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

AIDS2020

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

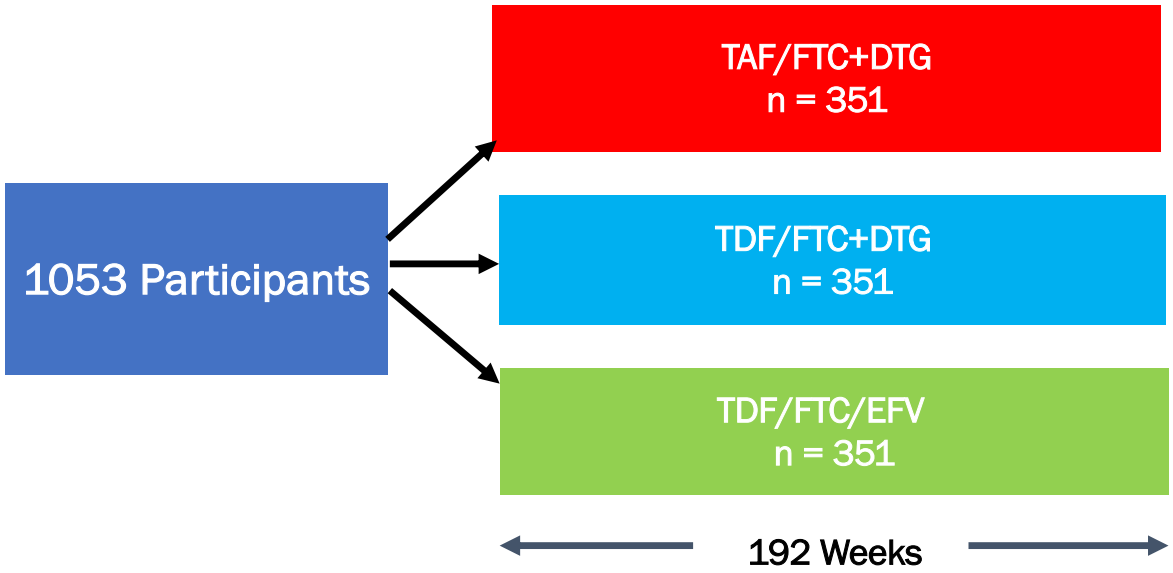
- South Africa background NNRTI resistance estimated 5-15% (Hunt, Antiviral Therapy, 2019)

- 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%)

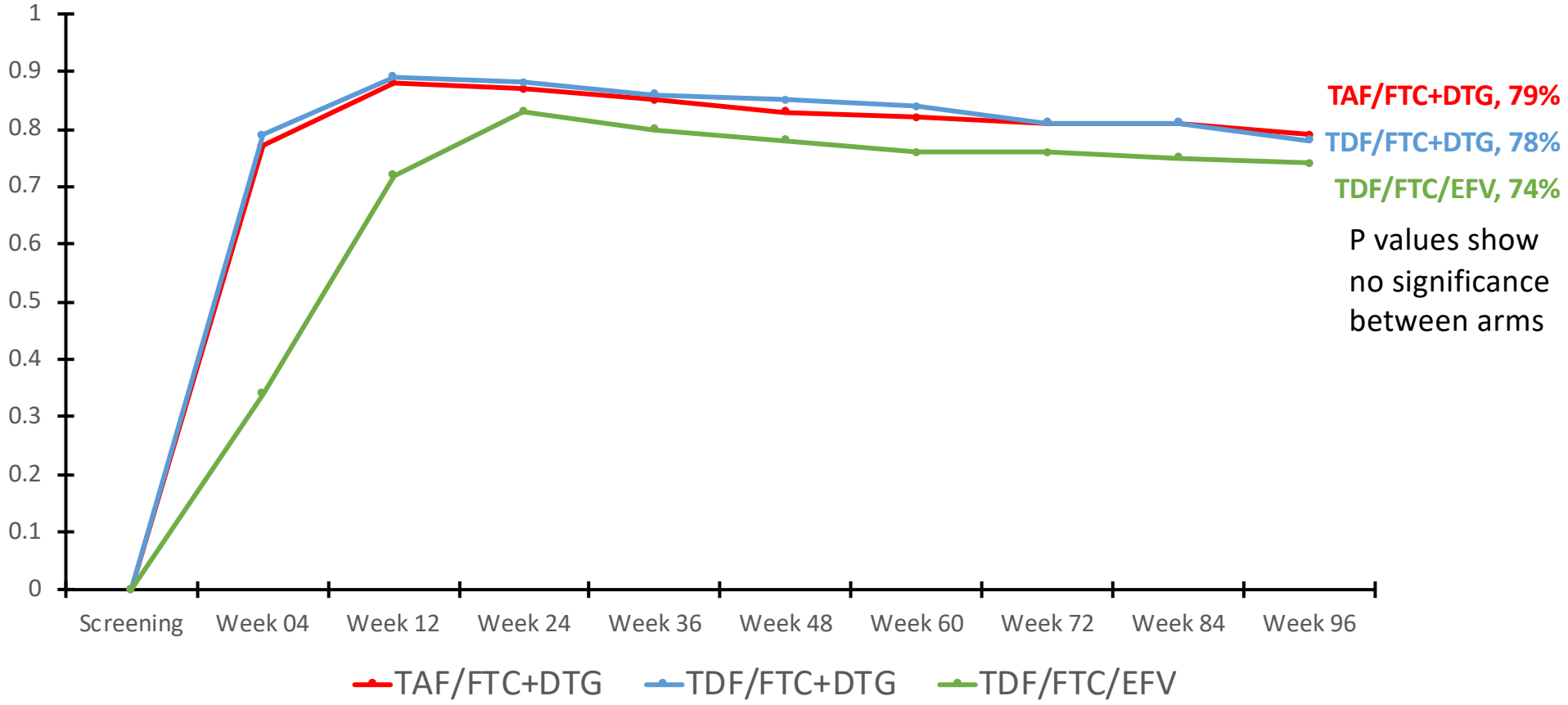
Primary efficacy endpoint: HIV RNA Analysis

- **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)



University of the Witwatersrand
WITS RHI

Treatment emergent resistance

Ezintsha
INVESTIGATE · INNOVATE · ADVANCE

	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%)

University of the Witwatersrand
WITS RHI

Ezintsha

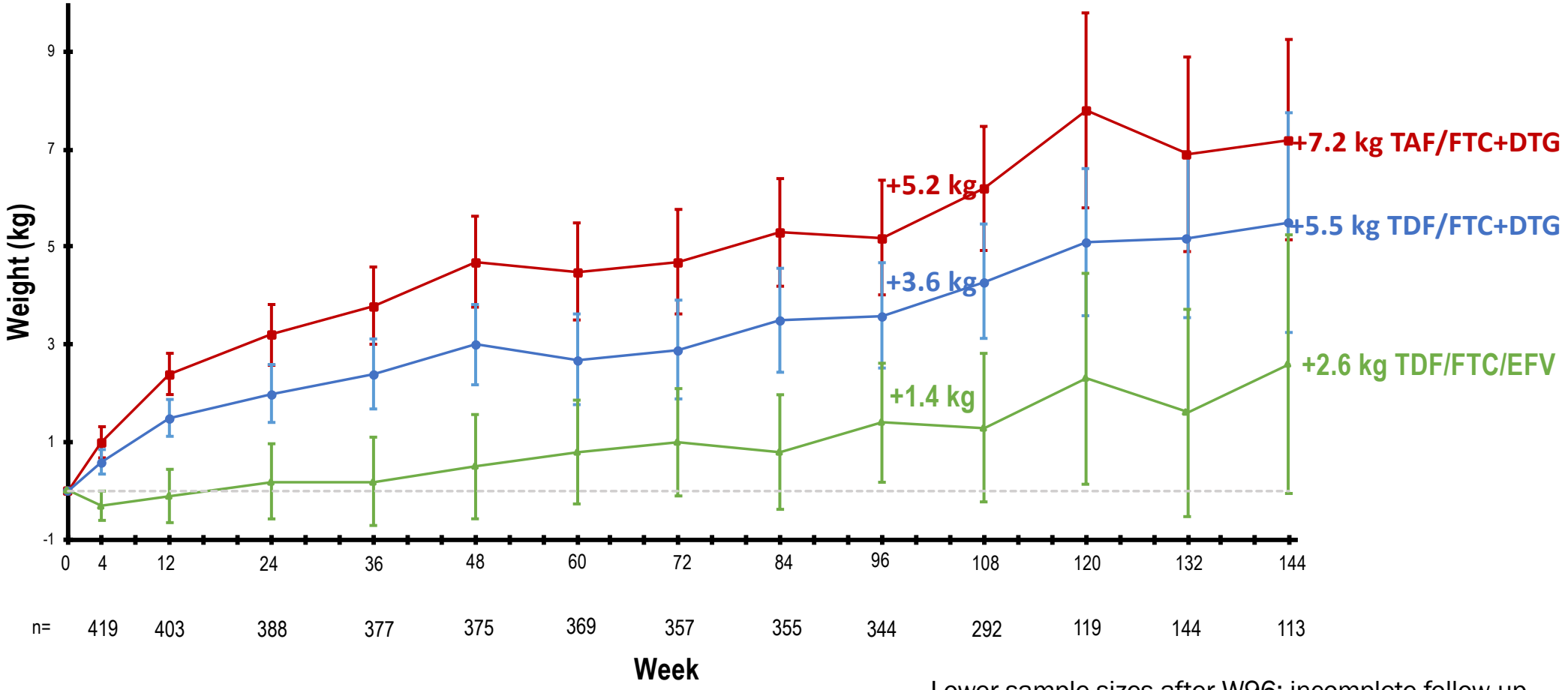
Grade 3 or 4 renal adverse events, renal markers and creatinine clearance

	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

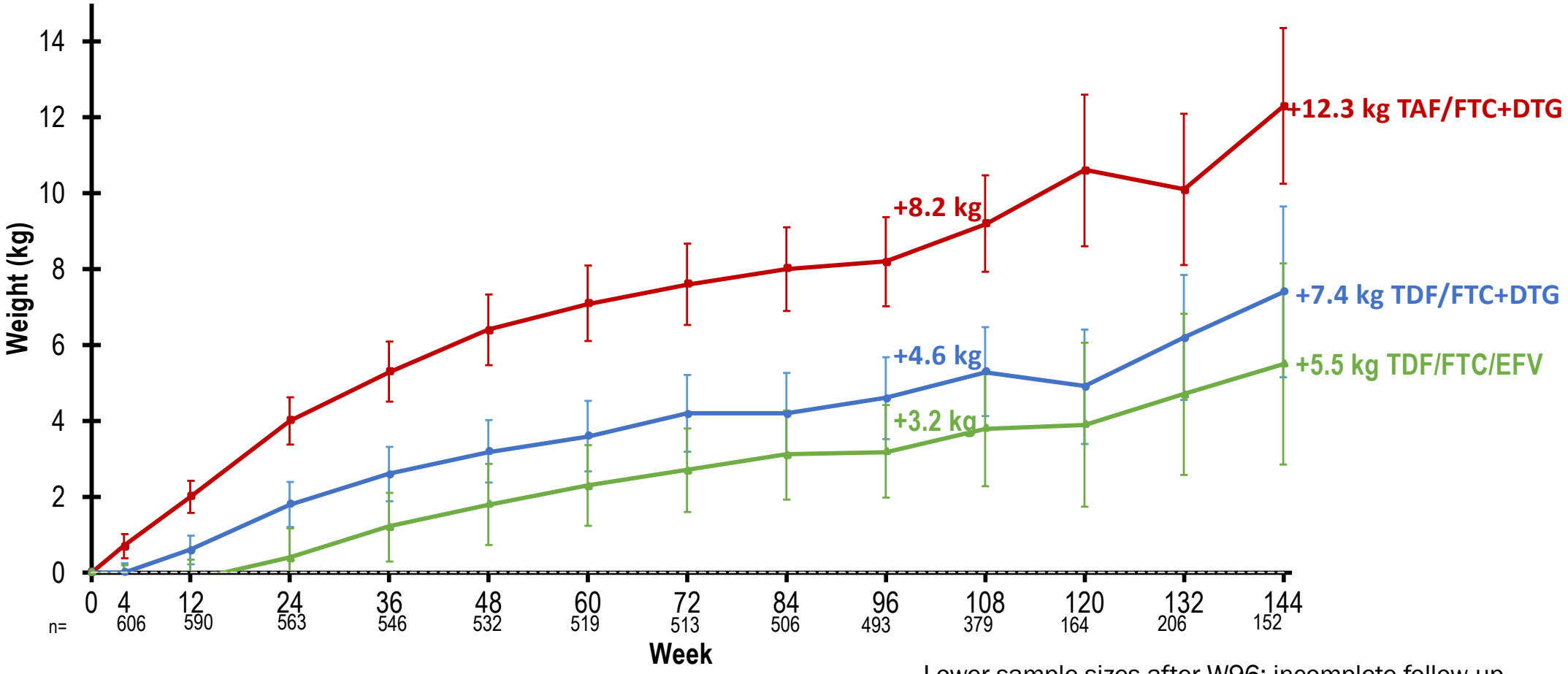
	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Hip			
Normal	291/307 (95%)	290/315 (92%)	260/293(89%)
Osteopenia	16/307(5%)	25/315 (8%)	33/293 (11%)
Lumbar Spine			
Normal	258/307 (84%)	252/315 (80%)	228/293 (78%)
Osteopenia	49/307 (16%)	63/315 (20%)	65/293 (22%)

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



Lower sample sizes after W96; incomplete follow-up

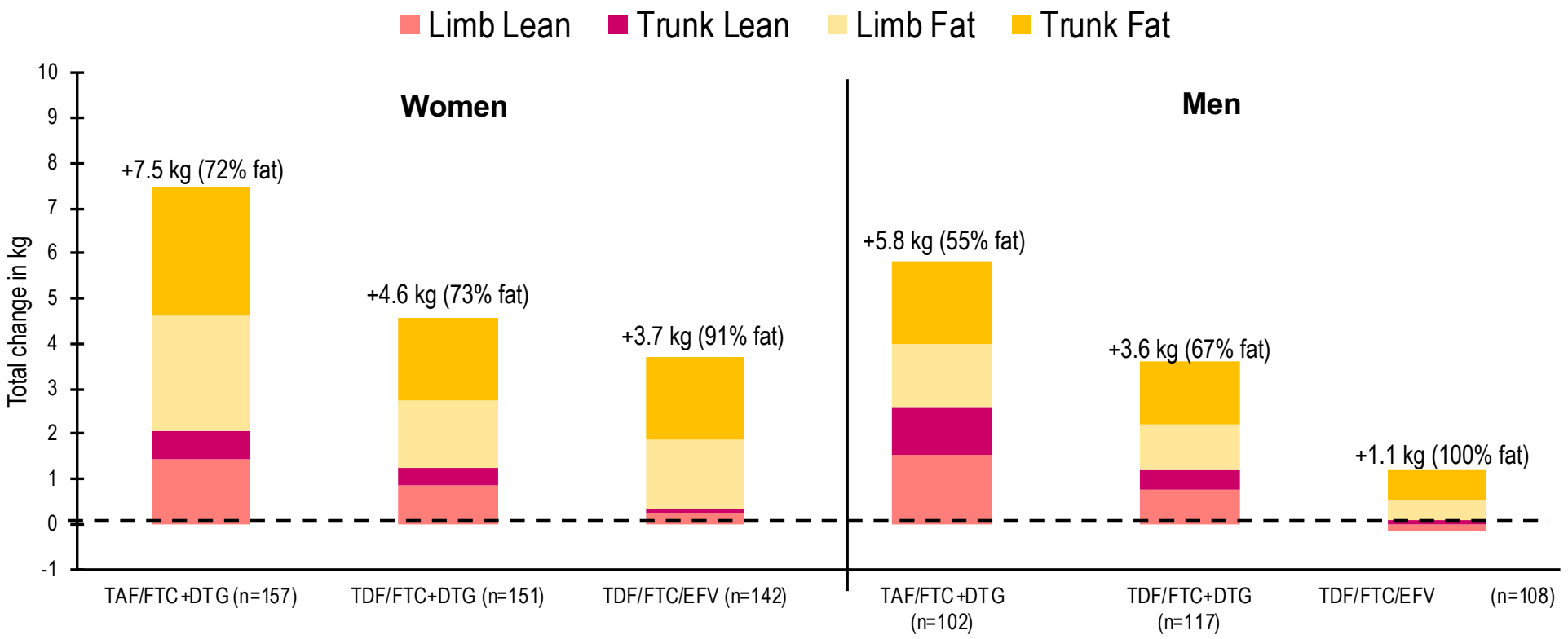
Mean change in weight (kg) to Week 96: Women



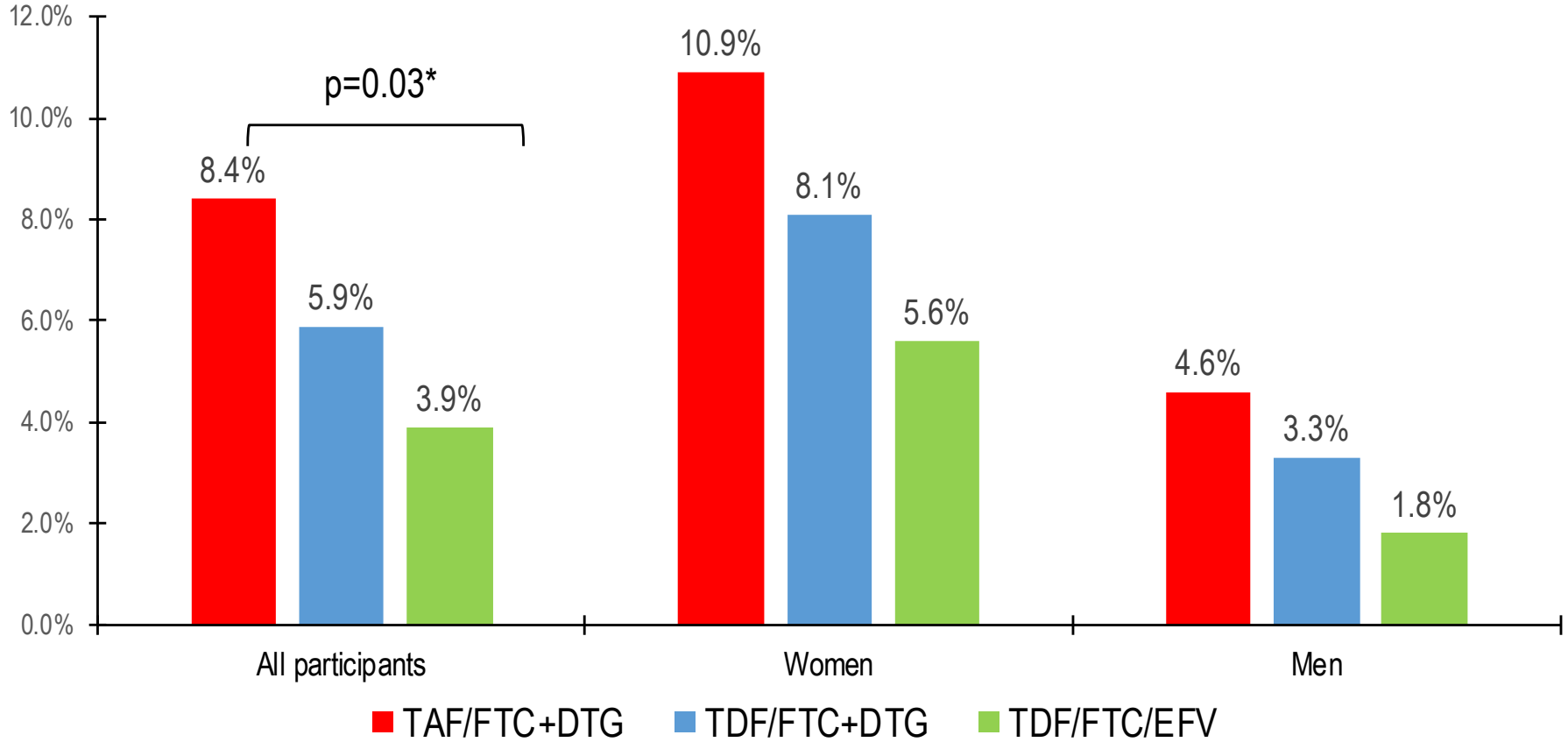
Lower sample sizes after W96; incomplete follow-up

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.

Thanks to:

Ezintsha, Wits RHI

Study participants

Andrew Hill and his team

Treatment Action Campaign and HIV i-Base

Yogan Pillay, Glaudina Loots and the South African government

WHO – especially Meg Doherty

Carole Wallis and BARC

Clinton Health Access Initiative

Committees who oversaw the study

Donors (including much technical support):

USAID

Unitaid

SA MRC

ViiV Healthcare

Drug donations and support

Gilead Sciences

ViiV Healthcare

Mylan

Acknowledgements

This study was supported by U.S. Agency for International Development (USAID), a key implementing agency of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), Unitaid and SAMRC, with study drugs donated by Gilead Sciences and ViiV Healthcare. The views expressed in this poster are those of the authors and do not necessarily reflect those of USAID, PEPFAR or the U.S. Government.

Unitaid finds new and better ways to prevent, test and treat HIV, tuberculosis and malaria quickly and more affordably. It takes game-changing ideas and turns those into practical solutions that can help accelerate the end of the three diseases. Established in 2006 by Brazil, Chile, France, Norway and the United Kingdom, Unitaid plays an important part in the global effort to defeat HIV, tuberculosis and malaria. For more information, please visit: www.unitaid.org

University of the Witwatersrand
WITS RHI

Thank you!

Ezintsha
INVESTIGATE · INNOVATE · ADVANCE