Dolutegravir, emtricitabine plus two prodrugs of tenofovir for the treatment of HIV-1 infection: ADVANCE trial

For the ADVANCE team: Francois Venter[1], Michelle Moorhouse[1], Simiso Sokhela[1], Nomathemba Chandiwana[1], Godspower Akpomiemie[1], Ambar Qavi[2], Kaitlyn McCann[2], Bryony Simmons[2], Celicia Serenata[1], Andrew Hill[3]

[1]Ezintsha, Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; [2]Imperial College, Faculty of Medicine, London, United Kingdom; [3]Liverpool University, Pharmacology, Liverpool, United Kingdom

Background

- Integrase inhibitors, including dolutegravir (DTG), have replaced non-nucleoside reverse transcriptase inhibitors (NNRTI), and tenofovir alafenamide (TAF) is an alternative to tenofovir disoproxil fumarate (TDF) in high-income countries' guidelines

- DTG and TAF offer toxicity and cost benefits; DTG offers resistance benefits in an era of rising NNRTI resistance

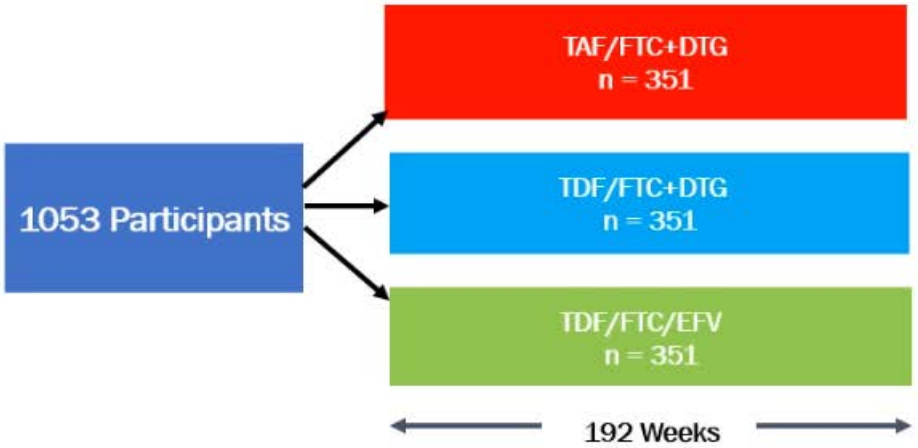
- South Africa background NNRTI resistance estimated 5-15% (Hunt, Antiviral Therapy, 2019)

- ADVANCE is a three arm, investigator-led, open-label, randomised 192-week study of first-line treatment for HIV infection, conducted in South Africa. Final week 96 visit was in March 2020.

- This analysis includes the 96-week primary efficacy analysis. Additional incomplete data are presented here, as well as earlier data (oral late breaker MOAX0102LB; poster WEPEB280).

ADVANCE: Study design

Inclusion criteria: Treatment-naïve, HIV-1 RNA level > 500 copies/mL, no TB or pregnancy, no baseline genotyping



Study visits: baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192

Baseline characteristics (ITT)

	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Median age (years)	32	32	32
Female	61%	59%	57%
Black	99%	100%	100%
Weight (median, kg)	66.1	66.4	66
BMI (kg/m^2)	24.1	24.1	24.1
Mean CD4+ cell count (cells/uL)	349	322	337
Baseline HIV RNA (copies/mL)			
HIV RNA <100,000	272 (77%)	279 (79%)	270 (77%)
HIV RNA 100-500,000	66 (19%)	62 (18%)	72 (21%)
HIV RNA >500,000	13 (4%)	10 (3%)	9 (3%)

