Predicting the risk of adverse pregnancy outcomes due to DTG-associated weight gain

Sumbul Asif[1], Evangelina Baxevanidi[1], Andrew Hill[2], Nomathemba Chandiwana[3], Lee Fairlie[4], Masebole Masenya[4], WD Francois Venter[3], Simiso Sokhela[3], Celicia Serenata[3]

1. Imperial College London, Faculty of Medicine, London, United Kingdom, 2. Liverpool University, Department of Translational Medicine, Liverpool, United Kingdom, 3. Ezintsha, Wits RHI, University of the Witwatersrand, Johannesburg, South Africa, 4. Wits RHI, University of the Witwatersrand, Johannesburg, South Africa

LIVE

Background

Dolutegravir (DTG) and and other integrase inhibitors have been associated with significant weight gain. This is higher if DTG is combined with tenofovir alafenamide (TAF/FTC). Rises in body weight are also associated with female sex and black race.

Pregnant women who are clinically obese have a higher risk of adverse birth outcomes, both for the mother and the infant

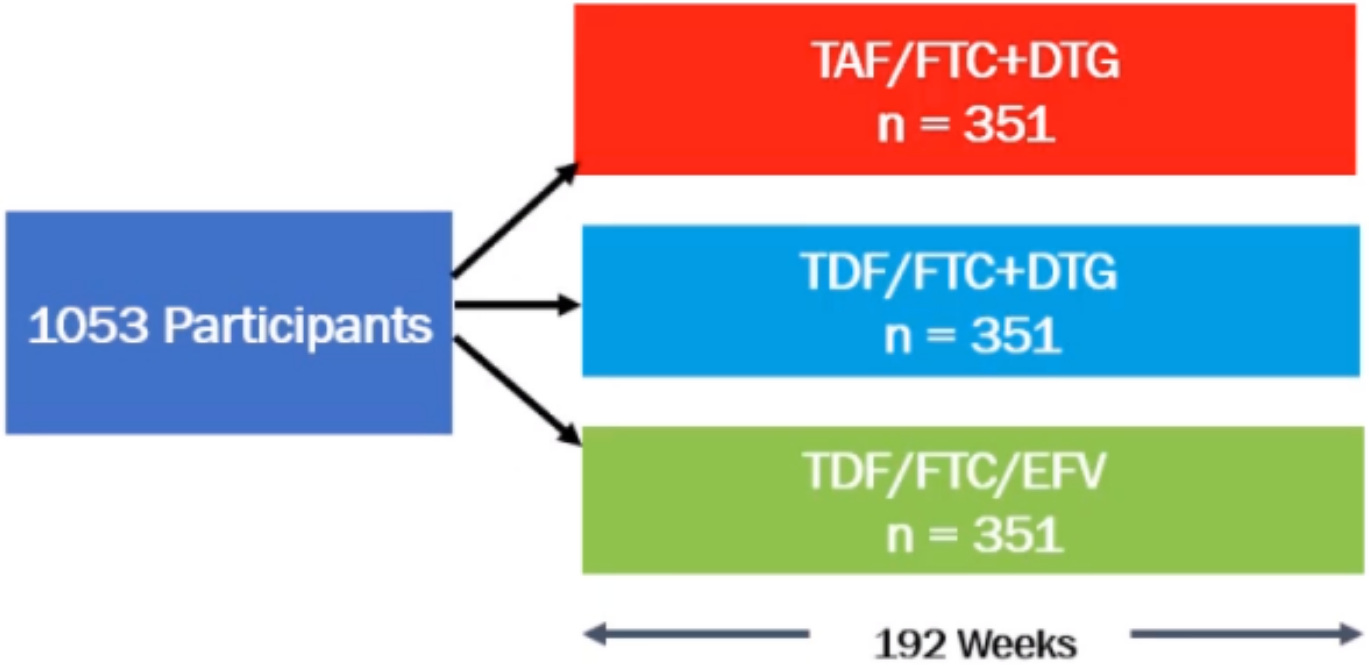
Short-term results from studies of DTG and TAF/FTC in pregnant women show no significant increase in risks of adverse birth outcomes.

Research question: If women become clinically obese after long-term antiretroviral treatment, is there an increased risk of adverse birth outcomes?

