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

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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.

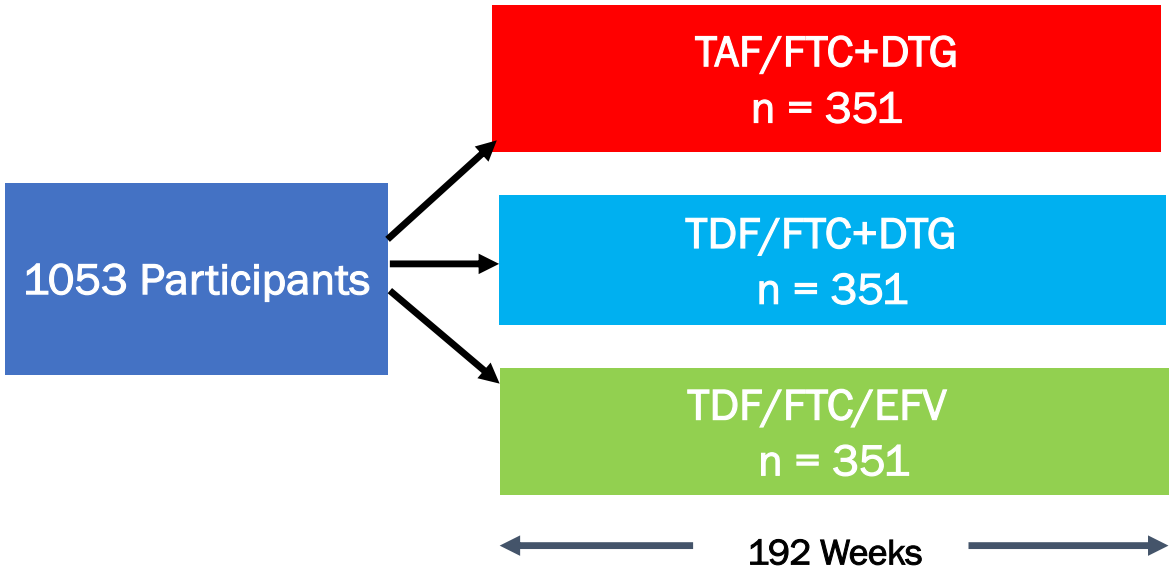
Pregnant women who are clinically obese have a higher risk of adverse birth outcomes, both for the mother and the infant

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?

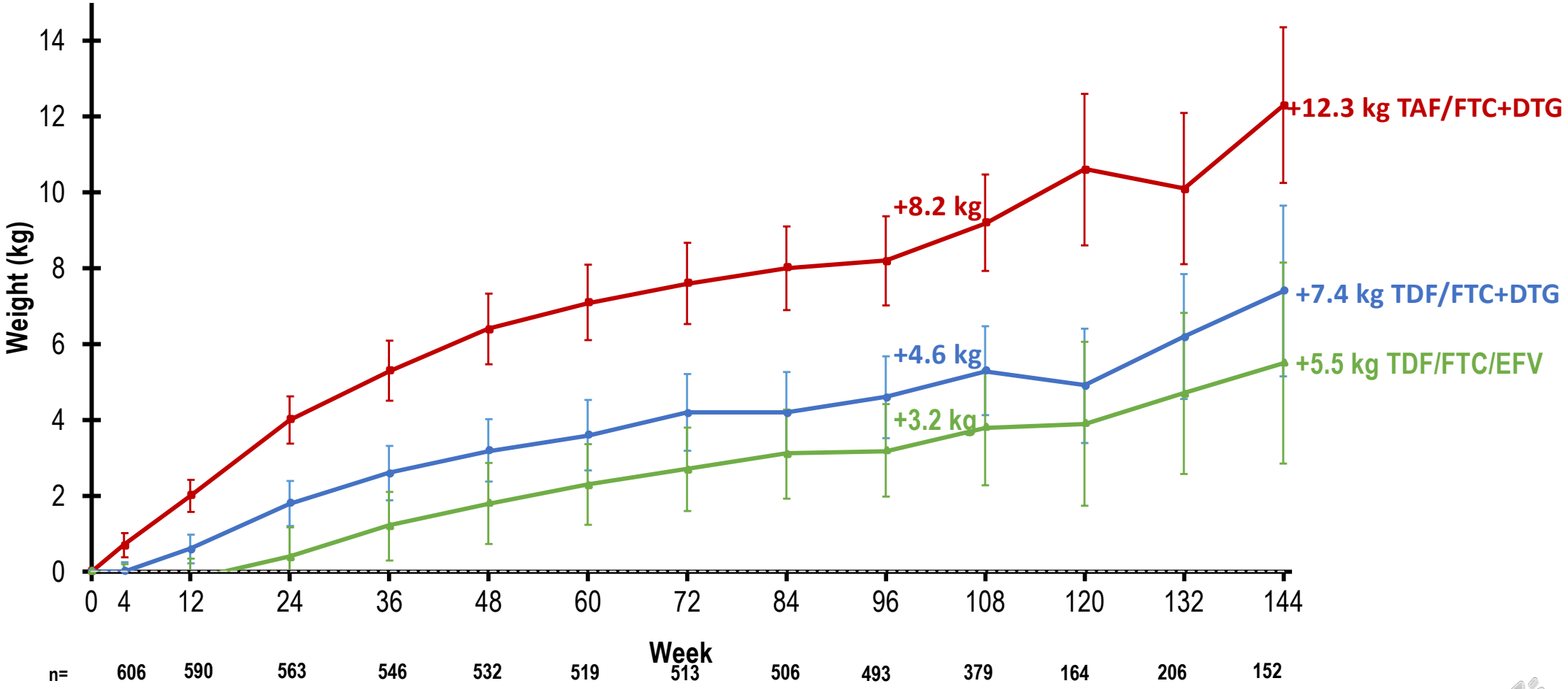
ADVANCE (South Africa): Study design

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

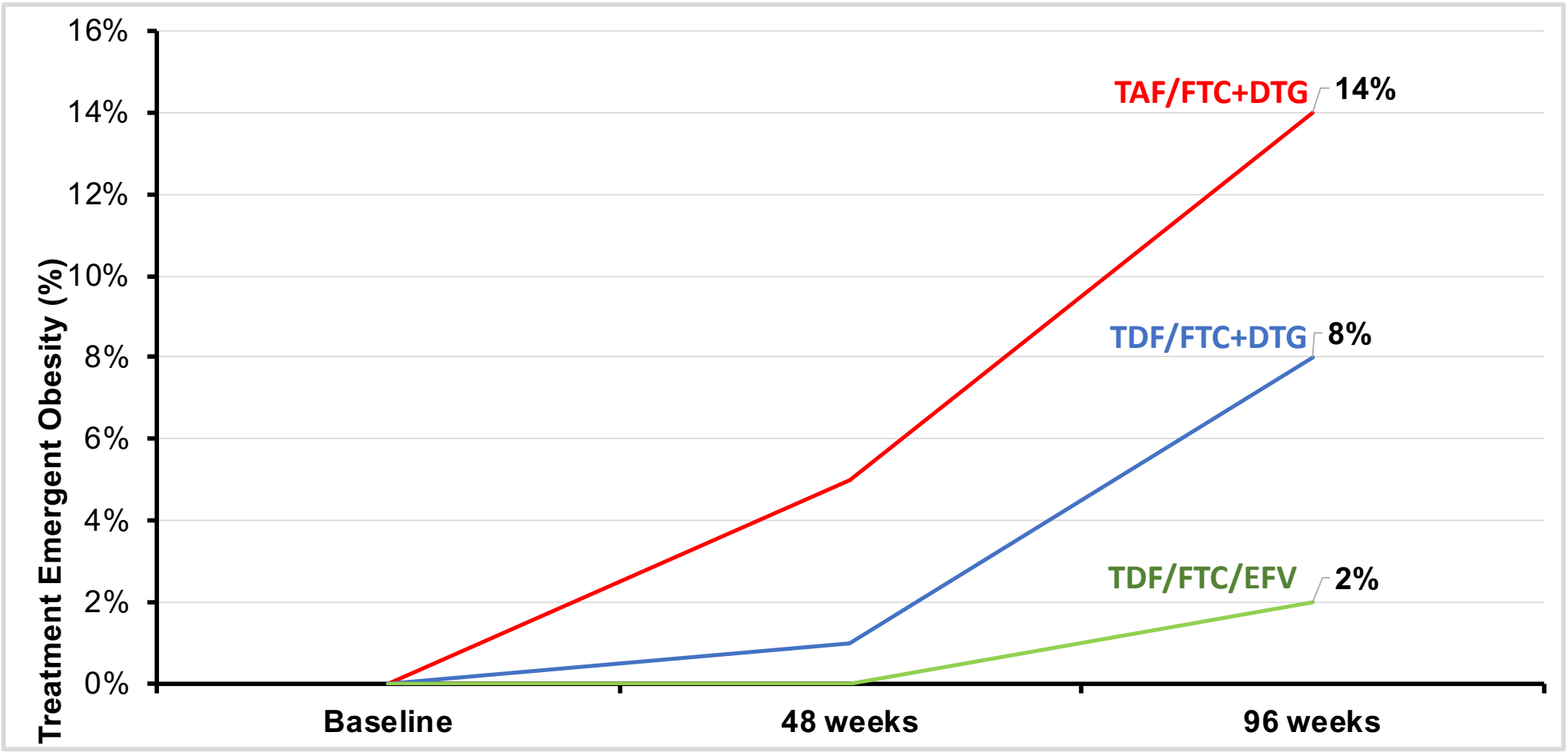


Study visits: baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 then every 24 weeks

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



Treatment Emergent Obesity: Women with normal baseline BMI



Systematic Review of adverse birth outcomes

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

Select**ed 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/m^2
Obese: ≥30 kg/m^2

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

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)

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

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

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

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

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

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 osteoporosis and/or impaired renal function**

Reference: WHO 2019 Treatment Guidelines
https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf