

Safety and Efficacy of DTG vs EFV and TDF vs TAF in Pregnancy: IMPAACT 2010 TRIAL

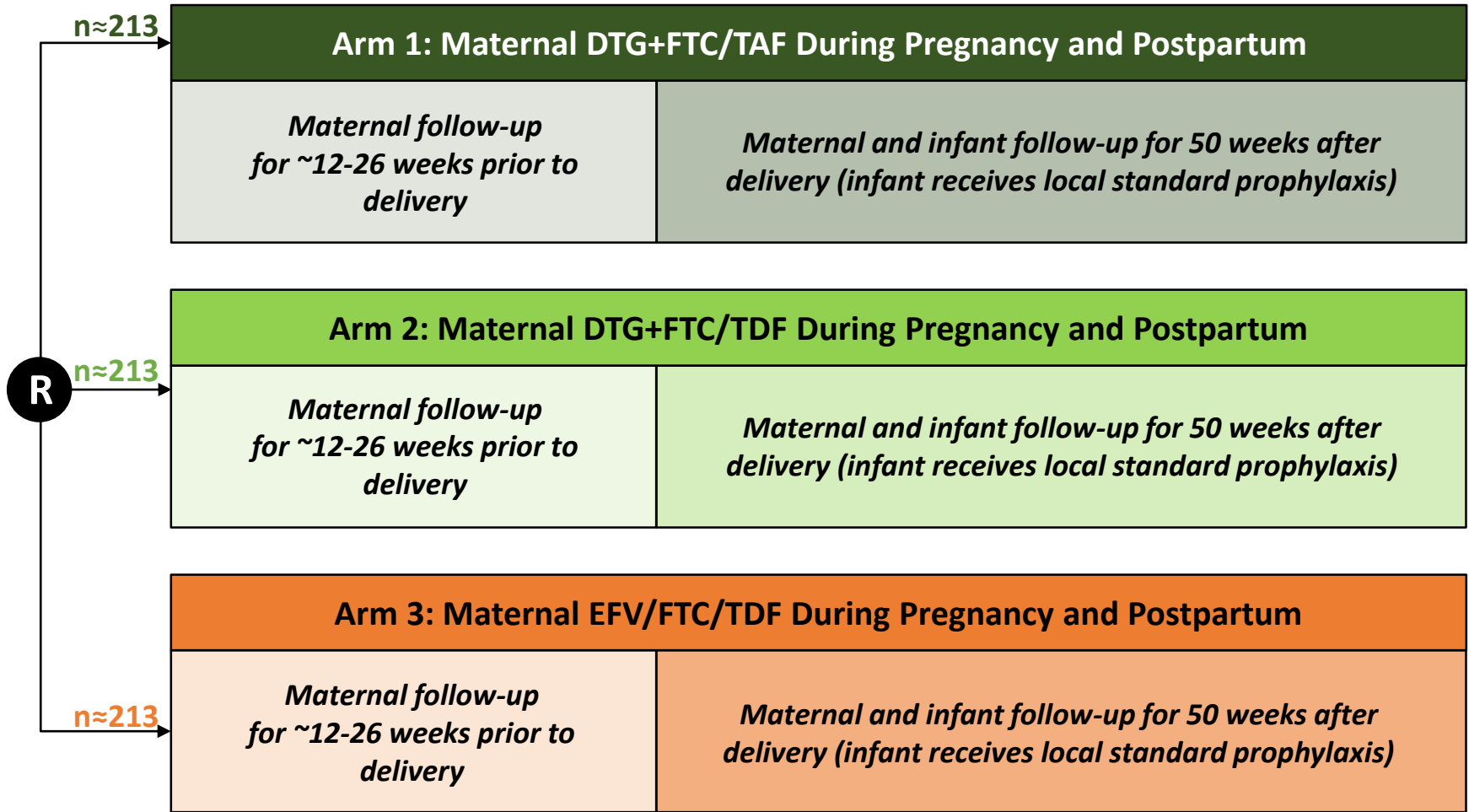
L Chinula, SS Brummel, L Ziemba, L Stranix-Chibanda, A Coletti, C Krotje,
P Jean-Philippe, L Fairlie, T Vhembo, D Wabwire, RM Hoffman, PE Sax,
JS Stringer, JS Currier, S Lockman, on behalf of the IMPAACT 2010 Study Team



Background and Rationale

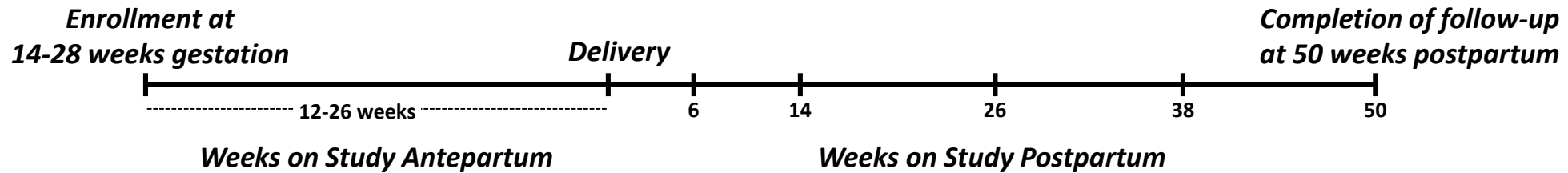
- WHO now recommends dolutegravir (DTG)-based antiretroviral treatment (ART) globally, given favorable efficacy, toxicity, resistance, and cost profiles
- Countries are transitioning from efavirenz (EFV)- to DTG-based first-line ART
 - Tenofovir alafenamide fumarate (TAF) is a recommended first-line agent for adults in the US
- ***It is essential to obtain pregnancy safety and efficacy data for agents that are expected to be widely used by women during pregnancy, such as DTG and TAF***
- We designed a Phase III, three-arm randomized open-label trial to compare the safety and virologic efficacy of three regimens started by women living with HIV (WLHIV) during pregnancy

IMPAACT 2010 Study Design



- Key Eligibility Criteria**
- Pregnant WLHIV 14-28 weeks gestation
 - ART-naïve (up to 14 days ART in current pregnancy allowed)

Participants were enrolled at 22 sites in 9 countries



Study Objectives: Virologic Efficacy

Whether treatment initiated during pregnancy with a **DTG-containing regimen (DTG arms combined)** is non-inferior to **EFV/FTC/TDF** with regard to HIV-1 RNA <200 copies/mL at delivery (primary)

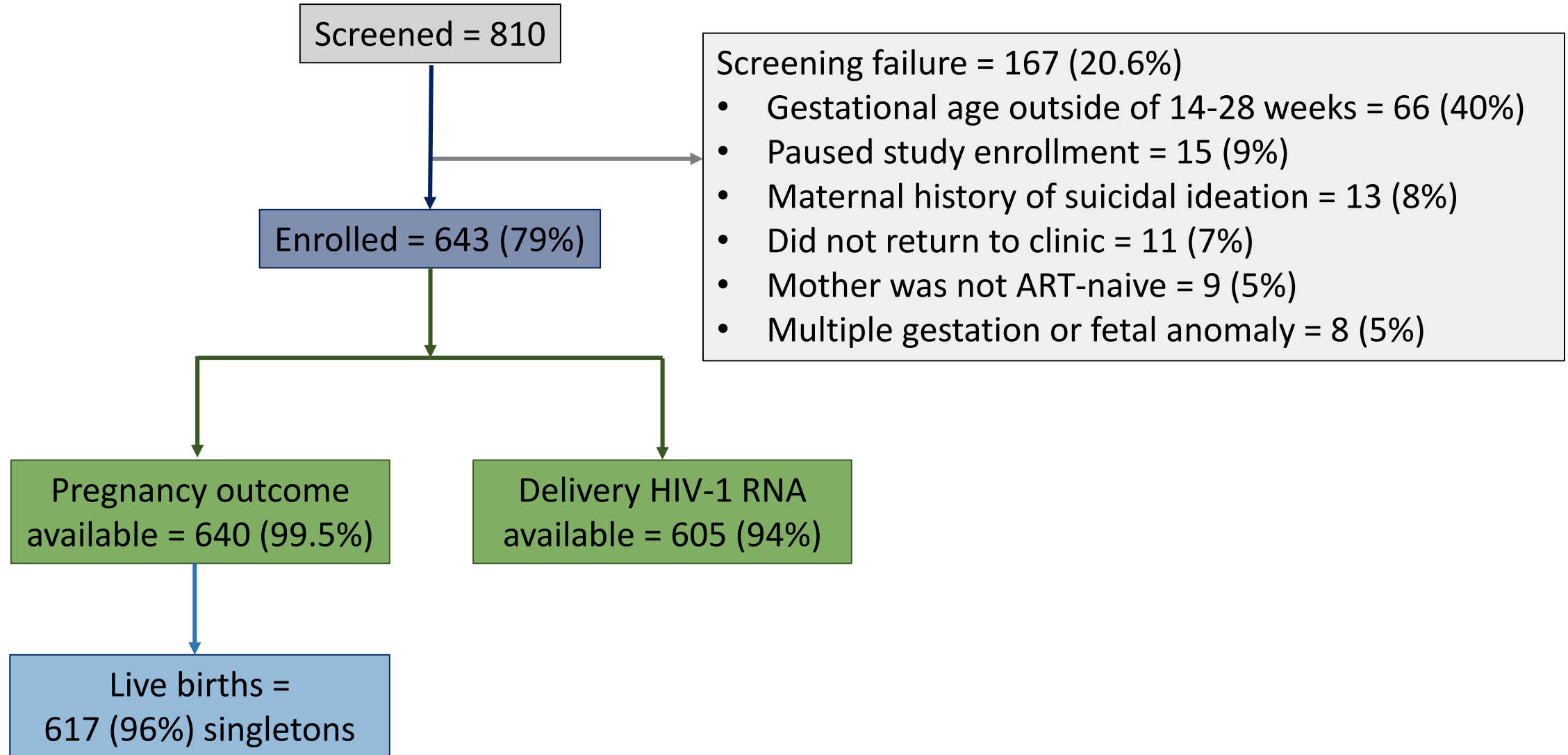
- -10% non-inferiority margin in favor of EFV for virologic efficacy
- Assessed superiority after establishing non-inferiority

