RANDOMIZED CLINICAL TRIAL OF TRANSGENDER WOMENSWITCHING TO B/F/TAF (MOBETTA TRIAL)

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AN Hyatt[1], H Feng[2], P Debroy[1], A Kettelhut[3], H Miao[2], L Peng[4], S Bhasin[4], TT Brown[5], N Funderburg[3], JE Lake[1]

[1]UTHealth McGovern Medical School, Houston, TX USA; [2]UTHealth School of Public Health Houston, TX USA; [3]The Ohio State University, Columbus, OH USA; [4]Brigham and Women's Hospital, Boston, MA USA; [5]Johns Hopkins University, Baltimore, MD USA

Correspondence:
Jordan E. Lake, M.D., M.Sc.
6431 Fannin St., MSB 2.112
Houston, TX 77030
Jordan.E.Lake@uth.tmc.edu

Background

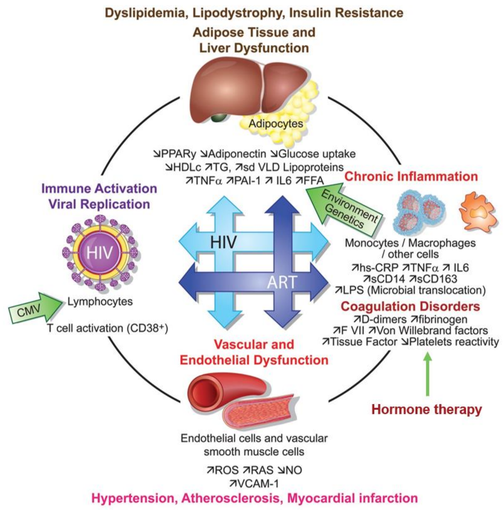


Fig. 1: Contributions of HIV and GAHT to metabolic and inflammatory disease. Adapted from Hemkens and Bucher. *Eur Heart J. 2014*

- Transgender women (TW) are disproportionally affected by HIV and have a high prevalence of modifiable cardiovascular disease (CVD) risk factors[1,2]
- HIV, antiretroviral therapy (ART), and gender-affirming hormone therapy (GAHT) have each been associated with altered body composition, inflammatory and coagulation pathway abnormalities, and cardiometabolic disturbances.[3-5]
- We evaluated the safety and tolerability of switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) vs continued current ART in TW living with HIV on GAHT.

Methods

Study Population:

- TW were recruited from the Thomas Street Health Center, a freestanding HIV clinic, and community-based organizations serving TW in Houston, TX, USA

Inclusion Criteria:

- Self-identification as a TW with current GAHT use
- Age ≥ 18 years
- HIV-1 RNA <50 copies/mL at screening and for >24 weeks
- Current ART including 2 nucleoside reverse transcriptase inhibitors (NRTIs) (tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF] or abacavir [ABC] with emtricitabine [FTC] or lamivudine [3TC]) and a third agent

Exclusion Criteria:

- Known resistance to integrase strand inhibitors (INSTI) or components of their current NRTI backbones
- Intention to significantly lose weight within the planned study period

Study Design:

- Single-center, open-label, phase IIb, randomized, two-arm study (NCT03348163)
- Participants were randomized 1:1 to switch current ART to B/F/TAF immediately (Arm A) or continue current ART (Arm B), each for a total of 48 weeks

Study Procedures and Analysis:

- Dual-energy X-ray absorptiometry (DXA) scan measured bone mineral density (BMD) and lean and fat mass
- Transient elastography (FibroScan®) for hepatic fat (controlled continuation parameter, CAP) and liver stiffness measurement (LSM) was performed locally by a single operator
- Cardiometabolic biomarkers and sex hormones were measured in batch centrally at end of study; fasting glucose and lipids were measured in real time
- Wilcoxon rank-sum/signed rank and $\chi 2$ tests compared continuous and categorical variables

