Assessing the safety and efficacy of dolutegravir in HIV-positive pregnant women in Sub-Saharan Africa: A meta-analysis

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

AIDS2020

Background

- The current recommended 1st line antiretroviral treatment for pregnant women consists of:

TDF + 3TC (or FTC) + DTG

Reference: Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019 (WHO/CDS/HIV/19.15). Licence: CC BY-NC-SA 3.0 IGO.

- Dolutegravir is part of the 1st line recommendation as it is well tolerated and causes a rapid reduction in the viral load

- With concerns regarding NNRTI drug resistance in Africa, dolutegravir is further favoured as it has a higher barrier to drug resistance

- **Aim: to analyse results from recent trials that have studied pregnant women to compare DTG-based treatments against the previous standard-of-care treatment (TDF /3TC or FTC /EFV)**

Trials Included

Trial	Location	Treatment Arms	Sample Size (pregnant women)		Total Sample: 1074 pregnant women
			DTG-Arm	EFV-Arm	
DolPHIN-1 (Enrolled in 3rd trimester)	South Africa, Uganda	TDF/XTC+DTG vs TDF/XTC/EFV	29	31	
DolPHIN-2 (Enrolled in 3rd trimester)	South Africa, Uganda	TDF/XTC+DTG vs TDF/XTC/EFV	137	131	
NAMSAL (from conception)	Cameroon	TDF/3TC+DTG vs TDF/3TC/EFV	13	12	
ADVANCE (from conception)	South Africa	TAF/FTC+DTG vs TDF/FTC+DTG vs TDF/FTC/EFV	26 25	30	
IMPAACT 2010 (Enrolled in 2nd/3rd trimester)	Brazil, Botswana, India, Tanzania, Thailand, South Africa, USA, Zimbabwe	TAF/FTC+DTG vs TDF/FTC+DTG vs TDF/FTC/EFV	216 213	211	

Meta-Analysis Endpoints

Efficacy endpoints:

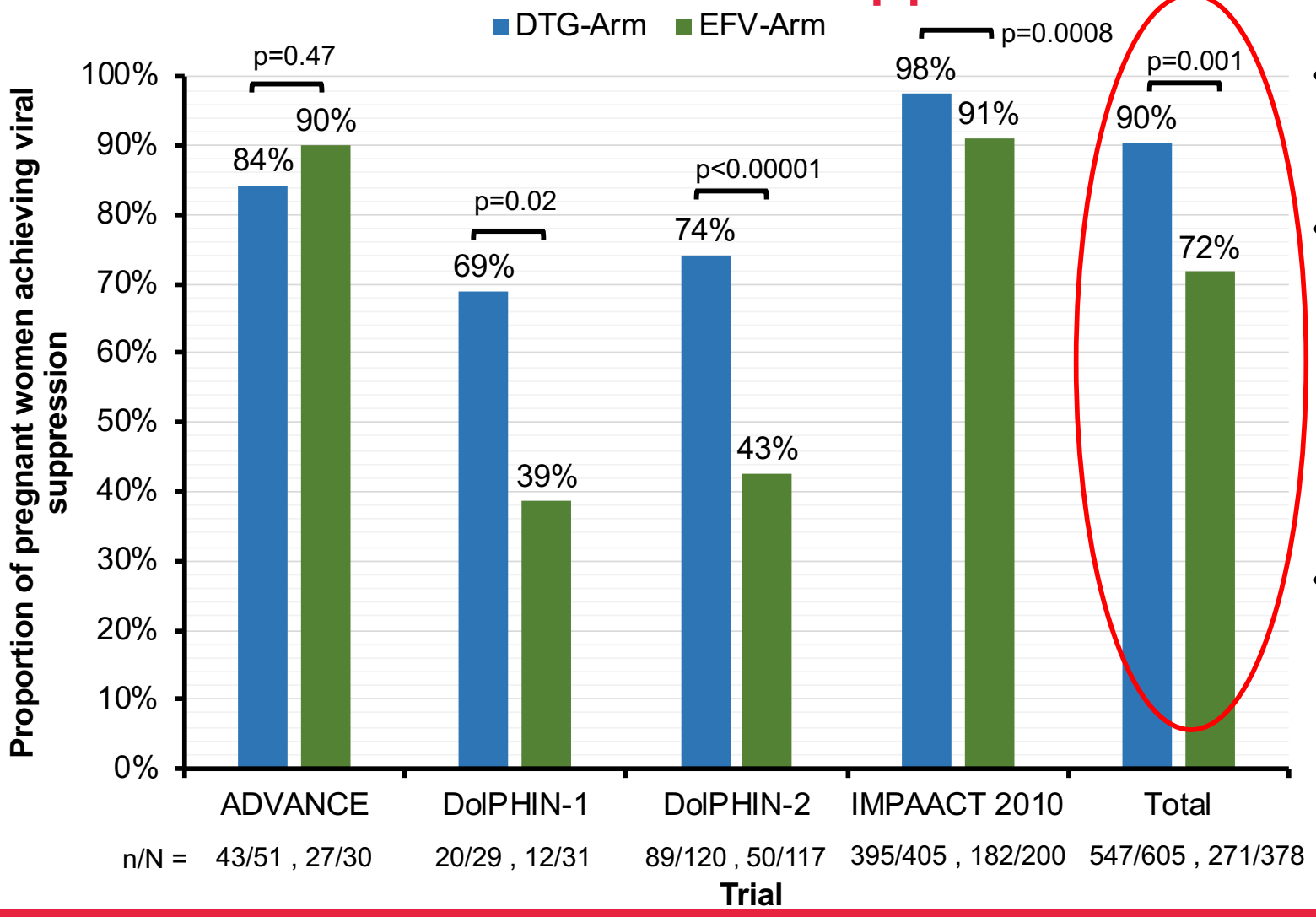
- Viral suppression rate
  (ADVANCE, DolPHIN-1, DolPHIN-2: <50 cp/mL, IMPAACT 2010: <200 cp/mL)
  (NAMSAL did not have viral suppression results for pregnant women)
- Mother-to-child-transmission cases (MTCTs)

