CLINICAL STUDY REPORT

THE BESTT WOMEN'S STUDY

Bone Evaluation in HIV positive women over 40 who Switch from TDF + 3TC/FTC + NNRTI to Triumeq - 'The BESTT women's Study'

Sponsor Protocol Code:	3552
EudraCT Number:	2015-005297-37
ClinicalTrials.gov Identifier:	180161 (CLRN portfolio nr)
REC Number:	16/LO/0019
Investigational Drugs (IMPs):	Triumeq
Indication:	HIV
Development Phase:	IV
Study Begin (FPFV):	04/05/2016
Study End (LPLV):	14/02/2020
Report Version & Issue Date:	v.3.0 - 22/11/2021
Sponsor Name and Address:	King's College NHS Foundation Trust
Sponsor contact details:	Amy Holton amy.holton@kcl.ac.uk
Chief Investigator:	Professor Frank Post

SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

Chief Investigator: Prof Frank Post

Printed name	**Signature**	**Date**
Frank Post		**22NOV2021**
…….	…….	…….

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APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board

The study protocol and amendments were reviewed and approved by a National Research Ethics Service (*London – City & East Research Ethics Committee*).

Ethical conduct of the study

The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent

Participants were provided with verbal and written information (participant information sheet) during routine clinic visits. They were provided with opportunities to ask questions and given at least 24 hours to decide whether to take part in the study. All participants provided written informed consent. Continued consent was confirmed at each study visit.

2. Data Monitoring

The independent Data and Safety Monitoring Committee (DSMC) monitored the main safety and efficacy outcome measures and the overall conduct of the trial, with the aim of protecting the safety and the interests of the trial participants.

3. Sponsors, Investigators and Trial Sites

Sponsors	*Amy Holton* *Quality Manager* ***King's Health Partners Clinical Trials Office*** ***Guy's Hospital*** ***London*** ***SE1 9RT***
Chief Investigator	***Professor Frank Post*** ***King's College NHS Foundation Trust*** ***Weston Education Centre*** ***Denmark Hill*** ***London*** ***SE5 9RJ***

4. Co-Investigators, Statistician, Laboratories, Database Management

Co-Investigators:	*Lisa Hamzah, Stephen Kegg, Julie Fox, Phillip Hay/Katia Prime, Chloe Orkin, Laura Waters, Margaret Johnson, Jonathan Ainsworth, Yvonne Gilleece*
Statistician:	*Fowzia Ibrahim*
Database Management:	*Bee Barbini – CASTOR EDC*
Laboratories:	*King's College NHS Foundation Trust Biochemistry and Virology Department* *Cambridge University Hospitals NHS Foundation Trust, Clinical Biochemistry, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0QQ*

5. Study Synopsis

Title of clinical trial	Bone Evaluation in HIV positive women over 40 who Switch from TDF + 3TC/FTC + NNRTI to Triumeq - 'The BESTT women's Study'
Protocol Short Title/Acronym	'The BESTT women's Study'
Study Phase	IV
Sponsor name	King's College NHS Foundation Trust
Chief Investigator	Prof Frank Post
Eudract number	2015-005297-37
REC number	16/LO/0019

IRAS project ID:	3552
Medical condition or disease under investigation	BMD in HIV positive women
Purpose of clinical trial	To investigate changes in bone mineral density (BMD) in HIV positive women who switch from an antiretroviral regimen consisting of tenofovir-DF/emtricitabine [TDF/FTC], or TDF/lamivudine [TDF/3TC] plus a non-nucleoside reverse transcriptase inhibitor [NNRTI]) to abacavir/lamivudine/dolutegravir (Triumeq).
Primary objective	Between study-arm changes from baseline in total hip BMD at week 48
Secondary objective (s)	- Changes in spine, total hip and neck of femur BMD at 24, 48 and 96 weeks - Changes in parathyroid hormone at 24, 48 and 96 weeks - Changes in bone turnover markers at 24, 48 and 96 weeks - Changes in renal function at 12, 24, 48 and 96 weeks - Changes in urinary albumin, protein, retinol-binding protein excretion and maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate (TmPO4/GFR) at 24, 48 and 96 weeks - Changes in body weight at 12, 24, 48, 72 and 96 weeks - Changes in insulin resistance at 48 weeks
Trial Design	The BESTT study is an ongoing 96-week, open-label, phase IV, randomised, controlled, multicentre clinical trial. Patients were randomized 1:2, stratified by age and seen at specialist HIV clinics in London and Brighton.
Endpoints	Primary endpoint: Between study-arm changes from baseline in total hip BMD at week 48 Secondary endpoints: Changes in spine, total hip and neck of femur BMD at 24, 48 and 96 weeks Changes in parathyroid hormone and bone turnover markers at 24, 48 and 96 weeks Changes in renal function at 12, 24, 48 and 96 weeks Changes in urinary albumin, protein, retinol-binding protein excretion and maximum rate of