Study Objectives: Safety

Whether rates of the following outcomes differ for any pairwise regimen comparison:

- **Adverse pregnancy composite outcome** (primary): occurrence of preterm delivery (PTD) <37 weeks, small for gestational age (SGA) <10th centile, stillbirth (SB) \geq 20 weeks, or spontaneous abortion (SAB) <20 weeks
- **Maternal grade 3 or higher adverse events** through 50 weeks postpartum (*this analysis includes follow-up through 14 days postpartum*)
- **Infant grade 3 or higher adverse events** through 50 weeks postpartum (*this analysis includes follow-up through 28 days after birth*)
- **Infant neonatal death** (\leq 28 days) (*post-hoc*)

Enrollment and Retention



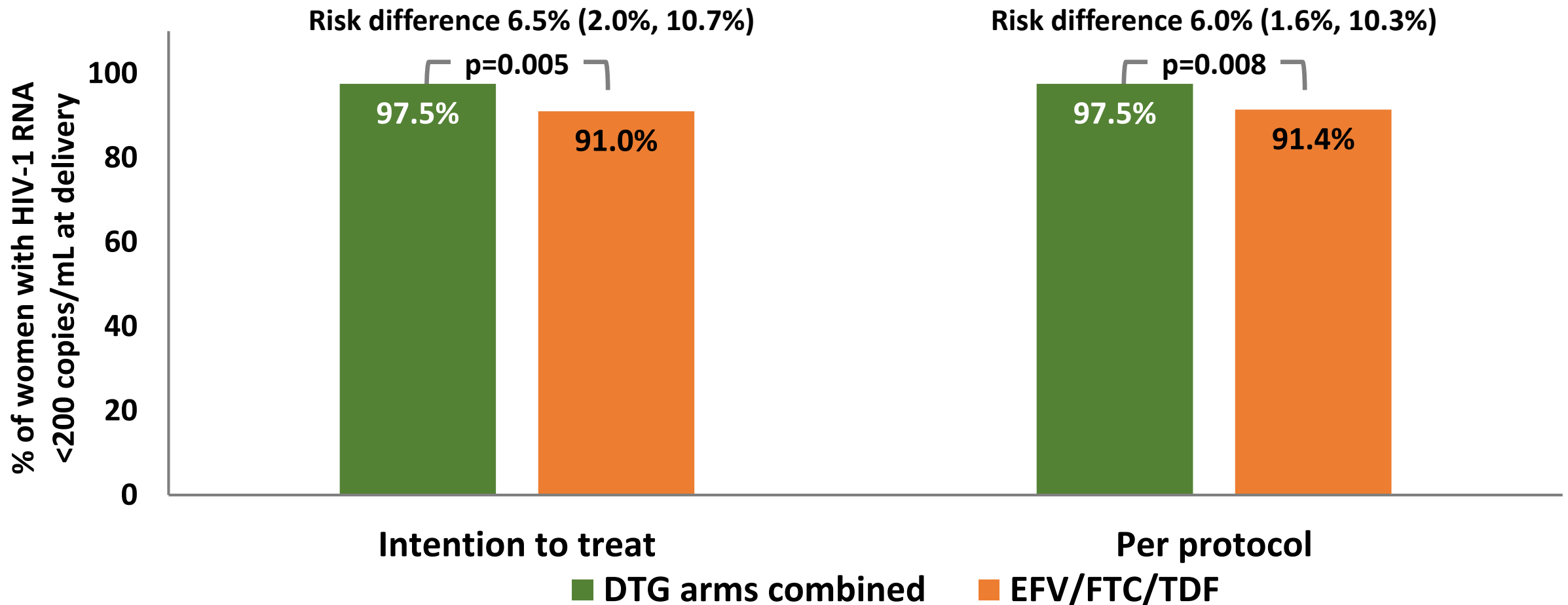
Maternal Baseline Characteristics

	DTG+FTC/TAF (N = 217)	DTG+FTC/TDF (N = 215)	EFV/FTC/TDF (N = 211)	Total (N = 643)
Age (median years)	26.8	26.0	26.6	26.6
Enrolled in Africa	187 (86%)	189 (88%)	188 (89%)	564 (88%)
Gestational age (median weeks)	22.1	21.3	22.1	21.9
CD4 count (median cells/mm³)	467	481	439	466
HIV-1 RNA (median copies/mL)	781	715	1357	903
HIV-1 RNA <50	36 (17%)	37 (17%)	27 (13%)	100 (16%)
ART in pregnancy prior to entry	176 (81%)	180 (84%)	176 (83%)	532 (83%)
Median days on ART	6	6	6	6