Safety endpoints:

- Stillbirths
- Neonatal deaths
- Small-for-gestational-age infants (SFGA)
- Preterm births
- Mothers and infants experiencing ≥1 adverse event

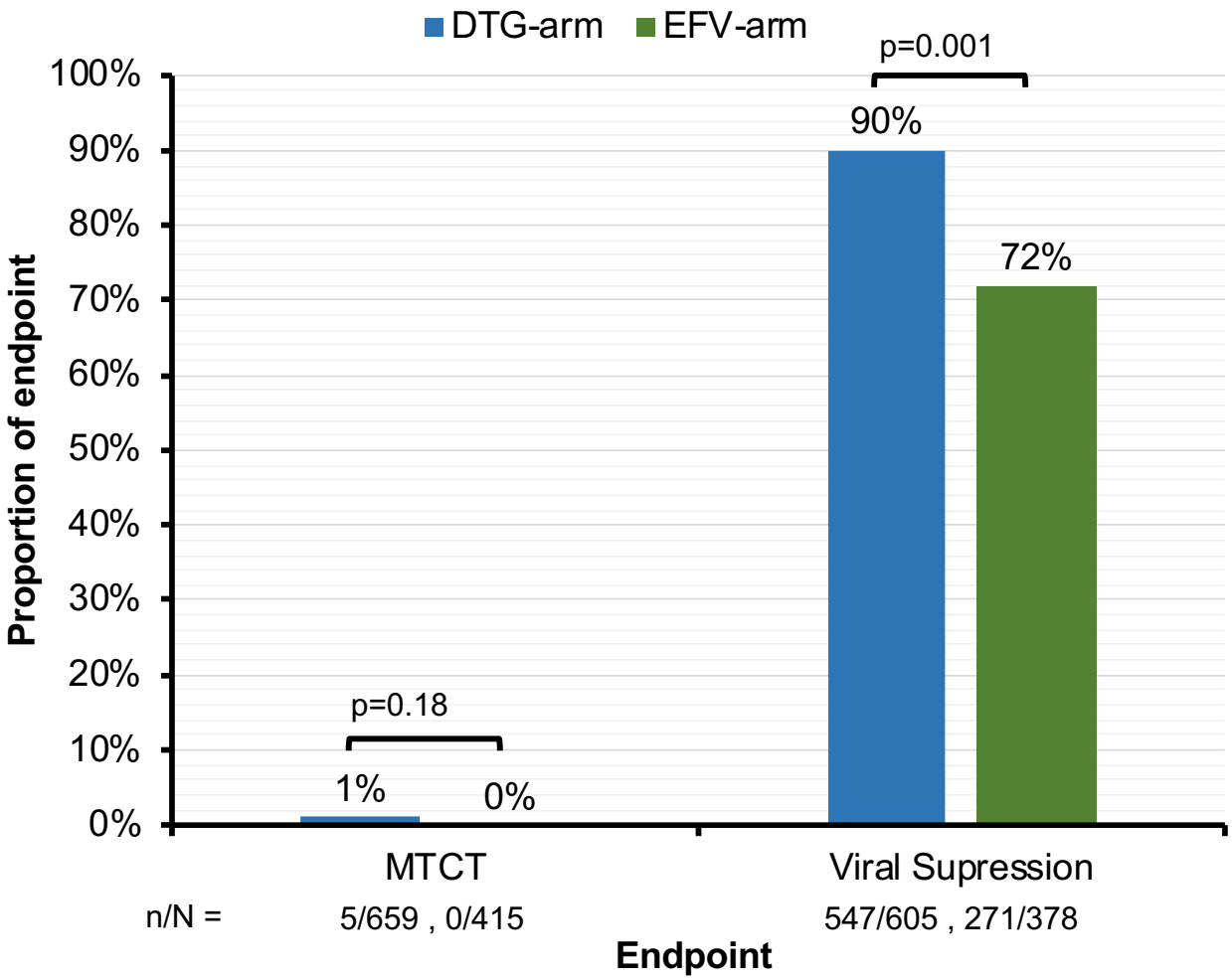
(DolPHIN-1, DolPHIN-2, IMPAACT 2010: ≥ Grade 3 Adverse Event, ADVANCE: Serious Adverse Event)