LIVE

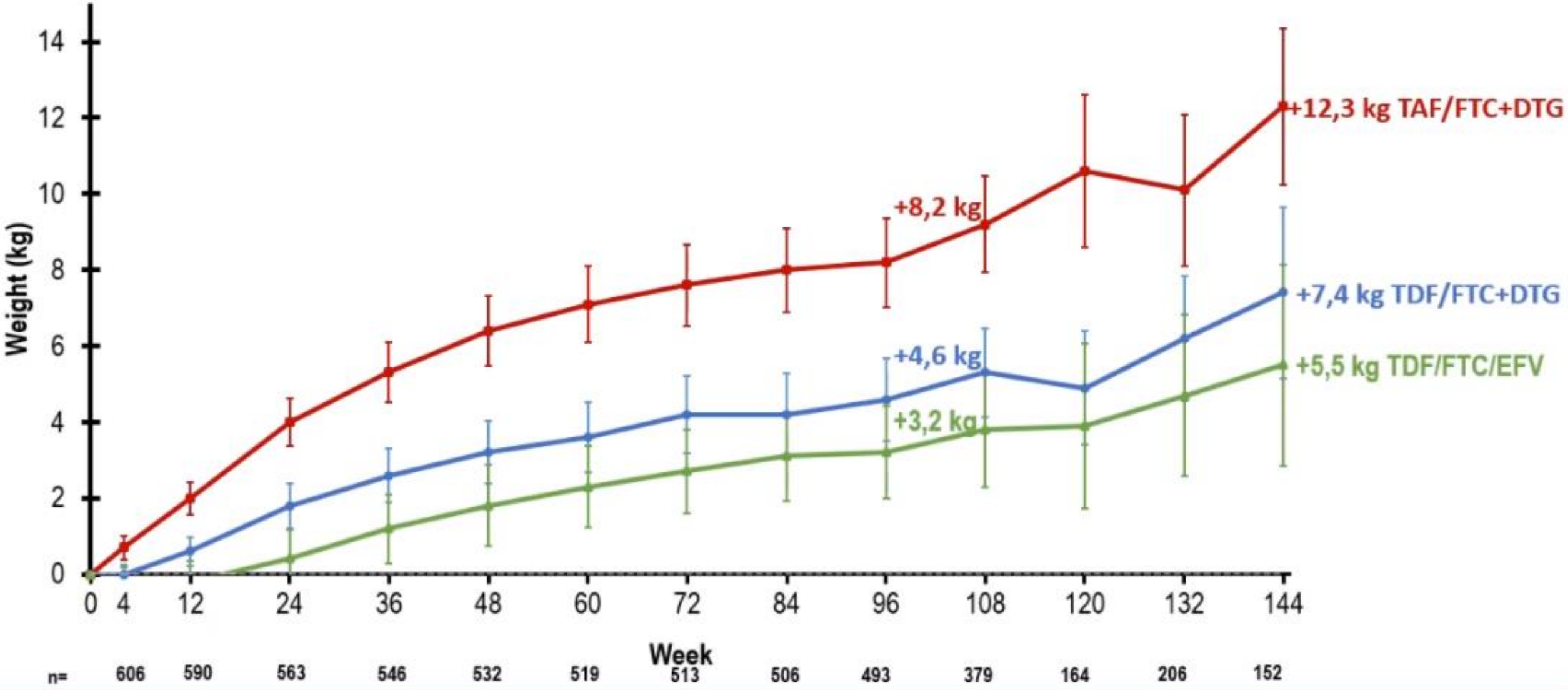
ADVANCE (South Africa): Study design

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



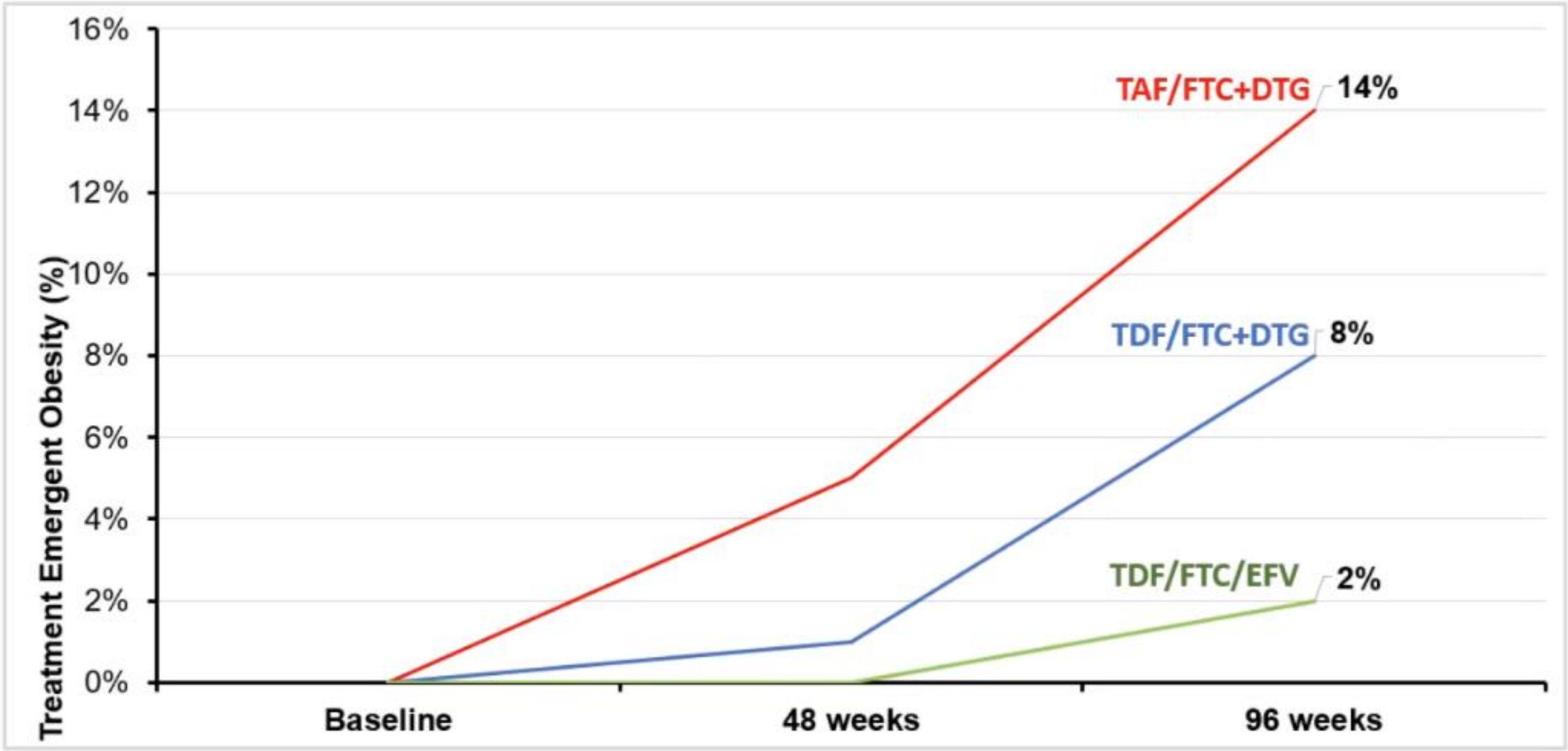
Study visits: baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 then every 24 weeks

Mean change in weight (kg) to Week 144: women



LIVE

Treatment Emergent Obesity: Women with normal baseline BMI



LIVE

Systematic Review of adverse birth outcomes

Medline, EMBASE, Maternal & Infant care and Global Health database searched

Selected **cohort studies** evaluating the impact of maternal obesity on adverse pregnancy outcomes

Compared the risk of adverse pregnancy outcomes in women with an **obese versus normal BMI**

25 studies were selected for analysis

Relative risk for each adverse outcome calculated using Revman 5.3 Software

Maternal Obesity:
BMI measured ≤16 weeks gestation

Normal: 18.5-24.9 kg/m²
Obese: ≥30 kg/m²

Adverse pregnancy outcomes selected in the analysis were based on the **most frequently occurring in standard clinical practice**

LIVE

Example: gestational diabetes

Background risk of gestational diabetes = 1.6% (systematic review)

So for 1000 women with normal weight, 16 would be expected to develop gestational diabetes

Clinical obesity increases risk of gestational diabetes: relative risk = 4.31 (systematic review): 6.9% (1.6 × 4.31 = 6.9)

