Impact of Antiretroviral Drugs on Fracture Risk in HIV-Infected Individuals: A Case–Control Study Nested Within the French Hospital Database on HIV (FHDH-ANRS CO4)

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Impact of antiretroviral drugs on fracture risk in HIV-infected individuals: A case-control study nested within the French Hospital Database on HIV (FHDH-ANRS CO4)

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Abstract

Background: HIV-infected patients have lower bone mineral density and a higher incidence of fractures than the general population of the same age and sex. To assess the impact of antiretroviral drugs (ARV) exposure on the risk of osteoporotic fractures, we conducted a nested case-control study.

Methods: Cases were individuals enrolled while ARV-naive, with a first prospectively recorded fracture between 2000 and 2010. Controls were randomly selected after matching for sex, age (±3 years), period of HIV diagnosis (<1997/$\geq$1997) and clinical centre. The risk of fracture was analysed with conditional logistic regression models, using different ways to model ARV exposure. All exposure variables and potential confounders were included in multivariable models.

Results: Among 861 reviewed cases, 261 fractures were osteoporotic and 254 of cases were matched to at least one control (376 controls). The median year of fracture diagnosis was 2007 (IQR 2004-2009): 49% of patients had been exposed to tenofovir disoproxil fumarate (TDF) and 82% to protease inhibitors (PIs).

After taking into account the transmission group, AIDS status, geographic origin, BMI, current smoking status, alcohol consumption, exposure to systemic glucocorticoids, and the period of enrolment, there was no association between the risk of fracture and exposure to TDF (OR for cumulative exposure: 1.04 [0.86-1.27], similar results for ever-exposed subjects), to NRTIs, or to PIs (OR for cumulative PI exposure: 1.02 [0.92-1.12]).

Conclusion: We found no evidence of an excess risk of fracture following exposure to TDF or PIs. This has important implications for the debate concerning tenofovir alafenamide versus generic TDF.

Introduction

People living with HIV (PLHIV) have a lower bone mineral density (BMD) [1] and a higher incidence of fractures than the general population of the same age and sex [2-7]. Data from randomized trials in antiretroviral treatment (ARV) naive patients show that BMD declines after ARV initiation [8,9], especially with tenofovir disoproxil fumarate (TDF) compared to other nucleoside reverse transcriptase inhibitors (NRTIs) both at the lumbar spine and the hip [10,11]. The decline was also greater with protease inhibitors (PIs) than with non nucleoside reverse transcriptase inhibitors (NNRTIs) at the lumbar spine [10,12]. The data concerning PIs might be artefactual being linked to an increase in visceral fat. A significant gain in fat mass correlating with a sharp drop in BMD has been observed during PI exposure [13]. Simulated increases in body fat reduced the mean Dual-energy X-ray absorptiometry (DXA) spine BMD but did not affect the mean DXA hip BMD, a finding that might explain the trial results [14]. In trials of pre-exposure prophylaxis (PrEP), in HIV-uninfected individuals, TDF was associated with a small decline in BMD [15,16]. In the SMART trial, ARV discontinuation was followed by an increase in BMD [17]. Ten studies (see supplementary table 1) have examined links between specific ARV and the risk of fracture [5,7,18-25]. They variously considered fractures, fractures at osteoporotic sites (or both), or low-energy fractures. They also differed in the confounders they took into account. In particular few considered classical risk factors for osteoporotic fractures such as the body mass index (BMI), ethnic origin, current smoking status, daily alcohol consumption exceeding two units, a family history of hip fracture, systemic glucocorticoids, rheumatoid arthritis, and menopausal status [26]. Few of these studies showed an association between an increased risk of fracture and exposure to TDF or to PIs (respectively 1/7 and 1/6), or of fractures at osteoporotic sites (respectively 2/6 and 2/3). In one of the study [5] showing a statistical association between ongoing PI exposure and an increased risk of fracture, the authors considered that the link was not causal. The purpose of the present study was to assess the possible impact of ARV on the risk of low-energy fractures at potential osteoporotic sites focusing on PIs and TDF.

Methods

The French Hospital Database on HIV (FHDH-ANRS CO4)

The FHDH is a hospital-based open multicentre cohort in which inclusions have been ongoing since 1989 [27]. Individuals are eligible if they have documented HIV-1 or HIV-2 infection and give their written informed consent to participate. Data are collected prospectively by trained research assistants on standardized forms, which include demographic characteristics, the date and type of clinical events recorded according to the International Disease Classification ART and biological markers. The FHDH project was approved by the French data protection authority (Commission National de l'Informatique et des Libertés on 27 November 1991, Journal Officiel, 17 January 1992).

Study design

The protocol, including a detailed statistical analysis plan, was written at the time of submission of the project to the French medicines agency (Agence Nationale de Sécurité du médicament et des produits de santé (ANSM)) and to France REcherche Nord & Sud Sida-hiv Hépatites (ANRS).

We conducted a case-control study nested in the FHDH and focusing on HIV-1 infected individuals who were enrolled in the FHDH while ARV-naive. We chose this approach because of the time-varying nature of ARV use, the large size of the cohort, and the long duration of follow-up [28]. Moreover, compared with a full cohort approach with a survival analysis using time-dependent variables, a nested case-control analysis provides estimates of odds ratios (ORs) from conditional logistic regression models that are unbiased estimates of relative risk (RR) [29].

Case definition

Cases were individuals enrolled in the FHDH while ARV-naive and who had a first prospectively reported low-energy fracture at a potential site of osteoporotic fracture between January 2000 and December 2010. Individuals who were selected as controls but for whom a fracture report was found

in their medical records when extracting the data were also considered as cases. The potential osteoporotic sites were the vertebrae, hip, wrist, upper humerus, lower femur, upper tibia, and simultaneous fracture of 3 or more ribs. A low-energy fracture was defined as a fracture sustained after mild trauma such as a fall from standing height.

Selection of controls

Controls were individuals enrolled in the FHDH while ARV-naive and with no history of fracture. They were randomly selected with the incidence density sampling method [30], after individual matching for sex, age (± 3 years), period of HIV diagnosis (<1997/≥1997), being under follow-up at the date of fracture in the corresponding case (± 3 months) and, if possible, the clinical centre.

Potential confounders

It was important to take into account pre-existing risk factors for fractures that might have influenced the choice of ARV during the study period. The following traditional risk factors were explored: geographic origin (sub-Saharan Africa/other), BMI (underweight (<18.5)/ normal (18.5≤BMI≤25)/ overweight (>25)), smoking status (no/past/current), alcohol consumption above two glasses per day (no/yes), family history of hip fracture (no/yes), prior exposure to systemic glucocorticoids (no/yes) and menopausal status for women (no/yes). We also studied the potential effect of the following HIV-related variables on the risk of fracture: period of enrolment in the FHDH (≤1996/1997-2001/2002-2010), transmission group (men who have sex with men (MSM)/other), period of ARV initiation (Naive/<1997/1997-2001/2002-2010), AIDS status, CD4 T-cell nadir, and anti-hepatitis C virus antibody status (HCV Ab-/HCV Ab+) before the date of fracture in the cases. In addition, we considered the CD4 T-cell count, CD8 T-cell count, CD4 to CD8 T-cell ratio and viral load (VL) measured within 6 months of the date of fracture in the cases. Finally, we collected available data on osteoporosis which could be on the causal pathway between ARV exposure and the risk of fracture and chronic kidney disease (dialysis or estimated glomerular filtration rate (eGFR) using the CKD-EPI equation from creatinine level < 60 mL/min/1.73m^2 (no/yes)) which may lie on the causal

pathway between TDF exposure and the risk of fracture. These last 2 variables were only to be used in sensitivity analyses if a significant association was found between exposure to any ARV and the risk of fracture.

