Bone mineral density, kidney function and participant-reported outcome measures in women who switch from TDF/FTC/NNRTI to ABC/3TC/DTG

Lucy Campbell[1,2], Fowzia Ibrahim[1], Birgit Barbini[2], Amanda Samarawickrama[3], Chloe Orkin[4], Julie Fox[1,5], Laura Waters[6], Yvonne Gilleece[7,8], Shema Tariq[9], Frank A. Post[1,2], on behalf of the BESTT Trial Team

Affiliations

[1]King's College London, [2]King's College Hospital NHS Foundation Trust, London, [3]Sexual Health South West London, [4]Queen Mary University of London and Barts Health NHS Trust, London, [5]Guy's and St Thomas' Hospitals NHS Foundation Trust, London, [6]Mortimer Market Centre, London, [7]University Hospitals Sussex NHS Trust, Brighton, [8]Brighton & Sussex Medical School, Brighton, [9]University College London, London, United Kingdom.

Word count: 2280; 44 references; 3 tables (+ 4 suppl. Tables and 4 suppl. Fig)

Keywords: Tenofovir, dolutegravir, bone, kidney, depression, sleep, women

Funding: ViiV Healthcare (investigator-sponsored study: 204658)

Corresponding author:

Prof Frank Post MMed FCP(SA) PhD FRCP

King's College Hospital NHS Foundation Trust

Weston Education Centre (rm 2.53), Cutcombe Road, London SE5 9RJ, United Kingdom

Tel: +44 207 848 5779, Fax: +44 207 848 5769

Email: frank.post@kcl.ac.uk

Abstract (word count: 248)

Background: Tenofovir disoproxil fumarate (TDF) is associated with reduced bone mineral density (BMD). We evaluated changes in BMD in women who switched from TDF, emtricitabine and a non-nucleoside reverse transcriptase inhibitor (TDF/FTC/NNRTI) to abacavir, lamivudine and dolutegravir (ABC/3TC/DTG).

Methods: We conducted a randomized controlled trial in which women aged ≥40 years were randomized 1:2 to continue TDF/FTC/NNRTI or switch to ABC/3TC/DTG. We analysed changes in BMD at the hip and lumbar spine from baseline through week 96 using linear regression, and markers of bone turnover, and kidney function using repeated measures mixed effects models with multiple imputation for missing data. We conducted exploratory analyses of weight, mental health, sleep, and symptoms attributed to HIV and antiretroviral therapy.

Results: Ninety-one women (mean age 50.4 [SD 6.6] years) were randomized. Women who switched to ABC/3TC/DTG maintained viral suppression and experienced improvements in BMD at the lumbar spine (but not neck of femur or total hip), bone resorption markers, proteinuria (total protein, albumin, and retinol-binding protein) and modest weight gain without change in body mass index. Although mean anxiety, depression and sleep scores did not differ between the two study arms, anxiety, depression, and sleep disturbance at baseline predicted ABC/3TC/DTG discontinuation for neuropsychiatric side effects (odds ratios 11.9 [95%CI 2.0-71.6], 16.0 [2.6-97.9] and10.0 [1.8-56.0] respectively).

Conclusions: Switching from TDF/FTC/NNRTI to ABC/3TC/DTG improved BMD of the lumbar spine and kidney function. These benefits need to be balanced against modest weight gain and the need for ART substitutions in a proportion of participants.

Introduction

Over half of the estimated 37.7 million people living with HIV globally in 2020 were female [1]. Increasingly effective and more widely available antiretroviral therapy (ART) means that HIV is now a long-term condition, with normal life expectancy for those who are virologically suppressed on ART [2], with the majority of people living with HIV expected to be aged 50 years and older by 2030 [3]. Over one-third of women seen for HIV care in 2019 (n=10,981) in the United Kingdom (UK) were aged 50 and over, a four-fold increase over a ten year period [4]. However, it is well-established that women remain under-represented in HIV clinical research [5]. This is of concern given that women's virological response to, and adverse effects from ART may differ from men's [6]. Furthermore, as women living with HIV reach menopausal age, oestrogen depletion increases their risk of comorbid conditions such as cardiovascular disease and low bone mineral density (BMD), making the investigation of the efficacy, safety, and tolerability of antiretroviral regimens in older women more pressing.

Tenofovir disoproxil fumarate (TDF) is associated with reductions in BMD [7], which may be of particular concern in older women. Clinical trials have shown improvements in BMD and kidney function in individuals who switch from TDF to tenofovir alafenamide (TAF) [8, 9] or other TDF-sparing antiretroviral therapy (ART) [10]. TDF may also adversely affect renal tubular function, particularly in an ageing population, manifesting as eGFR decline and proteinuria [11]. Improved kidney function has been reported in individuals who switch from TDF to tenofovir alafenamide (TAF) [8, 9] or other TDF-sparing ART [12, 13].

