Long-term risks of clinical obesity in the ADVANCE, NAMSAL and VISEND trials

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BACKGROUND

- Integrase inhibitor-based treatment and tenofovir alafenamide (TAF) have been associated with higher risks of weight gain and clinical obesity in a range of studies.
- Metabolic syndrome has been linked with a high risk of type II diabetes[1], cardiovascular disease[1], chronic kidney disease[2], obstructive sleep apnoea[3] etc.

RESULTS

- In ADVANCE, by week 192, probability of obesity was 29% for patients on TAF/FTC/DTG, 18% on TDF/FTC/DTG, and 11% on TDF/FTC/EFV
- In NAMSAL, by week 192, probability of obesity was 26% for TDF/3TC/DTG and 16% for TDF/3TC/EFV
- In VISEND, across both strata, probability of obesity varied from 10-15%
- Probabilities overall and by gender are shown in Table 2
- TAF/FTC/DTG was predictive of obesity in ADVANCE (p<0.001) and VISEND strata <1,000 copies/mL (p=0.002), but not in VISEND strata ≥1,000 copies/mL
- TDF/3TC/DTG was predictive of obesity in NAMSAL (p<0.001)
- In all three trials, predictors of clinical obesity were female gender, higher baseline HIV RNA, and higher baseline BMI

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

Central obesity (defined as waist circumference* with ethnicity specific values)

plus, any two of the following four factors:

Raised triglycerides	≥ 150 mg/dl (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	<40 mg/dL (1.03 mmol/L) in males <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure	Systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome

*if BMI is >30kg/m^2, central obesity can be assumed, and waist circumference does not need to be measured

Table 1: The new International Diabetes Federation (IDF) definition of metabolic syndrome

METHODS

- In ADVANCE, 1053 treatment-naïve participants in South Africa were randomized to either TAF/FTC/DTG, TDF/FTC/DTG, or TDF/FTC/EFV and followed up to week 192.
- In NAMSAL, 613 treatment-naïve participants in Cameroon were randomized to TDF/3TC/DTG or TDF/3TC/EFV for 192 weeks.
- In VISEND, 1201 NNRTI pre-treated patients in Zambia were randomized to TAF/FTC/DTG, TDF/FTC/DTG, or PI-based treatments for 144 weeks (stratified on baseline HIV RNA < or ≥1,000 copies/mL).
- Kaplan-Meier methods were used to evaluate probability of treatment-emergent clinical obesity (BMI ≥30 kg/m2), with multivariable predictors evaluated by Cox Proportional Hazard models.

Trial	Arm	Clinical obesity (probability)		
		Men	Women	Overall
ADVANCE (Week 192)	TAF/FTC/DTG	11%	42%	29%
	TDF/FTC/DTG	8%	28%	18%
	TDF/FTC/EFV	3%	20%	11%
NAMSAL (Week 192)	TDF/3TC/DTG	28%	25%	26%
	TDF/3TC/EFV	9%	20%	16%
VISEND BL<1,000 cp/mL (Week 96)	TAF/FTC/DTG	2%	22%	13%
	TDF/FTC/DTG	3%	14%	10%
VISEND BL≥1,000 cp/mL (Week 96)	TAF/FTC/DTG	6%	14%	11%
	TDF/FTC/DTG	1%	19%	12%
	ZDV/3TC/LPVr	4%	14%	11%
	ZDV/3TC/ATVr	7%	21%	15%

Table 2: Probabilities of obesity overall and by gender

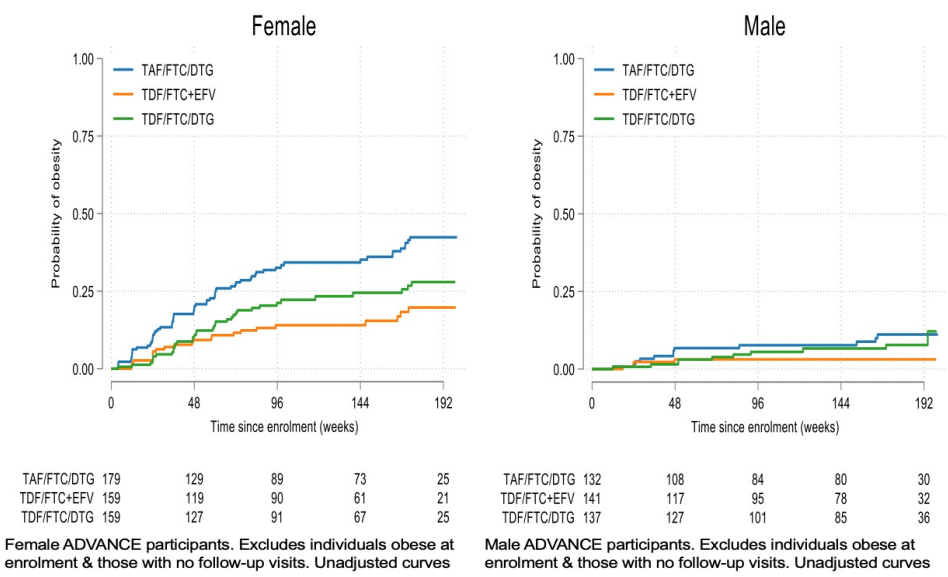
Treatment arm	TAF/FTC/DTG	TDF/FTC/DTG	TDF/FTC/EFV
All patients	50/335 (15%)	32/330 (10%)	23/337 (7%)
Women	40/199 (20%)	23/189 (12%)	29/191 (10%)
Men	10/136 (7%)	9/141 (6%)	4/145 (3%)

Risk is significantly higher for TAF/FTC/DTG (p<0.05) for all patients, and for women

Table 3: Treatment emergent metabolic syndrome - ADVANCE

Treatment arm	TDF/3TC/DTG	TDF/3TC/EFV	p
All patients	28/248 (11%)	6/219 (3%)	<0.001
Women	13/154 (8%)	5/151 (3%)	0.057
Men	15/94 (16%)	1/68 (1%)	0.002

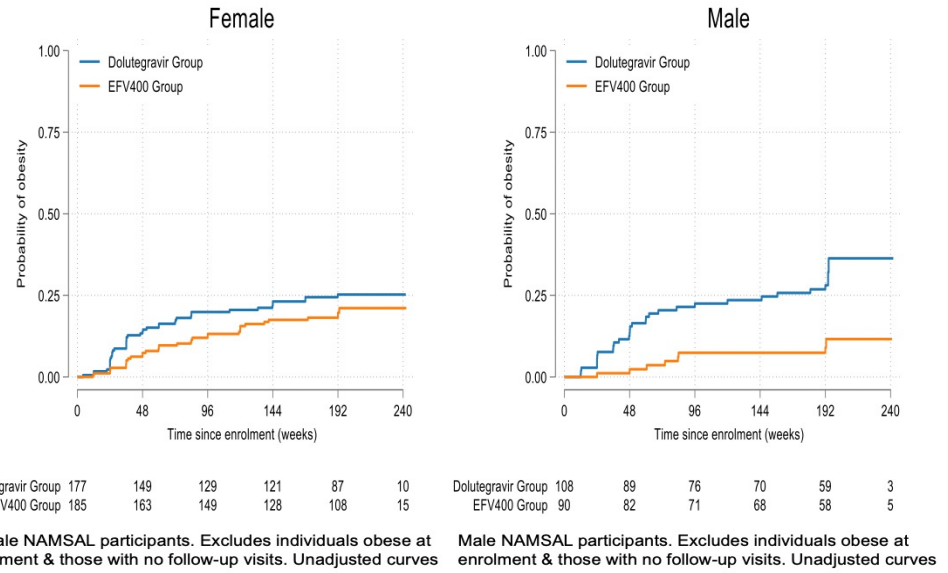
Table 4: Treatment emergent metabolic syndrome - NAMSAL



Female ADVANCE participants. Excludes individuals obese at enrolment & those with no follow-up visits. Unadjusted curves

Male ADVANCE participants. Excludes individuals obese at enrolment & those with no follow-up visits. Unadjusted curves

Figure 1: Time to clinical obesity - ADVANCE



Female NAMSAL participants. Excludes individuals obese at enrolment & those with no follow-up visits. Unadjusted curves

Male NAMSAL participants. Excludes individuals obese at enrolment & those with no follow-up visits. Unadjusted curves

Figure 2: Time to clinical obesity - NAMSAL

DISCUSSION AND CONCLUSION

- Across three randomized trials in 2867 patients, the risks of clinical obesity were significantly higher for DTG-based treatment, especially when combined with TAF/FTC.
- The adverse consequences of clinical obesity (e.g., diabetes, myocardial infarction) need to be factored into decisions on starting or switching to TAF/FTC/DTG, especially if already overweight at baseline.

References:

1. Alberti G, Zimmet P, Shaw J, Grundy SM. The IDF consensus worldwide definition of the Metabolic Syndrome. Belgium: International Diabetes Federation; 2006
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