	renal tubular reabsorption of phosphate to glomerular filtration rate (TmPO4/GFR) at 24, 48 and 96 weeks Changes in body weight at 12, 24, 48, 72 and 96 weeks Changes in insulin resistance at 48 weeks
Planned number of subjects	90 women
Summary of eligibility criteria	HIV positive women >40 years, Plasma HIV RNA < 50 copies/ml for at least 12 months on a stable regimen consisting of TDF/FTC or 3TC/NNRTI, HLA-B5701 negative, Agreeable not to get pregnant during the study
IMP, dosage and route of administration	Arm 1 – IMP: ORAL abacavir 600 mg daily, lamivudine 300 mg daily, and dolutegravir 50 mg daily (administered as Triumeq 1 tablet daily)
Active comparator product(s)	Arm 2 – Control: ORAL tenofovir (TDF) 245 mg daily, emtricitabine 200 mg or lamivudine (3TC) 300 mg daily, and an NNRTI (efavirenz (EFV) 600 mg daily, nevirapine (NVP) 400 mg daily, etravirine (ETV) 400 mg daily or rilpivirine (RPV) 25 mg daily
Maximum duration of treatment of a subject	96 weeks
Version and date of protocol amendments	V1.3 – 21/06/2016 V2.0 – 21/12/2016 V3.0 – 05/12/2017 V4.0 – 07/10/2019

6. Glossary of terms

N/A

7. Publication (reference)

- Ibrahim F, Samarawickrama A, Hamzah L, Vincent R, Gilleece Y, Waters L, Kegg S, Barbini B, Campbell L, Post FA. Bone mineral density, kidney function, weight gain and insulin resistance in women who switch from TDF/FTC/NNRTI to ABC/3TC/DTG. HIV Med 22: 83-91, 2021. PMID: 32985122.
- 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 35: 349-351, 2021. PMID: 33394676.
- The week 96 results have been submitted for publication.

8. Study period (years)

Study Start Date 04/05/2016 (FPFV)

Study End Date:	14/02/2020 (LPLV) (REC notification 16/04/2020). The LPLV should have been on 12/03/2020, however due to the COVID-19 pandemic, this visit did not take place.
Patient recruitment was completed	*30/03/2018*

9. Phase of development

This is a Phase IV RCT

10. Objectives

Primary endpoint

- Between study-arm changes from baseline in total hip BMD at week 48

Secondary endpoints

- Changes in spine, total hip and neck of femur BMD at 24, 48 and 96 weeks
- Changes in parathyroid hormone at 24, 48 and 96 weeks
- Changes in bone turnover markers at 24, 48 and 96 weeks
- Changes in renal function at 12, 24, 48 and 96 weeks
- Changes in urinary albumin, protein, retinol-binding protein excretion and maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate (TmPO4/GFR) at 24, 48 and 96 weeks
- Changes in body weight at 12, 24, 48, 72 and 96 weeks
- Changes in insulin resistance at 48 weeks

11. Background and Context

Combination antiretroviral therapy (cART) has revolutionised the management of HIV infection. When started before significant immunodeficiency has occurred, people living with HIV can aspire to live a normal lifespan. Several new drugs have recently been licensed for the treatment of HIV infection including the integrase inhibitor dolutegravir; the licensing trials for this and other drugs for HIV have predominantly included asymptomatic men, and the use of these agents in women remains poorly studied.

The use of cART has been associated with reductions in bone mineral density (BMD) and fractures, and the effects of cART on bone are of increasing importance in treatment strategies for older HIV positive men and post-menopausal women. Women are at risk of accelerated bone loss following the menopause, and bone preservation strategies including vitamin D and calcium supplementation, hormone replacement therapy and bisphosphonate treatment are widely employed to reduce fracture risk in this population. Antiretroviral switch may be an additional and attractive intervention to preserve bone mass in HIV positive patients. No data are available on the effects of ART switch on bone in women, and no studies to date have examined the effects of dolutegravir-containing antiretroviral therapy on BMD.