More recently, evidence has emerged that TDF may have weight-restricting properties in individuals without HIV taking TDF as pre-exposure prophylaxis (PrEP) [14, 15], and in people with HIV taking TDF-containing ART [16]. Efavirenz (EFV) may also have weight-restricting properties, especially in individuals with CYP2B6 polymorphisms rendering them slow metabolizers [17, 18]. By contrast, integrase strand-transfer inhibitors (INSTI) have been associated with weight gain, with women

disproportionally affected [16, 19, 20]. The mechanisms by which antiretrovirals affect weight are largely unknown.

Neuropsychiatric side effects, ranging from vivid dreams to overt depression and suicidality, have long been recognized as a complication of EFV use [21, 22]. Whereas the rate of neuropsychiatric events with INSTI in clinical trials has generally been similar to comparators [23, 24], cohort studies have suggested an increased rate of dolutegravir (DTG) discontinuations for neuropsychiatric symptoms including insomnia and sleep disturbance, anxiety and depression [25-28], particularly affecting women and/or older individuals [25, 26, 28].

We conducted a randomised controlled trial in virologically-suppressed women aged 40 years and over to examine the effect of switching from TDF/emtricitabine plus a non-nucleoside reverse-transcriptase inhibitor (TDF/FTC/NNRTI) to abacavir/lamivudine plus dolutegravir (ABC/3TC/DTG) on bone and kidney function. Here we report the changes in bone and renal outcomes at week 96, as well as changes in weight, mental health and sleep.

Methods

The design and inclusion criteria of the trial have been described previously [29]. Briefly, women aged 40 years and over with suppressed HIV RNA on TDF/FTC/NNRTI were enrolled and randomised 2:1 to switch to co-formulated ABC/3TC/DTG or to continue current ART, with stratification by age (above or below 50 years), using CASTOR EDC (Amsterdam, Netherlands). Postbaseline study visits occurred at weeks 4, 12, 24, 48, 72 and 96. All participants gave written, informed consent, and the study was approved by a National Health Service Research Ethics Committee (EudraCT 2015-005297-37).

BMD of the hip and lumbar spine was measured by dual energy x-ray absorptiometry at baseline and weeks 24, 48 and 96 using the same scanner at each site. Aliquots of stored plasma, serum and urine

were used to measure 25-hydroxy-vitamin D, parathyroid hormone (PTH), bone turnover (type I collagen cross-linked C-telopeptide [CTX] and procollagen type 1 N-terminal propeptide [P1NP]), albumin/creatinine ratio (ACR), protein/creatinine ratio (PCR), retinol-binding protein/creatinine ratio (RBPCR) in central laboratories. Height was measured at baseline, and weight at all study visits except week 4.

We used the Hospital Anxiety and Depression Scale (HADS) to evaluate mental health at baseline, week 48, and week 96. Items were scored from 0 to 3, with possible scores ranging from 0 to 21 for both the anxiety and the depression subscales. Cumulative scores of $\leq$7, 8-10, and $\geq$11 in each subscale were considered normal, borderline (indicating possible anxiety/depression) , and abnormal (indicating probable anxiety/depression) [30].

We used the Jenkins' sleep questionnaire to evaluate sleep quality at baseline and weeks 24, 48 and 96. Trouble falling asleep, awakening during sleep, trouble staying asleep, and feeling tired when waking from sleep each were evaluated using a 5-point Likert scale; the total score ranges from 0 to 20, with a higher score reflecting more severe sleep disturbance [31].

Statistical analysis

The planned sample size was 90 participants. With 1:2 randomisation (variable block size: 6-9-12) allowing 30 patients to continue TDF/FTC/NNRTI versus 60 switching to Triumeq, the study has 82% power to detect a 2% increase in total hip BMD in the Triumeq arm compared to the TDF/FTC/NNRTI arm (mean percentage change [SD] 0.02 [0.03] vs. 0.001 [0.03]).

Changes in BMD at week 96 were analysed using linear regression models with adjustment for age, ethnicity, BMI, time on TDF, NNRTI (efavirenz [EFV] vs. other) and BMD at baseline; biomarker measurements, weight, BMI, and waist circumference were analysed using repeated measures mixed-effects models (baseline through week 96) with an unstructured variance-covariance matrix with adjustment for age, ethnicity, BMI at baseline, time on TDF, and baseline measurements

(except weight, where weight at baseline instead of BMI at baseline was used). Missing observations were imputed regardless of the reason(s) they were missing. Predictive mean matching (with five nearest neighbours assuming unobserved measurements were missing at random) was used to impute primary and secondary outcomes [32].

Anxiety, depression, and sleep scores were calculated for each participant. We compared proportions of participants with anxiety, depression, and sleep disturbance by chi-squared test, mean anxiety, depression and sleep scores by T-test, and changes in anxiety, depression, and sleep scores from baseline to week 96 in repeated measures mixed-effects models adjusted for baseline scores and EFV use. All statistical analyses were done using STATA v16 (StataCorp, College Station, Tx).

Results

We enrolled 91 women, 59 of whom switched to ABC/3TC/DTG. Mean age at baseline was 50 years, 86% were of black ethnicity, and 55% were post-menopausal (Table 1). Eleven participants discontinued prior to week 24 (8 in the ABC/3TC/DTG arm and 3 in the TDF/FTC/NNRTI arm), and a further eight between weeks 48 and 96 (3 in the ABC/3TC/DTG arm and 5 in the TDF/FTC/NNRTI arm) (Figure S1 and Table S1). Treatment-limiting adverse events were experienced by 11 (18.6%) in the ABC/3TC/DTG arm and by one participant (3.1%) in the TDF/FTC/NNRTI arm. Treatment-limiting adverse events in the ABC/3TC/DTG arm included seven discontinuations for neuropsychiatric events (of which three with suicidality) and two hypersensitivity reactions (despite HLA-B5701 testing); five continued in the switch arm on a modified regimen (ABC/3TC plus raltegravir, rilpivirine, nevirapine or EFV). Acute kidney injury was the treatment-limiting adverse event in the TDF/FTC/NNRTI arm. No participants in either arm developed virological failure up to week 96 (Table S2).

BMD and biomarker data are shown in Table 2. Switching from TDF/FTC/NNRTI to ABC/3TC/DTG improved BMD at the lumbar spine at week 96 (adjusted mean difference 0.028 g/cm^2, p=0.022) while changes in BMD at the neck of femur and total hip were not statistically significant. Similar results were obtained when the BMD analyses were adjusted for changes in weight rather BMI from baseline to week 96 (Table S3); percentage change in BMD is shown in Table S4. Switching to ABC/3TC/DTG was associated with reduced bone resorption (CTX) and a reduction in urinary protein excretion (ACR, PCR, RBPCR). No significant changes in PTH, P1NP, FE-PO_4 or fasting lipids were seen. We found increases in serum creatinine and reductions in eGFR in the switch arm consistent with the known effect of DTG on tubular creatinine secretion. We also observed weight gain in the switch arm but no statistically significant increase in BMI or waist circumference; average weight stabilized from week 48 onwards (Figure S2).

Anxiety and depression scores are shown in Figure S3. Participants who withdrew from the trial prior to week 24 had higher mean anxiety (7.3 [SD 5.8] vs. 4.3 [3.7], p=0.02) and depression (5.0 [4.1] vs. 2.7 [3.2], p=0.03) scores at baseline compared to those who completed at least 48 weeks of follow up. Possible/probable anxiety and depression at baseline were prevalent among participants who discontinued DTG for neuropsychiatric side effects (anxiety 71.4% vs. 17.3%, p=0.002; depression 57.1% vs. 7.7%, p<0.001) and predicted DTG discontinuation for neuropsychiatric side effects (anxiety: odds ratio 11.9 [95%CI 2.0-71.6]; depression: odds ratio 16.0 [95%CI 2.6-97.9]). No significant change in anxiety and depression scores from baseline to week 96 was observed among participants in the two study-arms who completed at least 48 weeks of follow up (Table 3).

Sleep scores are shown in Figure S4. Participants who withdrew from the trial prior to week 24 had higher mean sleep scores (7.1 [5.7] vs. 3.6 [4.3], p=0.02) at baseline and were more likely to suffer from sleep disturbance (sleep score $\geq$11; 45.5% vs. 9.0%, p<0.001) than those who completed at least 48 weeks. Sleep disturbance was prevalent among participants who discontinued DTG for neuropsychiatric side effects (57.1% vs. 11.8%, p=0.003) and a predictor of DTG discontinuation for

neuropsychiatric side effects (odds ratio 10.0 [95%CI 1.8-56.0]). No significant change in sleep scores from baseline to week 96 was observed among participants in the two study-arms who completed at least 48 weeks of follow up (Table 3).

