**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]  Author conclusion:  No association | 1.41 [1.16-1.70]  Author conclusion:  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. [0.95-1.05]   Author conclusion:  No association | Use (index):  1.10 [0.98-1.39]  Cumulative exposure:  1.02 [0.99-1.05]  Author conclusion:  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]  Author conclusion:  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]  Author conclusion:  No association | Not analysed | Efavirenz:  1.1 [0.8-1.4]  Abacavir:  0.9 [0.7-1.2]  Author conclusion:  No association |
| Bedimo et al. [19]  AIDS 2012 | Cohort HIV+  (98% of male patients) | 951 | Cumulative exposure | Wrist, hip,  vertebral fractures.  Low-energy or high energy not reported | No HIV parameters | Age,ethnicity, BMI, tobacco use | Diabetes, chronic kidney disease, hepatitis C infection | Cox regression | 1.06 [0.99-1.14] (per year)  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. | 1.03 [0.97-1.09] (per year)  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] | Abacavir: NS  ZDV/D4T: NS  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:  Association with an reduced risk for fracture | 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 associated with DRV and SQV. | 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:  ≥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:  1.02 [0.91-1.14]  Author conclusion:  Not association |
| Borges AH [23]  CID 2017 | Cohort HIV+ | 132  619 in 496 individuals | Ever use  current use  cumulative exposure | fractures at wrist,hip,spine and arm  Low-energy or high energy not reported  All fractures | 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,recent cardiovascular disease | Poisson regression using generalized estimating equations | ever use: NS  current use: NS  cumulative exposure: NS  Author  conclusion:  no association  ever use:  1.40 [1.15-1.70]  current use:  1.25 [1.05-1.49]  cumulative exposure:  1.08 [0.94-1.25]  Author  conclusion:  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)  Author  conclusion:  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)  Author  conclusion:  No association |
| Gonciulea et al. [24]  AIDS 2017 | Cohort HIV+ men | 70  182 | Cumulative exposure/5 years | Fractures at  vertebral column, femur, wrist and humerus.  Low-energy or high energy not reported.  All fractures  except for those occuring at the face, skull or digits | 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  1.11 [0.86-1.45]  Author conclusion:  No association | 1.25 [0.94-1.67]  Author conclusion:  No association  1.14 [0.95-1.38]  Author conclusion:  No association | Not analysed |
| Garcia et al. [25]  Am J Ther | European pharmacovigildatabase between 2001 and November 10, 2016 | 181 with TDF exposure versus 67932 without TDF exposure out of 4,776,472 reports  13 with TDF | TDF presence (no/yes) | All fractures  Osteoporotic fractures |  |  |  | Proportional reporting ratios (PRR) | 1.11 [0.96-1.28]  Author conclusion:  No disproportionality  17.2 (9.9–30.0)  Author conclusion:  disproportionality was observed for osteoporotic fractures | 0.54 [0.45-0.64] |  |

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

|  |  | |  | OR model  Exposure (no/<2 years/≥2 years) | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Controls (n=376)**  % | **Cases (n=254)**  % |  | 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] |
| **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