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Greater change in bone turnover markers for efavirenz/emtricitabine/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naive adults over 144 weeks

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Objective: Antiretroviral therapy initiation has been linked to bone mineral density and bone biomarker changes. We assessed long-term bone turnover biomarker effects over 144 weeks in patients initiating dolutegravir (DTG) + abacavir/lamivudine (ABC/3TC) versus efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF).

Methods: Patients randomized in SINGLE received DTG (50 mg once daily) + ABC/3TC or fixed-dose combination EFV/FTC/TDF. We evaluated vitamin D serum levels and bone turnover markers (BTMs), including type 1 collagen cross-linked C-telopeptide (CTx), osteocalcin, bone-specific alkaline phosphatase (BSAP), and procollagen type 1 N-terminal propeptide (P1NP), at baseline and weeks 48, 96, and 144.

Results: Among the 833 enrolled patients (68% white, 85% men), baseline median age was 35 years (range 18–85), median $CD4^+$ was 338 cells/μl, and median BMI was 24 kg/m^2. Fifty-three percent of patients smoked, and 6% reported baseline vitamin D use, with no meaningful differences between groups. Relative to baseline, CTx, osteocalcin, BSAP, and P1NP increased; vitamin D decreased in both groups at weeks 48, 96, and 144. Changes from baseline typically peaked at weeks 48 or 96 and for the four analytes, excluding vitamin D, with the EFV/FTC/TDF group having significantly greater changes from baseline at all time points.

Conclusion: DTG + ABC/3TC in antiretroviral therapy-naive patients resulted in significantly lower increases in BTMs (CTx, osteocalcin, BSAP, P1NP) compared with EFV/FTC/TDF over 144 weeks. The observed changes are consistent with results from other smaller, randomized trials. These differences in BTMs likely correlate with changes in bone mineral density over time.

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Introduction

Understanding long-term consequences of exposure to individual antiretroviral therapy (ART) components is important in making an initial HIV treatment selection. Initiation of ART is associated with a decrease in bone mineral density (BMD). This initial bone loss is greater with some antiretrovirals, in particular, protease inhibitors [1–4] and tenofovir disoproxil fumarate (TDF) [1,5–9].

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The impact on bone health of the integrase strand transfer inhibitor (INSTI) class has not been well characterized. Few studies to date have evaluated the effects of INSTI-containing regimens [either raltegravir (RAL) or elvitegravir] on bone composition over 48 weeks or longer. BMD outcomes tended to be more favorable when RAL was administered as part of a protease inhibitor-sparing or TDF-sparing regimen [6,10–12]; elvitegravir was administered as part of a TDF-containing fixed-dose combination and showed similar decreases in BMD as a TDF-containing, protease inhibitor-based comparator regimen [13]. Dolutegravir (DTG) is the most recently approved INSTI, and no studies to date have evaluated long-term changes in BMD in individuals initiating a DTG-based regimen.

Measuring BMD in large, randomized trials is complex, as many sites do not have access to appropriate radiological facilities. As a consequence, most studies of BMD are done by monitoring changes after initiation of ART in a subset of the larger study, limiting the generalizability of conclusions and the participation to individuals seen in tertiary medical centers in the developed world.

Bone remodeling occurs throughout life. Changes in biochemical markers of bone remodeling [e.g. both resorption markers: type 1 collagen cross-linked C-telopeptide (CTx) and urinary N-telopeptide; and formation markers: serum bone-specific alkaline phosphatase (BSAP), osteocalcin, and procollagen type 1 N-terminal propeptide (P1NP)] can be used to predict the risk of fracture independently from bone density and the rapidity of bone loss in patients with untreated osteoporosis [14].

In the ASSERT study (NCT00549198), which compared abacavir/lamivudine (ABC/3TC) with TDF/emtricitabine (FTC) administered with efavirenz (EFV), results showed a significantly greater decline in BMD and a significant increase in bone turnover markers (BTMs) in the TDF/FTC arm over 96 weeks [8]. Changes in bone markers have been associated with changes in BMD in HIV-positive individuals: in the RADAR study (NCT00677300) and SMART Body Composition substudy (NCT00027352), early increases in CTx, osteocalcin, BSAP, or P1NP predicted decreases in BMD at 48 weeks [6,15]. The objective of this analysis is to evaluate the changes in BTMs in the SINGLE study (ING114467) through 144 weeks of treatment with either DTG + ABC/3TC or EFV/FTC/TDF.