12. Methodology

The Bone Evaluation in women over 40 who Switch from TDF + FTC/3TC + NNRTI to Triumeq study (BESTT women's study) examined the effects of a randomised switch from tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) or lamivudine (3TC) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) to abacavir (ABC)/3TC/dolutegravir (DTG) (Triumeq). We hypothesized that substitution of TDF/FTC or 3TC/NNRTI with Triumeq will result in improved BMD and reduced bone turnover while maintaining HIV control. The study was a 96-week open-label, randomised clinical trial. Participants are randomised 2:1 to switch to Triumeq. Post-baseline visits occurred at 4 (switch arm only), 12, 24, 48, 72 and 96 weeks. Safety assessments included symptom-directed physical examinations, kidney and bone profiles, as well as urine dipstick analysis at each visit. In addition, HIV RNA, CD4 cell count, fasting lipids and glucose, and pregnancy tests (women of childbearing potential only) were performed every 6 months. Aliquots of plasma, serum and urine were snap-frozen and stored at -70°C for biomarker analyses. Bone mineral density (expressed in g/cm^2) was assessed using dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine (L1 – L4) and the (non-dominant) total hip and femoral neck at baseline, and weeks 24, 48 and 96. Bone turnover was evaluated at by quantification of alkaline phosphatase (ALP), type I collagen cross-linked C-telopeptide (CTX) and pro-collagen type 1 N-terminal propeptide (P1NP), 25-hydroxy-vitamin D [25(OH)D] and parathyroid hormone (PTH); renal function by eGFR, serum cystatin C, albumin/creatinine ratio (ACR), protein/creatinine (PCR), retinol-binding protein/creatinine ratio (RBPCR) and fractional excretion of phosphate (FE-PO_4). In a post-hoc exploratory analysis, insulin was measured in stored samples at baseline and week 48, and insulin resistance was assessed by Homeostatic Model Assessment of Insulin Resistance (H0MA-IR), Quantitative Insulin Sensitivity Check Index (QUICKI) and Insulin Resistance index, and metabolic syndrome using the Adult Treatment Panel diagnostic criteria.

The following questionnaires were included: Hospital Anxiety and Depression Scale (HADS), symptoms associated with HIV and antiretroviral treatment, Jenkins Sleep Questionnaire, Adherence Questionnaire, and Menopause Questionnaire.