1000 pregnant women with normal body weight take TAF/FTC/DTG for 96 weeks, 14% become obese (percentage estimated based on the weight gain in ADVANCE at week 96)

140 with clinical obesity after Week 96, 6.9% risk = 9.6 cases ((6.9 × 140)/100)

860 not obese after Week 96, 1.6% risk = 13.8 cases ((1.6 × 860)/100)

1000 women given TAF/FTC/DTG for 96 weeks = 23.4 cases of gestational diabetes (+7 cases)

LIVE

Systematic review: risks of adverse maternal outcomes for obese versus normal weight pregnant women

Maternal outcome	Relative Risk	95% CI	P-value
Preterm delivery	1.33	[1.19,1.48]	p<0.0001
Gestational hypertension	3.68	[2.97,4.55]	p<0.00001
Gestational diabetes	4.31	[3.18,5.85]	p<0.00001
Pre-eclampsia	4.06	[3.09,5.33]	p<0.00001
Post-partum haemorrhage	1.23	[1.01,1.50]	p=0.04
Caesarean section	1.64	[1.55,1.73]	p<0.00001

LIVE

ADVANCE trial: predicted increased risks of adverse maternal outcomes (per 1000 pregnancies)

Adverse Maternal Outcomes	Baseline	TAF/FTC/DTG 96-weeks	TDF/FTC/DTG 96-weeks	TDF/FTC/EFV 96-weeks
Preterm delivery	70	73 (+3)	71 (+1)	70 (0)
Gestational hypertension	28	39 (+11)	34 (+6)	29 (+1)
Gestational diabetes	16	23 (+7)	19 (+3)	16 (0)
Pre-eclampsia	25	35 (+10)	30 (+5)	26 (+1)
Postpartum haemorrhage	112	115 (+3)	114 (+2)	112 (0)
Caesarean section	213	232 (+19)	224 (+11)	215 (+2)
Total effect:		**+53**	**+28**	**+4**

For each adverse birth outcome, treatment emergent obesity at Week 96 were combined with relative risks for obese versus normal weight pregnant women

LIVE

Systematic review: risks of adverse infant outcomes for obese versus normal weight pregnant women

Infant outcome	Relative Risk	95% CI	P-value
Large-for-gestational age	2.04	[1.65,2.52]	P<0.00001
Macrosomia	2.48	[2.10,2.93]	P<0.00001
Small-for-gestational age	0.84	[0.76,0.94]	P=0.0009
Neonatal death	1.57	[1.00,2.48]	P=0.05
Stillbirth	1.39	[1.01,1.92]	P=0.05
Neural tube defects	2.53	[1.15,5.55]	P=0.02

Risks for women with obese BMI significantly higher for most infant outcomes

LIVE

ADVANCE trial: predicted increased risks of adverse infant outcomes (per 1000 pregnancies)

Adverse Pregnancy Outcome	Baseline	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
		96-weeks	96-weeks	96-weeks
Small-for-gestational-age infants	89	87 (-2)	88 (-1)	89 (0)
Large-for-gestational-age infants	134	154 (+20)	145 (+11)	137 (+3)
Macrosomia	31	37 (+6)	34 (+3)	31 (0)
Stillbirth	4	4 (0)	4 (0)	4 (0)
Neonatal death	2	2 (0)	2 (0)	2 (0)
Neural tube defect	0	0 (0)	0 (0)	0 (0)
Total effect:		+24	+13	+3

For each adverse birth outcome, treatment emergent obesity at Week 96 were combined with relative risks for obese versus normal weight pregnant women

LIVE

Conclusion

- Among women with normal body weight at baseline in the ADVANCE trial, 14% became clinically obese after 96 weeks of TAF/FTC+DTG. Systematic reviews show clinical obesity significantly increases risks of adverse pregnancy outcomes, for both mothers and infants

- As a result, this analysis suggests higher risks of adverse maternal and infant birth outcomes after long-term treatment with TAF/FTC+DTG (+77 cases per 1000 births) and TDF/FTC+DTG (+41 cases per 1000 births)

- These risks could increase further for women treated longer-term: the risk of clinical obesity continues to rise after Week 96

- Further safety evaluation is required regarding the combination of TAF/FTC+DTG or other integrase inhibitors in treatment guidelines