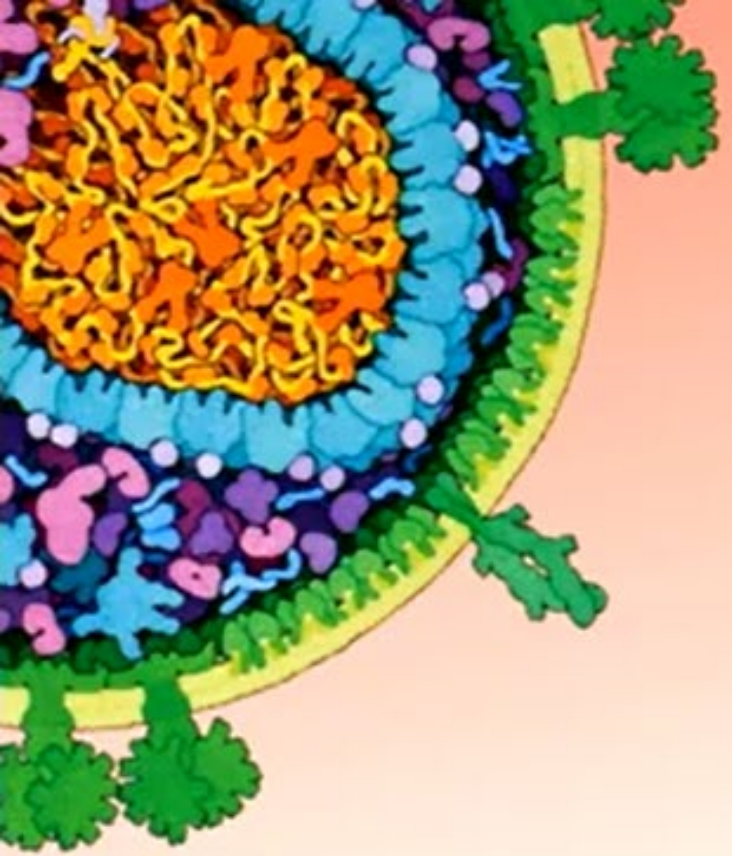


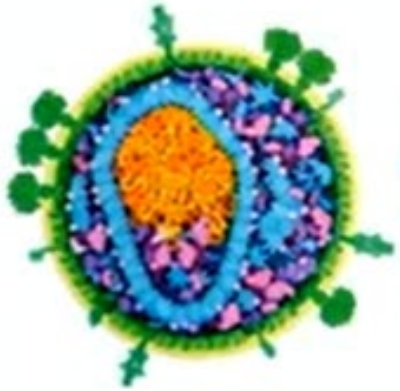
ORAL ABSTRACT: OL-07

Tuesday, March 10, 2020

RISKS OF METABOLIC SYNDROME, DIABETES, AND CARDIOVASCULAR DISEASE IN ADVANCE TRIAL

Andrew Hill

University of Liverpool
Liverpool, United Kingdom



CROI
Conference on Retroviruses and Opportunistic Infections

Predicted 10-year risks of diabetes and cardiovascular disease in the ADVANCE trial

Andrew Hill[1], Kaitlyn McCann[2], Ambar Qavi[2], Bryony Simmons[2] ,Victoria Pilkington[2], Michelle Moorhouse[3], Godspower Akopmiemie[3], , Simiso Sokhela[3], Celicia Serenata[3], Alinda Vos[4], Francois Venter[3]

[1] Liverpool University, Pharmacology, Liverpool, United Kingdom, [2] Imperial College London, Faculty of Medicine, Lond
[3] Ezintsha, Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; [4] University Medical Center Utrecht, I
Netherlands

Potential risks from clinical obesity (BMI >30)

Type II diabetes

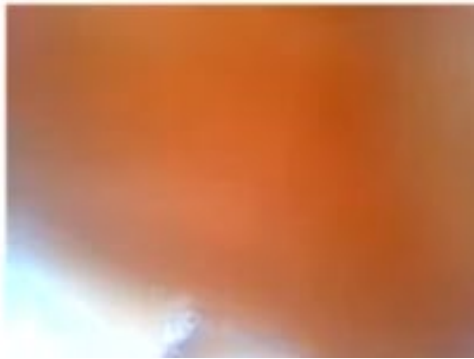
Cardiovascular disease: myocardial infarction / death

Alzheimer's disease

Obstetrics / birth outcomes: Gestational diabetes, pre-eclampsia, venous thromboembolism, maternal death, birth defects

Cancer

Reductions in life expectancy



Research questions

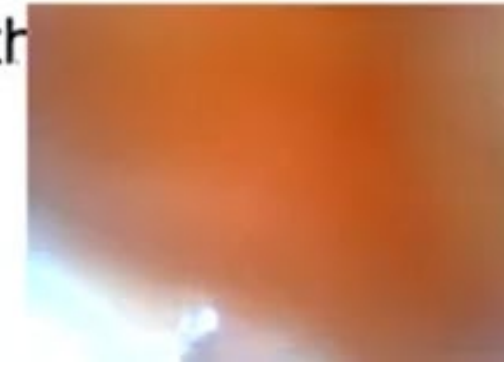
In the ADVANCE trial of treatment naïve patients in South Africa:

1. What changes are seen in markers of cardiovascular risk and diabetes?

2. Can we use risk equations to predict the risk of cardiovascular disease or diabetes from these changes?

Non-parametric tests used throughout analysis, given strong positive skew. Results repeated using log10 transformation and parametrics, with similar results

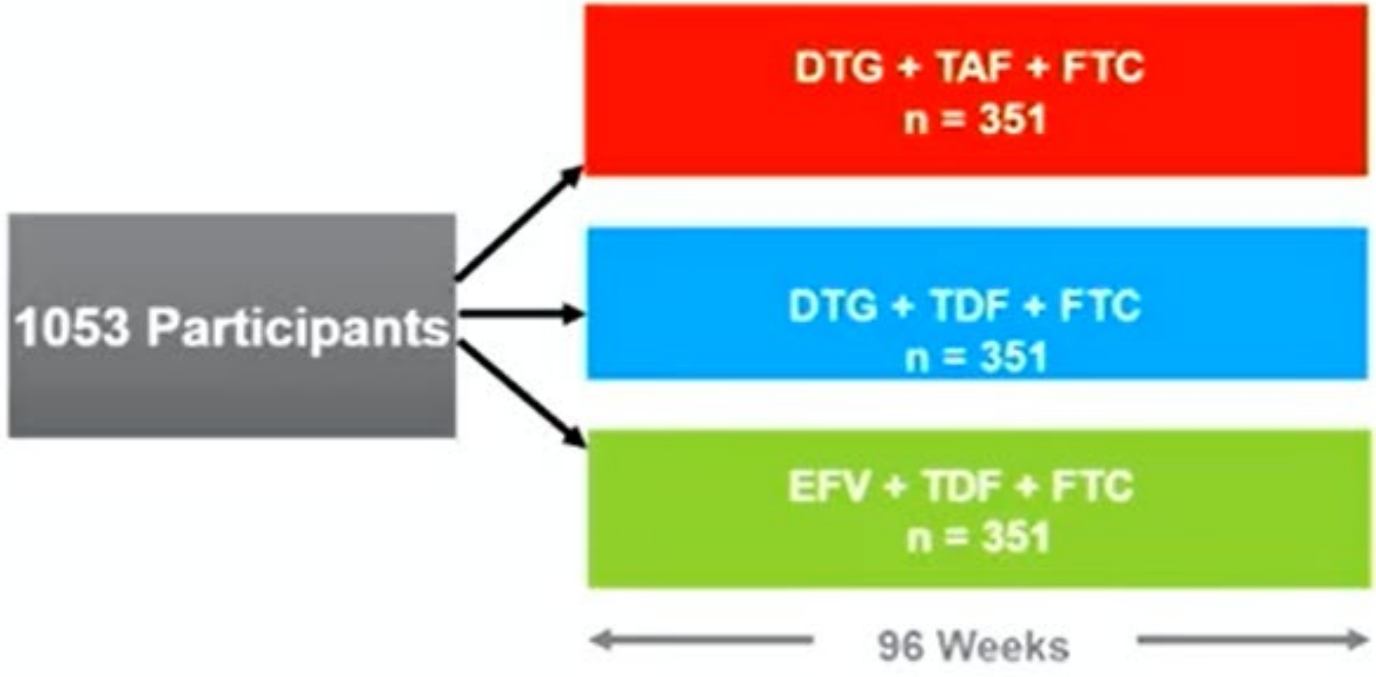
Bonferroni corrections used to adjust for multiple testing (p=0.017, th
comparisons).



ADVANCE study: Trial design

Inclusion criteria:

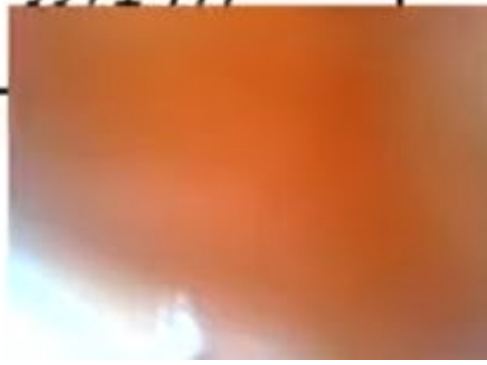
- Treatment-naïve, HIV-1 RNA level >500 copies/mL in the last 60 days



Open-label, 96-week study in Johannesburg, South Africa
Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84 and 96

Baseline characteristics (1/2)

Characteristic	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Age, mean (SD), years	33 ± 8	32 ± 8	32 ± 7
Female	61%	59%	57%
Black	99%	100%	100%
Baseline HIV-1 RNA			
≤100,000 copies/mL	78%	80%	77%
>100,000 copies/mL	22%	20%	23%
CD4+ cell count, mean (SD), cells/mm^3	349 ± 225	323 ± 234	337 ± 222