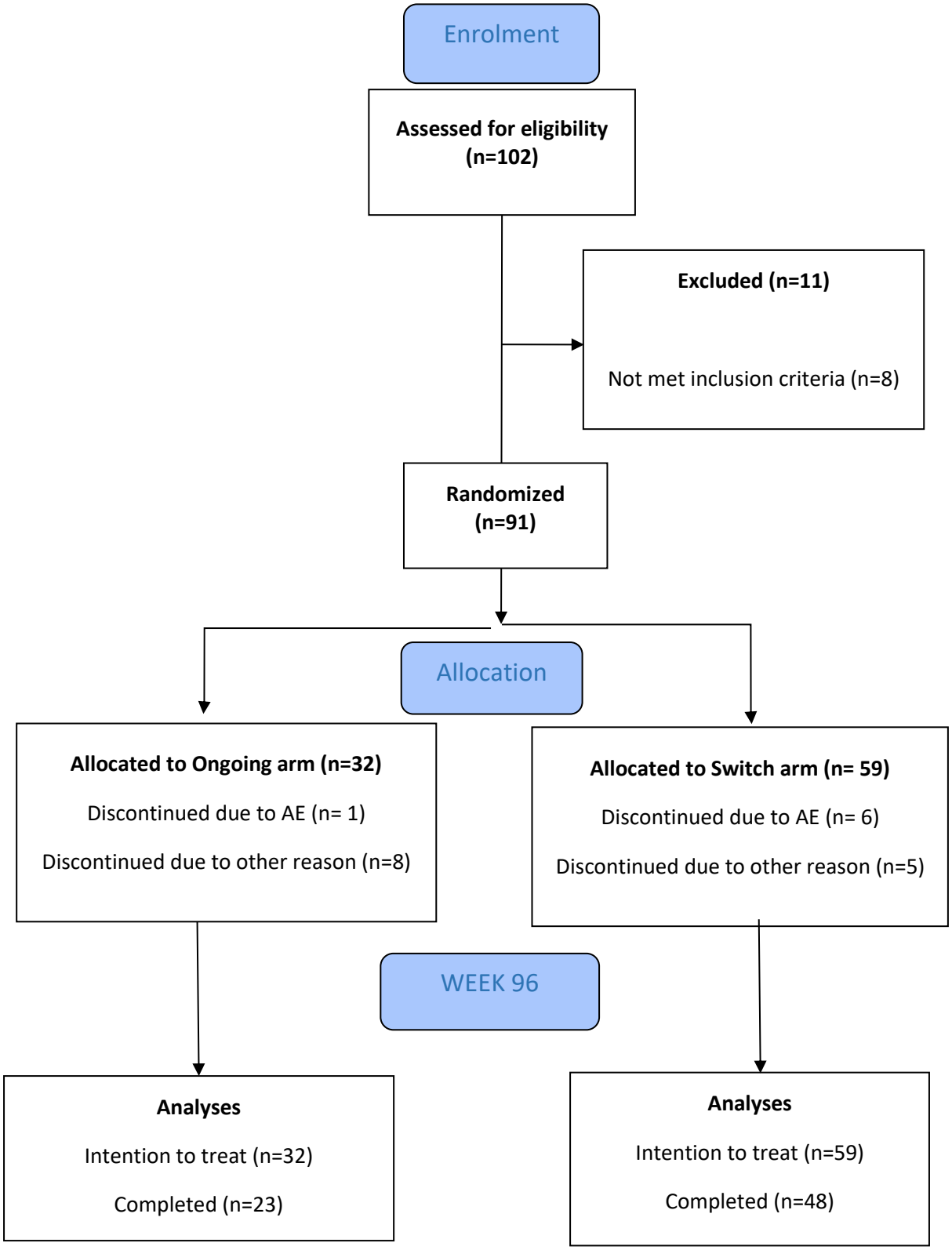
Schedule of Visits

Study Visit	Screening	Baseline	Follow up					
	Day -28 to -7	Day 0	Week 4 [9]	Week 12	Week 24	Week 48	Week 72	Week 96
Informed consent	x							
Review eligibility	x	x						
Medical history	x							
Randomisation		x						
Adherence, drug returns, pill count, adverse events, concomitant medications, dispensation/accountability of study medication		x	x	x	x	x	x	x
Physical examination [1]	x	x	x	x	x	x	x	x
Kidney/bone/liver profile [2]	x	x	x	x	x	x	x	x
Lipid profile plus glucose [3]		x			x	x		x
Full blood count	x	x			x	x		x
CD4+ lymphocyte count		x			x	x		x
Plasma HIV RNA	x	x	x		x	x	x	x
Thyroid function [4]	x							x
Follicle stimulating hormone		x						x
Hepatitis B/C status [5]	x							
Urine dipstick analysis	x	x	x	x	x	x	x	x
Pregnancy test [6]	x	x			x	x	x	x
Biobanking of blood/urine [7]		x		x	x	x		x
DXA scan (hip/spine)		x [8]			x	x		x
FRAX assessment	x	x						
Symptom and sleep questionnaires		x			x	x		x
Menopause questionnaire	x							x
HADS questionnaire		x	x	x	x	x		x
Reason for research participation questionnaire	x							

1	Physical Examination (symptom directed except at screening: full physical examination)	6	Women of child bearing potential
2	Should at least include the following: urea, creatinine, Na, K, Ca, P, albumin, bilirubin, ALP, ALT or AST, GGT	7	10 ml EDTA plasma, 10 ml serum, 5 ml urine (see appendix D)
3	Total Cholesterol, HDL, LDL, triglycerides (FASTING)	8	At or prior to baseline (see page 11)
4	Thyroid stimulating hormone (TSH)	9	Triumeq arm only
5	Hepatitis B surface antigen and hepatitis C IgG (plus, if HCV IgG positive, HCV RNA)	NB	Day 0 and week 24, 48 and 96 are fasting visits

13. Number of patients (planned and analysed)

The planned number of participants was: 90
We screened a total of 102 women.