Data collection

The date of fracture diagnosis, sex, age, geographic origin, and HIV parameters were extracted from the FHDH and validated in the medical records by trained medical assistants using a predefined case report form. We also collected the site and circumstances of the fracture, and potential confounders described above from the medical records. In addition, we used self administered questionnaire filled by the study participants to collect the date(s), site(s) and circumstance(s) of antecedent if any and referent fracture(s), smoking status, alcohol consumption above two units per day, a family history of hip fracture, systemic glucocorticoids, menopausal status, known osteoporosis, and dialysis. When data were recorded both in the medical records and in the questionnaire, we used the data from the questionnaire. When a value was missing both from the medical records and from the questionnaire, we used the value recorded in the FHDH if available.

Statistical analysis

Conditional logistic regression models were used to quantify the relation between exposure to individual antiretroviral drugs and the risk of fracture. Exposure to each drug was considered as the cumulative duration of exposure (model 1), or as "ever exposed" (yes/no) (model 2). In a 3rd model, the exposure variable for each antiretroviral drug was chosen according to the lowest values of Akaike's information criterion (AIC) in univariable models of the risk of fracture. In sensitivity analyses, exposure to each antiretroviral drug was modelled by a 3-category variable: never exposed, exposed for less than 2 years, and exposed for 2 years or more. ARV for which of less than 10% of controls were exposed was taken into account in the analyses, but the results are not reported. We also explored exposure to all PIs (darunavir (DRV), atazanavir (ATV), fosamprenavir/amprenavir

(FPV/AMP), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV)) and in separate models, exposure to first-generation PIs (all PIs except ATV and DRV).

Characteristics of the cases and controls were compared by using univariable conditional logistic regression. Known risk factors for fracture, except for menopausal status, were included in the multivariable models if they were present in at least 5% of individuals. Regarding factors related to HIV infection, these were included in the multivariable models if in the corresponding univariable conditional logistic regression model, the P value was below 0.10. For VL, CD4, the CD4 nadir, CD8, and CD4/CD8. The choice between continuous and categorical classification was based on the lowest AIC value in the corresponding univariable conditional logistic regression model.

All values missing for fewer than 50% of individuals were replaced by using a multiple imputation method, missing values being randomly sampled from their predicted distributions [29]. Ten sets of imputations were used to create 10 complete datasets. All 10 datasets were analyzed and combined with Rubin's rules. SAS software (v9.4; SAS Institute Inc, Cary, NC, USA) was used for all statistical analyses.

Results

Baseline characteristics of participants

The study flow chart is shown in figure 1. Among the 861 reviewed fractures, 261 low-energy fractures at a potential osteoporotic site were validated, and 254 of the patients concerned were matched with at least one control (376 controls). With a total of 254 cases and 376 controls, the odds ratios that could be detected with 80% power and a 5% type-one error were above 1.6 to 2.0 for exposure in the control group ranging from 50% to 10%. There were 285 self administered questionnaires completed of which 101 (41%) for the cases and 184 (49%) for the controls. Two hundred (78.7%) of the 254 cases had had only one fracture, 37 (14.6%) 2 fractures, 11 (4.3%) 3 fractures and 6 (2.4%) 4 fractures. There were 53 spine, 69 hip, 51 wrist, 30 humerus upper end, 11 femur lower end, 14 tibia upper end, 6 simultaneous 3-rib and 20 other fractures. The median year of

fracture diagnosis was 2007 [interquartile range (IQR), 2004-2009]. Characteristics of the cases and controls are shown in table 1. The rate of missing values was lower than 50% for all potential confounders: 15% for BMI, 7% for smoking status, 14% for alcohol consumption, 38% for a family history of hip fracture, 16% for prior systemic glucocorticoid exposure, 13% for chronic kidney disease, 1% for the CD4 nadir, 1% for CD4, 6% for CD8 and 2% for VL. In the case population, median age was 49 years, 67% of patients were men, and 71% were diagnosed with HIV infection before 1997. Their median CD4 cell count was 436/mm^3 [IQR, 293-592], their nadir CD4 cell count was 172/mm^3 [IQR, 75-298], and 65% of them had VL <50copies/mL. The corresponding values in controls were not significantly different. The proportion of individuals with AIDS was higher among the cases than the controls (31% versus 20%). Regarding classical fracture risk factors, the cases were less likely to be of sub-Saharan origin and more likely to have low BMI, alcohol consumption $\geq$ 2 glasses/day, and to have been exposed to systemic glucocorticoids. Unsurprisingly, osteoporosis had been diagnosed in more cases than controls.

The proportions of ARV-exposed cases and controls and the mean duration of exposure to individual ARVs are shown in table 2. At the date of fracture diagnosis, 49% of cases had been exposed to TDF and 82% to PIs, for 2.5 and 4.3 years respectively.

Less than 10% of controls had been exposed to darunavir, T20, raltegravir or maraviroc. In model 3, ARV exposure was modelled as follows: ever exposed (yes/no) to any ARV except EFV, ATV, DRV, FPV/APV and emtricitabine (FTC), the latter five drugs being modelled with their cumulative duration of exposure. In addition to ARV exposure, the multivariable models were adjusted for the period of FHDH enrolment, the HIV transmission group, prior AIDS-defining events, geographic origin, BMI, smoking status, alcohol consumption, and prior systemic glucocorticoid exposure.

Impact of ARV exposure on the risk of fracture

Univariable models of ARV exposure are shown in table 2. Multivariable models 1, 2, and 3 with adjustment for all ARV exposure and for all ARV exposure plus confounders are shown in table 3.

Models 1 and 3 had lower AIC values than model 2, whether they were adjusted for all ARVs alone or for ARVs and confounders.

Impact of TDF and PIs

In both the univariable and multivariable models, and regardless of how ARV exposure was modelled, no association was found between TDF and the risk of fracture: the OR was 1.21 (95% confidence interval (CI): [0.61-2.39]) in the ever-exposed model adjusted for ARV plus confounders and similar results were obtained for cumulative exposure (OR: 1.04, 95% CI [0.86-1.27]). Results were not changed after including existence of chronic kidney disease in the models (data not shown). Atazanavir was associated with an increased risk of fracture in univariable models using both cumulative exposure (OR: 1.32, 95% CI [1.08-1.62]), and ever exposure (OR: 1.59, 95% CI [1.01-2.51]). After accounting for other ARVs and confounding factors, we found no significant association in model 2 (OR: 1.89, 95% CI [0.96-3.72]), while the association was significant in model 1 (OR: 1.52, 95% CI [1.06-2.17]) and in model 3 (OR: 1.49, 95% CI [1.04-2.13]). In sensitivity analyses (supplementary table 2), atazanavir exposure for more than 2 years was associated with an increased risk of fracture in the univariable model (OR: 2.40, 95% CI [1.07-4.15]) but not after accounting for other ARVs and confounding factors (OR: 2.37, 95% CI [0.78-7.23]). We also checked whether there was an interaction between TDF and ATV and found no significant interaction (p-value=0.56 in Model 2 adjusted for ARV and confounders). Other PIs showed no significant association with the risk of fracture in any of the 3 multivariable models. Finally, there was no significant association between the risk of fracture and exposure to either all PIs or only to all first-generation PIs.

Impact of NRTI exposure

Zidovudine (ZDV) was associated with an increased risk of fracture in the univariable model using ever exposure (OR: 1.58, 95% CI [1.04-2.41]) but not cumulative exposure (OR: 1.01, 95% CI [0.96-1.06]). After accounting for other ARVs and confounding factors, ZDV was not associated with an increased risk of fracture in the 3 models. Zalcitabine (DDC) was not associated with the risk of

fracture in univariable models using either cumulative or ever exposure. After adjustment for ARV and confounders, cumulative exposure to DDC was associated with a lower risk of fracture in model 1 (OR: 0.66, 95% CI [0.45-0.97]), contrary to ever exposure to DDC. In adjusted models of sensitivity analyses, DDC exposure for more than 2 years was associated with a lower fracture risk (OR: 0.19, 95% CI [0.05-0.79]), while DDC exposure for less than 2 years was not associated with the risk of fracture. However, only 6% of controls and 2% of cases had been exposed to DDC for more than 2 years. No other association was found between NRTIs and the risk of fracture in any of the 3 models.