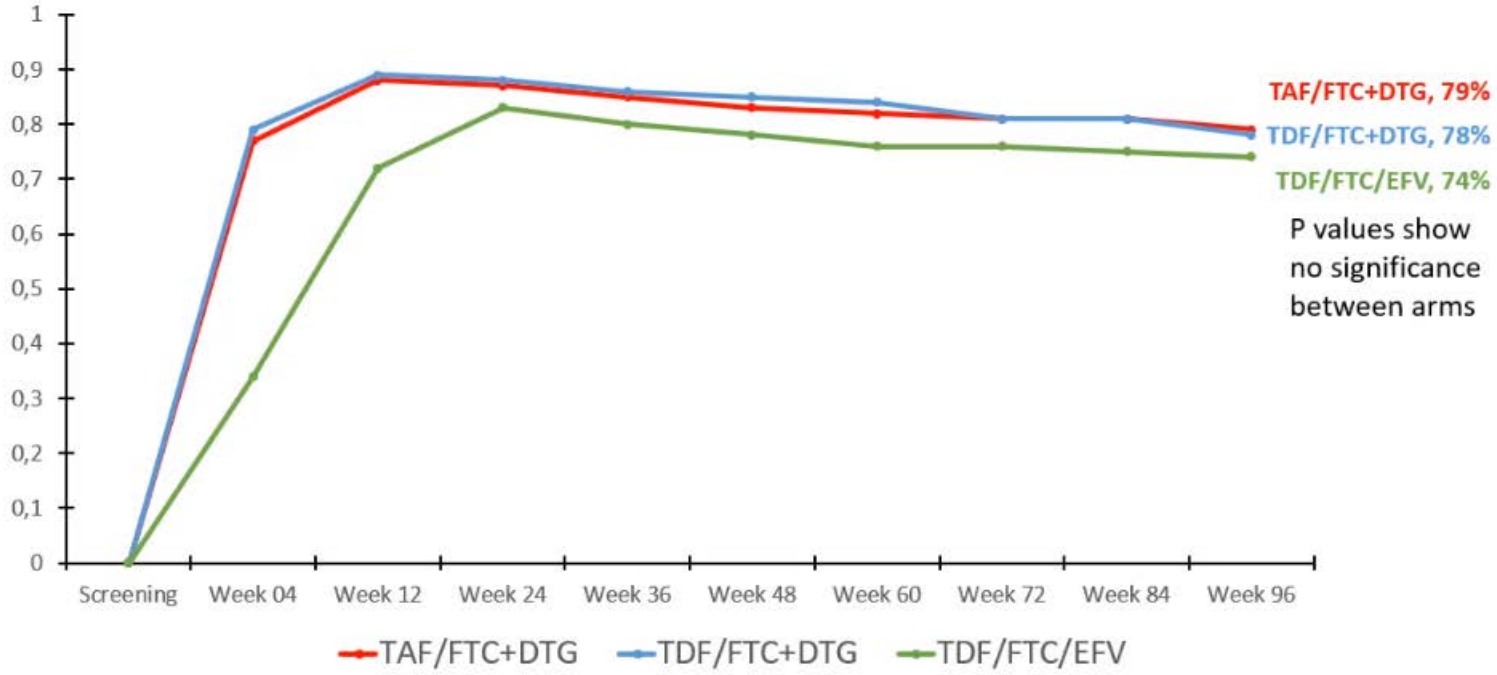
Primary efficacy endpoint: HIV RNA Analysis

- **Main efficacy endpoint: Intent to Treat, Missing equals failure analysis**

- This analysis used the last HIV RNA level for each patient in the Week 96 time window. Patients with missing data at Week 96 were classified as failures.
- Patients with HIV RNA > 50 copies/mL were counselled on adherence and re-tested within the Week 96 time window and during long-term follow-up.

- The trial was powered assuming a response rate of 80% at Week 96
- FDA non-inferiority margin for ARV-naïve studies = -10%
- Treatment arms first compared for non-inferiority, then superiority
- P value = 0.017 for superiority tests, to adjust for three pairwise comparisons

Proportion of participants with HIV-1 RNA level <50 copies/mL by time point (ITT)



TAF/FTC+DTG, 79%

TDF/FTC+DTG, 78%

TDF/FTC/EFV, 74%

P values show no significance between arms

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Treatment emergent resistance

	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
VF with resistance data at baseline & failure	12 (3%)	16 (5%)	21 (6%)
NRTI	0/12 (0%)	2/16 (13%)	9/21 (43%)
NNRTI	0/12 (0%)	0/16 (0%)	10/21 (48%)
Total: NRTI or NNRTI	**0/12 (0%)**	**2/16 (13%)***	**13/21(62%)**
INSTI	0/12 (0%)	0/16 (0%)	0/21 (0%)

*M184V mutations in both cases

Summary of clinical adverse events

	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Number of patients with:			
Serious Adverse Events	22 (6%)	20 (6%)	31 (9%)
Grade 3 and 4 AEs	54 (15%)	60 (17%)	96 (27%)*
Drug-related Grade 1-4 AEs	212 (60%)	246 (70%)	267 (76%)
Death	1 (0%)	2 (1%)	2 (1%)

*higher rates of Grade 3 or 4 adverse events in EFV arm mainly from short-term elevations in liver enzymes

Worst treatment emergent grade 3 or 4 laboratory abnormalities

	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Haematology			
Haemoglobin	4 (1%)	7 (2%)	10 (3%)
Platelets	2 (1%)	0 (0%)	2 (1%)
Neutrophil count	0 (0%)	0 (0%)	0 (0%)
Chemistry			
ALT	11 (3%)	7 (2%)	19 (5%)
AST	8 (2%)	6 (2%)	15 (4%)
GGT	7 (2%)	8 (2%)	35 (10%)
LDL	8 (2%)	1 (0%)	7 (2%)
Albumin	0 (0%)	0 (0%)	0 (0%)

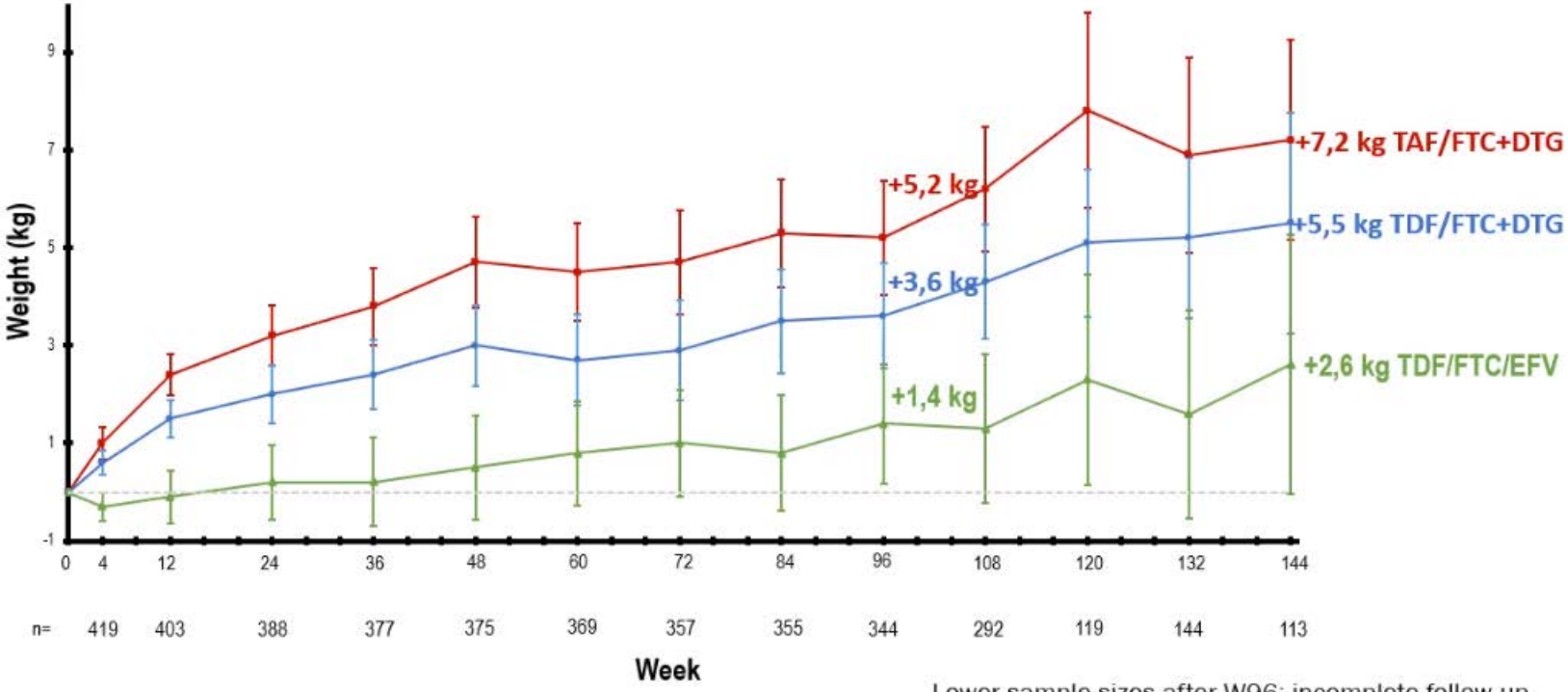
Grade 3 or 4 renal adverse events, renal markers and creatinine clearance