Discussion

Women who switched from TDF/FTC/NNRTI to ABC/3TC/DTG experienced increases in lumbar spine BMD and reductions in proteinuria. This is consistent with data from a trial in which predominantly male participants (85%; median age 49 years) who switched from TDF/FTC to TAF/FTC experienced increases in BMD (2.3% at the spine and 1.9% at the hip at 96 weeks) and reductions in total proteinuria, albuminuria and two low-molecular weight proteins (RBP and β_2-microglobulin) [8]. Exposure to TDF is thus a modifiable risk factor for low BMD which may be particularly relevant to post-menopausal women who already experience BMD reductions from loss of oestrogens although the extent to which these changes in BMD affect fracture risk remains uncertain [7, 33, 34]. High systemic tenofovir exposure may affect BMD via renal tubular dysfunction and increased bone turnover [35, 36] although measures of renal tubular dysfunction and bone turnover do not explain the association between TDF and low BMD suggesting direct or other indirect effects of tenofovir on bone may be more important [29, 37, 38]. Exposure to TDF is also a modifiable risk factor for chronic kidney disease, eGFR decline and proteinuria [39, 40], and discontinuation of TDF may reverse these manifestations of renal injury and preserve kidney function [12, 41].

Women who switched from TDF/FTC/NNRTI to ABC/3TC/DTG experienced modest weight gain which, consistent with previous studies [19], was largely restricted to the first 48 weeks. We previously reported this weight gain not to be associated with menopausal status or worsening insulin resistance [29, 42]. Consistent with previous studies, we observed no effect of DTG on anxiety, depression, and sleep in those who contributed at least 48 weeks of follow up [23, 43, 44]. By contrast, women who discontinued early from the trial had higher levels of anxiety, depression,

and sleep disturbance, and anxiety, depression, and sleep disturbance at baseline were predictive of DTG discontinuation for neuropsychiatric adverse events. Of note, participants in our trial were not screened for suicidality risk. If these findings are confirmed in other studies, older women should be counselled specifically about mood changes and sleep disturbance, which may overlap with symptoms of menopause, and that there may be a role for proactive screening for depression, anxiety, and sleep disruption in this patient group prior to switching to DTG.

Our study has several limitations. A relatively large number of participants did not complete the 96-week study assessments for administrative reasons including the effects of the COVID-19 pandemic or discontinuation due to adverse events; the resulting reduction in power was mitigated by utilizing multiple imputations for missing data in the renal and bone analyses. Changes in weight, BMI and waist circumference should be interpreted with a degree of caution as there was a substantial imbalance in weight and BMI at baseline between the participants who were randomised to switch to ABC/3TC/DTG and those who remained on TDF/FTC/NNRTI. Finally, as we enrolled no men, women younger than 40 years of age, and few women of non-black ethnicity (in whom peak bone mass, BMD, and bone turnover in relation to the vitamin D/parathyroid hormone axis may differ to black women), the results of our study cannot be generalised to these populations.

In conclusion, women aged 40 years and over who switched from TDF/FTC/NNRTI to ABC/3TC/DTG experienced improvements of lumbar spine BMD and proteinuria. These benefits need to be balanced against modest weight gain and the need for ART substitutions in a proportion of participants. Although we did not find evidence for an effect of DTG on mental health or sleep, women with anxiety, depression or sleep disturbance at baseline were at substantial risk of developing treatment-limiting neuropsychiatric adverse events. This highlights a potential need for caution when switching to DTG in those with mental health symptoms and/or sleep disturbance, both common symptoms during menopause. Finally, women are underrepresented in phase III clinical trials of people with HIV; this study demonstrates the feasibility of conducting interventional

studies exclusively in women who otherwise have unrestricted access to ART and adds to the growing literature on the efficacy, safety, and tolerability of ART in women.

Acknowledgements

The authors would like to thank the study participants, Prof Glen Blake for his assistance with quality assurance of the BMD data, Dr Keith Burling for his assistance with laboratory aspect of the trial, and all members of the BESTT Trial Team: KING'S COLLEGE HOSPITAL (Frank Post, Lucy Campbell, Oluwayomi Adegbaju, Birgit Barbini, Lisa Hamzah, Amanda Samarawickrama, Priya Bhagwandin, Ana Canoso, Fowzia Ibrahim); LEWISHAM AND GREENWICH NHS TRUST (Stephen Kegg, Tarik Moussaoui); GUY'S AND ST THOMAS' NHS FOUNDATION TRUST (Julie Fox, Julianne Lwanga, Alice Sharp, Mohammed Aminata, Ange John-Baptiste); ST GEORGE'S HEALTHCARE (Lisa Hamzah, Katia Prime, Olanike Okolo); BARTS HEALTH TRUST (Chloe Orkin, Anele Waters); MORTIMER MARKET CENTRE (Laura Waters, Andrea Cartier); ROYAL FREE HOSPITAL (Margaret Johnson, Alice Nightingale, Jonathan Edwards, Thomas Fernandez, Nargis Hemat); NORTH MIDDLESEX UNIVERSITY HOSPITAL (Jonathan Ainsworth, Rachel Vincent); BRIGHTON AND SUSSEX UNIVERSITY HOSPITALS (Yvonne Gilleece, Lisa Barbour, Sarah Kirk, Tanya Adams, Alyson Knott).