Methods

Study design and participants

SINGLE was a multicenter, multinational, double-blinded, phase III, 144-week study of ART-naive, HIV-1-infected HLA-B*5701-negative patients that evaluated the efficacy and safety of DTG (50 mg once daily) given in combination with ABC/3TC (600 mg/300 mg once daily) compared with a fixed-dose regimen of EFV/FTC/TDF (600 mg/200 mg/300 mg once daily). Details of the design and primary outcome – proportion of patients with plasma HIV-1 RNA less than 50 copies/ml through week 48 – have been previously reported [16].

At the week 96 visit, patients were unblinded to their study treatment and given the opportunity to continue open-label treatment with their assigned regimen to week 144 or to discontinue from the study.

Approval by the applicable ethics committee was obtained at participating centers in accordance with international standards. Participants provided written informed consent before any study-specific procedures were performed.

Assessments

Study visits were scheduled at baseline and weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48 and every 12 weeks thereafter. Samples for BTM (CTx, P1NP, osteocalcin, and BSAP) and vitamin D assessments were obtained at baseline and weeks 48, 96, 120, and 144. Adverse events were collected at every visit through week 144.

Statistical analysis

BTMs were analyzed using analysis of covariance models adjusting for age, sex, baseline viral load, baseline $CD4^+$ cell count, baseline biomarker level, BMI category, smoking status, and baseline vitamin D use. Age and baseline biomarker level were included as continuous variables and the other covariates as categorical variables. Covariates with P values at least 0.2 were subsequently excluded from the model in a stepwise manner. No adjustments for multiplicity were applied as these P values were considered exploratory. The safety population was used; it consisted of all individuals who received at least one dose of investigational product. In this population, individuals were analyzed according to the treatment they actually received, regardless of randomization; because no participant received a treatment differing from that assigned by the randomization schedule, the safety population was the same as the intent-to-treat population. Two post-hoc changes were made in the analysis plan of BTMs (i.e. changes in the analysis made after database freeze and unblinding). First, BMI, smoking history, and the concurrent use of vitamin D were added to the original list of covariates to be investigated in the statistical model. Second, BTMs were log transformed and percentage change from baseline was analyzed, rather than the change from baseline, to ease clinical interpretation.

Results

Patient characteristics

A total of 833 patients received at least one dose of study drug (DTG + ABC/3TC, $N = 414$; EFV/FTC/TDF, $N = 419$). Demographic and other baseline characteristics were well balanced between the groups (Table 1). The majority of patients were white (68%) and men (84%). Median age was 35 years; one patient in the DTG + ABC/3TC arm and six patients in the EFV/FTC/TDF arm were age 65 years or older. The median baseline $CD4^+$ cell count was 338 cells/μl, and 32% of patients had HIV-1 RNA more than 100 000 copies/ml at baseline. The median BMI for the study population was 24 kg/m^2. Fifty-three percent of patients were smokers, and 6% of patients reported vitamin D usage at baseline. Median baseline levels for CTx, osteocalcin, BSAP, P1NP, and vitamin D were all within the normal range.

Bone biomarkers

After the initiation of ART, levels of CTx (marker of bone resorption) were increased at all time points in both arms relative to baseline (Fig. 1). The largest increase was noted at week 48, after which there was a steady decline in both arms to week 144. Significant differences between the treatment arms were noted at all study points (weeks 48, 96, and 144), with more pronounced increases in the EFV/FTC/TDF arm ($P < 0.001$ at weeks 48 and 96, $P = 0.002$ at week 144).

Similar differences were seen for each of the three markers of bone formation (osteocalcin, BSAP, and P1NP), with increases relative to baseline evident in both arms at each time point. In all instances, the increase from baseline in the EFV/FTC/TDF arm was significantly greater than that of the DTG + ABC/3TC arm and the difference between arms was significant (Fig. 1).

Vitamin D levels decreased in both treatment arms relative to baseline at all three time points. At weeks 48, 96, and 144, vitamin D was decreased by 7, 5, and 2%, respectively, in the DTG + ABC/3TC arm and by 10, 10, and 4%, respectively, in the EFV/FTC/TDF arm. Unlike the BTMs, there was no significant difference between the treatment arms in changes in vitamin D levels.

Discussion

In adults, bone is constantly being remodeled. Changes in the rate of bone turnover are an important determinant of bone disease because alterations in bone turnover rate have been associated with an increased fracture risk. Patients with untreated HIV infection tend to have a state of low bone turnover [17] that is rapidly overcorrected with the initiation of ART and immunological recovery [1,18]. This phenomenon is so uniform that some have suggested that is a part of an immune reconstitution inflammatory syndrome (IRIS) [19]. As a result of this, patients with HIV infection have an increased risk of fractures when compared with the general population [20], particularly those receiving certain antiretroviral drugs including TDF and protease inhibitors [21].

The SINGLE study demonstrated the superiority of DTG + ABC/3TC compared with EFV/FTC/TDF [16] in the percentage of patients who maintained viral suppression to less than 50 copies/ml when measured at weeks 48, 96, and 144, a difference mediated primarily by the better tolerability with DTG + ABC/3TC. The present analysis compared changes in bone markers over 144 weeks in the SINGLE study, and the results confirmed that the differences seen at week 48 persisted through week 144, with significantly greater increases

Table 1. Characteristics of the study population.

Baseline characteristic	DTG + ABC/3TC arm $N = 414$	EFV/FTC/TDF arm $N = 419$	Total $N = 833$
Age in years, median (range)	36.0 (18, 68)	35.0 (18, 85)	35.0 (18, 85)
Women, *n* (%)	67 (16)	63 (15)	130 (16)
Hispanic/Latino ethnicity, *n* (%)	56 (14)	56 (13)	112 (13)
Race, *n* (%)			
African American/African heritage	98 (24)	99 (24)	197 (24)
American Indian or Alaska Native	13 (3)	17 (4)	30 (4)
Asian	9 (2)	9 (2)	18 (2)
White	284 (69)	285 (68)	569 (68)
Other[a]	10 (2)	8 (2)	18 (2)
HIV-1 RNA, median $\log_{10}$ c/ml	4.67	4.70	4.68
HIV-1 RNA ≤100 000, *n* (%)	280 (68)	288 (69)	568 (68)
HIV-1 RNA >100 000, *n* (%)	134 (32)	131 (31)	265 (32)
$CD4^+$ cells/μl, median (range)	334.5 (19, 1027)	339.0 (19, 1123)	338.0 (19, 1123)

3TC, lamivudine; ABC, abacavir; c/ml, copies per milliliter; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.
[a]Patients indicated more than one race.