Viral Suppression



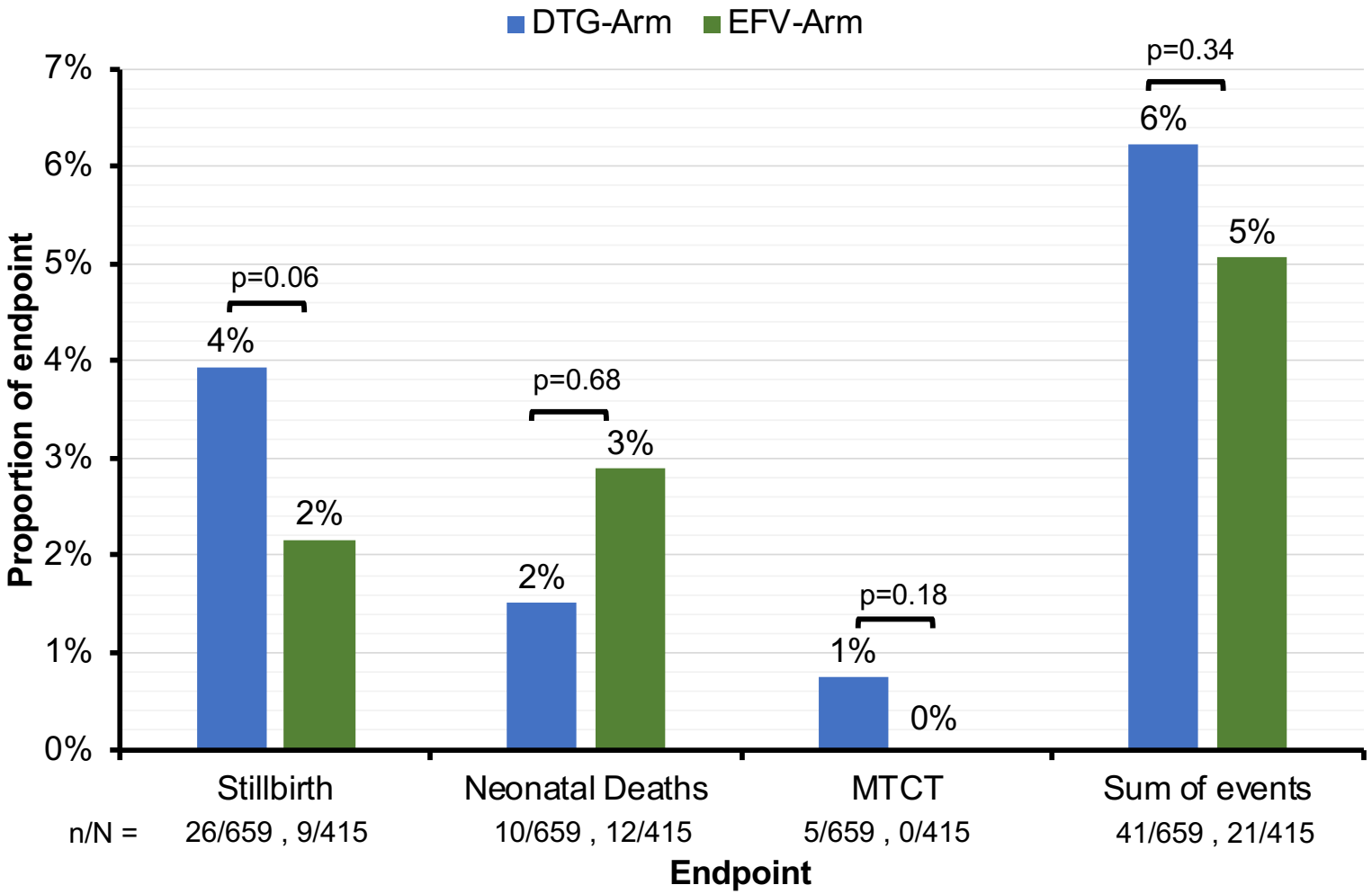
- Viral load was measured at delivery in each trial
- DTG was associated with significantly higher levels of viral suppression compared to EFV - OR: 2.90 , 95% CI: [1.54, 5.46], p=0.001
- Treatment duration was considerably longer in ADVANCE compared to DolPHIN-1, DolPHIN-2 and IMPAACT 2010

Viral Suppression vs MTCT



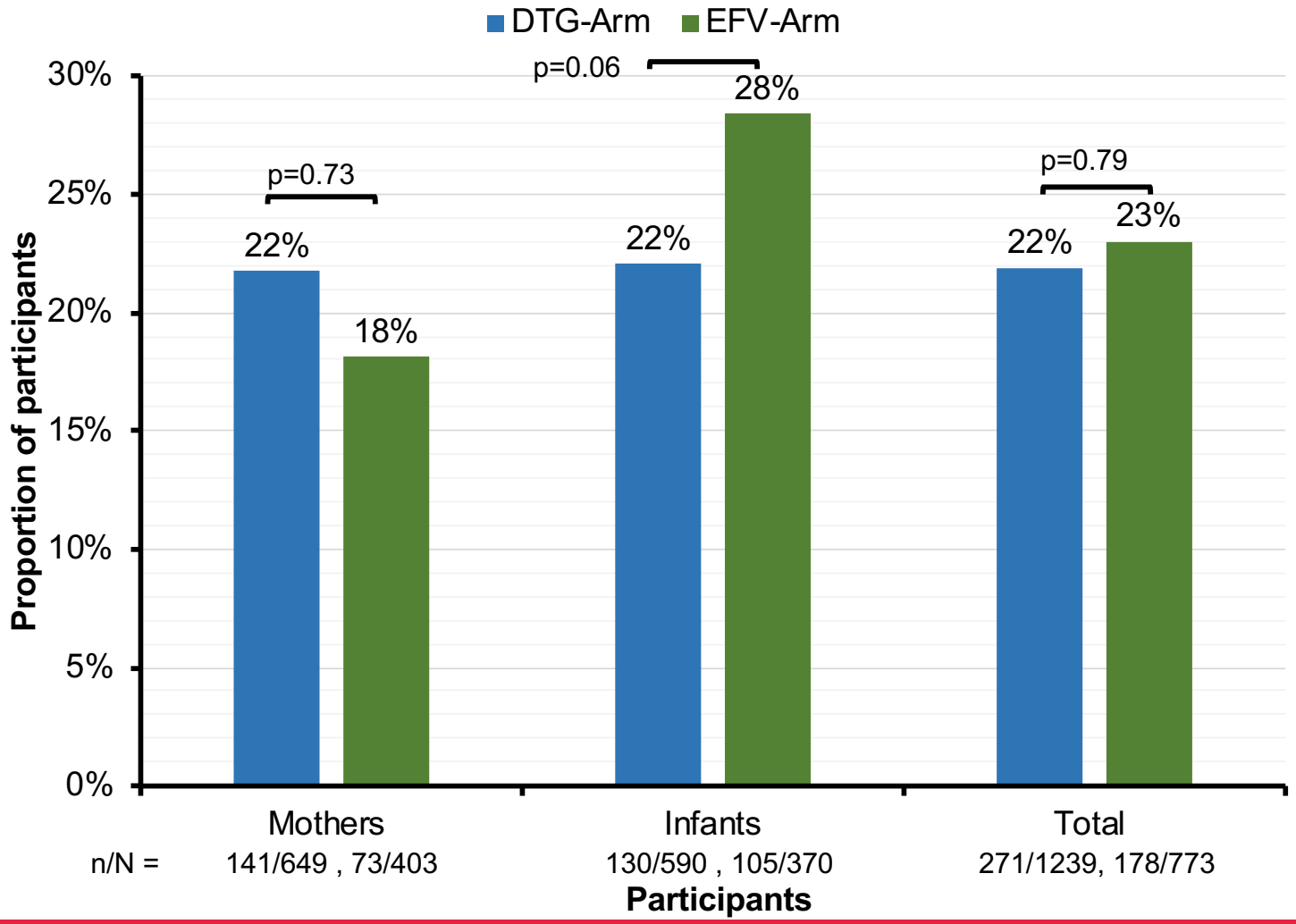
Trial	MTCT cases DTG-Arm (n/N)	MTCT cases EFV-Arm (n/N)
DolPHIN-1	0/29	0/31
DolPHIN-2	3/137	0/131
NAMSAL	0/13	0/12
ADVANCE	0/51	0/30
IMPAACT 2010	2/429	0/211
Total	**5/659**	**0/415**

Stillbirths, Neonatal Deaths, MTCTs



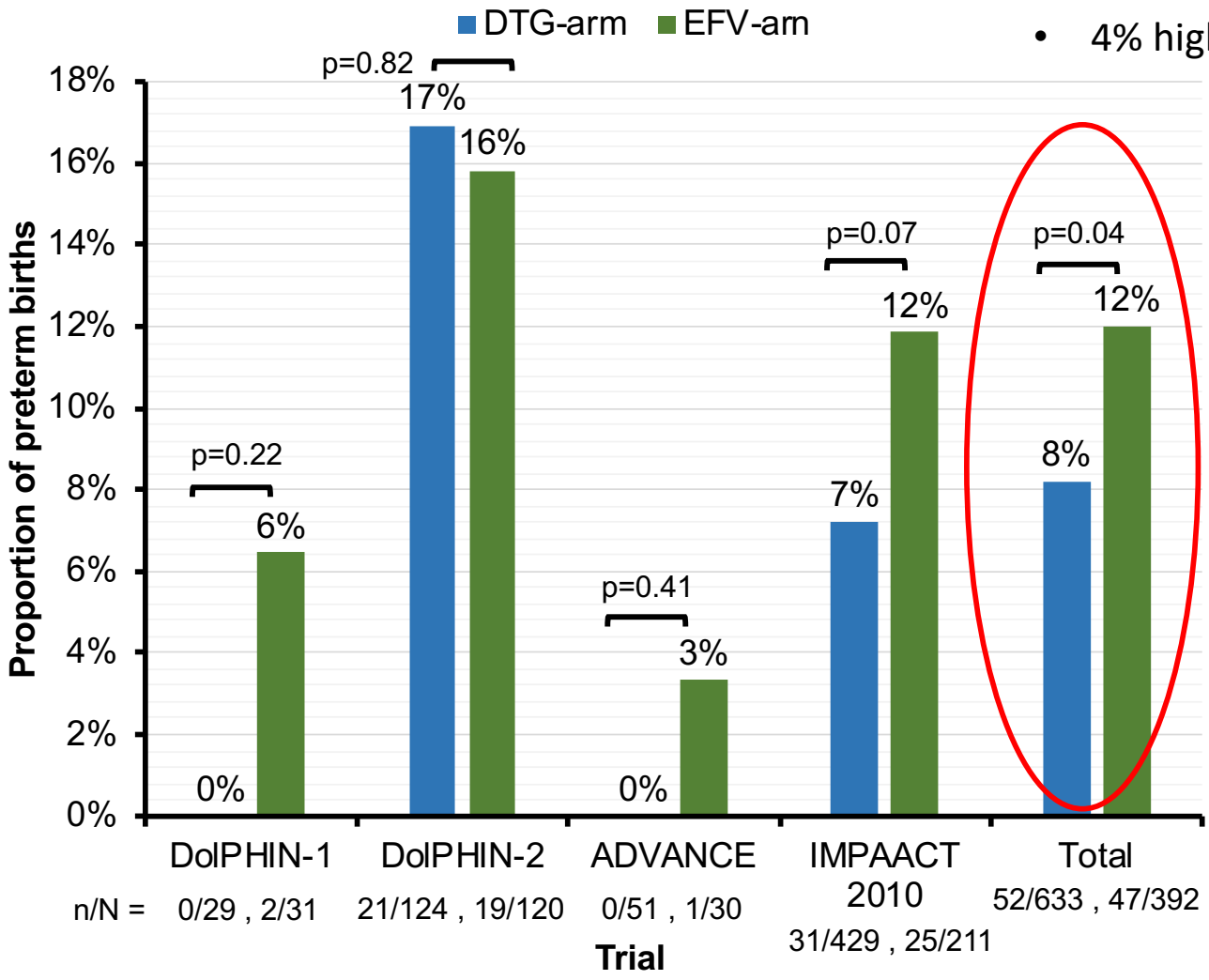
- No statistically significant difference for neonatal deaths and MTCT cases
- Borderline statistically significant difference for stillbirths – with a higher proportion occurring in the DTG-arm

Adverse Events: DTG vs EFV



- No statistically significant difference for mothers experiencing ≥1 adverse event
- Borderline statistically significant difference for infants experiencing ≥1 adverse event-with a higher proportion in the EFV-arm

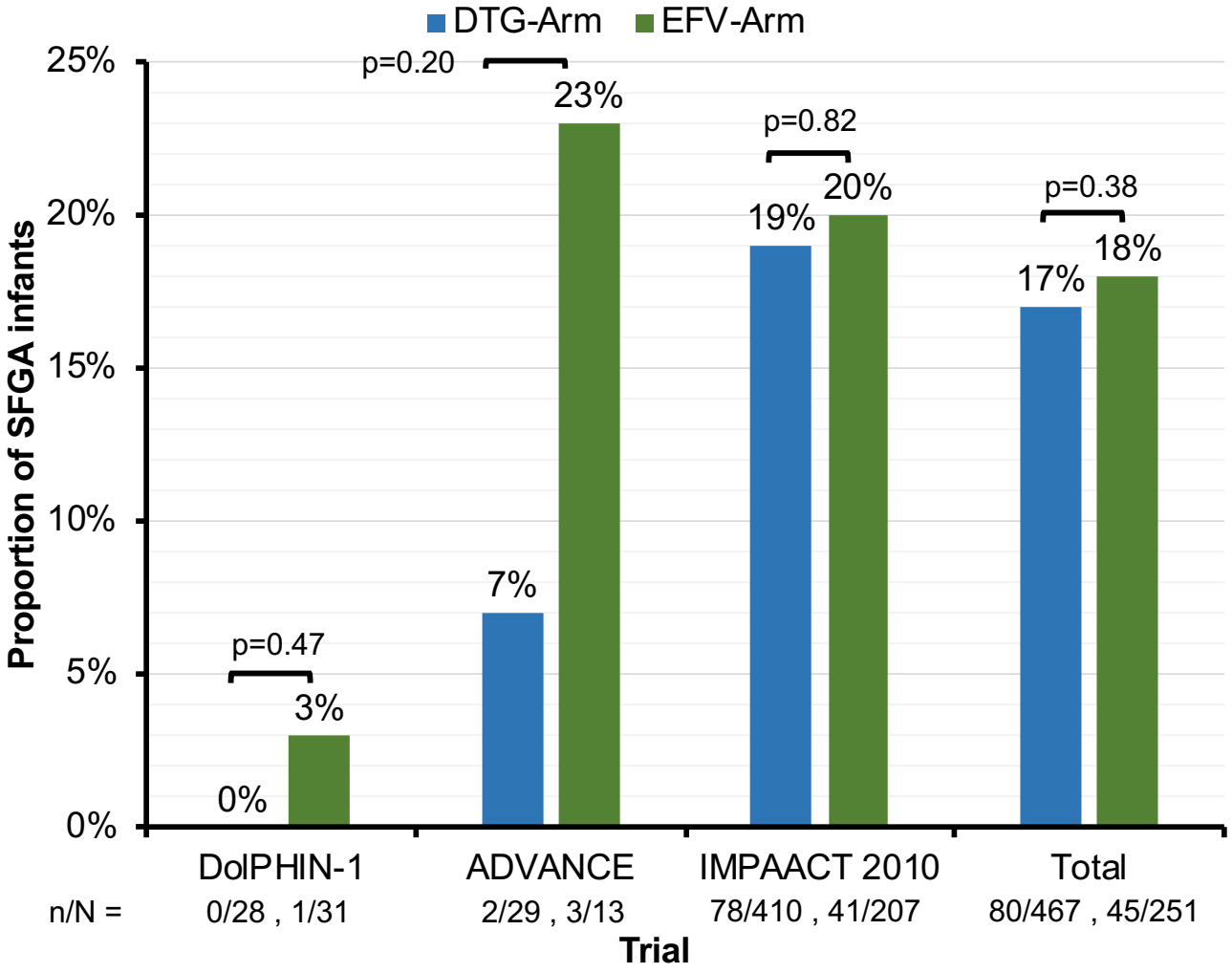
Preterm births



- 4% higher absolute risk of preterm births with EFV

Trial	DTG-Arm (n/N)	EFV-Arm (n/N)
DolPHIN-1	0/29 (0%)	2/31 (6%)
DolPHIN-2	21/124 (17%)	19/120 (16%)
ADVANCE	0/51 (0%)	1/30 (3%)
IMPAACT 2010	31/429 (7%)	25/211 (12%)
Total	**52/633 (8%)**	**47/392 (12%)**