Contributions

FAP designed the study with input from FI, AS, LH and LC. YG, LW, SK and FAP were principal investigators overseeing study conduct at their sites. BB and LC managed the trial. FI and LC performed the statistical analyses. FAP, ST and YG wrote the first draft of the paper. All authors contributed to and approved the final version of the manuscript.

Funding

Funding was provided by ViiV Healthcare for this investigator-sponsored study (204658). The funder provided study medication but was not involved in study design, data analysis or the decision to publish our findings. We notified the funder of our intention to submit this manuscript for publication, and the funder was provided with an opportunity to review and comment on the content of the manuscript.

Conflict of Interest Statement

LW reports speaker/advisory fees from Gilead, ViiV, MSD, Janssen, Mylan, and Cipla, and clinical trial support from Gilead, Janssen, and ViiV. YG has received fees for educational meetings, advisory board meetings and conference sponsorship from ViiV Healthcare, Janssen Pharmaceuticals, Gilead and MSD; CO reports lecture fees, honoraria, travel scholarships and research from GSK, MSD, Gilead and Janssen. ST reports speaker honoraria and funding for preparation of educational materials from Gilead Sciences; FAP reports grants and personal fees from Gilead Sciences, ViiV Healthcare, Janssen Pharmaceuticals, and MSD outside the submitted work. All others report no conflicts of interest.

References

1. UNAIDS. Data 2020. Available at: https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf.
2. May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. AIDS **2014**; 28(8): 1193-202.
3. Smit M, Brinkman K, Geerlings S, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis **2015**; 15(7): 810-8.
4. HIV: annual data tables. Available at: https://www.gov.uk/government/statistics/hiv-annual-data-tables.
5. Curno MJ, Rossi S, Hodges-Mameletzis I, Johnston R, Price MA, Heidari S. A Systematic Review of the Inclusion (or Exclusion) of Women in HIV Research: From Clinical Studies of Antiretrovirals and Vaccines to Cure Strategies. J Acquir Immune Defic Syndr **2016**; 71(2): 181-8.
6. Andany N, Walmsley SL. What's new for antiretroviral treatment in women with HIV. J Virus Erad **2016**; 2(2): 67-77.
7. Alvarez-Barco E, Mallon PWG. What's new in bone disease and fractures in HIV? Current Opinion in HIV and AIDS **2021**; 16(3): 186-91.
8. Raffi F, Orkin C, Clarke A, et al. Brief Report: Long-Term (96-Week) Efficacy and Safety After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in HIV-Infected, Virologically Suppressed Adults. J Acquir Immune Defic Syndr **2017**; 75(2): 226-31.
9. Post FA, Tebas P, Clarke A, et al. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Adults With Renal Impairment: 96-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. J Acquir Immune Defic Syndr **2017**; 74: 180-4.

10. McComsey GA, Lupo S, Parks D, et al. Switch from tenofovir disoproxil fumarate combination to dolutegravir with rilpivirine improves parameters of bone health. AIDS **2018**; 32(4): 477-85.

11. Yombi JC, Pozniak A, Boffito M, et al. Antiretrovirals and the kidney in current clinical practice: renal pharmacokinetics, alterations of renal function and renal toxicity. AIDS **2014**; 28(5): 621-32.

12. Jose S, Hamzah L, Campbell LJ, et al. Incomplete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure. J Infect Dis **2014**; 210(3): 363-73.

13. Cahn P, Madero JS, Arribas JR, et al. Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials. J Acquir Immune Defic Syndr **2020**; 83(3): 310-8.

14. Glidden DV, Mulligan K, McMahan V, et al. Metabolic Effects of Preexposure Prophylaxis With Coformulated Tenofovir Disoproxil Fumarate and Emtricitabine. Clin Infect Dis **2018**; 67(3): 411-9.

15. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet **2020**; 396(10246): 239-54.

16. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med **2019**; 381(9): 803-15.

17. Leonard MA, Cindi Z, Bradford Y, et al. Efavirenz Pharmacogenetics and Weight Gain following Switch to Integrase Inhibitor-containing Regimens. Clin Infect Dis **2020**.

18. Griesel R, Maartens G, Chirehwa M, et al. CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz. Clin Infect Dis **2020**.

19. Erlandson KM, Carter CC, Melbourne K, et al. Weight Change Following Antiretroviral Therapy Switch in People with Viral Suppression: Pooled Data from Randomized Clinical Trials. Clin Infect Dis **2021**.

20. Lake JE, Wu K, Bares SH, et al. Risk Factors for Weight Gain Following Switch to Integrase Inhibitor-Based Antiretroviral Therapy. Clin Infect Dis **2020**; 71(9): e471-e7.

21. Clifford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med **2005**; 143(10): 714-21.

22. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med **2014**; 161(1): 1-10.

23. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet HIV **2017**; 4(12): e536-e46.

24. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med **2013**; 369(19): 1807-18.

25. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med **2017**; 18(1): 56-63.

26. Peñafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. J Antimicrob Chemother **2017**; 72(6): 1752-9.

27. de Boer MG, van den Berk GE, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS **2016**; 30(18): 2831-4.

28. Greenberg L, Ryom L, Wandeler G, et al. Uptake and Discontinuation of Integrase Inhibitors (INSTIs) in a Large Cohort Setting. J Acquir Immune Defic Syndr **2020**; 83(3): 240-50.

29. Ibrahim F, Samarawickrama A, Hamzah L, et al. Bone mineral density, kidney function, weight gain and insulin resistance in women who switch from TDF/FTC/NNRTI to ABC/3TC/DTG. HIV Med **2021**; 22(2): 83-91.

30. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica **1983**; 67(6): 361-70.

31. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol **1988**; 41(4): 313-21.

32. Di Zio M, Guarnera U. Semiparametric predictive mean matching. AStA Advances in Statistical Analysis **2009**; 93(2): 175-86.

33. Borges AH, Hoy J, Florence E, et al. Antiretrovirals, Fractures, and Osteonecrosis in a Large International HIV Cohort. Clin Infect Dis **2017**; 64(10): 1413-21.

34. Costagliola D, Potard V, Lang S, et al. 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). J Acquir Immune Defic Syndr **2019**; 80(2): 214-23.

35. Hamzah L, Samarawickrama A, Campbell L, et al. Effects of renal tubular dysfunction on bone in tenofovir-exposed HIV-positive patients. AIDS **2015**; 29(14): 1785-92.

36. Casado JL, Santiuste C, Vazquez M, et al. Bone mineral density decline according to renal tubular dysfunction and phosphaturia in tenofovir-exposed HIV-infected patients. AIDS **2016**; 30(9): 1423-31.

37. Hamzah L, Tiraboschi JM, Iveson H, et al. Effects on vitamin D, bone and the kidney of switching from fixed-dose tenofovir disoproxil fumarate/emtricitabine/efavirenz to darunavir/ritonavir monotherapy: a randomized, controlled trial (MIDAS). Antivir Ther **2016**; 21(4): 287-96.

38. Alvarez-Barco E, Campbell L, Garcia A, et al. Low bone mineral density in older people with HIV: the rena;-bone axis and ART. Conference on Retroviruses and Opportunistic Infections. Boston, MA, **2020**.

39. Mocroft A, Lundgren JD, Ross M, et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. Lancet HIV **2016**; 3(1): e23-32.

40. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS **2012**; 26(7): 867-75.

41. Ibrahim F, Campbell L, Bailey AC, et al. Estimated glomerular filtration rate slopes on tenofovir alafenamide. HIV Med **2020**; 21(9): 607-12.

42. Hamzah L, Post FA. Effect of menopause on weight gain, insulin and waist circumference in women with HIV who switch antiretroviral therapy to abacavir/lamivudine/dolutegravir. Aids **2021**; 35(2): 349-51.

43. Hsu R, Fusco J, Henegar C, et al. Psychiatric outcomes observed in patients living with HIV using six common core antiretrovirals in the Observational Pharmaco-Epidemiology Research and Analysis database. Therapeutic advances in drug safety **2018**; 9(12): 675-86.

44. Elliot ER, Wang X, Singh S, et al. Increased Dolutegravir Peak Concentrations in People Living With Human Immunodeficiency Virus Aged 60 and Over, and Analysis of Sleep Quality and Cognition. Clin Infect Dis **2019**; 68(1): 87-95.

Table 1: Baseline characteristics of the study population

		TDF/FTC/NNRTI (n=32)	ABC/3TC/DTG (n=59)
Age, years	mean (SD)	49.5 (6.0)	50.9 (7.0)
Ethnicity			
Black	n (%)	27 (84.4)	51 (86.4)
White/Other	n (%)	5 (15.6)	8 (13.6)
Weight, kg	Mean (SD)	86.3 (16.2)	77.4 (17.0)
Body Mass Index, kg/m^2	Mean (SD)	32.7 (7.0)	29.0 (5.8)
Post-menopausal	n (%) *	16 (51.6)	33 (56.9)
Diabetes mellitus	n (%)	1 (3.1)	3 (5.1)
Hypertension	n (%)	8 (25.0)	13 (22.0)
Current smoker	n (%)	3 (9.4)	4 (9.8)
Time since HIV diagnosis, years	mean (SD)	11.7 (5.2)	13.9 (6.6)
Prior AIDS	n (%)	5 (15.6)	10 (17.0)
CD4 current, $cells/mm^3$	Median (IQR)	579 (510, 712)	612 (454, 807)
CD4 nadir, $cells/mm^3$	Median (IQR)	161 (88, 290)	195 (129, 323)
Viral load (<50 copies/mL)	n (%)	32 (100)	55 (96) **
Hepatitis B surface antigen negative	n (%)	32 (100)	59 (100)
Hepatitis C antibody negative	n (%)	32 (100)	59 (100)
Time on TDF, years	mean (SD)	7.3 (3.1)	8.7 (3.4)
Taking vitamin D containing supplements	n (%)	7 (21.9)	13 (22.0)
FRAX: major osteoporotic fracture	Median (IQR)	3.1 (2.5, 5.1)	3.2 (2.6, 5.5)
FRAX: hip fracture	Median (IQR)	0.2 (0.1, 0.4)	0.2 (0.1, 0.6)

Abbreviations: TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; SD = standard deviation; IQR = inter-quartile range; FRAX = risk of fracture (over 10 years)

* menopausal status (based on menstrual pattern and FSH data) could be determined for 89 participants** Viral load missing N=2 and <200 N=2

Table 2: Outcome measures by randomisation arm

	TDF/FTC/NNRTI N=32	ABC/3TC/DTG N=59	TDF/FTC/NNRTI N=32	ABC/3TC/DTG N=59	Adjusted mean difference between study arms	P-value
	Baseline		Week 96			
Bone mineral density						
Total hip, g/cm^2	1.03 (0.98, 1.08)	0.96 (0.92, 0.99)	1.02 (0.98,1.07)	0.96 (0.93, 1.00)	0.008 (-0.01, 0.03)	0.438
Neck of femur, g/cm^2	0.90 (0.85, 0.96)	0.87 (0.83, 0.90)	0.88 (0.84, 0.94)	0.87 (0.83, 0.91)	0.019 (-0.004, 0.043)	0.110
Lumbar spine, g/cm^2	1.07 (1.02, 1.12)	1.03 (0.99, 1.07)	1.05 (1.02, 1.11)	1.04 (1.00, 1.09)	0.028 (0.004, 0.051)	0.022
Bone biomarkers						
25(OH) vitamin D, nmol/L	40.8 (33.1, 48.4)	49.0 (42.9, 55.1)	41.5 (35.6, 47.3)	45.3 (39.0, 51.6)	1.63 (-2.42, 5.67)	0.431
Parathyroid hormone, ng/L	34.7 (29.3, 40.2)	32.5 (27.3, 37.7)	31.6 (27.1, 36.1)	33.1 (28.8, 37.5)	-1.55 (-5.23, 2.12)	0.407
Alkaline phosphatase, IU/L	89.9 (79.8, 100.0)	93.2 (84.7, 101.8)	91.3 (81.5, 101.2)	75.0 (69.2 ,80.9)	-15.86 (-20.7, -11.0)	<0.001
CTX, µg/L	0.44 (0.36, 0.51)	0.53 (0.45, 0.62)	0.31 (0.24, 0.37)	0.28 (0.25, 0.32)	-0.06 (-0.11, -0.01)	0.011
P1NP, µg/L	61.6 (54.6, 68.7)	68.7 (62.1, 75.3)	54.3 (47.1, 61.5)	52.4 (46.8, 58.0)	-2.20 (-7.94, 3.54)	0.452
Renal biomarkers						
Creatinine, µmol/L	67.7 (64.0, 71.4)	67.8 (65.4, 70.3)	71.7 (66.7, 76.6)	78.9 (75.5, 82.2)	5.7 (2.9, 8.4)	<0.001
eGFR (creatinine), mL/min/1.73m^2	103.5 (97.1, 109.9)	102.1 (98.1, 106.2)	97.5 (90.3, 104.8)	87.2 (82.6, 91.8)	-7.5 (-11.3, -3.8)	<0.001
Albumin/creatinine ratio, mg/mmol	1.78 (0.61, 2.95)	1.94 (0.79, 3.10)	2.60 (1.35, 3.85)	1.10 (0.68, 1.51)	-0.91 (-1.81, 0.00)	0.049
Protein/creatinine ratio, mg/mmol	10.74 (7.12, 14.35)	10.22 (8.05, 12.38)	12.9 (10.0, 15.8)	8.3 (6.6, 10.0)	-3.17 (-4.94, -1.40)	<0.001
Retinol-binding protein/creatinine ratio, µg/mmol	2.76 (0.97, 4.54)	2.31 (1.50, 3.12)	4.69 (2.14, 7.23)	2.74 (1.89, 3.59)	-1.68 (-3.35, -0.01)	0.049
Fractional excretion of phosphate, %	0.10 (0.07, 0.12)	0.10 (0.08, 0.11)	0.10 (0.08, 0.12)	0.11 (0.09, 0.12)	-0.004 (-0.02, 0.01)	0.687
Lipids						
Total cholesterol	5.1 (4.7, 5.4)	5.0 (4.8, 5.3)	5.0 (4.7, 5.4)	5.3 (5.0, 5.5)	0.07 (-0.13, 0.28)	0.469