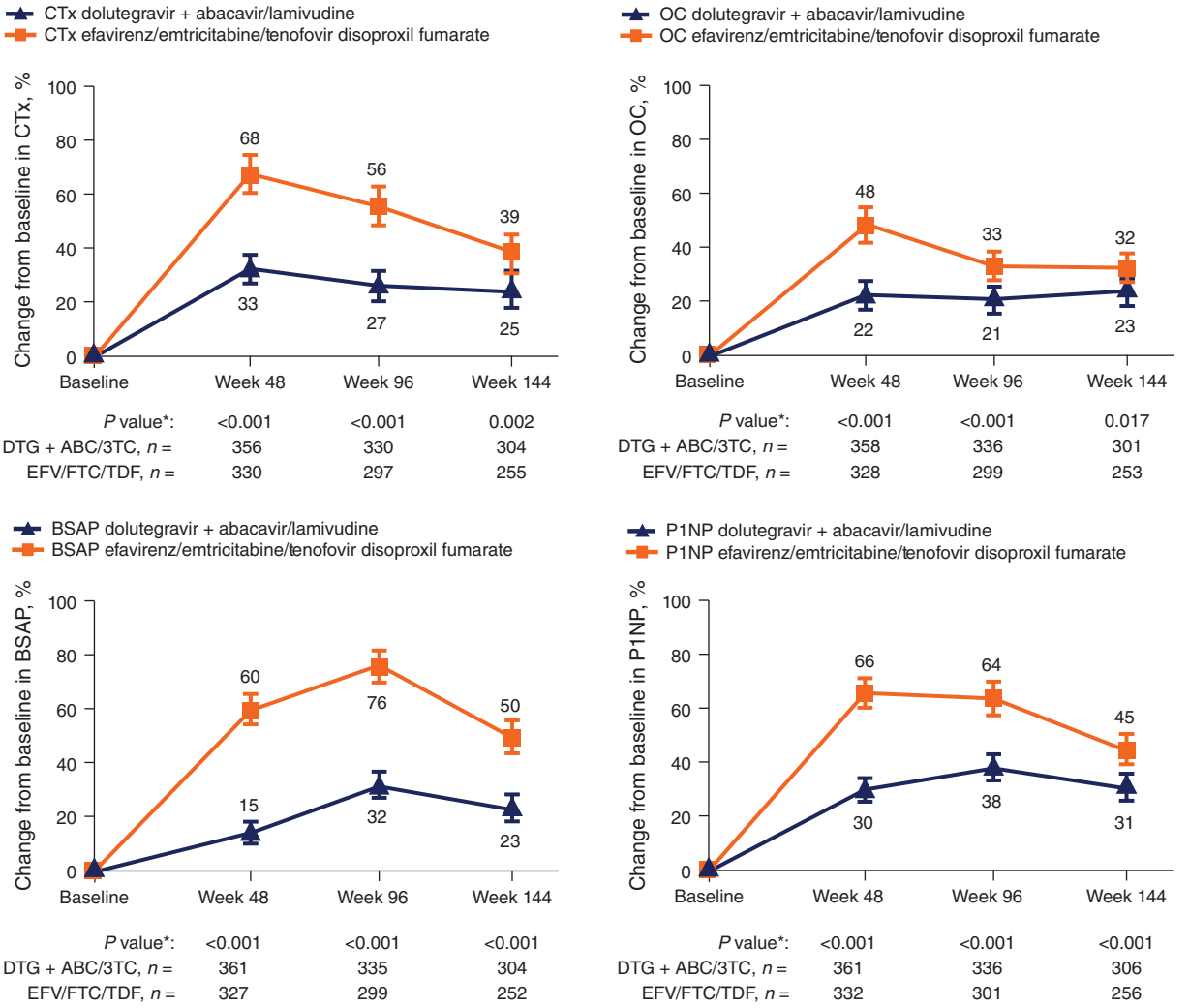

Fig. 1. Adjusted geometric mean percentage changes from baseline in bone biomarkers. *P values are for the difference between arms at each time point. 3TC, lamivudine; ABC, abacavir; BSAP, bone-specific alkaline phosphatase; CTx, type 1 collagen cross-linked C-telopeptide; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; OC, osteocalcin; P1NP, procollagen type 1 N-terminal propeptide; TDF, tenofovir disoproxil fumarate. Analysis of covariance models were used adjusting for age, sex, baseline viral load, baseline $CD4^+$ cell count, baseline biomarker level, BMI category, smoking status, and baseline vitamin D use. Covariates with P values at least 0.2 were subsequently excluded from the model in a stepwise manner.

from baseline in BTMs (CTx, osteocalcin, BSAP, and P1NP) occurring in patients receiving EFV/FTC/TDF [22]. The EFV/FTC/TDF arm also had greater changes from baseline in vitamin D compared with the DTG + ABC/3TC group, although the differences between groups were not significant. The ASSERT [8] and RADAR [6] studies also examined changes in BTMs for ART-naive patients initiating therapy (ASSERT study evaluated all four BTMs, and RADAR study evaluated CTx and P1NP). We are reluctant to make direct comparisons across studies since different statistical models were used, and the populations, time points, and treatment arms were also different. However, like in the SINGLE study, the TDF/FTC-containing arms in the ASSERT and RADAR studies consistently have higher changes from baseline in all BTMs versus the comparator (RAL in ASSERT study, ABC/3TC in RADAR study).

There are some limitations of the SINGLE analyses. One is that BMD was not directly assessed, meaning that the conclusions are based on bone markers alone. However, numerous studies have linked changes in bone markers with changes in BMD before the initiation of osteoporosis treatment and after a therapeutic intervention has been initiated. Some studies in HIV-infected individuals have shown similar results correlating changes in BTMs with changes in BMD measured by dual-energy X-ray absorptiometry (DEXA) after starting ART [6,15], but others have not confirmed the association [9,23]. Whether the findings of this study will translate to a decreased risk of osteopenia or osteoporosis and

ultimately bone fractures for patients taking DTG + ABC/3TC long term compared with EFV/FTC/TDF or other ART remains to be seen. Secondly, the generalizability of these results may be limited by the fact that a very high proportion of patients were men and white, and therefore not representative of the larger HIV population. There is, however, no biological reason to think that the results will differ in other populations [1]. The use of BTMs in this study allowed monitoring of the effects of ART on bone metabolism in a large multinational trial. If these markers accurately predict changes in BMD over time, their use could improve understanding of the long-term safety of ART regarding bone health in a more global population.

Changes in BTMs in this study were most evident early and tended to stabilize or even decrease over time. They remained above baseline levels for the duration of the study, suggesting that treated HIV infection becomes a state of persistent, relatively high bone turnover. This may explain why, in spite of successful ART, patients with HIV infection have a greater proportion of osteoporotic fractures than the general population [20,24–27]. Other studies have reported a similar trend in BTMs or BMD, wherein the largest changes occur early after ART initiation and decline at later time points [1,8,9].

The differences in BTMs in our study may be due to differences between the arms in the dual nucleoside/nucleotide reverse transcriptase inhibitor component, the third agent, or a combination of both. Studies comparing ABC/3TC and TDF/FTC have shown that TDF/FTC was associated with greater increases in BTM levels and greater decreases in BMD [1,8,9]. The changes tend to be worse when TDF is combined with a protease inhibitor [6]. Results of this study are consistent with observations in other studies of patients initiating ART. Regarding the comparison between INSTI-based ART and other regimens, it was noted in the metabolic substudy of AIDS Clinical Trials Group A5257 that there was a greater decease in hip and spine BMD in a combined protease inhibitor arm (atazanavir/ritonavir or DRV/ritonavir) than in the RAL arm [28]. In addition, in a separate trial, patients switching from a boosted protease inhibitor to RAL showed improvements in practically all locations [12]. Thus, including RAL as a component of ART may contribute to more favorable bone outcomes. Whether this is an INSTI class effect and whether DTG may contribute similarly favorable outcomes is still to be determined.

In summary, 144 weeks of treatment with DTG + ABC/3TC resulted in significantly lower increases in four BTMs (CTx, osteocalcin, BSAP, and P1NP) compared with a regimen of EFV/FTC/TDF. Over time, levels of bone biomarkers remained elevated in both groups. These results suggest that a regimen of DTG + ABC/3TC compared favorably concerning bone health to a fixed-dose combination regimen of EFV/FTC/TDF in patients initiating ART.

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Conflicts of interest

P.T. has received consultancy fees from GlaxoSmithKline and Merck, and his institution served as a study site and received a grant for its participation. P.K. has received consultancy fees, payment for lectures, including service on speakers' bureaus, and honoraria from Janssen and ViiV Healthcare; has received grants/has grants pending from GlaxoSmithKline, Janssen, and Merck; and has stock/stock options in Gilead Sciences, GlaxoSmithKline, Johnson & Johnson, Merck, and Pfizer. C.H. has received a grant and consulting fees or honorarium from ViiV Healthcare; has received consultancy fees from Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare; receives royalties from UpToDate, Inc; and is an associate editor for *New England Journal of Medicine* Journal Watch. B.W. is an employee of GlaxoSmithKline. C.G. and S.M. are employees of and have stock/stock options in GlaxoSmithKline. K.P. is an employee of and has stock/stock options in ViiV Healthcare.

References

1. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, *et al*. **Bone mineral density and fractures in antiretroviral-naive 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.

2. Duvivier C, Kolta S, Assoumou L, Ghosn J, Rozenberg S, Murphy RL, *et al*. **Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients.** *AIDS* 2009; **23**:817–824.
3. Brown TT, Qaqish RB. **Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review.** *AIDS* 2006; **20**:2165–2174.
4. Tebas P, Powderly WG, Claxton S, Marin D, Tantisiriwat W, Teitelbaum SL, Yarasheski KE. **Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy.** *AIDS* 2000; **14**:F63–F67.
5. Assoumou L, Katlama C, Viard JP, Bentata M, Simon A, Roux C, *et al*. **Changes in bone mineral density over a 2-year period in HIV-1-infected men under combined antiretroviral therapy with osteopenia.** *AIDS* 2013; **27**:2425–2430.
6. Bedimo RJ, Drechsler H, Jain M, Cutrell J, Zhang S, Li X, *et al*. **The RADAR study: week 48 safety and efficacy of RAltegravir combined with boosted DARunavir compared to tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naive patients. Impact on bone health.** *PLoS One* 2014; **9**:e106221.
7. Martin A, Moore C, Mallon PW, Hoy J, Emery S, Belloso W, *et al*. **Bone mineral density in HIV participants randomized to raltegravir and lopinavir/ritonavir compared with standard second line therapy.** *AIDS* 2013; **27**:2403–2411.
8. Moyle GJ, Stellbrink H-J, Compston J, Orkin C, Arribas JR, Domingo P, *et al*. **96-Week results of abacavir/lamivudine versus tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naive, HIV-1-infected adults: ASSERT study.** *Antivir Ther* 2013; **18**:905–913.
9. Haskelberg H, Hoy JF, Amin J, Ebeling PR, Emery S, Carr A, STEAL Study Group. **Changes in bone turnover and bone loss in HIV-infected patients changing treatment to tenofovir-emtricitabine or abacavir-lamivudine.** *PLoS One* 2012; **7**:e38377.
10. Fabbiani M, Mondi A, Colafigli M, D'Ettorre G, Paoletti F, D'Avino A, *et al*. **Safety and efficacy of treatment switch to raltegravir plus tenofovir/emtricitabine or abacavir/lamivudine in patients with optimal virological control: 48-week results from a randomized pilot study (Raltegravir Switch for Toxicity or Adverse Events, RASTA Study).** *Scand J Infect Dis* 2014; **46**:34–45.
11. Reynes J, Trinh R, Pulido F, Soto-Malave R, Gathe J, Qaqish R, *et al*. **Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS study.** *AIDS Res Hum Retroviruses* 2013; **29**:256–265.
12. Curran A, Martinez E, Saumoy M, del Rio L, Crespo M, Larrousse M, *et al*. **Body composition changes after switching from protease inhibitors to raltegravir: SPIRAL-LIP substudy.** *AIDS* 2012; **26**:475–481.
13. Rockstroh JK, DeJesus E, Henry K, Molina JM, Gathe J, Ramanathan S, *et al*. **A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results.** *J Acquir Immune Defic Syndr* 2013; **62**:483–486.
14. Burch J, Rice S, Yang H, Neilson A, Stirk L, Francis R, *et al*. **Systematic review of the use of bone turnover markers for monitoring the response to osteoporosis treatment: the secondary prevention of fractures, and primary prevention of fractures in high-risk groups.** *Health Technol Assess* 2014; **18**:1–180.
15. Hoy J, Grund B, Roediger M, Ensrud KE, Brar I, Colebunders R, *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**:1264–1274.
16. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, *et al*. **Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection.** *N Engl J Med* 2013; **369**:1807–1818.
17. Serrano S, Mariñoso ML, Soriano JC, Rubiés-Prat J, Aubia J, Coll J, *et al*. **Bone remodelling in human immunodeficiency virus-1-infected patients: a histomorphometric study.** *Bone* 1995; **16**:185–191.
18. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. **Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen.** *J Acquir Immune Defic Syndr* 2009; **51**:554–561.
19. Grant PM, Kitch D, McComsey GA, Dube MP, Haubrich R, Huang J, *et al*. **Low baseline CD4$^+$ count is associated with greater bone mineral density loss after antiretroviral therapy initiation.** *Clin Infect Dis* 2013; **57**:1483–1488.
20. 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.
21. 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.
22. Tebas P, Kumar P, Hicks C, Granier C, Wynne B, Pappa K, *et al*. **48 Week bone marker changes in dolutegravir (DTG/GSK1349572) plus abacavir/lamivudine (ABC/3TC) vs tenofovir/emtricitabine/efavirenz (EFV/TDF/FTC): the SINGLE trial.** [Abstract H-1461]. *53rd Interscience Conference on Antimicrobial Agents and Chemotherapy,* 10–13 September 2013, Denver, CO.
23. Mondy K, Yarasheski K, Powderly WG, Whyte M, Claxton S, DeMarco D, *et al*. **Longitudinal evolution of bone mineral density and bone markers in human immunodeficiency virus-infected individuals.** *Clin Infect Dis* 2003; **36**:482–490.
24. Shiau S, Broun EC, Arpadi SM, Yin MT. **Incident fractures in HIV-infected individuals: a systematic review and meta-analysis.** *AIDS* 2013; **27**:1949–1957.
25. Hansen AB, Gerstoft J, Kronborg G, Larsen CS, Pedersen C, Pedersen G, Obel N. **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.
26. Womack JA, Goulet JL, Gibert C, Brandt C, Chang CC, Gulanski B, *et al*. **Increased risk of fragility fractures among HIV infected compared to uninfected male veterans.** *PLoS One* 2011; **6**:e17217.
27. 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, 2000-2006.** *Clin Infect Dis* 2011; **52**:1061–1068.
28. Brown T, Moser C, Currier J, Ribaudo H, Rothenberg J, Dube M, *et al*. **Bone density changes after antiretroviral initiation with protease inhibitors or raltegravir.** [Abstract 779LB]. *21st Annual Conference on Retroviruses and Opportunistic Infections*, 3–6 March 2014, Boston, MA.