Enrolment
Assessed for eligibility (n=102)
Excluded (n=11)
Not met inclusion criteria (n=8)
Randomized (n=91)
Allocation
Allocated to Ongoing arm (n=32)
Discontinued due to AE (n= 1)
Discontinued due to other reason (n=8)
Allocated to Switch arm (n= 59)
Discontinued due to AE (n= 6)
Discontinued due to other reason (n=5)
WEEK 96
Analyses
Intention to treat (n=32)
Completed (n=23)
Analyses
Intention to treat (n=59)
Completed (n=48)

14. Diagnosis and main criteria for inclusion

Inclusion Criteria

- Documented HIV-1 antibody test
- Female aged ≥40 years
- Plasma HIV RNA < 50 copies/ml for at least 12 months on a stable regimen consisting of TDF/FTC or 3TC/NNRTI (single viral blip of 50-200 copies/ml allowed but this needs to be followed by an undetectable viral load (<50 c/ml) before a patient can be screened).Able to give informed consent
- HLA-B5701 negative
- Patient agreeable not to get pregnant during the study or female patients of child-bearing potential must agree to use one of the following methods of contraception to avoid pregnancy:
    - Complete abstinence from penile-vaginal intercourse from 2 weeks prior to baseline visit, throughout the study, and for at least 2 weeks after discontinuation of all study medications
    - Double barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide)
    - Any intrauterine device (IUD) with published data showing that the expected failure rate is <1% per year
    - Male partner sterilization ***confirmed prior to the female subject's entry into the study***, and this male is the sole partner for that subject
    - Hormonal contraception (unless currently taking efavirenz; see http://www.hiv-druginteractions.org/data/ExtraPrintableCharts/ExtraPrintableChartID13.pdf for further advice on choosing a reliable method of hormonal contraception

  Non-child-bearing potential is defined as 12 months of spontaneous amenorrhea in women ≥ 45 years of age), documented tubal ligation, hysterectomy or bilateral oophorectomy.

Exclusion Criteria

- At screening or any time since HIV diagnosis Hepatitis B surface antigen positive At screening Hepatitis C co-infection (HCV IgG positive AND HCV RNA positive) – patients can be included if HCV IgG positive but HCV RNA negative
- Subjects with moderate to severe hepatic impairment (Class B or greater) as determined by Child-Pugh classification
- Known HIV resistance mutations to any of the study drugs
- FRAX score-based 10 year risk estimate of major osteoporotic fracture above the NOGG treatment threshold*
- Current or planned use of bisphosphonates
- Screening laboratory parameters ≥ grade 3 (ACTG criteria – see appendix A)
- ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin)
- Creatinine clearance <50 mL/min (Cockcroft-Gault)
- Current alcohol use (>3 units daily for the past month) or drug dependence which would make the participant unable to comply with the protocol (investigator opinion)

- Active opportunistic infection within the last 4 weeks
- Significant co-morbidities (investigator opinion)
- Untreated hyper- or hypothyroidism (TSH below the lower limit or above the upper limit of the normal range, respectively)
- Female patients of child-bearing potential who have/are:
    - positive pregnancy test at screening or during the study
    - breast feeding
    - planning to become pregnant
    - unwilling to use adequate contraception throughout the study
- Individuals unable or unwilling to comply with the requirements of the study (investigator opinion)
- Known hypersensitivity to any of the active substances or excipients
- Current or likely use of any of the following substances:
    - carbamazepine, oxcarbazine, phenobarbitone, phenytoin, St John's wort, dofetilide

15. Test product, dose, and mode of administration

Triumeq

Pharmaceutical form:	Tablet
Unit strength:	600mg abacavir, 300mg lamivudine, 50mg dolutegravir
Daily dose:	1 tablet
Route of administration:	Oral

16. Duration of treatment

96 weeks

17. Reference therapy, dose, and mode of administration

Tenofovir disoproxil fumarate

Pharmaceutical form:	Tablet
Unit strength:	245mg tenofovir disoproxil fumarate
Daily dose:	1 tablet once daily
Route of administration:	Oral

Lamivudine

Pharmaceutical form:	Tablet
Unit strength:	150mg lamivudine or 300mg lamivudine
Daily dose:	300mg daily
Route of administration:	Oral

Truvada

Pharmaceutical form:	Tablet
Unit strength:	245mg tenofovir disoproxil fumarate, 200mg emtricitabine
Daily dose:	1 tablet
Route of administration:	Oral

Atripla

Pharmaceutical form:	Tablet

Unit strength:	Efavirenz 600mg, emtricitabine 200mg, tenofovir disoproxil fumarate 245mg
Daily dose:	1 tablet
Route of administration:	Oral

Eviplera

Pharmaceutical form:	Tablet
Unit strength:	Rilpivirine 25mg, emtricitabine 200mg, tenofovir disoproxil fumarate 245mg
Daily dose:	1 tablet
Route of administration:	Oral

Efavirenz

Pharmaceutical form:	Tablet or capsule
Unit strength:	Efavirenz 600mg tablet or 200mg capsule
Daily dose:	600mg
Route of administration:	Oral