Impact of NNRTI exposure

Univariable models showed no association between cumulative exposure or ever exposure to efavirenz. After accounting for ARV and confounding factors, cumulative efavirenz exposure was associated with a lower risk of fracture in models 1 and 3, with respective ORs of 0.81 [0.69-0.96] and 0.82 [0.70-0.96] per year of exposure. In sensitivity analyses, exposure to efavirenz for either less than 2 years or more than 2 years was not associated with the risk of fracture. The proportion of individuals exposed to EFV for more than 2 years was small (15%).

Univariable models, showed no association between cumulative exposure to nevirapine (NVP) whereas ever exposure to NVP was associated with an increased risk of fracture, with an OR of 1.93 [1.32-2.83]. After accounting for other ARVs and confounding factors, NVP exposure was associated with a higher risk of fracture only in model 2.

Discussion

We found no robust association between the risk of fracture in HIV-infected patients and exposure to antiretroviral drugs including to TDF and PIs. Some drugs, particularly EFV associated with a lower risk and ATV associated with a higher risk, were significantly associated to the fracture risk in some of the models we constructed, however, sensitivity analyses showed that these associations were not robust.

We used several approaches to minimize biases including the choice of a case-control design nested within the FHDH cohort, use of controls matched for age and sex, which are two important risk factors for fracture [26], as well as the period of HIV diagnosis (which influences exposure to the different ARVs), and adjustment for both HIV-related parameters and classical fracture risk factors. These classical risk factors were associated with the risk of fracture in our study, supporting the reliability of our data. HCV coinfection was not taken into account in the multivariable models, because its prevalence was low (6%). Adding the variable in the models did not change our results. Several published studies have shown an association between HCV coinfection and the risk of fracture in populations with a higher prevalence of HCV infection. We recognize that our study does not provide information on the most recent drugs such as darunavir, rilpivirine, raltegravir, dolutegravir or elvitegravir.

Only one previous study has linked TDF to an increased risk of all fractures [23]. The difference between the two analyses reported in this paper is surprising. If the impact of TDF on the risk of fracture is mediated by its effect on BMD, the hazard ratio (HR) should be larger when the analysis is restricted to osteoporotic fractures rather than all fractures. And even if the exact HR value for osteoporotic fractures was not reported, it does not appear to be the case when looking at the figures of this paper. This does not support a causal link of the reported association. In addition one study [19] concluded that there was a modestly increased osteoporotic fracture risk associated with an cumulative TDF exposure, however, the association was only significant when resticiting the analysis to participants enrolled after 1996. In the ACTG study A5202 [10], despite a significant impact of TDF on BMD compared to abacavir, there was no significant difference in the incidence of fractures. Finally, a study based on the proportional reporting ratios of fracture in the EudraVigilance database between 2001 and 2016 did not show a disproportionality for all fractures in patients treated with TDF, while the disproportionality observed for osteoporotic fractures was based on 13 cases only [25]. This may well be explained by difference in reporting rates in EudraVigilance when TDF is part of an antiretroviral regimen. All others studies (supplementary Table 1) did not report an

association between exposure to TDF and the risk of fractures. Exposure to TDF may affect BMD but not necessarily the risk of fractures, as the decline in BMD occurs mainly during the first two years of treatment. Recent studies have shown no effect of TDF on BMD except during treatment initiation [31,32]. In addition, only 10 to 44% of the risk of fractures can be attributed to low BMD [33]. In our study, the selected fractures occurred years after ARV initiation and only 9.0% of case patients started ARV with a TDF-containing combination.

Only three studies have shown an increased risk of fracture with some PI exposure [5,19, 20], but it was not necessarily causal in one study [5] and consisted only of a moderate, non significant increase in the risk of osteoporotic fracture in the study by Bedimo et al, where only exposure to lopinavir was significantly associated with the risk of fracture [19]. In the study by Mundy et al, while exposure to all PI was not associated with an increased risk of fracture; exposure to darunavir and to saquinavir were associated with an increased risk of fracture [20]. As in our study, PIs were not found to be associated with the fracture risk in the remaining studies [7,22-25]. This is not unexpected, as the observed decline in spine BMD after PI exposure [10,12] was recently suggested to be a measurement artifact: BMD measurement at lumbar spine is less accurate following weight gain [14].

Conclusion

We found no evidence of an excess risk of fracture following exposure to TDF or to PIs. It would be interesting to study this risk during a more recent period in order to include more individuals initiating ARV with a TDF. These results have important implications for the use of tenofovir alafenamide versus generic TDF.
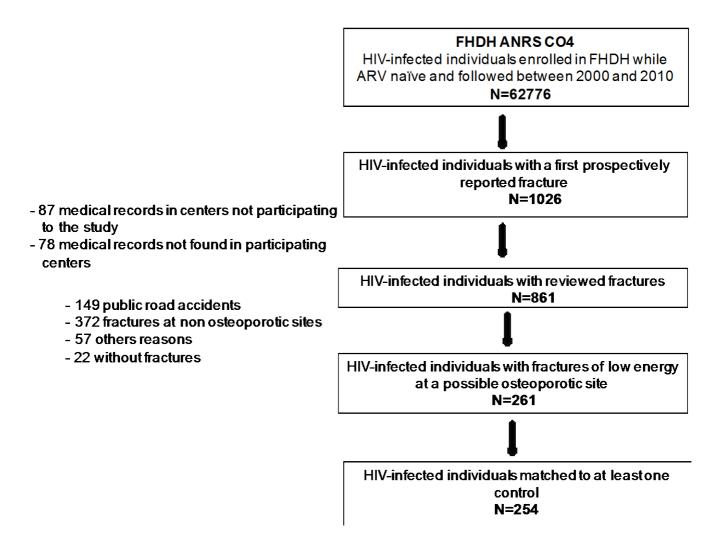
Acknowledgments

References

1. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS 2006; **20**: 2165-2174.

2. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. J Clin Endocrinol Metab 2008; **93**: 3499-3504.

3. Güerri-Fernandez R, Vestergaard P, Carbonell C, et al. HIV Infection Is Strongly Associated With Hip Fracture Risk, Independently of Age, Gender, and Comorbidities:A Population-Based Cohort Study. J. Bone Miner. Res. 2013; **28**: 1259–1263.

4. Prieto-Alhambra D, Güerri-Fernández R, De Vries F, et al. HIV Infection and Its Association With an Excess Risk of Clinical Fractures: A Nationwide Case–Control Study. JAIDS 2014; **66**: 90-95.

5. Womack JA, Goulet JL, Gibert C, et al. Increased risk of fragility fractures among HIV-infected compared to uninfected male veterans. PloS One 2011; **6**: e17217.

6. Young B, Dao CN, Buchacz K, Baker R, Brooks JT. Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS) compared with the US general population, 200-2006. Clin Infect Dis 2011; **52**: 1061-1068.

7. Sharma A, Shi Q, Hoover DR, et al. increased fracture incidence in middle-aged HIV-infected and uninfected women: updated results from the Women's Interagency HIV Study. JAIDS 2015; **70**: 54-61.

8. Grund B, Peng G, Gibert CL, et al. Continous antiretroviral therapy decreases bone mineral density. AIDS 2009; **23**: 1519-1529.

9. Hansen AB, Obel N, Nielsen H, Pedersen C, Gerstoft J. Bone mineral density changes in protease inhibitor-sparing vs. nucleoside reverse transcriptase inhibitor-sparing highly active antiretroviral therapy: data from randomized trial. HIV Med 2011; **12**: 157-165

10. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fracture in antiretroviral-naïve persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. J Infect Dis 2011; **203**: 1791-1801.

11. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis 2010; **51**: 963-972.

12. Duvivier C, Kolta S, Assoumou L, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with non nucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naïve patients. AIDS 2009; **23**: 817-824

13. Bonnet E, Ruidavets JB, Genoux A, et al. Early loss of bone mineral density is correlated with a gain of fat mass in patients starting a protease inhibitor containing regimen: the prospective Lipotrip study. BMC infection diseases 2013, **13**: 293

14. Yu EW, Thomas BJ, Brown JK, Finkelstein JS. Simulated increases in body fat and errors in bone mineral density measurements by DXA and QCT. J Bone Miner Res 2012, **27**: 119-24

15. Liu AY, Vittinghoff E, Sellmeyer DE, et al. Bone mineral density in HIV-negative men participating

in a tenofovir preexposure prophylaxis randomized clinical trial in San Francisco. PLoS One 2011; **6**: e23688

16. Mulligan K, Glidden DV, Anderson PE, Liu A, et al. Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in aRandomized, Double-Blind, Placebo-Controlled trial. CID 2015; **61**: 572-580

17. Hoy j, Grund B, Roediger M, et al. Interruption or deferral of antiretroviral therapy reduces markers of bone turnover compared with continuous therapy: the SMART Body Composition substudy. J Bone Miner Res 2013; **28**:1264-74

18. Hansen AB, Gerstoft J, Kronborg G, et al. Incidence of low and high-energy fractures in persons with and without HIV infection: a Danish population-based cohort study. AIDS 2012; **26**: 285-293

19. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS 2012; **26**: 825-831

20. Mundy LM, Youk AO, McComsey GA, Bowlin SJ. Overall benefit of antiretroviral treatment on the risk of fracture in HIV: nested case-control analysis in a health-insured population. AIDS 2012; **26**: 1073-1082

21. Gedmintas L, Wright EA, Dong Y, et al. Factors associated with fractures in HIV-infected persons: which factors matter? Osteoporos Int 2017; **28**: 239-244

22. Yin MT, Kendall MA, Wu Xingye, et al. Fracture after antiretroviral initiation. AIDS 2012; **26**: 2175-2184

23. Borges AH, Hoy J, Florence E, et al. Antiretrovirals, fractures and osteonecrosis in a large international HIV cohort. CID 2017; **64**: 1413-1421.

24. Gonciulea A, Wang R, Althoff KN, et al. An increased rate of fracture occurs a decade earlier in HIV+ compared with HIV- men. AIDS 2017; **31**: 1435-1443.

25. Garcia MG, Larrinaga-Torrontegui U, Eduardo Martinez M, Lertxundi U, Palacio-Zabalza I, Aguirre C. Fractures Related to Tenofovir: A Case/Noncase Study in the European Pharmacovigilance Database. Am J Ther. 2018

26. Kanis JA, Johnell O, Oden A, Johansson H, Mccloskey E. FRAXTM and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008; **19**: 385-397.

27. Mary-Krause M, Grabar S, Lièvre L, et al. Cohort Profile: French hospital database on HIV (FHDH-ANRS CO4). Int. J. Epidemiol. 2014; **43**: 1425-1436

28. Lang S, Mary-Krause M, Simon A, et al. HIV Replication and Immune Status Are Independent Predictors of the Risk of Myocardial Infarction in HIV-Infected Individuals. CID 2012; **55**: 600-607

29. Suissa S. Novel approaches to pharmacoepidemiology study design and statistical analysis. In: Strom B., ed. Pharmacoepidemiology. 4th ed. Wiley; 2005; 811-29.

30. Richardson DB. An incidence density sampling program for nested case-control analyses. Occup Environ Med 2004; **61**: e59

31. Tinago W, Cotter AG, Sabin CA, et al. Predictors of longitudinal change in bone mineral density in a cohort of HIV-positive and negative patients AIDS 2017; **31**: 643-652

32. Grant PM, Kitch D, McComsey GA, et al. Long-term Bone Mineral Density Changes in Antiretroviral-Treated HIV-Infected Individuals. JID 2016; **214**: 607-611

33. Stone KL, Seeley DG, Lui LY, et al for the study of Osteoporotic Fractures Research Group. BMD at multiple sites and risk of fractures of multiples types: long term results from the Study of Osteoporotic Fractures. J Bone Miner Res 2003; **18**: 1947-1954.

Fig. 1. Flow chart

FHDH ANRS CO4
HIV-infected individuals enrolled in FHDH while ARV naïve and followed between 2000 and 2010
N=62776

HIV-infected individuals with a first prospectively reported fracture
N=1026

- 87 medical records in centers not participating to the study
- 78 medical records not found in participating centers

HIV-infected individuals with reviewed fractures
N=861

- 149 public road accidents
- 372 fractures at non osteoporotic sites
- 57 others reasons
- 22 without fractures

HIV-infected individuals with fractures of low energy at a possible osteoporotic site
N=261

HIV-infected individuals matched to at least one control
N=254

254 cases matched to 376 controls

Table 1. Characteristics of participants

	Cases (n=254)		Controls (n=376)		Controls (n=376)
	n, median	n, median	n, median	%, [IQR]	
Age	49	[42-58]	49	[42-57]	
Gender					
Men	170	66.9	246	65.4	
Women	84	33.1	130	34.6	
HIV related factors:					
HIV-1 diagnosis period					
<1997	181	71.3	250	66.5	
≥1997	73	28.7	126	33.5	
Period of enrolment in FHDH					
≤1996	172	67.7	135	35.9	**<0.0001**
1997-2001	37	14.6	100	26.6	
2002-2010	45	17.7	141	37.5	
Transmission group					
MSM	86	33.9	74	19.7	**<0.0001**
Injecting drug use	56	22.0	39	10.4	
Other	112	44.1	263	69.9	
Period of ARV initiation					
Naïve	8		36		
<1997	104	42.3	134	39.4	0.636
1997-2001	73	29.7	103	30.3	
2002-2010	69	28.0	103	30.3	
Number of ARVs	6.0	[4.0-10.0]	5.0	[3.0-8.0]	**0.0003**
Cumulative duration of ARV exposure (months)	78.2	[34.9-119]	68.1	[21.7-123]	0.438
Nadir CD4 (cells/mm³) †	172	[75-298]	196	[82-287]	0.685**
CD4 (cells/mm³) at index date †	436	[293-592]	451	[310-612]	0.220**
CD8 (/mm³) at index date †	836	[589-1208]	872	[648-1151]	0.478**
CD4/CD8 at index date †	0.49	[0.32-0.76]	0.51	[0.35-0.74]	0.824**
Viral load (copies/ml) at index date †: <50 copies/ml	166	65.3	253	67.3	0.760**
Prior AIDS event					
No	175	68.9	302	80.3	**0.001**
Yes	79	31.1	74	19.7	
HCV antibody status					
Negative	235	92.5	356	94.7	0.314
Positive	19	7.5	20	5.3	
Classical risk factors for fracture:					
Sub-Saharan origin					
Yes	10	3.9	43	11.4	**0.002**
No	244	96.1	333	88.6	
BMI					
Missing	44	17.3	49	13.0	
Thin (< 18.5)	33	13.0	23	6.1	**0.045**
Normal (18.5 ≤ BMI ≤ 25)	137	53.9	214	56.9	
Overweight (> 25)	84	33.1	139	37.0	
Smoking status					
Missing	23	9.1	21	5.6	
No	105	41.3	181	48.1	0.132**
Past	54	21.3	61	16.3	
Current	95	37.4	134	35.6	
Alcohol consumption					
Missing	43	16.9	44	11.7	
≤2 glasses/day	193	76.0	326	86.7	**0.002**
>2 glasses/day	61	24.0	50	13.3	
History of hip fracture without major trauma in the father / mother					

	Cases (n=254)		Controls (n=376)		Controls (n=376)
	n, median	n, median	n, median	%, [IQR]	
Missing	120	47.2	121	32.2	
No	246	96.9	366	97.3	0.993**
Yes	8	3.1	10	2.7	
Prior systemic glucocorticoid exposure					
Missing	49	19.3	49	13.0	
No	229	90.2	362	96.3	**0.011****
Yes	25	9.8	14	3.7	
Chronic kidney disease: dialysis or eGFR (CKD-EPI<60)					
Missing	31	12.2	48	12.8	
No	222	87.4	336	89.4	0.282**
Yes	32	12.6	40	10.6	
Menopause before the fracture or age>50 years					
Missing	0	0.0	1	0.3	
No	38	45.8	64	49.6	0.431***
Yes	45	54.2	65	50.4	
Not relevant	171		247		
Known osteoporosis before the fracture					
Missing	124	48.8	121	32.2	
No	228	89.8	368	97.9	**0.002****
Yes	26	10.2	8	2.1	

* P values by conditional logistic regression

** P values after imputing missing values

*** Test restricted to women, after imputing missing values

† Number missing values for CD4 nadir: n=7, CD4: n=6, CD8: n=35, CD4/CD8: n=35, VL: n=10.

Table 2. ARV exposure

	Cases (n=254)	Controls (n=376)	Univariable models		
	n (% exposed)	n (% exposed)			
			OR (95% CI)	P	AIC
Exposure to tenofovir and to PIs:					
Tenofovir (TDF)	124 (48.8)	168 (44.7)	1.16 [0.81-1.66]	0.426	450
Mean duration ± sd (years)	1.21 ± 1.81	1.18 ± 1.87	0.99 [0.91-1.09]	0.905	450
Mean duration ± sd among exposed subjects	2.49 ± 1.88	2.65 ± 1.98			
Atazanavir (ATV)	53 (20.9)	57 (15.2)	1.59 [1.01-2.51]	0.047	445
Mean duration ± sd (years)	0.44 ± 1.10	0.25 ± 0.76	1.32 [1.08-1.62]	0.006	441
Mean duration ± sd among exposed subjects	2.09 ± 1.54	1.63 ± 1.27			
Fosamprenavir/amprenavir (FPV/AMP)	36 (14.2)	56 (14.9)	0.92 [0.58-1.48]	0.736	449
Mean duration ± sd (years)	0.27 ± 0.89	0.34± 1.09	0.91 [0.77-1.07]	0.242	448
Mean duration ± sd among exposed subjects	1.93 ± 1.55	2.27± 1.88			
Indinavir (IDV)	91 (35.8)	107 (28.5)	1.35 [0.94-1.94]	0.107	447
Mean duration ± sd (years)	0.75 ± 1.44	0.76 ± 1.85	0.98 [0.88-1.08]	0.633	449
Mean duration ± sd among exposed subjects	2.10 ± 1.72	2.66 ± 2.64			
Lopinavir (LPV)	104 (40.9)	113 (30.1)	1.70 [1.18-2.45]	0.005	441
Mean duration ± sd (years)	0.95 ± 1.83	0.70 ± 1.62	1.06 [0.97-1.17]	0.212	448
Mean duration ± sd among exposed subjects	2.32 ± 2.24	2.33 ± 2.23			
Nelfinavir (NFV)	85 (33.5)	103 (27.4)	1.23 [0.84-1.80]	0.281	448
Mean duration ± sd (years)	0.59 ± 1.25	0.60 ± 1.39	0.96 [0.84-1.09]	0.541	449
Mean duration ± sd among exposed subjects	1.76 ± 1.63	2.19 ± 1.90			
Saquinavir (SQV)	68 (26.8)	73 (19.4)	1.52 [1.00-2.32]	0.049	446
Mean duration ± sd (years)	0.53 ± 1.21	0.36 ± 1.01	1.15 [0.98-1.36]	0.092	447
Mean duration ± sd among exposed subjects	1.97 ± 1.63	1.83 ± 1.62			
1st generation PIs (all PIs except DRV and ATV)	191 (75.2)	257 (68.4)	1.40 [0.96-2.04]	0.049	446
Mean duration ± sd (years)	3.12 ± 3.28	2.70 ± 3.20	1.02 [0.97-1.08]	0.429	449
Mean duration ± sd among exposed subjects	4.15 ± 3.16	3.96 ± 3.17			
Any PIs	208 (81.9)	273 (72.6)	1.67 [1.11-2.50]	0.013	443
Mean duration ± sd (years)	3.55 ± 3.41	3.00 ± 3.35	1.04 [0.98-1.09]	0.171	448
Mean duration ± sd among exposed subjects	4.34 ± 3.29	4.13 ± 3.29			
Exposure to NRTIs:					
Abacavir (ABC)	111 (43.7)	140 (37.2)	1.26 [0.89-1.78]	0.193	448
Mean duration ± sd (years)	1.16 ± 2.05	1.11 ± 2.13	1.01 [0.93-1.10]	0.849	449
Mean duration ± sd among exposed subjects	2.65 ± 2.37	2.99 ± 2.57			
Didanosine (DDI)	142 (55.9)	177 (47.1)	1.39 [0.96-2.02]	0.080	446
Mean duration ± sd (years)	1.69 ± 2.38	1.51 ± 2.43	1.02 [0.94-1.09]	0.698	449
Mean duration ± sd among exposed subjects	3.01 ± 2.48	3.22 ± 2.66			
Emtricitabine (FTC)	74 (29.1)	112 (29.8)	0.92 [0.61-1.39]	0.689	449
Mean duration ± sd (years)	0.54 ± 1.15	0.59 ± 1.27	0.93 [0.80-1.09]	0.385	449
Mean duration ± sd among exposed subjects	1.85 ± 1.47	1.98 ± 1.65			
Lamivudine (3TC)	221 (87.0)	292 (77.7)	1.91 [1.19-3.08]	0.008	442
Mean duration ± sd (years)	3.63 ± 2.98	3.82 ± 3.54	0.96 [0.91-1.01]	0.129	447
Mean duration ± sd among exposed subjects	4.18 ± 2.82	4.92 ± 3.27			

	Cases (n=254)	Controls (n=376)	Univariable models		
	n (% exposed)	n (% exposed)			
			OR (95% CI)	P	AIC
Stavudine (D4T)	137 (53.9)	161 (42.8)	1.60 [1.10-2.32]	0.014	443
Mean duration ± sd (years)	1.58 ± 2.09	1.44 ± 2.23	1.02 [0.94-1.10]	0.666	449
Mean duration ± sd among exposed subjects	2.92 ± 2.05	3.36 ± 2.27			
Zalcitabine (DDC)	62 (24.4)	65 (17.3)	1.52 [1.00-2.32]	0.053	446
Mean duration ± sd (years)	0.25 ± 0.59	0.31 ± 0.92	0.85 [0.68-1.07]	0.166	447
Mean duration ± sd among exposed subjects	1.01 ± 0.82	1.77 ± 1.51			
Zidovudine (ZDV)	203 (79.9)	269 (71.5)	1.58 [1.04-2.41]	0.034	445
Mean duration ± sd (years)	3.14 ± 3.16	2.89 ± 3.40	1.01 [0.96-1.06]	0.634	449
Mean duration ± sd among exposed subjects	3.93 ± 3.06	4.04 ± 3.39			
Exposure to NNRTIs:					
Efavirenz (EFV)	95 (37.4)	127 (33.8)	1.17 [0.83-1.65]	0.386	449
Mean duration ± sd (years)	0.82 ± 1.78	1.03 ± 2.22	0.94 [0.86-1.02]	0.121	447
Mean duration ± sd among exposed subjects	2.19 ± 2.35	3.04 ± 2.92			
Nevirapine (NVP)	85 (33.5)	78 (20.7)	1.93 [1.32-2.83]	0.0007	438
Mean duration ± sd (years)	0.72 ± 1.68	0.57 ± 1.60	1.04 [0.94-1.15]	0.480	449
Mean duration ± sd among exposed subjects	2.14 ± 2.34	2.73 ± 2.55			

Table 3. Multivariable models of ARV exposure

	OR model 1 Cumulative exposure		OR model 2 Exposure (yes/no)		OR model 3 Exposure (yes/no) except for ATV, DRV, FPV, FTC, EFV	
	adjusted for ARV	adjusted for ARV+confounders*	adjusted for ARV	adjusted for ARV+confounders*	adjusted for ARV	adjusted for ARV+confounders*
	AIC=451	AIC=329	AIC=458	AIC=345	AIC=448	AIC=332
Exposure to TDF and to PIs:						
Tenofovir (TDF)	1.07 [0.93-1.22]	1.04 [0.86-1.27]	1.05 [0.63-1.75]	1.21 [0.61-2.39]	1.09 [0.70-1.69]	1.37 [0.74-2.53]
Atazanavir (ATV)	1.46 [1.15-1.85]	1.52 [1.06-2.17]	1.67 [1.01-2.73]	1.89 [0.96-3.72]	1.41 [1.12-1.77]	1.49 [1.04-2.13]
Fosamprenavir/amprenavir (FPV/AMP)	0.98 [0.81-1.19]	1.02 [0.75-1.38]	0.82 [0.48-1.41]	0.72 [0.34-1.53]	0.90 [0.74-1.09]	0.98 [0.72-1.33]
Indinavir (IDV)	1.02 [0.89-1.16]	1.09 [0.88-1.34]	1.00 [0.64-1.56]	1.18 [0.66-2.14]	1.04 [0.67-1.63]	1.29 [0.70-2.38]
Lopinavir (LPV)	1.10 [0.98-1.23]	1.04 [0.87-1.25]	1.47 [0.98-2.22]	1.29 [0.73-2.27]	1.46 [0.95-2.22]	1.13 [0.63-2.04]
Nelfinavir (NFV)	0.93 [0.80-1.07]	0.95 [0.77-1.16]	0.89 [0.57-1.40]	0.89 [0.49-1.62]	0.84 [0.53-1.35]	0.87 [0.47-1.64]
Saquinavir (SQV)	1.19 [0.99-1.44]	1.00 [0.78-1.27]	1.11 [0.67-1.84]	0.80 [0.42-1.52]	1.07 [0.64-1.78]	0.73 [0.38-1.41]
1st generation PIs**	1.06 [0.99-1.13]	1.01 [0.91-1.12]	1.02 [0.65-1.61]	0.96 [0.51-1.80]	1.00 [0.63-1.59]	0.95 [0.50-1.82]
Any PI	1.06 [1.00-1.14]	1.02 [0.92-1.12]	1.39 [0.87-2.21]	1.25 [0.66-2.35]	1.27 [0.80-2.04]	1.10 [0.58-2.10]
Exposure to NRTIs:						
Abacavir (ABC)	0.99 [0.90-1.09]	0.98 [0.86-1.12]	1.04 [0.68-1.57]	1.41 [0.80-2.48]	1.08 [0.71-1.64]	1.45 [0.82-2.56]
Didanosine (DDI)	0.98 [0.89-1.07]	0.95 [0.83-1.08]	0.97 [0.61-1.53]	0.80 [0.44-1.45]	0.98 [0.61-1.55]	0.79 [0.43-1.47]
Emtricitabine (FTC)	0.80 [0.64-1.01]	0.84 [0.60-1.18]	0.80 [0.45-1.44]	0.97 [0.45-2.08]	0.86 [0.70-1.06]	0.87 [0.65-1.17]
Lamivudine (3TC)	0.86 [0.78-0.95]	0.85 [0.74-0.98]	1.22 [0.62-2.43]	1.31 [0.55-3.13]	1.33 [0.67-2.67]	1.36 [0.56-3.32]
Stavudine (D4T)	1.15 [1.01-1.30]	1.04 [0.87-1.24]	1.16 [0.70-1.91]	0.71 [0.36-1.41]	1.22 [0.73-2.02]	0.77 [0.38-1.55]
Zalcitabine (DDC)	0.69 [0.53-0.91]	0.66 [0.45-0.97]	1.27 [0.77-2.08]	0.79[0.40-1.56]	1.32 [0.80-2.19]	0.86 [0.42-1.74]
Zidovudine (ZDV)	1.13 [1.04-1.22]	1.11 [0.99-1.24]	1.08 [0.59-1.96]	1.07 [0.50-2.30]	1.01 [0.55-1.86]	0.99 [0.45-2.21]
Exposure to NNRTIs:						
Efavirenz (EFV)	0.98 [0.88-1.09]	0.81 [0.69-0.96]	1.09 [0.74-1.61]	0.90 [0.54-1.51]	0.95 [0.86-1.05]	0.82 [0.70-0.96]
Nevirapine (NVP)	1.05 [0.93-1.18]	0.98 [0.83-1.16]	1.79 [1.17-2.73]	1.81 [1.05-3.13]	1.70 [1.09-2.63]	1.60 [0.89-2.87]

*Potential confounders: HIV transmission group (MSM/injecting drug use/others), geographic origin (Sub-Saharan Africa/others), AIDS status (yes/no), BMI ([18.5-25.0]/<18.5/>25.0), smoking status (no/past/current), alcohol consumption (≤2glasses/day/>2glasses/day), exposure to systemic glucocorticoids (no/yes), period of enrolment (≤1996/1997-2001/≥2002).

**All PIs except darunavir and atazanavir

Supplementary Table 1. Summary of studies on the association between eposure to ARV and the risk of fracture.

Study	Study design	Fracture, n	Exposure measurement	Definition fracture	Adjustement factors			Statistic model	Results on ARVs		
					HIV parameters	Fractures risk factors	Others factors		TDF effect	PI effect	Others ARVs effect
Womack et al. [5] Plos One 2011	Cohort HIV+ Men	Number of fractures in HIV patients was not reported By calulation can be estimated as 602	Current use Cumulative exposure	Hip,vertebral and humeral fractures of low and high energy	Current CD4 count	Age,ethnicity,BMI, current cigarette smoking, corticosteroid use, alcohol abuse	proton pump inhibitor, congestive heart failure, pulmonary disease, peripheral vascular disease, diabetes melitus, major depressive disorder, coronary artery disease, liver disease, renal insufficiency	Cox regression	Current use: 1.29 [0.99-1.70] <u>Author conclusion:</u> No association	1.41 [1.16-1.70] <u>Author conclusion:</u> Association not necessarily causal	Not analysed
Sharma et al. [7] JAIDS 2015	Cohort HIV+ women	300	Use at index visit Cumulative exposure	Any fractures (fragility or non-fragility) at any body site				Bivariate analysis	Use (index): 1.24 [0.98-1.56] Cumulative exposure: 1.0 [0.95-1.05] <u>Author conclusion:</u> No association	Use (index): 1.10 [0.98-1.39] Cumulative exposure: 1.02 [0.99-1.05] <u>Author conclusion:</u> No association	NRTI use: 1.01 [0.77-1.33] NNRTI use: 0.10 [0.78-1.27] Cumulative exposure NRTI: 1.02 [0.99-1.05] Cumulative exposure NNRTI: 1.01 [0.98-1.05] <u>Author conclusion:</u> No association
Hansen et al. [18] AIDS 2012	Cohort HIV+ not infected by HCV who started cArt	375	Any use	Wrist, humerus, hip,vertebral or other fractures of low-energy	CD4 before start of cART, AIDS status, HIV diagnostic before or after 1 jan. 1995	Age, sex, ethnicity	Charlson comorbidity index (CCI)	Cox regression	1.2 [0.8-1.7] <u>Author conclusion:</u> No association	Not analysed	Efavirenz: 1.1 [0.8-1.4] Abacavir: 0.9 [0.7-1.2] <u>Author conclusion:</u> No association
Bedimo et al. [19]	Cohort HIV+	951	Cumulative exposure	Wrist, hip,	No HIV parameters	Age,ethnicity, BMI, tobacco use	Diabetes, chronic kidney	Cox regression	1.06 [0.99-1.14] (per year)	1.03 [0.97-1.09] (per year)	Abacavir: NS ZDV/D4T: NS

Study	Study design	Fracture, n	Exposure measurement	Definition fracture	Adjustement factors			Statistic model	Results on ARVs		
					HIV parameters	Fractures risk factors	Others factors		TDF effect	PI effect	Others ARVs effect
AIDS 2012	(98% of male patients)			vertebral fractures. Low-energy or high energy not reported			disease, hepatitis C infection		Author conclusion: Association with a modestly increased osteoporotic fracture risk, no longer significant after controlling for traditional osteoporotic risk factors When restricting the analysis to individuals entering the cohort in the cART era (1996-2009) 1.12 [1.03–1.21] Cumulative exposure to TDF was independently predictive of increased risk of osteoporotic fracture in the HAART era.	Author conclusion: Association with a modestly increased osteoporotic fracture risk, no longer significant after controlling for traditional osteoporotic risk factors When restricting the analysis to individuals entering the cohort in the cART era (1996-2009) 1.05 [0.97–1.13] LPV/RTV had 1.09 [1.00-1.20]	NNRTI: NS Author conclusion: No association
Mundy et al. [20] AIDS 2012	Nested case-control matched on sex and age in cohort HIV+	2477 9144 controls	Cumulative exposure except for ARV with 30 or less exposed cases as darunavir was unexposed/ exposed	sites of fractures not reported low-energy fractures	advanced HIV AIDS (category B/C)	Low body weight, excess steroid use, alcohol abuse, treatment for osteoporosis with bisphosphonates	Prior fracture, low physical activity, hepatitis C infection,	Conditional logistic regression	Decreased risk: Not exposed: 1 <3.5 months: 0.83 [0.68-1.01] [3.5- 8[months: 0.78 [0.64-0.96] [8- 17[months: 0.68 [0.56-0.82] ≥17 months: 0.65 [0.53-0.79] Author conclusion:	Overall PI: NS However for Darunavir: 1.95 [1.05-3.56] Saquinavir: <3 months vs not exposed: 1.93 [1.27-2.93] Author conclusion: An increased risk for fracture	Decreased risk: NRTI: <4.5 months vs not exposed: 0.83 [0.72-0.97] NNRTI: ≥18 months: 0.59 [0.49-0.70] Efavirenz: ≥16 months: 0.55 [0.45-0.67] Emtricitabine:

Study	Study design	Fracture, n	Exposure measurement	Definition fracture	Adjustement factors			Statistic model	Results on ARVs		
					HIV parameters	Fractures risk factors	Others factors		TDF effect	PI effect	Others ARVs effect
									Association with an reduced risk for fracture	associated with DRV and SQV.	≥12 months: 0.51 [0.40-0.65] Lamivudine: ≥19.5 months: 0.64 [0.55-0.75] Zidovudine ≥19 months: 0.63 [0.52-0.77] Abacavir: NS Didanosine: NS Stavudine: NS Zalcitabine: NS T20: NS Author conclusion: A reduced risk for fracture associated with efavirenz, emtricitabine, lamivudine, and zidovudine
Gedmintas et al. [21] Osteopor Int 2017	Cohort HIV+	180	TDF users (no/yes)	Fractures at any site of low and high energy	Nadir CD4, history of an AIDS-defining illness	Age, sex, ethnicity, corticosteroid use, alcohol abuse, vitamin D supplement use, osteonecrosis, osteoporosis	Prior fracture, history of falls, obstructive lung disease, hepatitis C infection, study entry year	Pooled logistic regression	0.8 [0.6-1.1] Author conclusion: No association	Not analysed	Not analysed
Yin et al. [22] AIDS 2012	Cohort HIV+	80	Cumulative exposure	fractures at wrist, hip, spine, ankle, foot, rib, clavicle, hand and pelvis low or high energy not reported				Cox regression	1.02 [0.86-1.22] (per year) Author conclusion: No association	1.04 [0.93-1.17] (per year) Author conclusion: No association	NRTI: 1.00 [0.91-1.10] NNRTI: 1.00 [0.89-1.12] Abacavir: 1.09 [0.97-1.22] Lamivudine: 1.05 [0.94-1.17] Stavudine: 0.93 [0.81-1.07] Zalcitabine: 1.01 [0.93-1.09] efavirenz:

Study	Study design	Fracture, n	Exposure measurement	Definition fracture	Adjustement factors			Statistic model	Results on ARVs		
					HIV parameters	Fractures risk factors	Others factors		TDF effect	PI effect	Others ARVs effect
											1.02 [0.91-1.14] <u>Author conclusion:</u> Not association
Borges AH [23] CID 2017	Cohort HIV+	132	Ever use current use cumulative exposure	fractures at wrist,hip,spine and arm Low-energy or high energy not reported	HIV transmission group, nadir CD4, CD4,viral load,	Age, race,Europeen region,BMI	Prior fracture, year of follow-up,Hepatitis C, AIDS defining malignancy, non malignant AIDS event, non AIDS defining malignancy,re cent cardiovascular disease	Poisson regression using generalized estimating equations	ever use: NS current use: NS cumulative exposure: NS <u>Author conclusion:</u> no association		
		619 in 496 individuals		All fractures					ever use: 1.40 [1.15-1.70] current use: 1.25 [1.05-1.49] cumulative exposure: 1.08 [0.94-1.25] <u>Author conclusion:</u> Association with an increased risk of fractures	Whether modeled as ever, current, or cumulative, no association between exposure to any of the other investigated antiretrovirals and fracture risk was observed (data not shown) <u>Author conclusion:</u> No association	Whether modeled as ever, current, or cumulative, no association between exposure to any of the other investigated antiretrovirals and fracture risk was observed (data not shown) <u>Author conclusion:</u> No association

Study	Study design	Fracture, n	Exposure measurement	Definition fracture	Adjustement factors			Statistic model	Results on ARVs		
					HIV parameters	Fractures risk factors	Others factors		TDF effect	PI effect	Others ARVs effect
Gonciulea et al. [24] AIDS 2017	Cohort HIV+ men	70	Cumulative exposure/5 years	Fractures at vertebral column, femur, wrist and humerus. Low-energy or high energy not reported.	CD4, viral load, history of an AIDS-defining illness, current ART use	Age, race, BMI, current smoking, alcohol use	Hypertension, diabetes, estimated glomerular filtration rate (eGFR)	Poisson regression model	0.95 [0.62-1.44] Author conclusion: No association	1.25 [0.94-1.67] Author conclusion: No association	Not analysed
		182		All fractures except for those occuring at the face, skull or digits					1.11 [0.86-1.45] Author conclusion: No association	1.14 [0.95-1.38] Author conclusion: No association	
Garcia et al. [25] Am J Ther	European pharmacovigil database between 2001 and November 10, 2016	181 with TDF exposure versus 67932 without TDF exposure out of 4,776,472 reports	TDF presence (no/yes)	All fractures				Proportional reporting ratios (PRR)	1.11 [0.96-1.28] Author conclusion: No disproportionality	0.54 [0.45-0.64]	
		13 with TDF		Osteoporotic fractures					17.2 (9.9–30.0) Author conclusion: disproportionality was observed for osteoporotic fractures		

Supplementary Table 2. Models for exposure to ARV measured by not/<2years/≥2years exposed

	Controls (n=376) %	Cases (n=254) %	OR model Exposure (no/<2 years/≥2 years)		
			Unajusted	Adusted for ARV*	Ajusted for ARV*+confounders**
Exposure to TDF and to PIs:					
Tenofovir (TDF): not exposed	55.3	51.2	1	1	1
<2 years	19.7	23.2	1.25 [0.80-1.95]	1.18 [0.72-1.91]	1.52 [0.78-2.96]
≥2 years	25.0	25.6	1.08 [0.70-1.66]	0.92 [0.51-1.68]	1.09 [0.48-2.46]
Atazanavir (ATV): not exposed	84.8	79.1	1	1	1
<2 years	9.3	11.0	1.34 [0.77-2.31]	1.22 [0.67-2.21]	1.20 [0.55-2.65]
≥2 years	5.9	9.9	2.40 [1.07-4.15]	2.15 [1.00-4.63]	2.37 [0.78-7.23]
Fosamprenavir/amprenavir (FPV/AMP)): not exposed	85.1	85.8	1	1	1
<2 years	8.8	8.7	1.09 [0.60-1.98]	0.93 [0.46-1.86]	0.67 [0.27-1.65]
≥2 years	6.1	5.5	0.73 [0.36-1.51]	0.75 [0.33-1.71]	1.22 [0.32-4.56]
Indinavir (IDV): not exposed	71.5	64.2	1	1	1
<2 years	14.9	20.1	1.48 [0.94-2.32]	1.10 [0.63-1.92]	1.26 [0.60-2.68]
≥2 years	13.6	15.7	1.22 [0.76-1.95]	0.99 [0.57-1.71]	1.32 [0.62-2.80]
Lopinavir (LPV): not exposed	69.9	59.1	1	1	1
<2 years	18.6	23.2	1.64 [1.07-2.52]	1.36 [0.84-2.21]	1.10 [0.57-2.11]
≥2 years	11.4	17.7	1.80 [1.09-2.97]	1.63 [0.91-2.92]	1.19 [0.51-2.76]
Nelfinavir (NFV): not exposed	72.6	66.5	1	1	1
<2 years	17.3	23.2	1.37 [0.90-2.11]	1.00 [0.58-1.71]	1.05 [0.51-2.19]
≥2 years	10.1	10.3	0.98 [0.55-1.73]	0.65 [0.34-1.24]	0.69 [0.31-1.54]
Saquinavir (SQV): not exposed	80.6	73.2	1	1	1
<2 years	13.6	16.1	1.34 [0.83-2.16]	0.84 [0.46-1.52]	0.54 [0.24-1.19]
≥2 years	5.8	10.7	2.02 [1.06-3.85]	1.63 [0.80-3.34]	1.13 [0.47-2.72]
1st generation PIs*:** not exposed	31.6	24.8	1	1	1
<2 years	21.8	22.4	1.43 [0.89-2.30]	1.12 [0.67-1.87]	0.97 [0.48-1.96]
≥2 years	46.5	52.8	1.38 [0.92-2.08]	0.86 [0.52-1.41]	0.81 [0.39-1.65]
Any PIs: not exposed	27.4	18.1	1	1	1
<2 years	21.3	22.4	1.64 [1.00-2.70]	1.38 [0.81-2.34]	1.02 [0.50-2.06]
≥2 years	51.3	59.4	1.68 [1.09-2.59]	1.18 [0.70-1.99]	1.22 [0.59-2.55]
Exposure to NRTIs:					
Abacavir (ABC): not exposed	62.8	56.3	1	1	1
<2 years	17.0	22.0	1.35 [0.89-2.06]	1.21 [0.75-1.96]	1.72 [0.90-3.31]
≥2 years	20.2	21.7	1.16 [0.75-1.81]	0.92 [0.54-1.57]	1.12 [0.53-2.36]
Didanosine (DDI): not exposed	52.9	44.1	1	1	1
<2 years	19.9	24.0	1.46 [0.94-2.26]	1.01 [0.61-1.69]	0.83 [0.42-1.63]
≥2 years	27.2	31.9	1.33 [0.86-2.06]	0.93 [0.53-1.61]	0.73 [0.34-1.58]
Emtricitabine (FTC): not exposed	70.2	70.9	1	1	1
<2 years	17.6	16.9	0.93 [0.58-1.48]	0.82 [0.44-1.53]	0.92 [0.41-2.11]
≥2 years	12.2	12.2	0.91 [0.50-1.64]	0.70 [0.32-1.53]	1.09 [0.37-3.19]
Lamivudine (3TC): not exposed	22.3	13.0	1	1	1
<2 years	18.4	22.0	2.30 [1.28-4.13]	1.46 [0.70-3.06]	1.48 [0.58-3.76]
≥2 years	59.3	65.0	1.81 [1.12-2.95]	1.23 [0.59-2.55]	1.21 [0.46-3.19]
Stavudine (D4T): not exposed	57.2	46.1	1	1	1
<2 years	14.4	21.3	1.94 [1.19-3.15]	1.51 [0.83-2.73]	0.94 [0.41-2.16]
≥2 years	28.4	32.6	1.41 [0.92-2.15]	1.03 [0.59-1.81]	0.65 [0.30-1.44]
Zalcitabine (DDC): not exposed	82.7	75.6	1	1	1
<2 years	10.9	22.0	2.06 [1.29-3.27]	1.84 [1.05-3.22]	1.34 [0.60-2.97]
≥2 years	6.4	2.4	0.37 [0.14-1.00]	0.26 [0.09-0.79]	0.19 [0.05-0.79]

	Controls (n=376) %	Cases (n=254) %	OR model Exposure (no/<2 years/≥2 years) Unajusted	Adusted for ARV*	Ajusted for ARV*+confounders**
Zidovudine (ZDV): not exposed	28.5	20.1	1	1	1
<2 years	22.9	22.8	1.50 [0.90-2.49]	0.85 [0.43-1.68]	0.90 [0.37-2.21]
≥2 years	48.7	57.1	1.62 [1.04-2.51]	1.11 [0.59-2.09]	1.04 [0.46-2.38]
Exposure to NNRTIs:					
Efavirenz (EFV): not exposed	66.2	62.6	1	1	1
<2 years	17.8	23.2	1.41 [0.93-2.12]	1.23 [0.78-1.96]	1.11 [0.60-2.07]
≥2 years	16.0	14.2	0.89 [0.55-1.43]	0.96 [0.55-1.67]	0.64 [0.30-1.36]
Nevirapine (NVP): not exposed	79.3	66.5	1	1	1
<2 years	11.4	20.5	2.23 [1.40-3.55]	1.88 [1.12-3.18]	1.98 [0.99-3.99]
≥2 years	9.3	13.0	1.58 [0.93-2.69]	1.45 [0.79-2.66]	1.14 [0.49-2.61]

* ARV exposure coding in model 3

**Potential confounders: transmission group (MSM/injecting drug users/others), geographic origin (Sub-Sahara/others), AIDS-stage (yes/no), BMI ([18.5-25.0]/<18.5/>25.0), smoking status (no/past/current), alcohol consumption (≤2glasses/day/>2glasses/day), exposure to systemic glucocorticoids (no/yes), period of enrolment (≤1996/1997-2001/≥2002).

***All PIs except darunavir and atazanavir