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The predicted risk of adverse pregnancy outcomes as a result of treatment-associated obesity in a hypothetical population receiving tenofovir alafenamide/emtricitabine/dolutegravir, tenofovir disoproxil fumarate/emtricitabine/dolutegravir or tenofovir disoproxil fumarate/emtricitabine/efavirenz

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Objective: Integrase inhibitors, including dolutegravir (DTG), are associated with weight gain and obesity, especially when combined with tenofovir alafenamide (TAF). Obesity increases the risk of adverse pregnancy outcomes (APOs). This study aimed to predict the risk of APOs caused by treatment-associated obesity, using a hypothetical sample based on the ADVANCE trial.

Design: Risk prediction.

Methods: Firstly, a meta-analysis was performed to determine the relative risk (RR) for APOs in women with obese (≥30) versus normal prepregnancy BMIs (18.5–24.9). For the hypothetical sample, 3000 nonpregnant women with normal BMIs at Week 0 of treatment were evenly allocated across the following treatment arms: TAF/FTC+DTG, TDF/FTC+DTG, TDF/FTC/EFV. The treatment-associated obesity rates from ADVANCE were used to calculate the number of women with obese and normal BMIs expected at Week 96 in our sample. This was combined with the APO RRs to predict the number of women at risk of APOs, in each treatment arm, assuming they conceived at Week 96.

Results: At Week 96, the percentage of women predicted to be obese was 14.1% with TAF/FTC+DTG, 7.9% with TDF/FTC+DTG and 1.5% with TDF/FTC/EFV. The RR in women with obese versus normal BMIs was significantly higher for most APOs. Therefore, the number of women at risk of APOs was higher with TAF/FTC+DTG than TDF/FTC+DTG and TDF/FTC/EFV. For example, 11/1000 additional gestational hypertension cases were predicted with TAF/FTC+DTG, 6/1000 with TDF/FTC+DTG and 1/1000 with TDF/FTC/EFV.

Conclusion: Treatment-associated obesity increased the APO risk in women. This risk is likely to increase, as preliminary data from ADVANCE demonstrates ongoing weight gain beyond Week 96. Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Since 2018, the WHO has recommended the first-line antiretroviral therapy (ART) to be a combination of tenofovir disoproxil fumarate (TDF) and either lamivudine (3TC) or emtricitabine (FTC) with the integrase strand transfer inhibitor (INSTI), dolutegravir (DTG) [1]. DTG replaced the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz (EFV), in the updated ART guidelines [2]. This update occurred in light of evidence from the SINGLE trial reporting that DTG had more favourable tolerability and a higher barrier to resistance in comparison to EFV [3,4].

In the current WHO guidelines, tenofovir alafenamide (TAF) is included in the triple-drug therapy for patients with osteoporosis or impaired renal function, as a substitute for TDF [1]. Due to its renal and bone safety benefits, the use of TAF in the North American and European ART guidelines has been expanded to the wider population living with HIV [5–8].

With ART drug resistance emerging in low-and-middle-income countries (LMICs), the low-cost generic formulations of DTG and TAF are attractive options that would allow LMICs to scale up their HIV treatment programmes [9–11]. However, both TAF and INSTIs, including DTG, have been associated with increased levels of weight gain [12–16].

The WHO defines obesity as a BMI of at least 30. It is calculated using the weight in kilograms divided by the height in metres squared (kg/m^2) [17]. Obesity and its associated morbidities are a global health concern as over 650 million people worldwide fall into this category [18]. South Africa accounts for the highest proportion of people living with HIV globally and has one of the highest levels of obesity in Sub-Saharan Africa, with one in five women having a BMI of at least 35 [19,20].

ADVANCE and NAMSAL are randomized controlled trials (RCTs) that are one of the few Phase III trials to investigate the effects of DTG, specifically on body weight, in a predominantly black, African population [4,14,16,21–24]. Black ethnic groups face the heaviest burden of the HIV epidemic but remain the most underrepresented population in ART drug trials; therefore, the results from ADVANCE and NAMSAL are of significant value [25]. Both studies have reported significant weight gain with ART combinations containing DTG.

ADVANCE is an ongoing trial that began in 2017, based in South Africa. The trial is comparing the efficacy and safety of two DTG-based regimens (TAF/FTC+DTG, TDF/FTC+DTG) against the previous standard treatment (TDF/FTC/EFV). There are 1053 participants who have been evenly assigned across the three treatment arms to receive long-term follow-ups. Currently, results have been published for Week 48 and Week 96 [14,26]. Higher levels of weight gain have been reported with the DTG-based regimens, particularly in the TAF/FTC+DTG treatment arm. Furthermore, the weight gain has been more pronounced amongst the black female participants compared to the black male participants. At Week 96, the mean weight gain in women was 8.1 kg with TAF/FTC+DTG compared to only 3.2 kg with TDF/FTC/EFV [14]. Similarly, the NAMSAL trial, based in Cameroon, reported a median weight gain of 6 kg with TDF/3TC+DTG and 3 kg with TDF/3TC/EFV amongst the women in the trial at Week 96 [21].

Aside from the recognized association between obesity and cardiovascular disease, there is extensive research highlighting an association between maternal obesity and adverse pregnancy outcomes. For example, a retrospective cohort study in Nigeria comparing adverse pregnancy outcomes in women with an obese BMI versus a normal BMI reported an increased risk of several adverse outcomes with obesity, including antepartum haemorrhage [odds ratio (OR): 2.78, 95% confidence interval (95% CI): 1.02–7.93], preeclampsia (OR: 2.31, 95% CI: 1.72–4.48) and postpartum haemorrhage (PPH, OR: 2.2, 95% CI: 1.18–5.20) [27]. A study assessing macrosomia (infant birthweight more than the 90th percentile of the country-specific birthweight) across 23 countries reported that macrosomia was more common in obese women (OR for Africa: 2.00, 95% CI: 1.85–2.17) [28]. Other frequently recorded adverse pregnancy outcomes with maternal obesity include gestational diabetes, large-for-gestational age infants and neonatal deaths [29–31].

Although current evidence shows DTG to be effective and well-tolerated during pregnancy (DolPHIN-1, DolPHIN-2, IMPAACT 2010) [32–34], it is important to consider that these trials have only measured the short-term safety and efficacy outcomes of DTG. Participants in these trials recieved DTG for only a few months, whilst they were pregnant. The long-term effects of DTG, specifically, the effects on a subsequent pregnancy after longer periods of use, prior to conception, and the treatment-associated weight gain is unknown.

Therefore, this study aimed to assess the consequences of DTG-associated maternal obesity (at conception) on adverse pregnancy outcomes for a hypothetical population of 3000 women, evenly allocated to receive TAF/FTC+DTG, TDF/FTC+DTG or TDF/FTC/EFV.

Materials and methods

The method was divided into two steps, which are outlined as follows.

Meta-analysis

Firstly, a meta-analysis was performed to determine the effects of maternal obesity on adverse pregnancy outcomes. The methodology was carried out in line with the Cochrane Guidelines for Systematic Reviews and the PRISMA Guidelines [35,36].

Before performing the literature search for the meta-analysis, a scoping review of the literature was carried out to identify frequently reported adverse pregnancy outcomes in studies. This was used to decide the key outcomes to be measured in the meta-analysis and form parts of the inclusion criteria.

Four databases (MEDLINE, EMBASE, Maternal & Infant Care and Global Health) were searched to retrieve studies evaluating an association between adverse pregnancy outcomes and maternal obesity. A search strategy was developed using the 'population, intervention, comparison, outcome' framework. Search terms included '*prepregnancy BMI', 'pregnancy complications'* and *'maternal obesity'*. No language, country or date restrictions were applied (Supplementary 1: PRISMA Diagram, Supplementary 2: Search Terms, http://links.lww.com/QAD/C242). Studies were transferred into the systematic review management software, Covidence [37], for title and abstract screening and full-text eligibility assessment.

Study selection

Studies were required to assess at least one of the following adverse maternal pregnancy outcomes: preterm delivery, gestational hypertension, gestational diabetes mellitus, caesarean section or preeclampsia and at least one of the following adverse infant outcomes: small-for-gestational age (SGA), large-for-gestational age (LGA), low birthweight, macrosomia or stillbirth. Studies reporting neural tube defects (NTDs) were also selected.

Women with a normal BMI were compared against women with an obese BMI. Studies were required to define weight categories using the International WHO BMI classification (normal: 18.5–24.9, obese: $\geq$30) [17]. It was necessary for all the studies to clearly state that the maternal BMI was measured prepregnancy or measured at 16 weeks of gestation or less; we did not extend beyond this as the BMI would be influenced too heavily by gestational weight gain.

Studies were eligible for inclusion if they were cohort in design. Only studies with sufficient reporting of raw data values were selected to allow for appropriate data extraction and analysis. (Supplementary 3: Inclusion and Exclusion Criteria, http://links.lww.com/QAD/C242)

Following the initial scoping review, there were a limited selection of cohort studies measuring an association between maternal obesity and NTDs. Therefore, the BMI classification inclusion criterion was not applied when screening the studies reporting this specific outcome. It was important to investigate this outcome in our meta-analysis considering the global safety signal that was released for DTG use during pregnancy in 2018. This occurred following the release of preliminary results from a birth surveillance programme in Botswana, which reported an increased risk of NTDs in infants exposed to DTG *in utero.* Fortunately, further analysis and research has now shown this risk to be nonsignificant and small [38,39].

The quality assessment of the cohort studies was done using the 9* Newcastle-Ottawa Tool [40].

Data extraction and analysis

The BMI classifications, outcome definitions and raw values were extracted from the selected studies. After the full-text assessments, PPH and neonatal deaths were adopted as additional outcomes for the meta-analysis, as these outcomes were consistently reported in many of the studies.

Statistical analysis was conducted using RevMan Software Version 5.3 [41]. The relative risk (RR) for each adverse pregnancy outcome in women with normal versus obese BMIs was calculated, using the Mantel–Haenszel tests. Random-effects modelling accounted for clinical diversity in the studies. Statistical heterogeneity was calculated using the Chi-squared test (I^2) and guidance from the Cochrane Handbook was used for interpretation [42]. Values of $30\% \leq I^2 < 50\%$ were defined as moderate heterogeneity, $50\% \leq I^2 < 75\%$ as substantial and at least 75% as considerable.

Risk prediction

The risk prediction calculations were performed using a hypothetical sample based on the ADVANCE trial, across a 10-year time-frame. In the hypothetical sample, 3000 nonpregnant women with normal BMIs at baseline (i.e. at Week 0 of treatment) were evenly divided across the following treatment arms: TAF/FTC+DTG, TDF/FTC+DTG and TDF/FTC/EFV, to receive 96 weeks of treatment.

The rationale for this hypothetical sample is described as follows.

Firstly, we assumed that 3000 nonpregnant women with normal BMIs at baseline were evenly divided to use TAF/FTC+DTG, TDF/FTC+DTG or TDF/FTC/EFV. Within each treatment arm, an annual pregnancy rate of 10% was applied (based on the real annual pregnancy rate from the ADVANCE trial). Therefore, 100 women in each treatment arm were expected to become pregnant whilst receiving treatment. Across a 10-year timeframe, this created a sample of 1000 women in each treatment

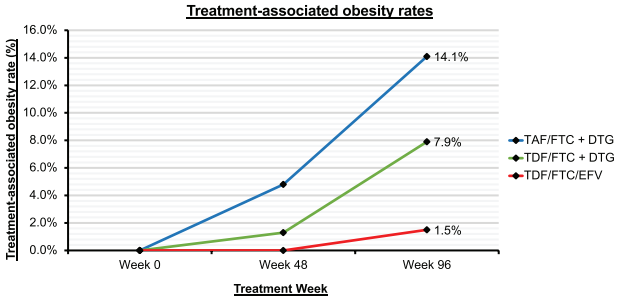

Fig. 1. The treatment-associated obesity rates for women with a normal baseline BMI in each treatment arm of the ADVANCE trial. Baseline = at Week 0 of treatment.

arm, with normal BMIs at baseline who became pregnant during treatment, resulting in a total sample of 3000 women.

The hypothetical sample requires the assumption that each woman became pregnant only once whilst taking the treatment. It also assumes that all the women were of reproductive age with no underlying conditions affecting their fertility and pregnancy.

We estimated the number of women expected to become obese or remain with a normal BMI at Week 96 of treatment in the hypothetical sample. The real ADVANCE treatment-associated obesity rates for Week 96 in women with a normal BMI at baseline were used for the calculation (14.1% for TAF/FTC+DTG, 7.9% for TDF/FTC+DTG and 1.5% for TDF/FTC/EFV) (Fig. 1). For example, in the hypothetical TAF/FTC+DTG arm, we estimated 141 women would have an obese BMI and 859 women would remain with a normal BMI at Week 96 of treatment.

From the meta-analysis, we extracted the RR and the absolute percentage of women with normal and obese BMIs experiencing each adverse pregnancy outcome. These results were combined with the hypothetical Week 96 BMI estimates to predict the number of women at risk of each adverse pregnancy outcome at Week 96 of treatment, assuming they conceived at Week 96 (i.e. at their Week 96 prepregnancy BMI)

We compared this to the number of women at risk of each adverse pregnancy outcome if they conceived at their baseline BMI (i.e. at their Week 0 prepregnancy BMI),

Finally, the number of women at risk of each adverse pregnancy outcome was aggregated for each treatment arm, for Week 0 and Week 96.

Figure 2 shows a flow-chart to aid the visualization of the methodology.

A 10-year timeframe was used for the risk prediction because we aimed to predict and illustrate the possible long-term health burden of treatment-associated weight gain (as seen in the results of the ADVANCE trial) on a large cohort of women becoming pregnant whilst receiving DTG-based ART.

The hypothetical sample only considered women with a normal BMI at baseline because it was based on the real participant demographics of the ADVANCE trial. In the ADVANCE trial, the normal baseline BMI category had the highest proportion of female participants. It would be areas for future research to perform similar risk prediction calculations for the other BMI categories. The 10% annual pregnancy rate from the ADVANCE trial was used over the 10-year time period for similar reasons.

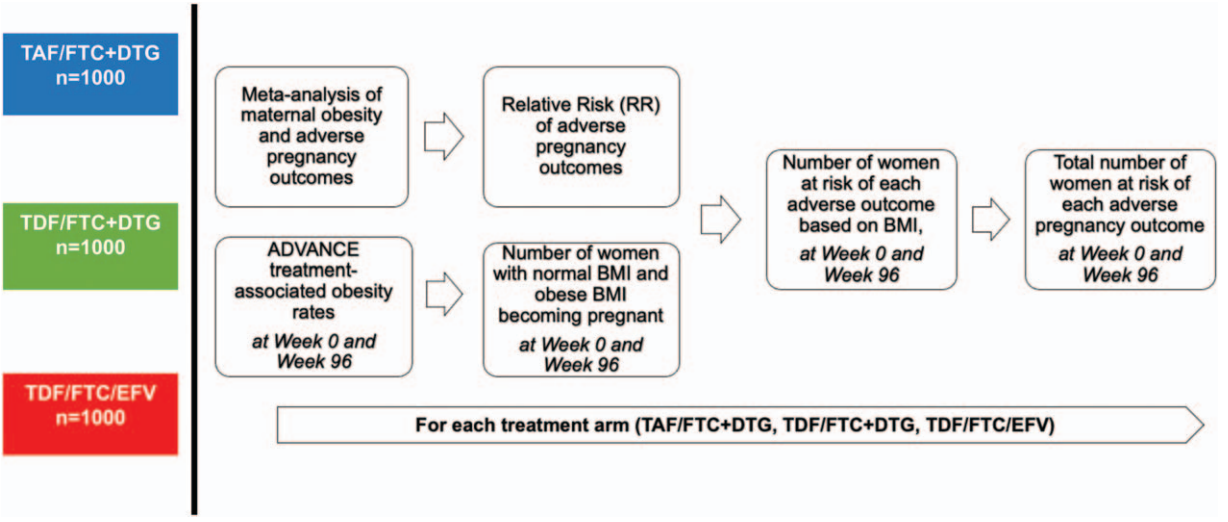

Fig. 2. A flow-chart to illustrate the methodology. DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 1. Relative risk of adverse pregnancy outcomes.

Adverse pregnancy outcome	Raw values (%)		Relative risk (RR)	95% CI	*P*
	Normal BMI	Obese BMI			
Preterm delivery*	24 998/359 032 (7.0)	6096/88 746 (6.9)	1.33	[1.19–1.48]	<0.0001
Gestational hypertension*	7391/261 776 (2.8)	3845/63 123 (6.1)	3.68	[2.97–4.55]	<0.00001
Gestational diabetes mellitus*	7986/514 908 (1.6)	6272/110 224 (5.7)	4.31	[3.18–5.85]	<0.00001
Preeclampsia*	8898/361 935 (2.5)	4741/76 208 (6.2)	4.06	[3.09–5.33]	<0.00001
Postpartum haemorrhage*	35 004/313 050 (11.2)	3895/47 933 (8.1)	1.23	[1.01–1.50]	0.04
Caesarean section*	115 351/540 994 (21.3)	37 829/117 232 (32.3)	1.64	[1.55–1.73]	<0.00001
Small-for-gestational age*	19 872/223 542 (8.9)	3500/44 757 (7.8)	0.84	[0.76–0.94]	0.0009
Large-for-gestational age*	32 481/241 531 (13.5)	12 440/51 813 (24.0)	2.04	[1.65–2.52]	<0.00001
Macrosomia*	13 050/427 496 (3.1)	5560/76 278 (7.3)	2.48	[2.10–2.93]	<0.00001
Low birthweight	1777/27 582 (6.5)	410/4969 (8.3)	1.01	[0.56–1.80]	0.98
Neonatal death*	115/53 637 (0.2)	284/176 335 (0.2)	1.57	[1.00–2.48]	0.05
Stillbirth*	1517/432 873 (0.4)	632/101 894 (0.6)	1.39	[1.01–1.92]	0.05
Neural tube defect*	593/2 696 807 (0.02)	90/142 291 (0.06)	2.53	[1.15–5.55]	0.02

*Outcomes were statistically significant, $P \leq 0.05$.

The risk prediction calculations did not include the actual pregnancy outcomes experienced by women in the ADVANCE trial. The adverse pregnancy outcomes and predictions were derived from the studies found in the literature search. Details on the real pregnancy outcomes reported in the ADVANCE trial can be found in the published papers of the Week 48 and Week 96 results [14,26].

Results

Meta-analysis

The meta-analysis included 25 studies. The majority of the studies assessed women with singleton pregnancies. The studies were from a broad range of countries with the mean gestational age and gestational age at delivery being similar **(**Supplementary 4: Study details, http://links.lww.com/QAD/C242).

The RR for each adverse pregnancy outcome is displayed in Table 1 (Supplementary 5: Forest Plots, http://links.lww.com/QAD/C242). All the adverse pregnancy outcomes except for low birthweight infants ($P = 0.98$) had a statistically significant association with maternal prepregnancy obesity. Prepregnancy obesity increased the risk for all the measured adverse pregnancy outcomes apart from SGA infants. The risk of SGA infants was lower with obesity; the RR was 0.84 (95% CI: 0.76–0.94). Regarding adverse maternal pregnancy outcomes, obese mothers were at a higher risk of preeclampsia, gestational diabetes and gestational hypertension. Regarding adverse infant outcomes, obese mothers were at a higher risk of LGA infants or infants with macrosomia.

Risk prediction

As mentioned in the methodology, the ADVANCE treatment-associated obesity rates at Week 96 for women with a normal BMI at baseline were 14.1% for TAF/FTC+DTG, 7.9% for TDF/FTC+DTG and 1.5% for TDF/FTC/EFV (Fig. 1). Women in all three treatment arms gained weight after starting the ART regimens. Therefore, in our hypothetical sample, there was an overall rise in the number of women predicted to experience adverse pregnancy outcomes if they conceived at Week 96 versus Week 0 of treatment (i.e. at their Week 96 prepregnancy BMI versus Week 0 prepregnancy BMI), in all the treatment arms, across a 10-year timeframe.

Overall, the percentage increase in the number of women predicted to experience adverse pregnancy outcomes at their Week 0 BMI versus Week 96 BMI was 10% with TAF/FTC+DTG and 5% with TDF/FTC+DTG compared to only 1% with TDF/FTC/EV. The estimated predictions for each adverse pregnancy outcome are outlined in Table 2.

Looking at specific outcomes, if women conceived at their Week 96 BMI, there would be 7/1000 additional predicted cases of gestational diabetes mellitus with TAF/FTC+DTG, 3/1000 cases with TDF/FTC+DTG and none with TDF/FTC/EFV across a 10-year time frame. Likewise, there would be 6/1000 additional predicted cases of macrosomia with TAF/FTC+DTG, 3/1000 with TDF/FTC+DTG and none with TDF/FTC/EFV across a 10-year time frame. No cases of NTDs were predicted to occur.

Discussion

Women in Africa already have a higher background risk to adverse pregnancy outcomes due to the high prevalence of maternal risk factors such as malaria, anaemia, sexually transmitted infections and HIV [43,44]. This study suggests that the maternal and infant risks associated with maternal prepregnancy obesity may be

Table 2. The number of women predicted to be at risk of each adverse pregnancy outcomes if they conceived at their baseline BMI (i.e. normal BMI at Week 0) and at their Week 96 BMI, for each treatment arm (TAF/FTC+DTG, TDF/FTC+DTG, TDF/FTC/EFV).

	TAF/FTC+DTG			TDF/FTC+DTG			TDF/FTC/EFV		
Adverse pregnancy outcome	Week 0	Week 96	Percentage change	Week 0	Week 96	Percentage change	Week 0	Week 96	Percentage change
Preterm delivery	70	73	+4%	70	71	+1%	70	70	±0%
Gestational hypertension	28	39	+39%	28	34	+21%	28	29	+4%
Gestational diabetes mellitus	16	23	+44%	16	19	+19%	16	16	±0%
Preeclampsia	25	35	+40%	25	30	+20%	25	26	+4%
Postpartum haemorrhage	112	115	+3%	112	114	+2%	112	112	±0%
Caesarean section	213	232	+9%	213	224	+5%	213	215	+1%
Small-for-gestational age	89	87	−2%	89	88	−1%	89	89	±0%
Large-for-gestational age	134	154	+15%	134	145	+8%	134	137	+2%
Low birthweight	64	65	+2%	64	64	±0%	64	64	±0%
Macrosomia	31	37	+19%	31	34	+10%	31	31	±0%
Stillbirth	4	4	±0%	4	4	±0%	4	4	±0%
Neonatal death	2	2	±0%	2	2	±0%	2	2	±0%
Neural tube defect	0	0	±0%	0	0	±0%	0	0	±0%
Total	788	866	+10%	788	829	+5%	788	795	+1%

DTG, dolutegravir; EFV, efavirenz; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

significant with the use of DTG, especially in combination with TAF, and increase this background risk.

From the meta-analysis, it was concluded that maternal prepregnancy obesity is significantly associated with a higher risk of several adverse outcomes such as gestational hypertension (RR: 3.68, 95% CI: 2.97–4.55) and gestational diabetes mellitus (RR: 4.31, 95% CI: 3.18–5.85). However, maternal prepregnancy obesity was protective for adverse outcomes such as low birthweight and SGA infants. These results are in line with systematic reviews that have carried out similar assessments of maternal obesity and adverse pregnancy outcomes [29,45].

As higher rates of obesity occurred with DTG-based regimens in the ADVANCE trial, our calculations illustrated that ART regimen using DTG posed the highest predicted risk of adverse pregnancy outcomes in women.

The underlying mechanism for the DTG-associated weight gain is unclear, however, whilst most of the evidence suggests DTG has weight-inducing effects, it is important to consider a possible weight-suppression effect occurring with EFV. Participants in the ADVANCE trial with a mutation in the CYP2B6 metaboliser genotype, causing a slower metabolism of EFV, were suggested to have inhibited weight gain [46]. As seen in the ADVANCE trial, TAF is also associated with significant weight gain. It is proposed that although TDF induces weight loss, TAF either lacks a weight suppression effect or induces weight gain. Therefore, TAF likely has additive effects on the weight gain when used in combination with DTG [16].

DTG-associated obesity places users, particularly black women, at a higher risk of adverse outcomes. These adverse outcomes are not limited to pregnancy and may contribute to the development of metabolic syndrome and cardiac insufficiency [47]. As several countries in Africa face the highest uptake of ART globally, a large proportion of the black ethnicities would face the risks of DTG-associated obesity and the consequent adverse outcomes. Although the primary concern is rising obesity, it is also important to consider that a small minority of underweight women may benefit from the weight gain. This weight gain would push them into the normal BMI category and improve their health outcomes. For example, a study reported that the risk of preterm births follow a U-shaped curve in relation to gestational weight gain and maternal prepregnancy BMI. Therefore, the extremes of the BMI categories face an increased risk of this adverse pregnancy outcome [48].

One of the limitations in this study is that we only considered a small selection of adverse pregnancy outcomes in the risk prediction calculations. In clinical practice, other important adverse pregnancy outcomes such as neonatal ICU admissions, antepartum haemorrhage and puerperal infections are seen but were not evaluated. We were also unable to account for the influence of other factors such as past medical and family history that would increase the underlying risk of some women for adverse pregnancy outcomes.

Similarly, we did not factor in the variation and confounding influence of ethnicity on adverse pregnancy outcomes. Ethnicity is known to create variation amongst populations and their risk of adverse pregnancy outcomes [49]. As most of the studies included in the meta-analysis were conducted in higher-income countries, the RR of the adverse pregnancy outcomes are less applicable to the specific population being assessed in our hypothetical sample, that is, black women who are most likely to face the burden of HIV and require DTG–based ART.

Furthermore, several assumptions were needed for our predictions to be valid. For example, we assumed that women became pregnant only once during their treatment, at Week 96 of treatment. We also assumed these women had no additional risk factors (apart from treatment-associated obesity) that may increase their chance of adverse pregnancy outcomes. We also assumed that there were no external factors apart from the ART that may cause fluctuations in their BMI.

The ADVANCE trial has extended past 96 weeks and the weight gain with TAF/FTC+DTG and TDF/FTC+DTG shows no indication of plateauing. At 144 weeks, though with incomplete data, women using TAF/FTC+DTG experienced an average weight gain of 12.8 kg compared with just 5.5 kg with TDF/FTC/EFV [50]. The predictions of the adverse pregnancy outcome risk will almost certainly increase as the treatment-associated obesity continues to rise over time in ADVANCE.

DTG-associated obesity is a slow-developing effect, with most of the DTG RCTs failing to have sufficient follow-up periods to see the manifestation of obesity-associated adverse events, including during and after pregnancy. Hence, these results should be interpreted with caution until adequately powered cohorts provide clinical data.

Weight gain is a complex issue before and during pregnancy (being underweight is also associated with poorer outcomes), and TAF and DTG are not the only antiretrovirals implicated. There is an urgent need to extend the follow-up period of ongoing and future DTG and other ART trials to assess the positive weight gain trend and understand the long-term and short-term implications of this drug. True safety and efficacy conclusions cannot be made until there is further information on the long-term impacts of this treatment.

Conclusion

DTG-associated obesity, especially in combination with TAF, may increase the risk of adverse pregnancy outcomes in women who are obese prior to conception, based on our predictions. Widespread use of TAF with DTG may need to be reconsidered until there are better long-term clinical data to inform decision-making.

There is a need for careful discussions on the benefits and risks of using newer antiretroviral agents and address the safety and efficacy of available alternatives amongst women of children-bearing age, without heightening the additional burden of obesity and the associated non-communicable diseases. These discussions are essential for healthcare providers to make evidence-based decisions regarding ART regimens.

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Sumbul Asif performed the analysis and wrote the article. Evangelia Baxevanidi checked the analysis and reviewed the article. Andrew Hill ran the overall project, checked the analysis and the article. Celicia Serenata, Willem D.F. Venter, Lee Fairlie, Masebole Masenya, Simiso Sokhela and Nomathemba Chandiwana conducted the ADVANCE study in South Africa, collected the outcomes data and reviewed the article.

Conflicts of interest

There are no conflicts of interest.

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