Nevirapine

Pharmaceutical form:	Tablet
Unit strength:	Nevirapine 400mg prolonged release (PR) or 200mg tablet
Daily dose:	400mg
Route of administration:	Oral

Etravirine

Pharmaceutical form:	Tablet
Unit strength:	200mg
Daily dose:	Etravirine 400mg
Route of administration:	Oral

Rilpivirine

Pharmaceutical form:	Tablet
Unit strength:	Rilpivirine 25mg
Daily dose:	25mg
Route of administration:	Oral

18. Criteria for evaluation: Endpoints

Primary end-point: Changes in total hip BMD at week 48 between study treatment arms

Secondary end-points: Changes in BMD and the lumbar spine and femoral neck; bone turnover; kidney function; anxiety, depression, sleep; efficacy (HIV RNA <50 copies/mL) and safety (discontinuations and adverse events).

19. Statistical Methods

Analyses were by intention-to-treat. Baseline characteristics were summarized by randomization group as means and standard deviations (continuous normally distributed variables), medians and interquartile ranges (IQRs, non-normally distributed variables), and frequencies and percentages (categorical variables). 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 BMI, where weight 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 biomarker outcomes.

20. Summary – Conclusions

20.1 Demographic and clinical characteristics

		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 (%)] *	14 (50.0)	26 (52.0)
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 could be determined for 78 participants; ** Viral load missing N=2 and <200 N=2

Age stratification: 18-64 years and 64 years and over:

Age, years	TDF/FTC/NNRTI (n=32)	ABC/3TC/DTG (n=59)
18-64	31	56
>64	1	3

20.2 Primary outcome

	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

Abbreviations: TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir

20.3 Secondary outcomes

	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 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

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

20.4 Safety results: adverse events

Several women who switched to ABC/3TC/DTG experienced (worsening) anxiety or depression, which in N=3 was accompanied by suicidality. Participants who switched ART also experienced weight gain. Further details of the reported adverse events are provided in the appendix.

Total number of subjects that experienced at least 1 AE in each arm:

	BESTT (n=91)	TDF/XTC/NNRTI (N=32)	ABC/3TC/DTG (N=59)
Any adverse event (N=264)	77 (84.6%)	25 (78.1%)	52 (88.1%)

20.5 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.

21. Date of Report

This is version 3.0 of the Clinical Study Report synopsis, dated 22/NOVEMBER/2021.

APPENDIX

Summary of treatment-emergent AEs in the per protocol population

System Organ Class	Preferred Term	Number of Subjects Experiencing the AE in Active Arm (ABC/3TC/DTG)	Total Number of Occurrences of the AE in the Active Arm (ABC/3TC/DTG)	Number of Subjects Experiencing the AE in Control Arm	Total Number of Occurrences of the AE in Control Arm
		n / 59		n / 32	
Eye Disorders	Conjunctivitis	0	0	1	1
Eye Disorders	Blepharitis	0	0	1	1
Eye Disorders	Itchy eyes	1	1	0	0
Eye Disorders	Bilateral red eyelids, burning sensation around eyes	1	1	0	0
Eye Disorders	Dry eyes	1	1	0	0
Eye Disorders	Sty	1	1	0	0
Gastrointestinal disorders	Toothache	0	0	1	1
Gastrointestinal disorders	Tooth infection	0	0	1	1

Gastrointestinal disorders	Root canal	0	0	1	1
Gastrointestinal disorders	Tooth abscess	1	1	1	1
Gastrointestinal disorders	Tooth erosion	1	1	0	0
Gastrointestinal disorders	Abdominal feeling of heat, nausea, vomiting and sore throat	1	1	0	0
Gastrointestinal disorders	Abdominal pain	0	0	1	1
Gastrointestinal disorders	Constipation	2	2	0	0
Gastrointestinal disorders	Diarrhoea	5	6	2	3
Gastrointestinal disorders	Dyspepsia	1	1	0	0
Gastrointestinal disorders	Flatulence	1	1	0	0
Gastrointestinal disorders	Gastroenteritis	0	0	1	1
Gastrointestinal disorders	Nausea	1	1	1	1
Gastrointestinal disorders	Reflux	2	2	0	0
Gastrointestinal disorders	Stomach pain	3	3	0	0
Gastrointestinal disorders	Vomiting	0	0	1	1
General disorders and administration site conditions	Hypothyroid	0	0	1	1
General disorders and administration site conditions	Abnormal dreams	3	3	0	0

General disorders and administration site conditions	Insomnia	3	4	0	0
General disorders and administration site conditions	Parasomnia	4	4	0	0
Immune system disorders	Allergic reaction	0	0	1	2
Immune system disorders	Anaemia	0	0	1	1
Immune system disorders	Folic acid deficiency	1	1	0	0
Immune system disorders	Hayfever	3	3	0	0
Immune system disorders	Low B12 and folate deficiency	1	1	0	0
Immune system disorders	Vitamin D deficiency	4	5	1	1
Infections and infestations	Ear pain	2	2	1	1
Infections and infestations	Fever	1	1	0	0
Infections and infestations	Influenza	5	5	0	0
Infections and infestations	Respiratory infection	3	3	0	0
Metabolism and nutritional disorders	Anorexia	0	0	1	1
Metabolism and nutritional disorders	Weight gain / change in body shape or abdominal girth	3	4	0	0
Musculoskeletal and connective tissue disorders	All over body pain	1	1	0	0

Musculoskeletal and connective tissue disorders	Painful ankles (due to falls)	1	1	0	0
Musculoskeletal and connective tissue disorders	Arm pain	2	2	0	0
Musculoskeletal and connective tissue disorders	Back pain	2	2	3	3
Musculoskeletal and connective tissue disorders	Lower back muscle spasm	0	0	1	1
Musculoskeletal and connective tissue disorders	Body aches	1	1	1	1
Musculoskeletal and connective tissue disorders	Early changes of degeneration in spine	1	1	0	0
Musculoskeletal and connective tissue disorders	Golfer's elbow	1	1	0	0
Musculoskeletal and connective tissue disorders	Hip pain	1	1	1	1
Musculoskeletal and connective tissue disorders	Insertional Tendinopathy	1	1	0	0
Musculoskeletal and connective tissue disorders	Intermittent bilateral bony elbow pain	1	1	0	0
Musculoskeletal and connective tissue disorders	Jaw pain	1	1	0	0
Musculoskeletal and connective tissue disorders	Joint pain / stiffness	1	1	2	2
Musculoskeletal and connective tissue disorders	Knee / ankle pain	2	2	1	1
Musculoskeletal and connective tissue disorders	Leg pain	0	0	1	1
Musculoskeletal and connective tissue disorders	Medial epicondylitis	1	1	0	0

Musculoskeletal and connective tissue disorders	Musculoskeletal pain (chest / arm / shoulder)	2	2	1	1
Musculoskeletal and connective tissue disorders	Neck strain	0	0	1	1
Musculoskeletal and connective tissue disorders	Rheumatoid Arthritis / Osteoarthritis	1	1	1	1
Musculoskeletal and connective tissue disorders	Right gluteal tendonitis and bursitis	1	1	0	0
Musculoskeletal and connective tissue disorders	Medial foot pain	1	1	0	0
Musculoskeletal and connective tissue disorders	Sciatica nerve pain	1	1	0	0
Musculoskeletal and connective tissue disorders	Shoulder / scapular pain	5	5	1	1
Musculoskeletal and connective tissue disorders	Finger stiffness	2	2	0	0
Musculoskeletal and connective tissue disorders	Swollen feet	1	1	0	0
Musculoskeletal and connective tissue disorders	Thigh pain	1	1	0	0
Musculoskeletal and connective tissue disorders	Tingling in arms and legs	1	1	0	0
Musculoskeletal and connective tissue disorders	Weak joints	1	1	0	0
Musculoskeletal and connective tissue disorders	Ankle oedema	1	1	0	0
Musculoskeletal and connective tissue disorders	Burn on buttock	0	0	1	1

Musculoskeletal and connective tissue disorders	Banged knee	0	0	1	1
Musculoskeletal and connective tissue disorders	Enlarged heart	1	1	0	0
Musculoskeletal and connective tissue disorders	Left leg weakness after road traffic accident	1	1	0	0
Musculoskeletal and connective tissue disorders	Cut left middle finger after fall	1	1	0	0
Musculoskeletal and connective tissue disorders	Left foot injury	1	1	0	0
Musculoskeletal and connective tissue disorders	Pain in right side of face, ear and head	0	0	1	1
Nervous system disorders	Dizziness	5	5	3	3
Nervous system disorders	Fatigue	5	5	2	2
Nervous system disorders	Headache	4	4	2	3
Nervous system disorders	Migraine	0	0	1	2
Nervous system disorders	Neurocognitive symptoms	0	0	1	1
Nervous system disorders	Memory issues	1	1	0	0
Psychiatric disorders	Anxiety	2	2	0	0
Psychiatric disorders	Depression	0	0	2	2
Psychiatric disorders	Fleeting suicidal thoughts	1	1	0	0

Psychiatric disorders	Low mood	4	4	3	3
Renal and urinary disorders	Haematuria	1	1	0	0
Renal and urinary disorders	Proteinuria	0	0	1	1
Renal and urinary disorders	Kidney infection	0	0	1	1
Renal and urinary disorders	Urinary tract infection	2	2	2	2
Renal and urinary disorders	Pain / difficulty on micturation	2	2	0	0
Reproductive system and breast disorders	Adnexal mass	1	1	0	0
Reproductive system and breast disorders	Bulky uterus	1	1	0	0
Reproductive system and breast disorders	Dysmenorrhea	0	0	1	1
Reproductive system and breast disorders	Endometrial thickening and hysteroscopy	1	1	0	0
Reproductive system and breast disorders	Fibroids	1	1	0	0
Reproductive system and breast disorders	Menorrhagia	2	2	0	0
Reproductive system and breast disorders	Postmenopausal bleeding	0	0	1	1
Reproductive system and breast disorders	Vaginal bleeding	1	1	0	0
Reproductive system and breast disorders	Vaginal candidiasis	1	1	1	1
Respiratory, thoracic and mediastinal disorders	Chest infection	3	3	2	2

Respiratory, thoracic and mediastinal disorders	Cold / coryzal symptoms	5	5	6	6
Respiratory, thoracic and mediastinal disorders	Cough	9	10	2	2
Respiratory, thoracic and mediastinal disorders	Post nasal drip	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Sore throat / throat irritation	3	3	1	1
Respiratory, thoracic and mediastinal disorders	Sinusitis	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	1	1	0	0
Skin and subcutaneous tissue disorders	Abscess	0	0	1	1
Skin and subcutaneous tissue disorders	Localised rash	4	4	1	1
Skin and subcutaneous tissue disorders	Athletes foot	1	1	0	0
Skin and subcutaneous tissue disorders	Blister / Ulcer	1	1	0	0
Skin and subcutaneous tissue disorders	Coldsores around mouth	1	1	0	0
Skin and subcutaneous tissue disorders	Darkened patches of skin to feet and toes	1	1	0	0
Skin and subcutaneous tissue disorders	Eczema	2	2	0	0
Skin and subcutaneous tissue disorders	Right 4th finger skin infection	1	2	0	0
Skin and subcutaneous tissue disorders	Swollen index finger	1	2	0	0

Skin and subcutaneous tissue disorders	Fungal skin infection	1	1	0	0
Skin and subcutaneous tissue disorders	Haemarrhoids	1	1	0	0
Skin and subcutaneous tissue disorders	Hot flushes	1	1	1	1
Skin and subcutaneous tissue disorders	Infected hair follicle	1	1	0	0
Skin and subcutaneous tissue disorders	Infection of wound on chest	1	2	0	0
Skin and subcutaneous tissue disorders	Itchiness	4	4	0	0
Skin and subcutaneous tissue disorders	Lichen planus	1	1	0	0
Skin and subcutaneous tissue disorders	Lipodystrophy	1	1	0	0
Skin and subcutaneous tissue disorders	Lump over right shoulder	1	1	0	0
Skin and subcutaneous tissue disorders	Dry skin	2	2	0	0
Skin and subcutaneous tissue disorders	Skin lesion on neck	1	1	0	0
Skin and subcutaneous tissue disorders	Solar keratosis	1	1	0	0
Vascular disorders	Hypertension	2	2	0	0

Summary of treatment-emergent SAEs, IMEs and SARs in the study population:

Serious adverse events (N=11): of which SAE (n=6), IME (n=3), SAR (n=1), Pregnancy (n=1)

	BESTT (n=91)	TDF/XTC/NNRTI (N=32)	ABC/3TC/DTG (N=59)
Serious adverse events	11	2	9
Suicidal Ideation (Low mood) **IME**	1		1
Attempted suicide **SAR**	1		1
Low mood with insomnia **IME**	1		1
Elective TAH/BSO - Adult Granulosa cell tumour FIGO Stage 1A	1		1
Respiratory distress, hepatitis and acute kidney injury.	1	1	
Perianal abscess	1		1
Pregnancy	1		1
Cellulitis of Hand	1	1	
Lower respiratory infection	1		1
Papillary Carcinoma	1		1
Thyroidectomy **IME**	1		1