LDL-cholesterol, mmol/L	2.9 (2.6, 3.2)	2.9 (2.7, 3.2)	2.9 (2.5, 3.2)	3.0 (2.8, 3.2)	0.02 (-0.12, 0.17)	0.744
HDL-cholesterol, mmol/L	1.6 (1.5, 1.9)	1.7 (1.6, 1.9)	1.6 (1.5, 1.8)	1.7 (1.6, 1.9)	0.003 (-0.08, 0.09)	0.948
Triglycerides, mmol/L	1.1 (1.0, 1.3)	1.0 (1.0, 1.2)	1.2 (1.0, 1.5)	1.1 (0.9, 1.2)	-0.02 (-0.11, 0.08)	0.703
Weight and body mass index						
Weight (kg)	86.3 (79.7, 93.0)	77.4 (72.7, 82.1)	85.8 (79.1, 92.5)	78.5 (74.2, 82.8)	1.36 (0.09, 2.62)	0.036
Body mass index (kg/m^2)	32.7 (30.2, 35.1)	29.0 (27.5, 30.5)	29.3 (25.1, 33.5)	30.0 (27.9, 31.4)	2.88 (-1.00, 6.77)	0.146
Waist circumference (cm)	99.6 (96.5, 103.9)	92.8 (89.0, 96.7)	102.3 (97.3, 107.3)	97.1 (93.8, 100.4)	0.09 (-2.99, 3.16)	0.956

Data are expressed as mean (95%CI); bone mineral density is adjusted for age, ethnicity, BMI at baseline, time on TDF, non-nucleoside reverse transcriptase inhibitor (efavirenz vs. other) and bone mineral density at baseline; all other secondary outcomes were adjusted for age, ethnicity, BMI at baseline, time on TDF, and baseline measurements except weight (where weight at baseline was used instead of BMI at baseline). Five participants in the TDF/FTC/NNRTI arm and 3 in the ABC/3TC/DTG arm transitioned from pre-menopausal at baseline to post-menopausal at week 96.

Abbreviations: TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; CTX = type I collagen cross-linked C-telopeptide; P1NP = procollagen type 1 N-terminal propeptide; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein

Table 3: Outcome measures by randomisation arm

	TDF/FTC/NNRTI N=28	ABC/3TC/DTG N=51	TDF/FTC/NNRTI N=23	ABC/3TC/DTG N=43	Adjusted mean difference between study arms	P-value
	Baseline		Week 96			
Anxiety and Depression						
HADS Anxiety score	3.30 (2.21, 4.40)	4.73 (3.44, 6.01)	3.74 (1.85, 5.63)	4.80 (3.35, 6.24)	-0.08 (-2.07, 1.91)	0.94
HADS Depression score	2.43 (0.95, 3.91)	2.93 (1.92, 3.95)	3.26 (1.56, 4.96)	3.32 (2.03, 4.61)	-1.14 (-2.79, 0.50)	0.17
Sleep						
Jenkins sleep score	2.78 (1.43, 4.14)	4.07 (2.45, 5.69)	4.14 (2.17, 6.10)	5.20 (3.50, 6.90)	-1.39 (-3.24, 0.45)	0.14

Data are expressed as mean (95%CI); anxiety, depression and sleep scores are adjusted for baseline measurements and efavirenz use.

Abbreviations: TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; CTX = type I collagen cross-linked C-telopeptide; P1NP = procollagen type 1 N-terminal propeptide; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein