

<b>GSK Medicine:</b> abacavir, zidovudine/lamivudine, lamivudine/abacavir, lamivudine, zidovudine/lamivudine/abacavir, zidovudine, fosamprenavir, amprenavir
<b>Study No.:</b> WWE111950/WEUSKOP2048
<b>Title:</b> Fractures over time stratified by HIV infection and ART exposure
<b>Rationale:</b> The risk-benefit of combination antiretroviral (ARV) therapy is dependent on both benefit of the treatment and the long-term complications of receiving treatment. Bone disorders such as fracture have recently been implicated as one of several long-term complications of combination ARV use. Fractures are common and costly. To date, there are little published data (beyond case series) about the interactions of aging, HIV infection, and ARV treatment for fracture events.
<b>Objectives:</b> 1. To determine the incidence of bone fractures among persons with and without HIV infection. 2. To compare risk factors for bone fractures among persons with and without HIV infection. 3. To examine the association of ARV treatment exposure and incidence of fracture among persons with HIV infection.
<b>Indication:</b> HIV infection
<b>Study Investigators/Centers:</b> GlaxoSmithKline: LM Mundy, S St. Laurent, H Li (cohort study), SJ Bowlin. Case Western Reserve University and University Hospitals: GA McComsey (nested case-control study). University of Pittsburgh: AO Youk (nested case-control study). Medco Health Solutions, Inc. and Medco Research Institute, LLC: SJ Bowlin.
<b>Research Methods:</b> Retrospective cohort study and nested case-control study.
<b>Data Source:</b> The Ingenix Impact National Benchmark Database™ (INBD), an administrative claims database comprised of over 74 million members from the United States (US); previously called the Integrated Health Care Information System (IHCIS).
<b>Study Design:</b> Cohort study (objectives 1 & 2); nested case-control study (objective 3)
<b>Study Population:</b> <i>Cohort study:</i> 238,336 adult participants with confirmed Ingenix continuous enrollment and pharmacy-claims eligibility between January 1, 1997 and March 31, 2008. There were 59,584 persons with HIV infection and 178,758 persons without HIV infection who were 1:3 matched on gender and date of INBD enrolment. <i>Nested case-control study:</i> From the cohort study population, cases were 2,477 participants with HIV infection and low-impact, non-traumatic fracture identified by ICD-9-CM codes. Non-cases were 1:4 matched and without fracture (N= 9,144).
<b>Study Exposures, Outcomes:</b> Exposures: age, gender, geographic census region, year of enrolment, excess alcohol use, low physical activity, severity of illness (HIV versus acquired immune deficiency syndrome), prior fracture, low body weight, lipodystrophy, co-infection with hepatitis B virus, co-infection with hepatitis C virus, and prescription drug exposures of excess glucocorticosteroids, vitamin D or calcium supplements, bisphosphonates; and ARV drug exposures by class (NRTI, non-NNRTI, PI, fusion inhibitor, and entry inhibitor), duration, and drug-specific treatment. Outcome: low impact, nontraumatic fracture.
<b>Data Analysis Methods:</b> <b>Cohort study:</b> For computation of incidence rates (IR) and IR ratios (IRR), person-years of follow-up were used in rate denominators. Person-years were accumulated across all participants. Cox regression models were used to assess the relationship between time to first fracture, identified risks, and potential confounders; statistical modeling was done using SAS for Windows, Version 9 (Cary, North Carolina). Calendar time contributions were time-varying using left-truncation methods. All other predictors occurred at or prior to an outcome event (fracture) or end of observation and included demographic factors, clinical factors, and ARV drug exposures. <b>Nested case-control study:</b> We estimated odds ratios (OR) and 95% confidence intervals (CI) using exact conditional logistic regression programs in Stata (Stata, College Station, TX). The OR for each of the primary demographic, prescription history, and ARV exposure variables were also adjusted for potential confounding factors if warranted. All ARV drug exposure variables were categorized a priori into

approximately equal exposure groups based on the distribution of fractures in an attempt to balance the precision of the risk estimates across subgroups. Multivariate models were adjusted for prior fracture, excess alcohol use, low physical activity, low body weight, hepatitis C virus (HCV) infection, excess steroid use, and treatment for osteoporosis with bisphosphonates. We assessed the statistical significance of each main effect (expressed as a global P-value) with a likelihood ratio statistic and conducted tests for linear trend (expressed as a trend P-value) using equally spaced scores.

**Limitations:** We acknowledge potential ascertainment, information, and measurement biases associated with the use of a retrospective study design and an administrative US claims database.

**Study Results:**

*Cohort study:* There were a total of 9,027 incident fractures, with 6,550 fractures in persons without HIV infection and 2,477 fractures in persons with HIV infection. These incident fractures included 6,730 single closed fractures, 1706 multiple-closed fractures, and 591 pathological fractures. Among these incident fractures, the IR of fracture per 100 person-years was 1.77 (95% CI 1.73-1.82) among persons without HIV infection and 2.02 (95% CI 1.94-2.1) among persons with HIV infection; the unadjusted IR ratio was 1.14 when HIV-infected persons were compared to persons without HIV infection. Prior fracture was consistently the covariate with the highest hazard for incident fracture in the full- and age-adjusted models.

*Nested case-control study:* Exposure to ARV therapy by drug class and by duration (any drug/class) was associated with reduced risk for fracture. Drug-specific ARV exposures over time identified an increased risk for fracture associated with darunavir, delavirdine and saquinavir while reduced risk was associated with efavirenz, emtricitabine, lamivudine, tenofovir, and zidovudine. An initial null risk became a reduced risk with increased duration for nevirapine. In a similar pattern, abacavir, didanosine, nelfinavir, ritonavir and stavudine were initially associated with increased risk for fracture, after which the risk became null with increased duration of exposure. Null or uncertain risk for fracture was associated with amprenavir, atazanavir, enfuvirtide, fosamprenavir, indinavir, lopinavir, tipranavir, and zalcitabine

Demographics/Baseline Characteristics	Study Group	Comparison Group
<i>Cohort Study</i>	<b>HIV</b>	<b>Non-HIV</b>
Age		
<65 years	58,619 (98.4)	167,907 (93.9)
≥65 years	965 (1.6)	10,845 (6.1)
Comorbidities		
Prior fractures	1,182 (2.0)	3,319 (1.9)
Low body weight	4,725 (7.9)	2,926 (1.6)
Lipodystrophy	2,011 (3.4)	78 (0.04)
Hepatitis B virus	2,459 (4.1)	419 (0.2)
Hepatitis C virus	3,868 (6.5)	1,043 (0.6)
<i>Nested case-control study</i>	<b>Case</b>	<b>Non-case</b>
Demographics		
Sex (female)	694	2,480
Geographic region (non-northeast)	1,133	4,285
Enrollment year* (2003-2008)	1,714	6,388
Comorbidities		
Prior fractures	163	168
Low body weight	315	891
Lipodystrophy	154	510
Hepatitis B virus	120	426
Hepatitis C virus	244	732

Primary and Secondary Outcome(s)	Study Group	Comparison Group	Evaluation of Study Outcome
Cohort study: Fracture incidence	HIV infection	No HIV infection	IR 2.02 ( 95% CI 1.94-2.10) versus 1.77 (95%CI 1.73-1.82)
Nested case-control study: fracture	ARV	No ARV	OR 0.64, 95% CI 0.58-0.71; p <.0001
<p><b>Conclusion:</b>  <i>Cohort study:</i> HIV infection was associated with higher fracture incidence rate in this large, population-based study. Prior fracture was the strongest predictor of fracture. Differential age-stratified risks for fracture in this study provide a framework for age-stratified risk assessment in other study populations and have implications for patient education and treatment.  <i>Nested case-control study:</i> Our findings suggest an overall reduced risk for fracture in persons treated versus not treated with ARV drugs for HIV infection. Differential drug-specific exposure-response relationships for fracture will need to be further evaluated in other study populations.</p>			