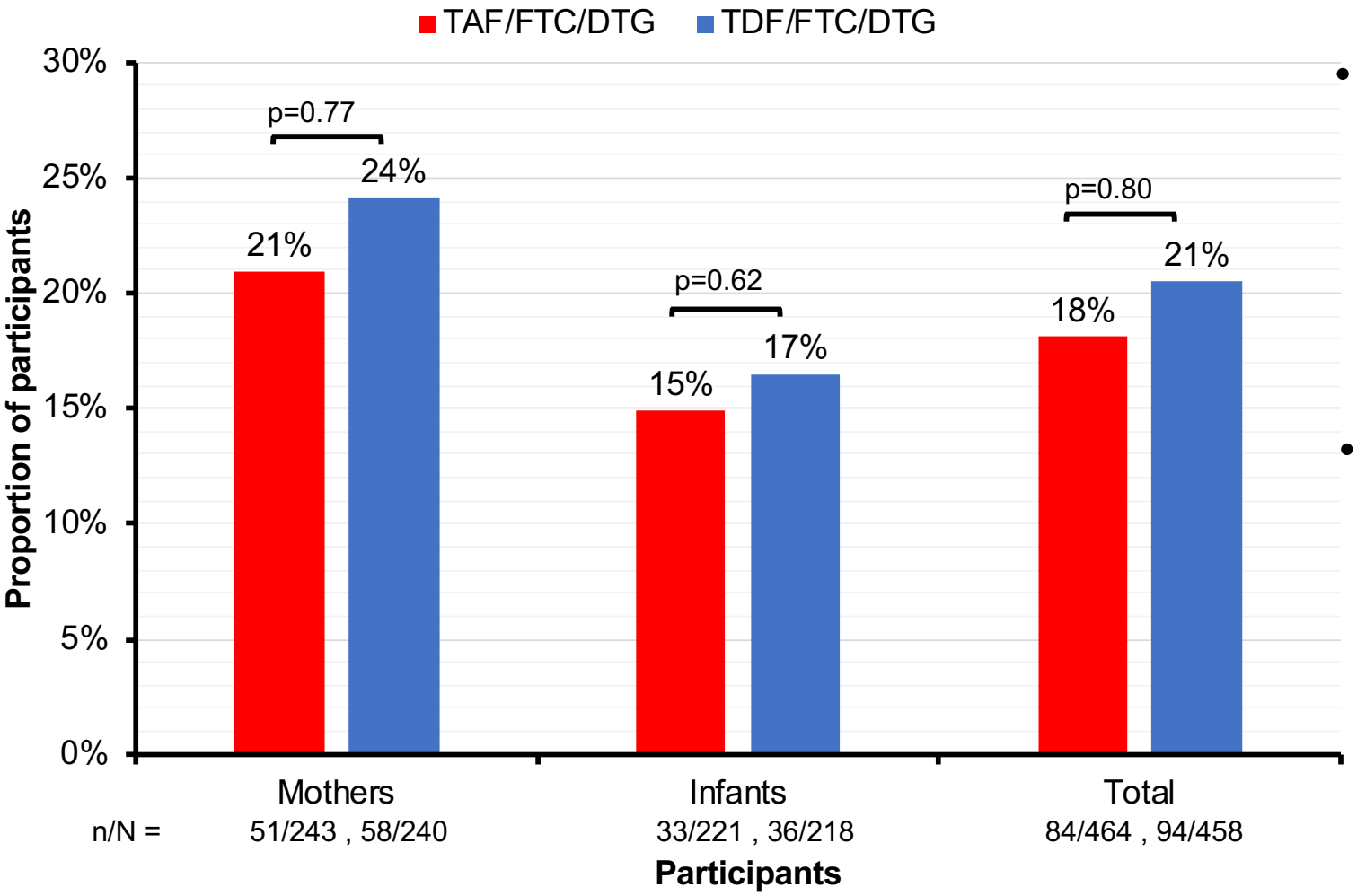
SFGA Infants



Trial	DTG-Arm (n/N)	EFV-Arm (n/N)
DolPHIN-1	0/28 (0%)	1/31 (3%)
ADVANCE	2/29 (7%)	3/13 (23%)
IMPAACT 2010	78/410 (19%)	41/207 (20%)
Total	**80/467 (17%)**	**45/251 (18%)**

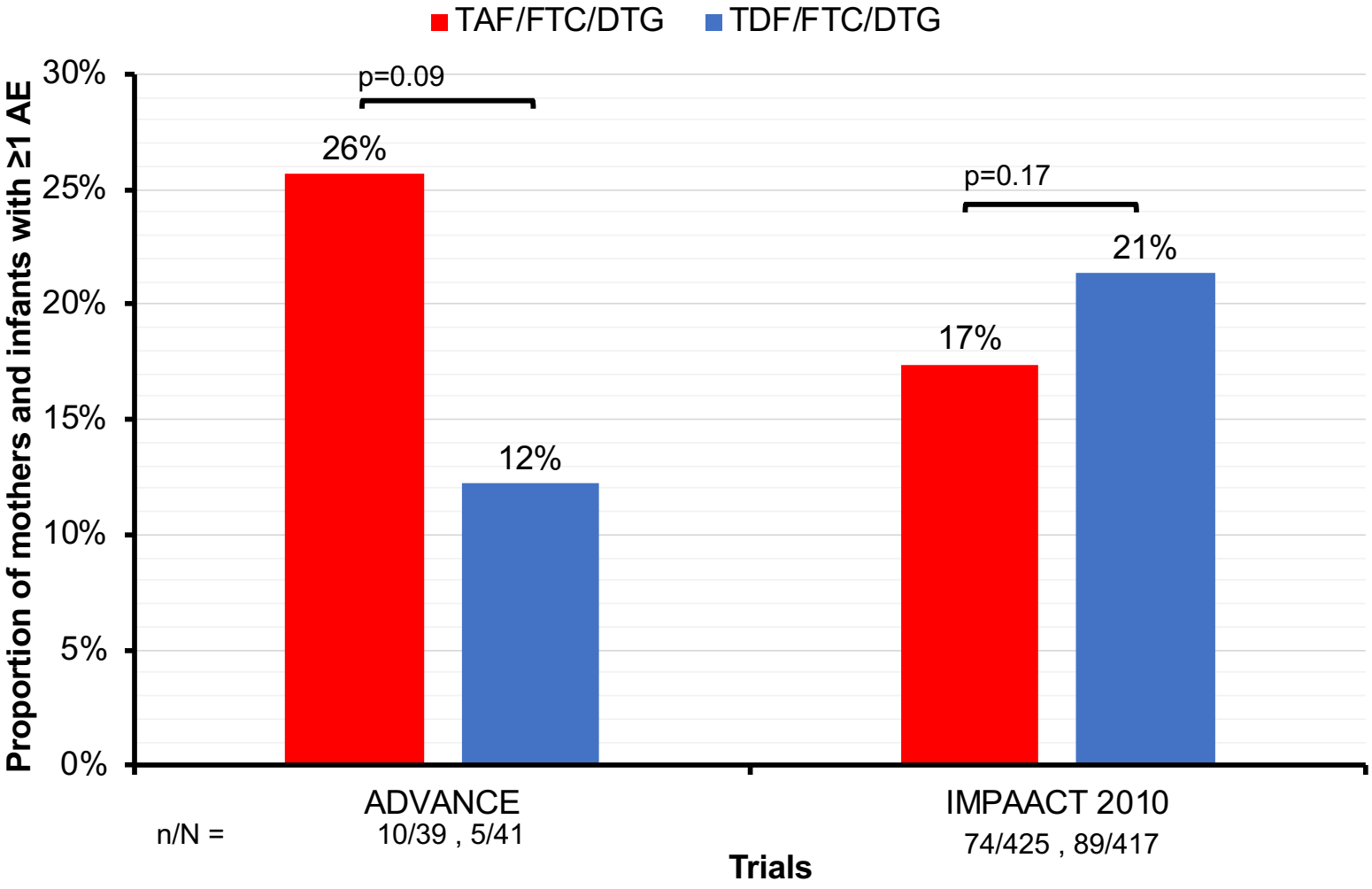
*N-number of live infants

Adverse Events: TAF/FTC/]+DTG vs TDF/FTC+DTG



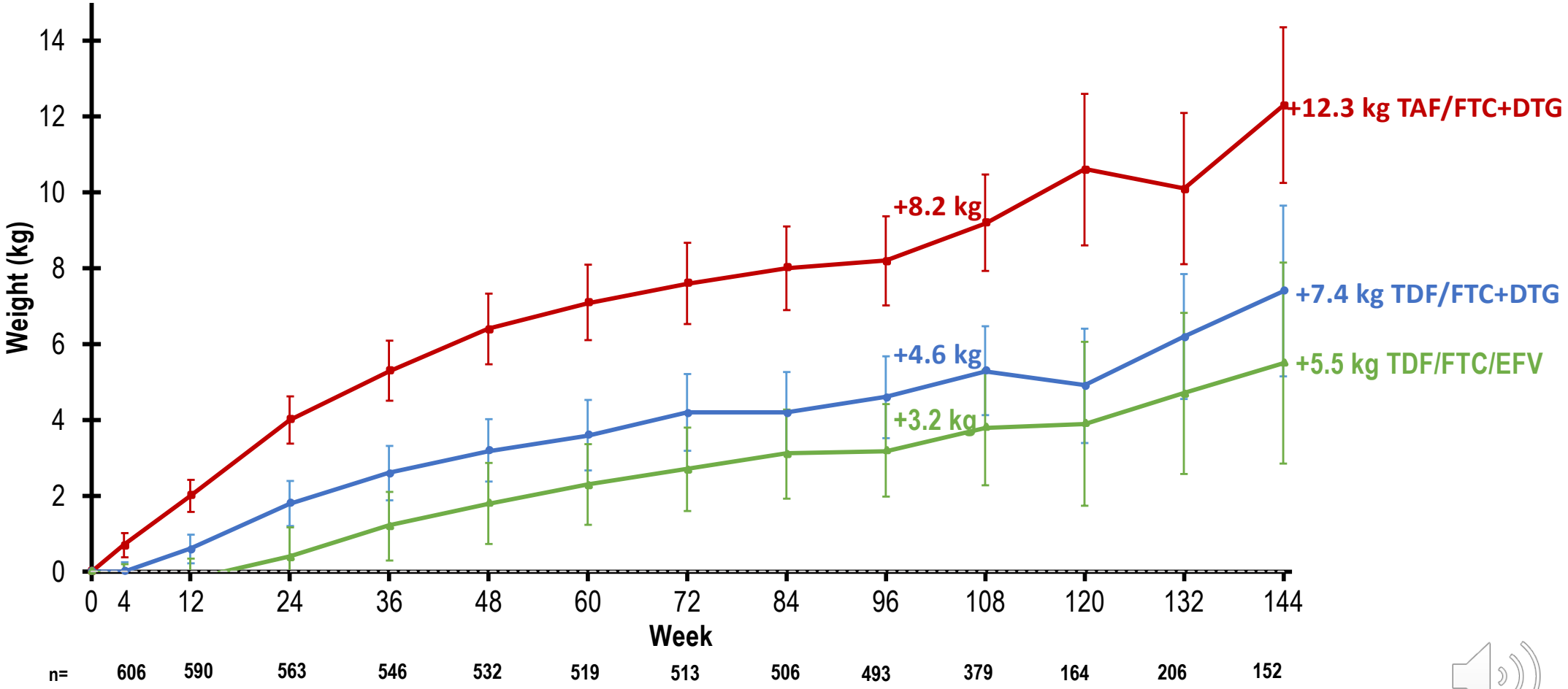
- ADVANCE and IMPAACT 2010 had two DTG-based treatment arms:
  TAF/FTC+DTG
  TDF/FTC+DTG
- No statistically significant difference for mothers and infants experiencing ≥1 adverse event

Adverse Events: TAF/FTC/DTG vs TDF/FTC/DTG



- Trend of more mothers and infants with ≥1 adverse with TDF/FTC+DTG in IMPAACT 2010
- Trend of more mothers and infants with ≥1 adverse with TAF/FTC+DTG in ADVANCE
- Overall no significant difference between the treatments

ADVANCE Trial: Mean change in weight (kg) to Week 96: Women



Implications + Limitations

- The safety profile of dolutegravir and efavirenz are similar in the results of this meta-analysis
- However, these results only illustrate the short-term effects of dolutegravir and TAF/FTC
- Pregnant women in these trials received antiretroviral treatment for a short duration with a limited long-term follow-up
- In reality, most women are likely to become pregnant after receiving antiretroviral treatment for years
- Future assessment is needed (studies, observational cohorts) on the long-term safety profile of dolutegravir due to its association with weight gain – being noticeably higher in black females
- There are concerns regarding the dolutegravir-associated weight gain possibly increasing the risk of obesity-associated adverse birth outcomes in its users

Conclusion

Efficacy:

- Dolutegravir was associated with greater virologic suppression than efavirenz
- As dolutegravir had significantly superior viral efficacy, it was unexpected to find five MTCT cases with dolutegravir versus none with efavirenz

Safety

- There were marginal differences between the treatment safety of dolutegravir and efavirenz
- The number of mothers and infants experiencing ≥1 adverse event was similar
- There was a trend for more stillbirths with dolutegravir but more preterm births with efavirenz
- There was no significant difference between the safety of TAF/FTC/DTG and TDF/FTC/DTG

Thanks to:

Study participants in each of the trials
Andrew Hill and his team