

Incidence of low- and high-energy fractures in persons with and without HIV-infection: a Danish population-based cohort study

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Objective: To compare fracture risk in persons with and without HIV-infection and to examine the influence of HAART initiation on risk of fracture.

Design: Population-based nationwide cohort study using Danish registries.

Methods: Outcome measures were time to first fracture at any site, time to first low-energy and high-energy fracture in HIV-infected patients (n = 5,306) compared with a general population control cohort (n = 26,530) matched by sex and age during the study period 1995 to 2009. Cox regression analyses were used to estimate incidence rate ratios (IRR).

Results: HIV-infected patients had increased risk of fracture [IRR: 1.5 (95% CI; 1.4–1.7)] compared with population controls. The relative risk was lower in HIV-mono-infected patients [IRR: 1.3 (95% CI; 1.2–1.4)] than in HIV/HCV-coinfected patients [IRR: 2.9 (95% CI; 2.5–3.4)].

Both HIV-monoinfected and HIV/HCV-coinfected patients had increased risk of low-energy fracture, IRR of 1.6 (95% CI; 1.4–1.8) and 3.8 (95% CI; 3.0–4.9). However, only HIV/HCV-coinfected patients had increased risk of high-energy fracture, IRR of 2.4 (95% CI; 2.0–2.9). Among HIV-monoinfected patients the risk of low-energy fracture was only significantly increased after HAART-exposure, IRR of 1.8 (95% CI; 1.5–2.1). The increased risk in HAART-exposed patients was not associated with CD4 cell count, prior AIDS, tenofovir or efavirenz exposure, but with comorbidity and smoking.

Conclusions: HIV-infected patients had increased risk of fracture compared with population controls. Among HIV-monoinfected patients the increased risk was observed for low-energy but not for high-energy fractures, and the increased risk of low-energy fracture was only observed in HAART-exposed patients.

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Introduction

Increased prevalence of osteopenia and osteoporosis is well documented in both antiretroviral naïve and antiretroviral treated HIV-infected persons [1]. Chronic

HIV-infection is associated with immune-activation, chronic inflammation, and low body mass index (BMI), which are all established risk factors for low bone mineral density (BMD). Antiretroviral treatment may also cause accelerated bone loss. A number of

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randomized controlled trials have demonstrated accelerated bone loss in the initial six to twelve months after highly active antiretroviral therapy (HAART) initiation followed by stabilization of BMD hereafter [2–4]. Further, prospective studies of patients on established HAART showed stable or increasing BMD [5,6]. Although there are drug and drug class differences, especially tenofovir causes a larger initial bone loss [2,4], the initial BMD loss after HAART initiation has been observed for all combinations of major drug classes in the HAART regimen [3,7–9]. Recent studies have also shown low BMD in MSM with primary HIV-infection [10] and in HIV-negative MSM at high risk of HIV-infection [11] thus suggesting importance of risk factors associated with both risk of HIV-infection and with low BMD.

The clinical impact of the changes in BMD remains uncertain. Most studies have found increased fracture rates among HIV-infected individuals compared with HIV-negative controls [12–15] whereas a study of premenopausal women did not [16]. Especially the influence of the short-term bone loss associated with HAART initiation on long-term risk of fracture is not well described. Only few studies have specifically addresses the influence of HAART treatment on subsequent fracture risk. Two American studies found no association between HAART exposure and risk of fracture [14,16]; recently Bedimo et al found increased fracture risk in the HAART era compared with the pre-HAART era but primarily ascribed the increased risk to non HIV-related risk factors [17]. Some of the published studies have been hampered by small study populations, absence of information on hepatitis C status, included mainly intravenous drug users, or did not conduct separate analyses for low-energy and high-energy fractures.

We aimed to compare the overall incidence of fractures and the incidence of low-energy and high-energy fractures in antiretroviral-naïve and HAART-treated HIV-infected patients with the general population during the period January 1 1995 to January 1 2010. Linking data from the population-based Danish HIV Cohort Study with the Danish Civil Registration System and Danish National Hospital Registry allowed us to capture all fractures diagnosed at hospital admissions and at outpatient or emergency visits for both HIV-infected persons and matched general population controls.

Methods

Setting

The adult population of Denmark is 4.3 million with an estimated HIV prevalence of 0.09% [18]. Patients with HIV-infection are treated in one of the country's eight specialized medical centres, where they are seen on an outpatient basis at intended intervals of 12 weeks.

Antiretroviral treatment is provided free of charge to all HIV-infected residents in Denmark and prescribed according to international guidelines.

Data sources

We used the unique 10-digit civil registration number assigned to all individuals in Denmark at birth or upon immigration to link the data sources described below.

The Danish HIV Cohort study (DHCS) is a population-based prospective nationwide cohort study of all HIV-infected individuals 16 years or older and who have been treated at Danish HIV centres since 1 January 1995 [18,19]. Patients are consecutively enrolled, and multiple registrations are avoided through the use of the unique civil registration number. Data are updated yearly and include demographics, date of HIV-infection, AIDS defining events, smoking status, date and cause of death and antiretroviral treatment. CD4⁺ cell counts and HIV-RNA measurements are extracted electronically from laboratory data files.

From the Danish Civil Registration System (CRS), which has stored information on all Danish residents since 1968, we extracted information on vital status, residency, immigration and emigration [20].

The Danish National Hospital Register (DNHR) was initiated in 1977 and contains information on all patients discharged from Danish non-psychiatric hospitals. Since 1995 data on outpatients and emergency patients have been included as well. Each record includes the dates of admission and discharge, one primary and up to 19 secondary discharge diagnosis coded according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter. From this register, we extracted date of first fracture diagnosis, date of first low-energy and date of first high-energy fracture diagnosis [21].

HIV-infected and population control study populations

We included all HIV patients from the DHCS who received a diagnosis of HIV after the age of 16 years and lived in Denmark at time of HIV diagnosis. For the HIV-infected patients we defined the index date as 1 January 1995 or the date of the HIV diagnosis which ever came last. From the CRS we identified five population controls for each HIV-infected patient, matched by age (month and year of birth) and sex. For the population controls, the index date was defined as the index date of the HIV-infected patients to whom they were matched. The population controls had to be alive and living in Denmark on the index date.

Outcomes

We had three outcomes: The main outcomes were time to the first fracture at any site (ICD10-codes: M48.4–

M48.5, M84.3, S02.0–S02.9, S12.0–S12.9, S22.0–S22.9, S32.0–S32.9, S42.0–S42.9, S52.0–S52.9, S62.0–S62.9, S72.0–S72.9, S82.0–S82.9, S92.0–S92.9, T02.0–T02.9, T10.0, T10.9, T12.0, T12.9, T14.2) and time to first low-energy fracture. The secondary endpoint was time to first high-energy fracture. Similar to the approach used by Lippuner *et al* [22], we defined low-energy fractures as fractures possibly due to osteoporosis, typically those caused by low-energy trauma. The group comprised 28 relevant ICD-10 codes: M48.4 (Vertebral fatigue fracture), M48.5 (Vertebral compression fracture, not classified elsewhere), M84.3 (Stress fracture, not classified elsewhere), S22.0 (Fracture of the thoracic spine), S22.1 (Multiple fractures of the thoracic spine), S22.3 (Rib fracture), S32.0 (Fracture of the lumbar spine), S32.1 (Fracture of the sacrum), S32.5 (Fracture of the pubis), S32.7 (Multiple fractures of the lumbar spine), S32.8 (Other fractures of the lumbar spine), S42.2 (Fracture of the proximal humerus), S42.3 (Fracture of the humerus shaft), S52.2 (Fracture of the ulna shaft), S52.5 (Fracture of the distal radius), S52.6 (Combined fracture of the distal radius/ulna), S72.0 (Fracture of the femoral neck), S72.1 (Pertrochanteric fracture), S72.2 (Subtrochanteric fracture), S72.4 (Fracture of the femur, distal), S72.8 (Fracture of the femur, other), S72.9 (Fracture of the femur, no further mention), S82.1 (Fracture of the tibia, proximal), S82.2 (Fracture of the tibia shaft), S82.3 (Fracture of the tibia, distal), S82.4 (Fracture of the fibula), S82.5 (Fracture of the malleolar int.), S82.6 (Fracture of the malleolar ext.).

To further explore the risk of low-energy fracture, we grouped the low-energy fractures as wrist, humerus, hip, vertebral, or other low-energy fractures.

High-energy fractures were defined as fractures unlikely to be due to osteoporosis, typically those caused by high-energy trauma [22]. High-energy fractures comprised 29 relevant ICD-10 codes:

S42.0 (fracture clavícula), S42.4 (fracture humerus distal), S42.7 (multiple fractures clavícula), S42.8 (other fractures of the shoulder, upper arm), S42.9 (fracture of the shoulder, no further mention), S52.0 (fracture ulna proximal), S52.1 (fracture radius proximal), S52.3 (fracture of the radius shaft), S52.4 (combined fracture of the radius/ulna), S52.7 (multiple fractures of the forearm), S52.8 (fracture of the forearm, other), S52.9 (fracture of the forearm, no further mention), S62 (fracture of the hand and wrist), S72.3 (fracture of the femur shaft), S72.7 (multiple fractures femur), S82.0 (fracture patella), S82.7 (multiple fractures of the lower leg), S82.8 (fractures of the lower leg, other), S82.9 (fracture of the lower leg, no further mention), S92 (fracture of the foot, excluding ankle), T02.1 (fractures involving thoracic and lumbar spine and pelvis), T02.2 (multiple fractures of the upper limb), T02.3 (multiple fractures of the lower limb), T02.4 (multiple fractures of

both upper limbs), T02.5 (multiple fractures of both lower limbs), T02.6 (multiple fractures of the lower and upper limbs), T02.7 (fractures involving thoracic and lumbar spine and pelvis and limbs), T02.8 (other combined fractures), T02.9 (multiple fractures, no further mention).

Comorbidity:

Patients with at least one positive hepatitis C virus (HCV)-antibody test or a positive HCV-RNA test were considered HCV-positive.

Comorbidity was included in the analyses as a modified Charlson Comorbidity Index (CCI) based on discharge diagnoses registered in the DNHR prior to the index date for both populations. The CCI assigns a score between one and six to a range of diseases recorded during previous hospital contacts, with the sum of scores serving as the co-morbidity measure for each patient (21). We captured the co-morbid diseases using the ICD-8 and ICD-10 codes. AIDS-defining diagnoses were not included. We defined three modified co-morbidity levels according to the CCI: low (score 0); medium (score 1–2); or high (score >2) [23,24].

HAART was defined as either combination antiretroviral treatment with at least three drugs that included a protease inhibitor (PI), a non-nucleoside reverse-transcriptase inhibitor (NNRTI), an integrase-inhibitor, and/or abacavir; or a combination of a ritonavir-boosted PI with an NNRTI or an integrase-inhibitor.

Statistical analyses

We computed time from the index date to date of first fracture, death, lost to follow-up, emigration or January 1, 2010 whichever came first. Similarly, we computed time from index date to first low-energy or to first high-energy fracture, death, lost to follow-up, emigration or January 1, 2010 whichever came first. As a measure of relative risk of contracting a fracture we used Cox regression analysis to compute unadjusted incidence rate ratios (IRRs). For low-energy fractures we further estimated IRR adjusted for comorbidity. In Denmark, HCV-infection is a marker of intravenous drug use and therefore we conducted separate analyses for HIV-monoinfected and HIV/HCV-coinfected patients [25].

For HIV-monoinfected patients, HIV/HCV-coinfected patients and population controls, we computed the cumulative incidence of low-energy and high-energy fractures respectively. Further for HIV-monoinfected patients and corresponding population controls we computed cumulative incidence of low-energy and high-energy fractures stratified by HAART treatment. In the analysis of fracture incidence before HAART initiation patients and corresponding population controls were followed from study entry until date of HAART initiation or censoring. In the analysis of fracture

incidence after HAART initiation patients and corresponding controls were followed from date of HAART initiation until end of study.

Cumulative incidence of fracture was computed with death as competing risk to avoid overestimation of fracture risk [26]. By using Schoenfeld residuals we determined that hazard ratios were constant within follow-up after HAART initiation.

To evaluate predictors of low-energy fractures for HIV-monoinfected patients on HAART we fitted a model including CD4 cell count before start of HAART, prior AIDS defining event, gender, age (<35 years, 35–49 years, \geq 50 years), race, Charlson Comorbidity Index, and time of HIV-diagnosis before or after January 1 1995. We did not have complete data on smoking, therefore we estimated the effect of smoking (ever vs. never) on fracture risk in a separate model.

As tenofovir has been associated with more accelerated bone loss [2,4] and efavirenz has been associated with vitamin D deficiency [27,28] we performed analyses in which the start date of tenofovir or efavirenz was introduced as time dependent variables from date of first exposure to the drug of interest until end of study. Tenofovir has been approved later than most other nucleoside reverse-transcriptase inhibitors (NRTIs), which could introduce confounding. Abacavir has also been introduced later than other NRTIs and we undertook a similar analysis in which start date of abacavir was the time-dependent variable to allow comparison of the effect of tenofovir versus abacavir.

For low-energy fractures, incidence rates (IRs) were calculated for 1,000 person years at risk (PYR) with 95% confidence intervals (CIs) for three time periods (1995–1996, 1997–2003, and 2004–2009).

SPSS statistical software (Norusis; SPSS Inc., Chicago, Illinois, USA) and R software, version 2.8.1, was used for data analysis.

Approvals and permissions

The Danish Data Protection Agency approved the establishment of the cohort study and the record linkage with CRS and DNHR.

Results

Characteristics of the study population.

The study population included 5306 HIV-infected patients and 26,530 individuals in the general population control cohort (Table 1). Patients and population controls were well matched in terms of age at index date and sex, and furthermore, they were equally distributed in terms

of emigration and loss to follow-up. Median age was 37 years and the male-to-female ratio was 3:1. Almost two thirds of the HIV-infected patients (62%) had received a diagnosis of HIV-infection after 1 January 1995, and 78% percent of the HIV-infected patients started HAART during the study period. Co-infection with HCV was observed in 851 (16%) of the HIV-infected patients.

Total number of fractures

We observed 806 fractures in the HIV-infected cohort during 38,456 person-years (PYR) [IR of 21.0/1000 PYR (95% CI; 19.8–22.2)], and 3312 fractures in the general population control cohort during 245,315 PYR [IR of 13.5/1000 PYR (95% CI; 13.1–13.9)]. HIV-infected patients had increased fracture risk compared with population controls, IRR of 1.5. Fracture risk was increased in both HAART-naïve (IRR of 1.4) and HAART-exposed patients (IRR of 1.6). Compared with corresponding population controls both HIV-monoinfected patients (IRR of 1.3) and HIV/HCV-coinfected patients (IRR of 2.9) had increased risk of fracture. Table 2 displays IRRs with 95% CI.

Low-energy fractures

For HIV-monoinfected patients the IR of low-energy fracture was 7.4/1000 PYR (95% CI; 6.7–8.2), for HIV/HCV-coinfected patients the IR was 17.7/1000 PYR (15.3–20.5), and for the population controls cohort the IR was 4.8/1000 PYR (4.6–5.0). Compared with the population controls both HIV-monoinfected patients (IRR of 1.6) and HIV/HCV-coinfected patients (IRR of 3.8) had increased risk of low-energy fracture. Figure 1 displays cumulative incidence of low-energy fractures for the three groups.

All subgroups of low-energy fractures contributed to the increased risk of low-energy fracture observed in HIV-monoinfected patients. For HIV/HCV-coinfected patients the relative risk of hip fractures was substantially higher than risk of other low-energy fractures, IRR of 16.0, while vertebral fractures seemed under-represented (Table 2).

High-energy fractures

For HIV-infected patients the IR of high-energy fracture was 9.5/1000 PYR (95% CI; 8.7–9.5), for HIV/HCV-monoinfected patients the IR was 22.7/1000 PYR (19.9–25.9), and for population controls the IR was 8.7/1000 PYR (8.4–9.0). Thus HIV-monoinfected patients and population controls had comparable risks of high-energy fractures, while HIV/HCV-coinfected patients had increased risk of high-energy fractures compared with population controls, IRR of 2.4 (Fig. 1).

Low-energy fractures in HAART-naïve versus HAART treated HIV-monoinfected patients

Figure 2 displays cumulative incidence of low-energy fractures stratified by time before and after HAART

Table 1. Characteristics of HIV-infected patients and controls.

	HIV-infected N = 5306	Population controls N = 26530
Age, years, median (IQR)	36.7 (30.5–44.5)	36.7 (30.5–44.5)
Male, no (%)	4042 (76%)	20210 (76%)
Duration of follow up, years, median (IQR)	6.5 (2.5–12.1)	9.6 (4.6–15.0)
Loss to follow up, no (%)	22 (0.4%)	44 (0.2%)
Migration, no (%)	219 (4.1%)	1082 (4.1%)
Died (%)	1341 (25.3%)	1256 (4.7%)
Infection risk factor, no (%)		
MSM	2408 (45%)	
Heterosexual	1929 (36%)	
IDU	563 (11%)	
Caucasian, no (%)	4172 (80%)	
Diag. Of HIV before 1 Jan 1995	2009 (38%)	
HAART during study period, no (%)	4113 (78%)	
CD4 cell count at index date, median (IQR)	274 (103–470)	
HCV-coinfection, no (%)	851 (16%)	
Fractures, no (%)	806 (15%)	3312 (12%)

IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men.

exposure in HIV-monoinfected patients and corresponding population controls. As illustrated, there was no significant difference in fracture risk between HAART-naïve patients and population controls. In contrast, HAART-exposed patients had increased risk of low-energy fracture [IRR of 1.8 (95% CI; 1.5–2.1)] compared with population controls. After adjusting for comorbidity the IRR was 1.6 (95% CI: 1.36–1.87). A plot of Schoenfeld residuals proved that the risk of low-energy fracture was constant over time after HAART initiation (data not shown).

Risk-factors for low-energy fractures in HAART-exposed HIV-monoinfected patients

For HIV-monoinfected patients, we estimated the effect of age, gender, an AIDS defining diagnosis prior to HAART, CD4 cell count and race in univariate and

multivariate analyses restricted to time after HAART initiation (Table 3). We found no significant association between CD4 cell count, prior AIDS diagnosis or gender and risk of low-energy fracture. Caucasian race, increasing age and medium or high comorbidity score was associated with increased fracture risk in both univariate and multivariate analyses. We had only information on smoking in 69% of the patients (of whom 67% were current or former smokers) and therefore evaluated the effect of smoking in a separate model. Smoking was associated with increased fracture risk, unadjusted IRR of 2.0 and adjusted IRR of 2.0.

Use of tenofovir did not increase the risk of fracture, IRR of 1.2 (95% CI; 0.8–1.7); neither did the use of efavirenz, IRR of 1.1 (0.8–1.4). The IRR for use of abacavir was 0.9 (0.7–1.2).

Table 2. Overall risk of fracture, risk of low-energy fracture and risk of high-energy fracture compared with the population controls.

Fracture type	HIV		HIV-monoinfected.		HIV/HCV-coinfected	
	No	IRR (95% CI)	No	IRR (95% CI)	No	IRR (95% CI)
All	806 ^a	1.5 (1.4–1.7)	562	1.3 (1.2–1.4)	244	2.9 (2.5–3.4)
Low-Energy	375	1.9 (1.7–2.2)	256	1.6 (1.4–1.8)	119	3.8 (3.0–4.9)
Before HAART	104	1.6 (1.3–1.9)	57	^b	47	3.2 (2.2–4.5)
After HAART	271	2.1 (1.8–2.4)	199	1.8 (1.5–2.1)	72	4.6 (3.4–6.2)
By type of fracture:						
Wrist	94	1.7 (1.3–2.1)	60 (23)	1.3 (1.0–1.7)	34 (29)	3.8 (2.6–5.7)
Humerus	57	3.5 (2.6–4.9)	42 (16)	3.3 (2.3–4.7)	15 (13)	4.5 (2.3–5.7)
Hip	51	4.1 (2.9–5.9)	27 (11)	2.5 (1.6–3.8)	24 (20)	16.0 (8.0–32.3)
Vertebra	18	1.2 (0.75–2.1)	17 (7)	1.4 (1.1–1.7)	1 (1)	0.5 (0.1–3.8)
Other	155	1.6 (1.4–1.9)	110 (43)	1.4 (1.1–1.7)	45 (38)	3.0 (2.1–4.2)
High-energy	467	1.3 (1.2–1.5)	320	1.1 (0.97–1.2)	147	2.4 (2.0–2.9)
Before HAART	163	1.3 (1.2–1.5)	95	1.0 (0.8–1.2)	68	2.3 (1.7–3.0)
After HAART	304	1.3 (1.1–1.5)	225	1.2 (1.0–1.3)	79	2.5 (2.0–3.3)

CI, Confidence interval; IRR, Incidence rate ratio.

^aAmong the 806 fractures observed among the HIV-infected patients, 292 fractures were categorized as low-energy fractures, 396 were categorized as high-energy fractures, and 118 did not fall into any of the two categories. In the overall analyses some patients have been censored by another type of fracture before the occurrence of a low-energy fracture or high-energy fracture and therefore the number of these fractures is lower in this analyses than in the subsequent analyses of time to first low-energy or first high-energy fractures.

^bIRR was not calculated as the proportional hazard assumption was not fulfilled (Figure 2 left).

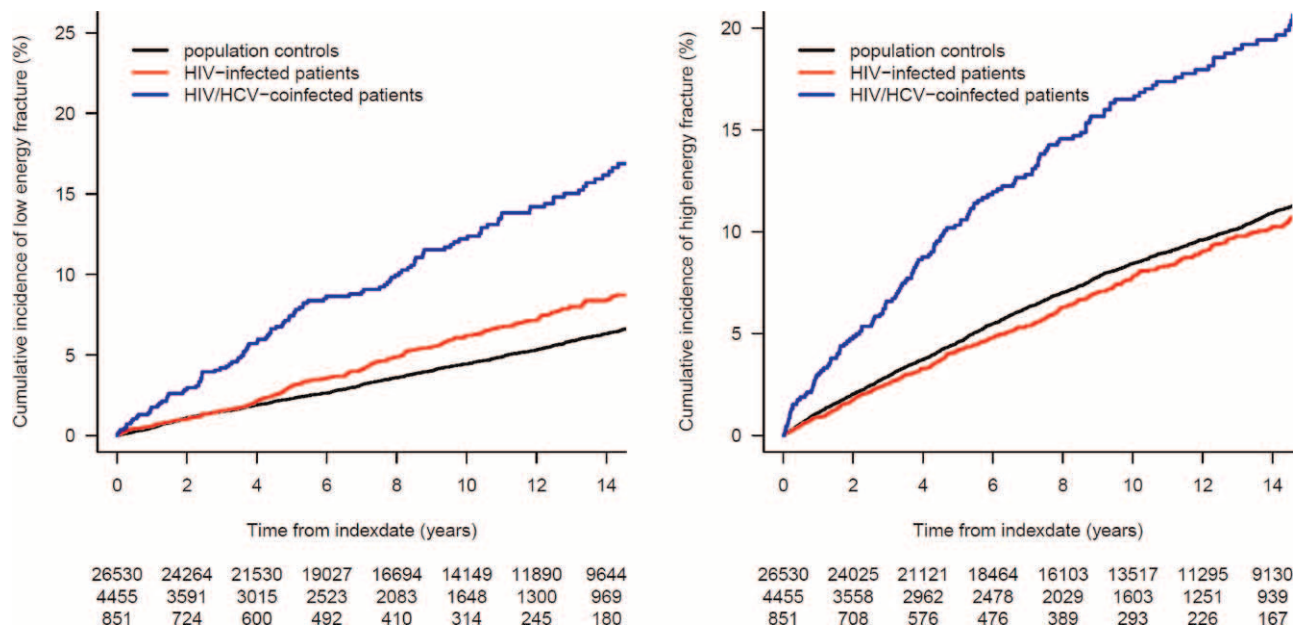


Fig. 1. Cumulative incidence of low-energy fractures (left) and high-energy fractures (right) in HIV-monoinfected patients, HIV/HCV-coinfected patients and population controls.

Temporal trends in incidence rates of low-energy fractures

For HIV-monoinfected subjects the IR increased from 3.5/1000 PYR (95% CI; 2.2–5.7) for the pre-HAART period (1996–1997) to 8.3/1000 PYR (95% CI; 7.2–9.7) for the period 1997–2003 and 7.5/1000 PYR (95% CI; 6.5–8.6) for the period 2004–2009.

For HIV/HCV-infected subject the IR remained stable during the three periods, 16.7/1000 PYR (11.1–25.3), 17.9/1000 PYR (14.4–22.2) and 17.8/1000 PYR (14.1–22.4), respectively.

For the population control cohort the IR were 6.2/1000 PYR (5.4–7.1) for 1995–1996, 4.6/1000 PYR (4.3–4.9) for 1997–2003, and 4.7/1000 PYR (4.4–5.0) for 2004–2009.

Discussion

In this nationwide population-based cohort study we found that HIV-monoinfected patients had increased risk of low-energy fractures driven by the period after HAART exposure compared with population controls. In contrast, we observed similar risks of high-energy fractures in HIV-monoinfected patients and controls.

The risk of fractures is determined by a combination of bone strength and a relevant trauma [13]. The fracture risk in HIV/HCV-coinfected patients with considerably increased risk of both low-energy and high-energy fractures was substantially different from that observed in

HIV-monoinfected patients We have previously shown that HIV/HCV-coinfected patients had a poorer prognosis irrespective of recorded HIV transmission group [29], and further that HCV co-infection was a very sensitive marker of past or ongoing intravenous drug use and of lifestyle-related risk factors [25,30]. Thus the markedly increased fracture risk in HIV/HCV-coinfected patients may be associated with consequences of intravenous drug use or increased alcohol use including increased fall or trauma risk [16]. To reduce confounding by lifestyle-related factors and more precisely explore the influence of HIV-infection and HAART exposure on risk of fracture we therefore performed analyses restricted to HIV-monoinfected patients.

HIV-monoinfected individuals had increased risk of low-energy fractures compared with population controls, and importantly this risk was only increased in HAART-exposed patients. Our study is the first to highlight an association between HAART exposure and subsequent fracture risk. Only few previous studies have analyzed data on HAART initiation and subsequent fracture risk; Yin *et al* found no association with cumulative use of HAART and fracture risk [16]; Young *et al* found that HAART exposure was associated with a hazard rate of 1.39 for fracture [14], but their result was not statistically significant.

As in all observational studies we can identify associations but cannot attribute causality. We found an association between HAART-exposure and increased risk of low-energy fracture but cannot determine whether this increased risk is induced by the alterations in BMD observed after HAART initiation or by differences

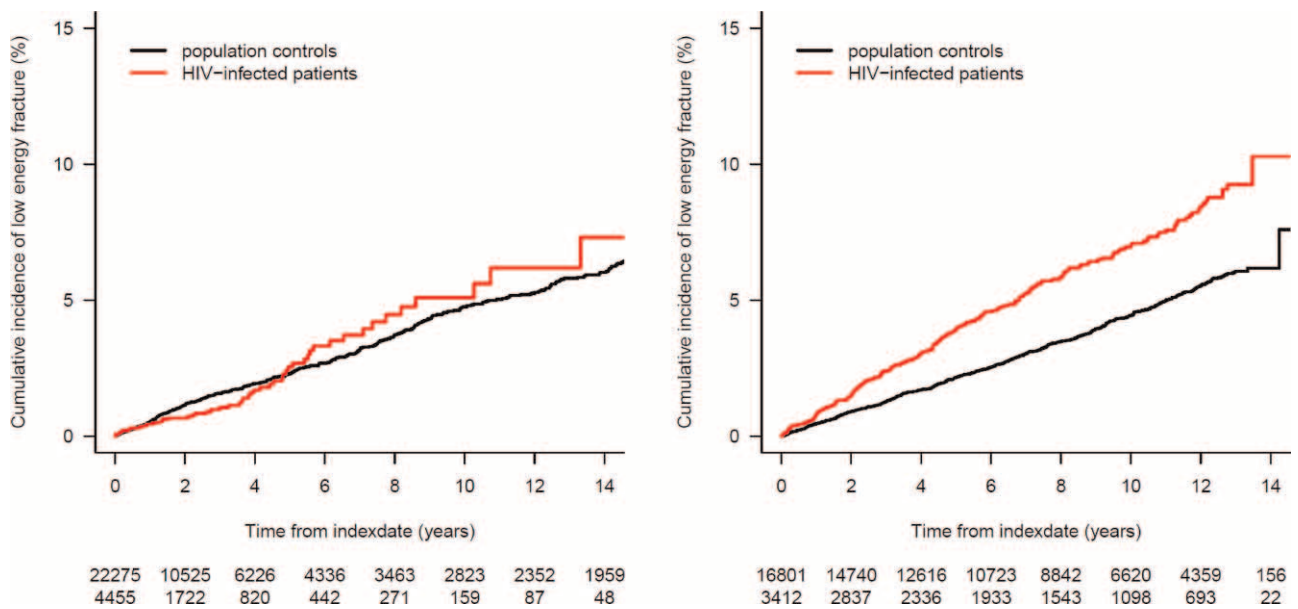


Fig. 2. Cumulative incidence of low-energy fractures before and after HAART initiation in HIV-monoinfected patients and matched population controls. The left figure shows timing of fracture from entry into the study until initiation of HAART or censoring which ever comes first. The right figure shows timing of fracture from initiation of HAART until censoring.

between HAART-treated and HAART-naïve patients. Use of HAART may be a marker of duration and/or severity of HIV-infection, and the two groups may therefore have different immunological profiles and response to HIV-infection. Previous studies have shown association between low CD4 cell count and increased BMD loss after start of HAART [3,7]. While one study [14] found an association between low CD4 cell count and fracture risk others did not [13,16]. In our study, neither pre-HAART CD4 cell count nor pre-HAART AIDS defining diagnosis were significantly associated with subsequent fracture risk

Adjusting for comorbidity attenuated the difference in fracture risk between HIV-infected patients and controls. We were not able to adjust for other traditional risk factors for osteoporosis such as low BMI, smoking and steroid exposure that may also be more common in HIV-infected patients than in general population controls. Among HAART-exposed patients smoking was associated with a two-fold increased risk of low-energy fracture. Thus, increased prevalence of smoking among HIV-infected patients [31] may explain part of the excess risk. Concerns have been raised about the long-term effect of tenofovir on bone strengths. However, similar to three other studies we found no association between use of tenofovir and

Table 3. Predictors of low-energy fracture after HAART initiation in HIV-monoinfected patients.

	Unadjusted IRR (95% CI)	Adjusted IRR ^a (95% CI)
Age		
<35 years (ref)	1	1
35–49 years	1.30 (0.92–1.83)	1.18 (0.82–1.70)
≥ 50 years	2.45 (1.7–3.53)	1.91 (1.28–2.86)
Previous AIDS	1.16 (0.84–1.58)	1.09 (0.77–1.55)
CD4 cell count>200	0.97 (0.73–1.29)	1.02 (0.75–1.38)
Female	0.82 (0.58–1.16)	1.20 (0.80–1.78)
Caucasian	2.00 (1.32–3.04)	1.74 (1.06–2.84)
Charlsons Comorbidity Index		
Low, score 0 (ref)	1	1
Medium, score 1–2	2.05 (1.37–3.06)	1.71 (1.13–2.58)
High, score>2	2.08 (0.98–4.43)	1.45 (0.64–3.30)
HIV after 1995	0.95 (0.72–1.27)	0.99 (0.74–1.33)
Smoking	1.97 (1.27–3.05)	2.05 (1.28–3.27)

CI, Confidence interval; IRR, Incidence rate ratio.

^aAll variables except smoking included in the adjusted analyses. Adjusted IRR for smoking was estimated in a separate model including all other variables.

fracture risk [4,13,16]. As in most other studies, Caucasian race and increasing age were associated with increased fracture risk.

The strengths of our study include the use of population-based nationwide cohorts; long and nearly complete follow-up; access to detailed data on fracture and comorbidity in DNHR; and for the HIV-patients clinical information on use of antiretroviral treatment, AIDS defining events, CD4 cell count and viral load. Our study also had limitations. Fracture data were incomplete before 1995 as the DNHR only included data on outpatients and emergency patients since 1995. Therefore we could not exclude persons with low-energy fracture before the index date.

We used a wider definition of low-energy fractures than the major osteoporotic fractures at spine, forearm, hip and shoulder [32], and therefore we also present relative risks for each type of low-energy fracture. Another potential shortcoming is inaccuracies in fracture diagnoses reported to DNHR. However, the positive predictive value of the registry diagnoses is generally high (70% to 99%) [33], and the positive predictive value of hip fractures in DNHR has been shown to be as high as 93% [34].

In conclusion, we found that HIV-infected patients had increased risk of fracture at any site. HIV-infected patients without HCV-coinfection had increased risk of low-energy fractures but not of high-energy fractures. The risk of low-energy fracture was associated with HAART-exposure but also with traditional risk factors such as age, comorbidity and smoking. The risk associated with HAART was moderate and did not increase over time. Future research should explore mechanisms behind the HAART-associated initial BMD loss and investigate possible interventions in patients at high risk of osteoporosis.

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Contributions: AH, JG, and NO designed the study and analysed and interpreted the data; AH wrote the manuscript; JG, GK, CL, CP, GP and NO revised the manuscript critically; JG, GK, CL, CP, GP and NO collected the data.

Conflicts of interest

Potential conflicts of interest: Ann-Brit Eg Hansen has received travel grants from Bristol-Myers Squibb and Gilead.

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