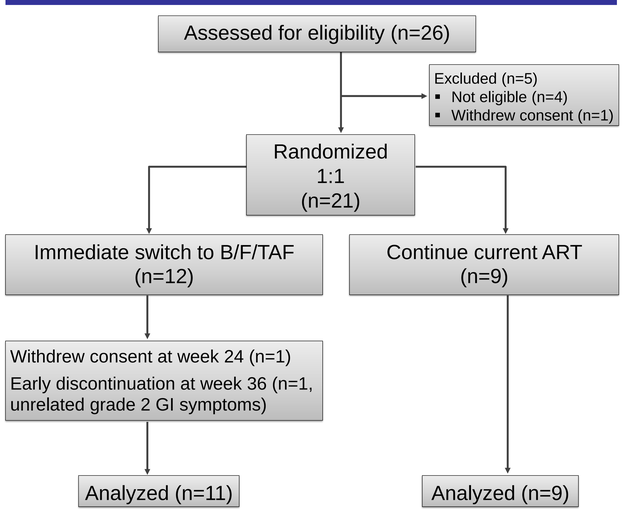
Results

Table 1. Baseline Characteristics

	ARM A N=12	ARM B N=9
Age (years)	44 (36, 56)	48 (44, 50)
Race		
Hispanic	58%	45%
Black	25%	22%
Native American	0%	22%
Asian	17%	0%
White	0%	11%
Hypertension	17%	44%
Diabetes mellitus	0%	11%
Dyslipidemia	50%	78%
Hepatitis C History	0%	11%
Current Smoker	42%	56%
BMI (kg/m^2)	27 (25, 30)	30 (27, 33)
Heavy Alcohol Use [a]	17%	0%
Years living with HIV	8	10
ART regimen		
INSTI-based	67%	67%
EVG	58%	22%
DTG	8%	44%
RAL	0%	0%
NNRTI-based	25%	33%
EFV	8%	11%
RPV	8%	11%
NVP	0%	11%
DOR	8%	0%
PI (ATV)-based	8%	0%
TAF	67%	44%
ABC	8%	44%
TDF	25%	11%
CD4$^+$ T lymphocyte count (cells/μL)	650 (439, 859)	891 (381, 1002)
History of CD4$^+$ T lymphocyte nadir <200 (cells/μL) or ever AIDS-defining diagnosis	25%	22%

Frequency or median (interquartile range) presented. a Heavy alcohol use: ≥21 drinks/week or binge drinking (>6 drinks on one occasion); BMI: body mass index; ART: antiretroviral therapy; INSTI: integrase strand transfer inhibitor; EVG: elvitegravir; DTG: dolutegravir; RAL: raltegravir; NNRTI: non-nucleoside reverse transcriptase inhibitor; EFV: efavirenz; RPV: rilpivirine; NVP: nevirapine; DOR: doravirine; PI: protease inhibitor; ATV: atazanavir; TAF: tenofovir alafenamide; ABC: abacavir; TDF: tenofovir disoproxil fumarate

Fig. 1. Patient Disposition



- **There were no study drug-related Grade ≥3 lab or clinical events**
- **At week 48, 91% of participants in Arm A and 89% in Arm B had HIV-1 RNA <50 copies/mL**

Table 2. Body Composition, Bone Mineral Density, Hepatic Fat, and Liver Stiffness Changes

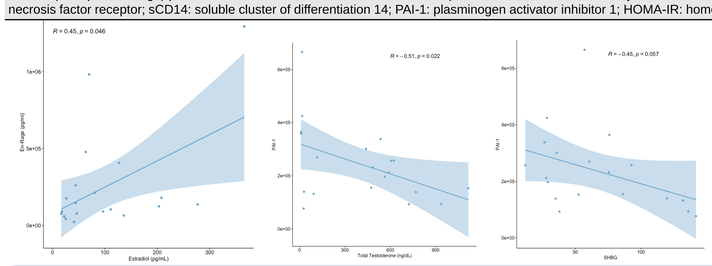
	Arm A			Arm B		
	W0 (n=12)	W48 (n=11)	change	W0 (n=9)	W48 (n=9)	change
Body Composition						
Lean mass (lbs)						
Total	108.7 (99.7, 121.6)	110.2 (101.3, 116.7)	0.79 (-2.6, 3.1)	124.4 (112.1, 146.1)	137.4 (111.4, 150.4)	0.1 (-1.6, 2)
Limb	49.8 (43.4, 54.2)	48.6 (43.5, 55.1)	0.01 (-0.9, 1.4)	50.1 (47.3, 59.9)	56.3 (47.7, 66.7)	-0.8 (-2, 1.78)
Fat mass (lbs)						
Total	53.5 (49.2, 59.1)	62.1 (53.1, 71.3)	6.5 (3.2, 9.6) *	55.4 (52.8, 72.8)	71.6 (47.2, 77.4)	3.1 (-2, 10.7)
Trunk	30.8 (27.8, 38.1)	34.8 (31.4, 44)	2.8 (1.8, 5.5) *	42.2 (22.3, 46.9)	44.8 (29, 53.8)	-0.4 (-1.4, 2.4)
Limb	21.1 (16.2, 23.5)	23.6 (17.9, 25.5)	2.9 (1.5, 3.9) *	19.6 (12.3, 20.8)	22.5 (16.3, 35.4)	-0.2 (-0.9, 3.4)
Android/gynoid ratio	1.2 (1.1, 1.5)	1.2 (1.1, 1.4)	-0.01 (-0.06, 0.04)	1.1 (0.9, 1.4)	1.2 (1.1, 1.3)	0.06 (-0.01, 0.3)
BMD (g/cm^2)						
Femur Neck Mean	0.9 (0.9, 1.1)	1 (0.9, 1.1)	0.03 (0.01, 0.04)	0.9 (0.9, 1)	0.99 (0.9, 1)	0.01 (-0.01, 0.03)
Spine L1-L4	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	0.00 (-0.02, 0.03)	1.2 (1.1, 1.3)	1.2 (1.2, 1.3)	0.04 (0.02, 0.06) *
Hip Total	1.1 (1, 1.1)	1.1 (1, 1.1)	0.02 (0.02, 0.03) *	0.9 (0.9, 1.2)	1 (0.9, 1.2)	0.03 (0.01, 0.04) *
Age-matched BMD (Z-score)						
Femur Neck Mean	-0.3 (-0.8, 0)	-0.3 (-0.7, 0.4)	0.3 (0.02, 0.3)	-1 (-1.4, -0.4)	-0.9 (-1.2, -0.3)	0.1 (-0.1, 0.3)
Spine L1-L4	-0.5 (-1.6, 0.2)	-0.9 (-1.6, -0.1)	0 (-0.1, 0.2)	-0.8 (-1.4, 0.3)	-0.1 (-1.1, 0.6)	0.5 (0.2, 0.6) *
Hip Total	-0.2 (-1.1, 0.4)	-0.5 (-0.9, 0.5)	0.2 (0.1, 0.3)	-1.3 (-1.6, 0.1)	-0.9 (-1.3, 0.3)	0.3 (0.2, 0.4)
Bone Disease Category						
Normal	41%	55%	+N/A; -9%	62%	62%	+N/A; -0%
Osteopenia	42%	36%	+27%; -0%	25%	38%	+0%; -0%
Osteoporosis	17%	9%	+9%; N/A	13%	0%	+13%; -N/A
Liver disease						
CAP Score (dB/m) †	254 (234.5, 297.5)	253 (236.5, 309.5)	3 (-13, 37.5)	301 (271, 318)	256 (235, 294)	-25 (-62, -17)
LSM (kPa)	4.4 (4.2, 4.5)	4.3 (3.8, 5.2)	0.1 (-0.7, 0.8)	4.4 (4.1, 4.6)	3.9 (3.8, 5.1)	-0.20 (-1, 1)

Median (interquartile range) presented unless noted. W0: Week 0; w48: week 48 of follow-up; BMD: Bone mineral density; Z-score matched for age, weight and ethnicity; Osteopenia: T-score between −1 and −2.5 SD at any site; Osteoporosis: T-score of −2.5 or lower at any site; CAP: Hepatic fat content as measured by FibroScan® controlled attenuation parameter; LSM: Liver stiffness measurement; (+): improved Bone Disease Category; (-): worsened Bone Disease Category;†Between-arm change at w48 p-value<0.05; *Within-arm change at w48 p-value <0.05

Table 3. Biomarker Changes

	Arm A			Arm B		
	w0	w48	change	w0	w48	change
Adiponectin (ng/mL)	5616 (2761, 6253)	3120 (2762, 5491)	13 (-2143, 252)	3472 (2444, 3792)	3681 (2154, 5908)	190 (-776, 1249)
Endothelin-1 (pg/mL)	1.3 (1.1, 3.7)	2.6 (1.7, 3.9)	0.18 (-0.5, 1.1)	3.3 (1.5, 4.5)	5.2 (2.5, 8)	1.1 (-2.2, 4.6)
EN-RAGE (pg/mL)	13658 (8329, 29269)	12332 (7594, 21189)	-2123 (-6461, 1531)	10380 (7759, 21149)	15149 (7379, 20759)	939 (-2006, 7472)
sTNFRI (pg/mL)	1033 (957, 1282)	1077 (971, 1167)	1 (-184, 89)	1266 (997, 1420)	1119 (1045, 1222)	-59 (-142, 101)
sTNFRII (pg/mL)	2552 (2043, 2724)	2307 (2011, 2931)	-34 (-453, 342)	2718 (2236, 3487)	2389 (2166, 2541)	-177 (-567, 76)
D dimer (ng/mL)	194 (179, 287)	279 (198, 325)	0.98 (-41, 86)	196 (136, 265)	198 (136, 427)	-3 (-62, 254)
Tissue factor (pg/mL)	38 (13, 72)	37 (13, 63)	3 (-15, 17)	58 (34, 91)	44 (40, 71)	-5 (-22, 17)
sCD14 (μg/mL)	1.4 (1.2, 1.4)	1.3 (1.2, 1.4)	-0.04 (-0.1, 0.05)	1.4 (1.3, 1.8)	1.3 (1.1, 1.8)	-0.1 (-0.2, 0.02)
PAI-1 (ng/mL)	155 (136, 279)	246 (191, 346)	111 (-11, 174)	256 (197, 338)	155 (143, 291)	-56 (-116, 397)
Oxidized LDL (mU/mL)	40 (27, 54)	44 (27, 47)	-6 (-9, 0.2)	46 (29, 52)	35 (32, 45)	-37 (-12, 7)
HOMA-IR	2.6 (1.8, 3.6)	1.8 (1.1, 3.1)	-0.2 (-1, 0.4)	3.5 (1.3, 9.9)	3.9 (2, 7.5)	0.3 (-0.8, 3.8)

Median (interquartile range) presented. W0: Week 0; w48: week 48 of follow-up; EN-RAGE: extracellular newly-identified receptor for advanced glycation end-products; sTNFR: soluble tumor necrosis factor receptor; sCD14: soluble cluster of differentiation 14; PAI-1: plasminogen activator inhibitor 1; HOMA-IR: homeostatic model assessment of insulin resistance



- **Higher estradiol concentrations correlated with higher EN-RAGE concentrations**
- **Lower total testosterone and lower SHBG concentrations correlated with higher PAI-1 concentrations at baseline**

- **Reported median cumulative duration of estrogen supplementation (any form) was 1.4 (IQR 0.3, 3.5) years.**
- **No TW had a history of gonadectomy**
- **Overall baseline median (IQR) estradiol concentrations: 70 (41, 136) pg/mL; total testosterone: 473 (26, 605) ng/dL**
- **Sex hormone concentrations did not strongly correlate with hepatic fat content, liver stiffness, or BMD in either arm**

Summary & Conclusions

- **In the first randomized trial of exclusively TW living with HIV on GAHT, switch to B/F/TAF was safe and metabolically neutral.**
- **However, switch to B/F/TAF was associated with greater trunk and limb fat gain.**
- **Larger studies are needed to optimize ART for TW on GAHT and dissect subtle differences between ART regimens, particularly between-INSTI differences.**

References and Acknowledgements

[1]CDC. 2019-2020 [2]Am J Public Health 2019; 109(1): e1-e8 [3]Lancet Infect Dis 2013; 13(11): 964-75 [4]Eur J Endocrinol 2018; 178(2): 163-71 [5]PLoS One 2022; 17(3): e0261312

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