	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Renal	**1 (0%)**	**2 (1%)**	**3 (1%)**
Acute kidney injury	0 (0%)	0 (0%)	1 (0%)
Haematuria	0 (0%)	0 (0%)	1 (0%)
Hydronephrosis	0 (0%)	0 (0%)	1 (0%)
Lupus nephritis	0 (0%)	1 (0%)	0 (0%)
Proteinuria	0 (0%)	1 (0%)	0 (0%)
Renal impairment	1 (0%)	0 (0%)	0 (0%)
Creatinine clearance			
Grade 3 or 4	6 (2%)	46 (13%)	14 (4%)

Bone DXA: WHO category at week 96

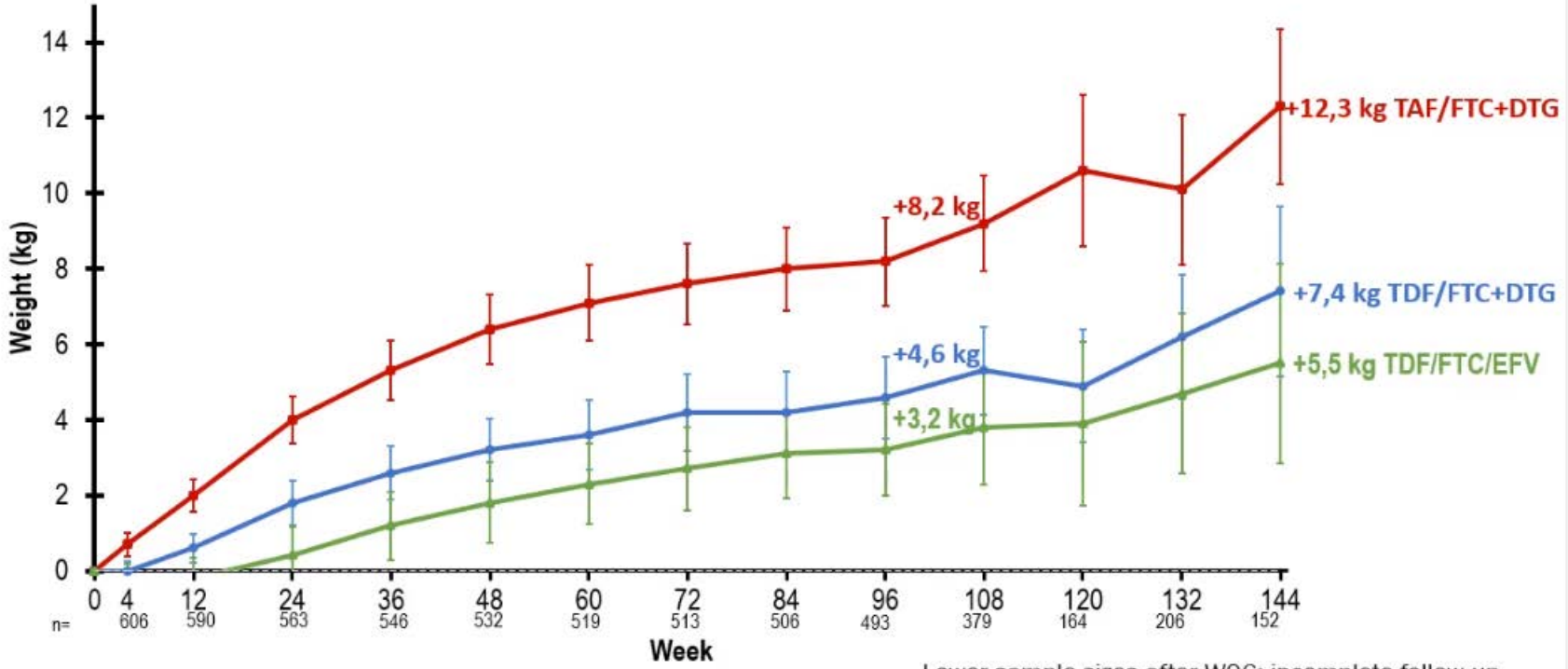
	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Hip			
Normal	291/307 (95%)	290/315 (92%)	260/293(89%)
Osteopenia	16/307(5%)	25/315 (8%)	33/293 (11%)
Lumbar Spine			
Normal	258/307 (84%)	252/315 (80%)	228/293 (78%)
Osteopenia	49/307 (16%)	63/315 (20%)	65/293 (22%)

Mean change in weight (kg) to Week 96: Men



Lower sample sizes after W96; incomplete follow-up

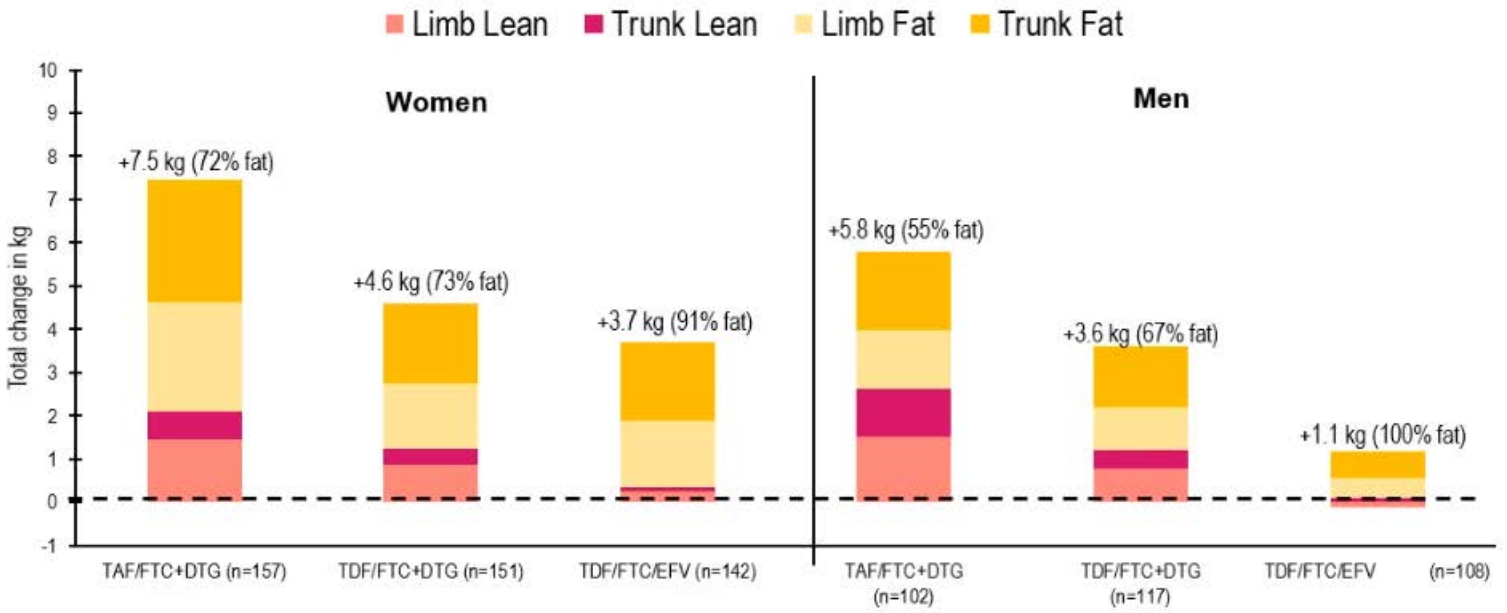
Mean change in weight (kg) to Week 96: Women



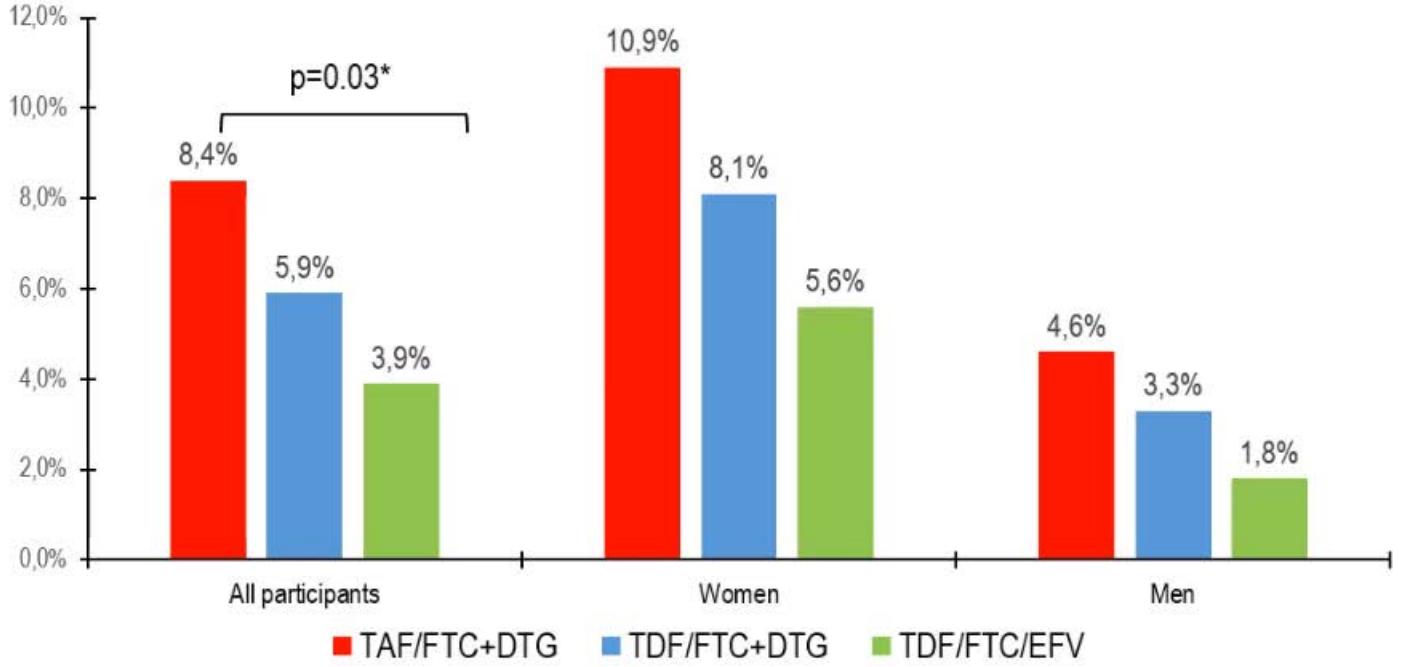
Lower sample sizes after W96; incomplete follow-up

Changes in body composition to week 96

- Mass increases were largely fat over lean gain and were distributed between trunk and limbs in all arms
- Gain in fat mass was significantly higher in females compared to males (p<0.001)



Treatment emergent metabolic syndrome: Week 96



* no other statistically significant differences between arms

Conclusions

- In the ADVANCE trial, there was no statistically significance in HIV RNA suppression rates <50 copies/mL between TDF/FTC+DTG, TDF/FTC+DTG and TDF/FTC/EFV at 96 weeks. This was seen in both the Intent to Treat and Observed Data analyses.

- There was a slightly higher risk of treatment-emergent NRTI and NNRTI resistance in the TDF/FTC/EFV arm

- Patients in the TAF/FTC+DTG had significantly higher mean rises in body weight which were greatest in women and continued post Week 96. There were greater rises in Trunk Fat and a higher risk of metabolic syndrome for TAF/FTC+DTG

- These results support current WHO treatment guidelines, which reserve TAF/FTC+DTG only for patients with osteoporosis or impaired renal function.

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University of the Witwatersrand
WITS RHI

Thank you!

Ezintsha

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