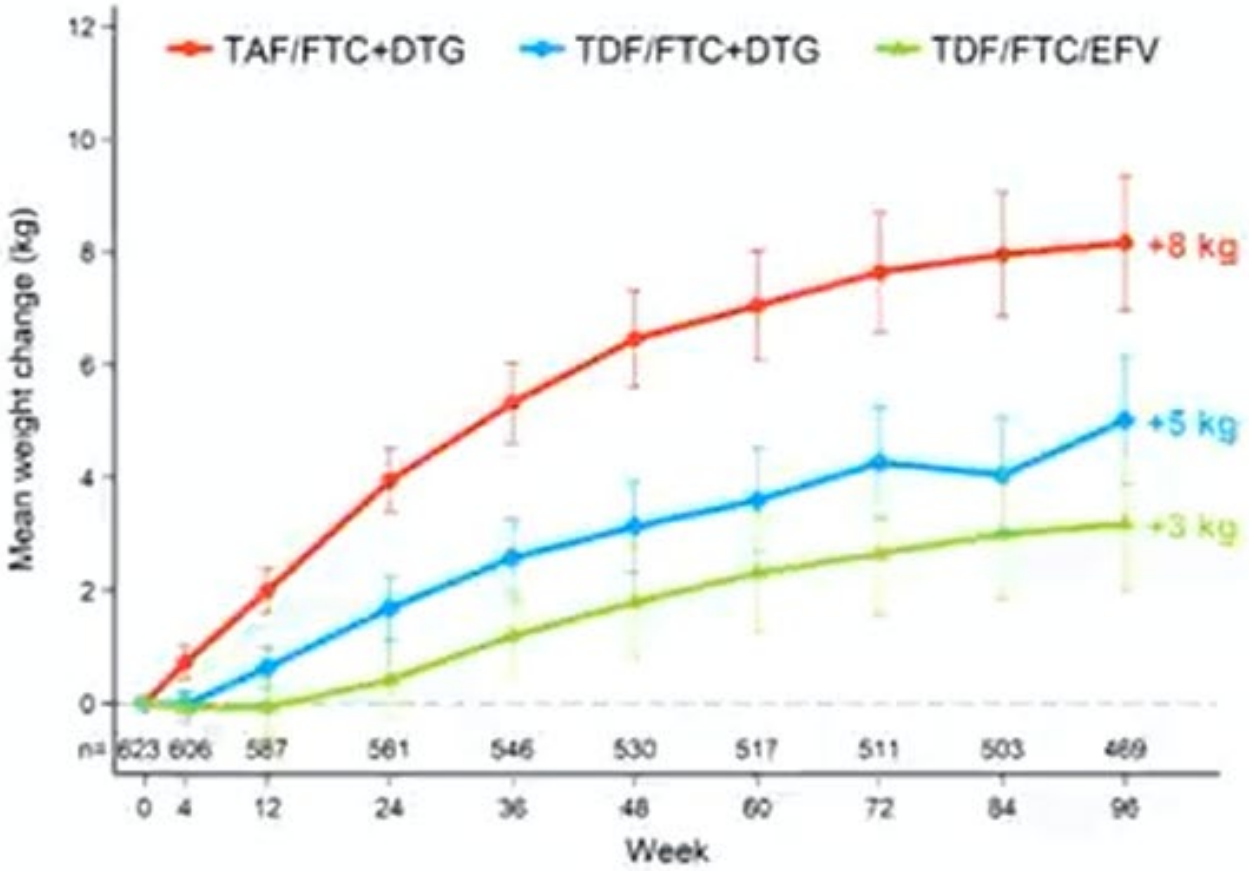


Baseline characteristics (2/2)

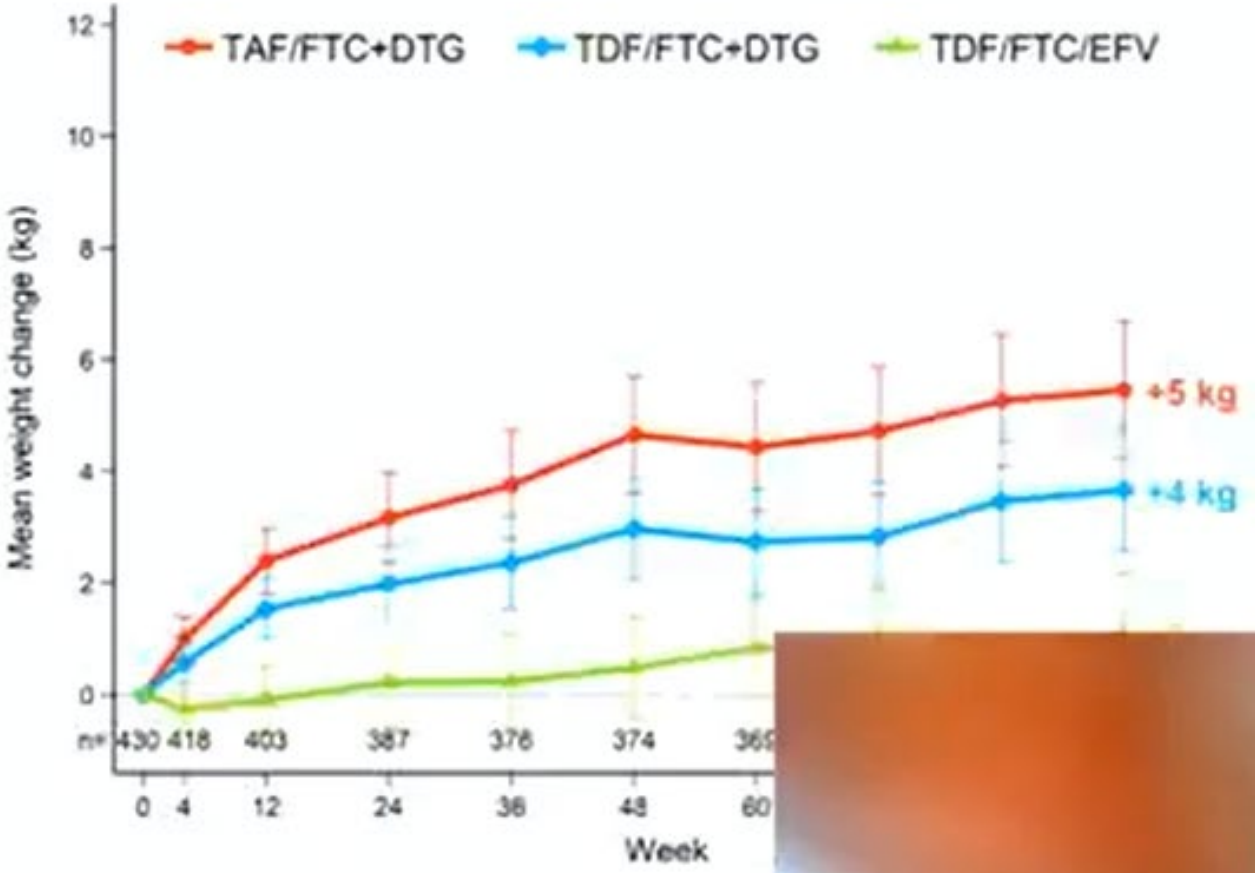
Characteristic	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Weight, mean (kg)			
Male	67.9	67.1	67.3
Female	68.8	69.5	70.2
BMI, mean (kg/m²)			
Male	21.7	21.6	21.8
Female	25.6	26.1	26.1
Categories of BMI, n (%)			
Underweight (< 18.5)	42 (12%)	35 (10%)	37 (11%)
Normal (18.5-25)	177 (51%)	190 (54%)	
Overweight (25-30)	96 (27%)	78 (22%)	
Obese (> 30)	35 (10%)	48 (14%)	

Mean change in weight (kg) to Week 96

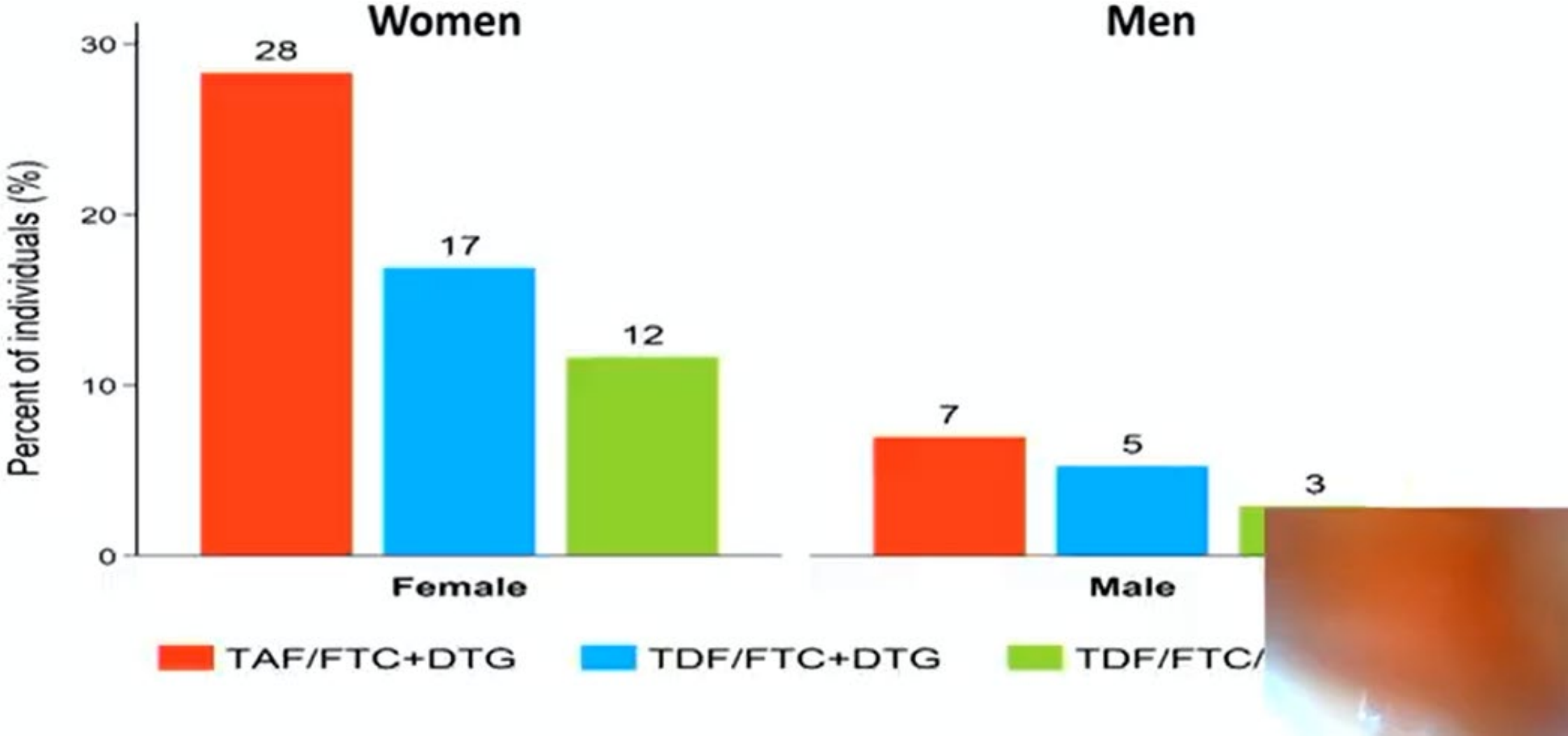
Women



Men

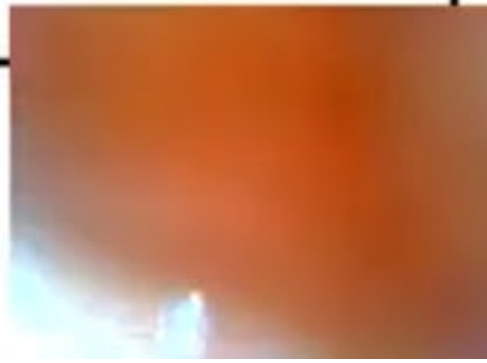


Treatment-emergent obesity to Week 96

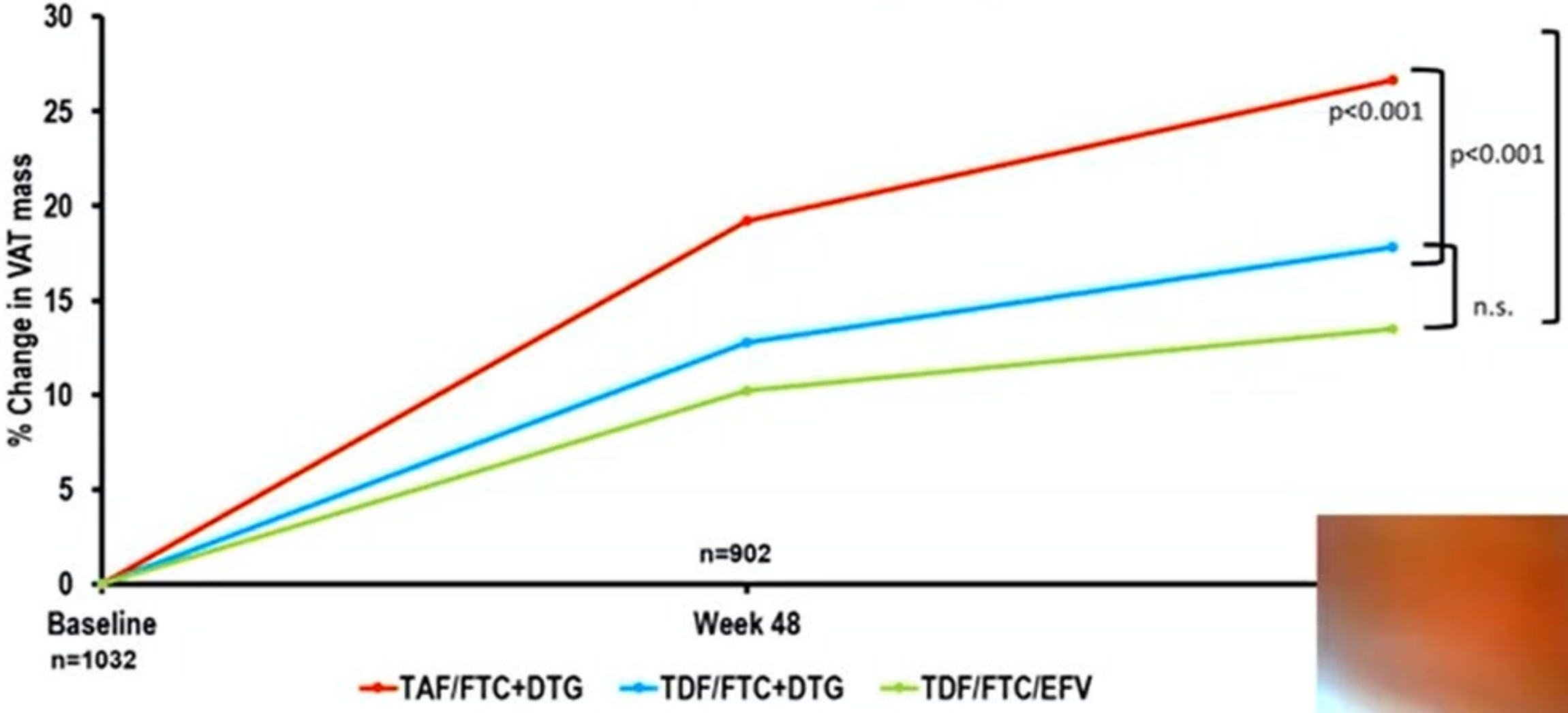


Changes in Lab parameters to week 96, median (IQR)

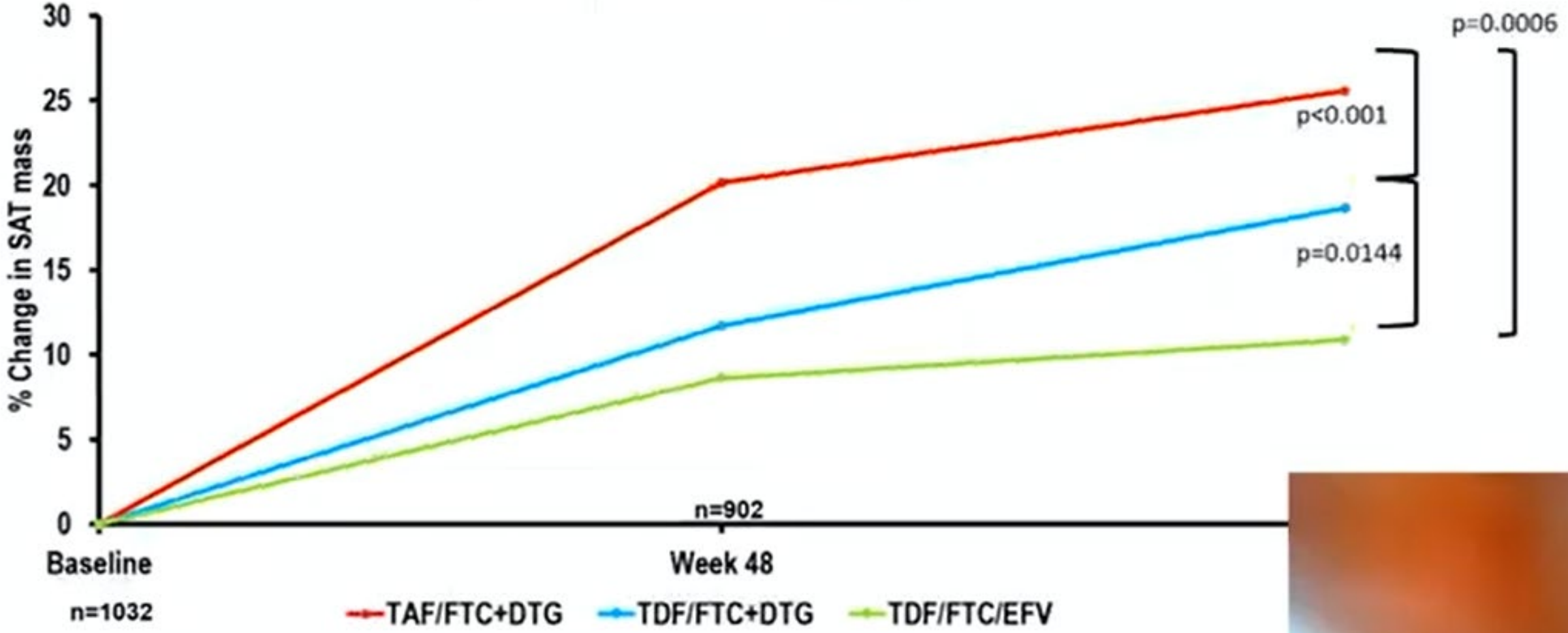
	TAF/FTC+DTG (n=185)	TDF/FTC+DTG (n=187)	TDF/FTC/EFV (n=191)			
Week 96				Group 1 vs. 3	Group 1 vs. 2	Group 2 vs. 3
Total cholesterol (mg/dL)	10.4 (-5.4, 24.0)	1.5 (-13.1, 19.7)	13.1 (-1.9,33.3)	P=0.022	p=0.007	p<0.001
LDL (mg/dL)	8.5 (-6.2, 20.5)	2.3 (-10.8, 12.4)	6.2 (-5.0 , 22.0)	p=0.82	p=0.007	P=0.013
HDL (mg/dL)	4.6 (-2.3, 12.0)	3.9 (-2.3, 12.0)	9.7 (2.3, 19.3)	p<0.001	p=0.73	p<0.001
Fasting glucose (mg/dL)	19.3 (7.7, 34.8)	19.3 (0.00, 34.8)	27.1 (11.6, 42.5)	0.0049	p=0.21	p<0.001
Systolic BP (mmHg)	3.0 (-7.0,11.0)	-1.0 (-12.0,8.0)	0.50(-9.0 8.0)	p=0.19		



Median % change in Visceral Adipose Tissue (VAT) from baseline to week 96 (DXA)



Median % change in Subcutaneous Adipose Tissue (SAT) to week 96 (DXA)



Metabolic syndrome: Definition

Assessed using the International Diabetes Federation (IDF) definition:

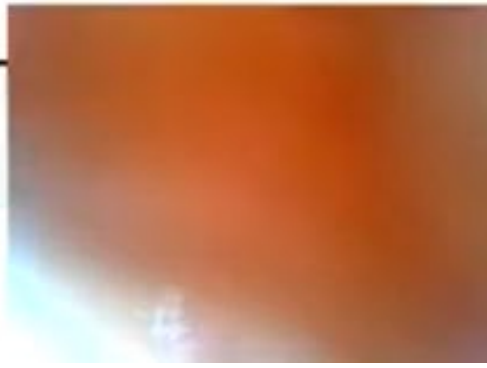
- **Clinical obesity (BMI > 30 kg/m^2)**
- **AND** any two of the following factors

Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) *OR* on treatment for this lipid abnormality
Reduced HDL cholesterol	Males: ≤ 40 mg/dL (1.03 mmol/L) Females: ≤ 50 mg/dL (1.29 mmol/L) *OR* on treatment for this lipid abnormality
Raised blood pressure	Systolic BP ≥ 130 mmHg Diastolic BP ≥ 85 mmHg *OR* on treatment for previously diagnosed hypertension
Raised fasting glucose	≥ 100 mg/dL (5.6 mmol/L) *OR* diagnosis of Type 2 diabetes

Metabolic syndrome at Week 96

	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
Baseline prevalence	16/351 (5%)	21/351 (6%)	14/351 (4%)
Treatment-emergent metabolic syndrome			
Week 96	20/259 (8%)	15/258 (6%)	8/242 (3%)

Statistically significant differences between TAF/FTC+DTG and TDF/F
at Week 96 (p=0.031).



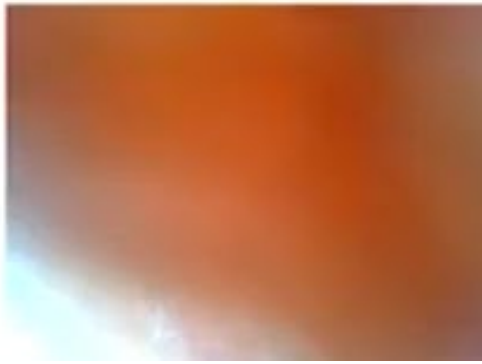
Framingham Risk Equation

Estimates 10-year risk of myocardial infarction or coronary death

https://reference.medscape.com/calculator/framingham-cardiovascular-disease-risk

Variables included in equation:

- Age
- Sex
- Systolic BP
- Total cholesterol
- HDL cholesterol
- On hypertension medication
- Smoking status
- Diabetes



Framingham Risk Equation results

Predicted results over time:

Treatment arm / 10-year risk	Baseline	Median change to: Wk 48	Wk 96
TAF/FTC+DTG:	2.37%	0.00%	+0.43%
TDF/FTC+DTG:	2.53%	-0.06%	+0.22%
TDF/FTC/EFV:	2.24%	-0.08%	+0.28%

No significant differences between arms at Week 96

QRISK Equation

Estimates 10-year risk of developing a heart attack or stroke

https://qrisk.org/three/

Variables included in equation

- Age (25-84)
- Sex
- Ethnicity (Black African included)
- Cholesterol ratio
- Systolic BP
- BMI
- Family history of heart attack/angina*
- Smoking status
- Diabetes
- Chronic kidney disease (stages 3,4, or 5)
- Atrial fibrillation
- Migraines
- Rheumatoid arthritis
- Systemic lupus erythematous (SLE)
- Severe mental illness (schizophrenia, bipolar disorder, moderate/severe depression
- On treatment for hypertension
- On atypical antipsychotic med
- On regular steroid tablets
- Erectile disfunction

*information not available

QRisk Equation results:

Predicted results over time:

Treatment arm / 10-year risk	Baseline	Median change to:	
		Wk 48	Wk 96
TAF/FTC+DTG:	0.60%	+0.10%	+0.20%
TDF/FTC+DTG:	0.60%	+0.10%	+0.20%
TDF/FTC/EFV:	0.50%	0.00%	+0.10%

Borderline significant differences between TAF/FTC+DTG and TDF/FTC/EFV at week 96 (p=0.027)

QDIABETES Equation

Website / reference: https://qdiabetes.org/

Estimates the 10-year risk of developing diabetes

Variables included in equation:

- Age (25-84)
- Sex
- Ethnicity (Black African included)
- Fasting blood glucose
- HBA1c*
- BMI
- Smoking status
- Family history of diabetes*
- On treatment for hypertension
- Heart attack/angina/stroke/TIA
- Learning disabilities
- Manic depression/schizophrenia
- On regular steroid tablets
- On statins
- On atypical antipsychotic medication
- Polycystic ovaries
- Gestational diabetes

*information not available

QDIABETES Equation results:

Predicted results over time:

Treatment arm / 10-year risk	Baseline	Median change to: Wk 48	Wk 96
TAF/FTC+DTG:	0.30%	+0.70%*	+0.90%*
TDF/FTC+DTG:	0.40%	+0.40%	+0.50%
TDF/FTC/EFV:	0.30%	+0.60%**	+0.70%**

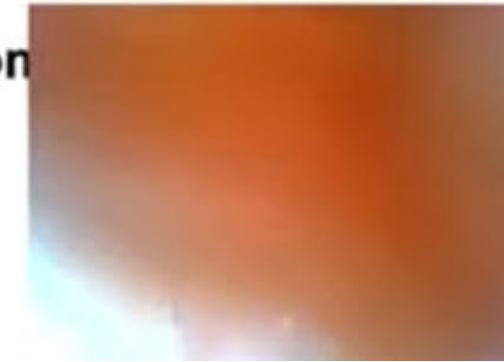
*TAF/FTC+DTG risk significantly higher than TDF/FTC+DTG at Week 48 (p=0.008) and Week 96 (p=0.004)

**TDF/FTC/EFV risk significantly higher than TDF/FTC+DTG at Week 48 (p=0.0
96 (p=0.005)

No significant differences between TAF/FTC/DTG and TDF/FTC/EFV at Weeks

Limitations of the current analysis

- The ADVANCE population is young (median 31 years), when the risk of MI and diabetes is relatively low.
- Among women treated with TAF/FTC+DTG, weight is continuing to rise to Week 96, with no sign of a plateau. The predictive models do not account for additional weight gain after week 96.
- ADVANCE is in treatment naïve patients; increases in weight could be partly a "return to health" effect. However this does not explain the higher weight gains for TAF/FTC/DTG versus TDF/FTC/DTG.
- Other NCDs need to be evaluate: Cancer, Alzheimer's, adverse birth outcon



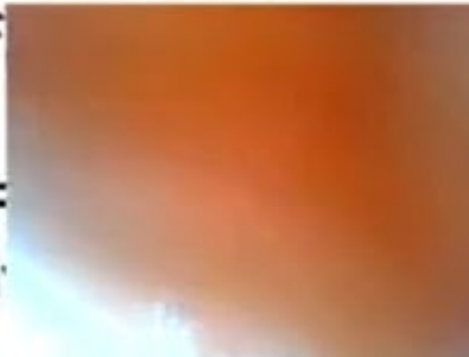
Conclusions

In the ADVANCE Trial, TAF/FTC+DTG was associated with a significantly higher risk of:

- Clinical obesity
- Metabolic syndrome
- Rises in VAT and SAT
- Predicted risk of diabetes

The predicted risk of MI from these changes is not significant. However, there is a predicted increase in the risk of diabetes – 4 cases per 1000 people treated with TAF/FTC+DTG versus TDF/FTC+DTG. Additional risks for TDF/FTC/EF

These analyses should be repeated for other studies evaluating TAF/F
integrase inhibitors in other patient populations and lines of treatmen

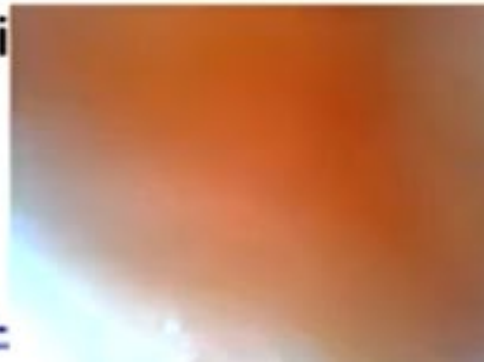


WHO – first-line treatment guidelines

Preferred	Alternative	Special Circumstances only
TDF/XTC/DTG	TDF/XTC/EFV400	TDF/XTC/EFV600 ZDV/3TC/EFV600 TDF/3TC/PI/r TDF/3TC/RAL **TAF/3TC/DTG*** ABC/XTC/DTG

***TAF may be considered for patients with established osteoporosi and/or impaired renal function**

Reference: WHO 2019 Treatment Guidelines
https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-



Acknowledgements

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Ezintsha

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(be sure to include presenter's name in question)

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