Median duration of antepartum follow-up: 17.4 weeks

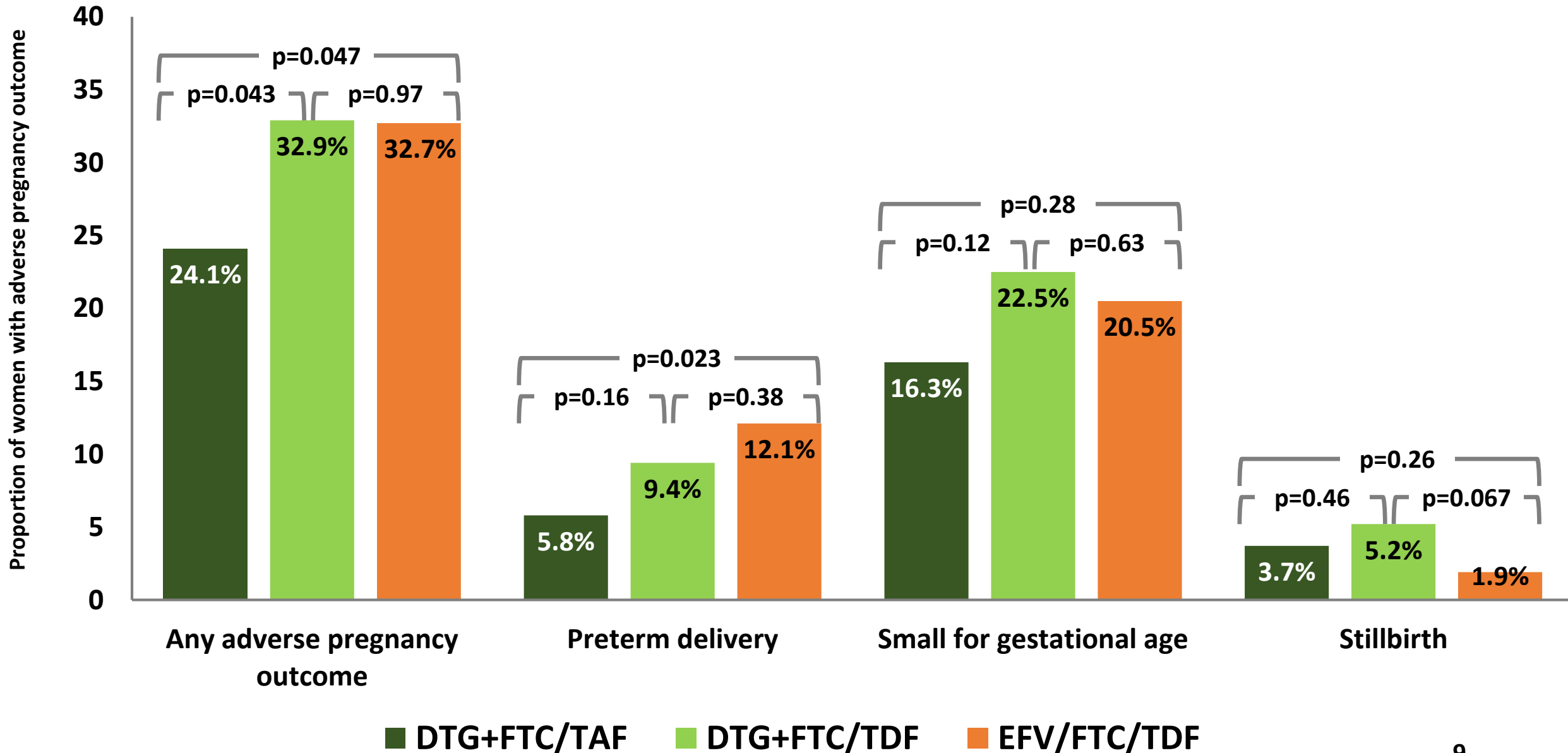
Virologic Suppression at Delivery was Significantly Higher in the DTG Arms Compared with EFV Arm

Proportion of women with HIV-1 RNA <200 copies/mL at delivery visit:
Combined DTG-ART arms vs EFV/FTC/TDF arm



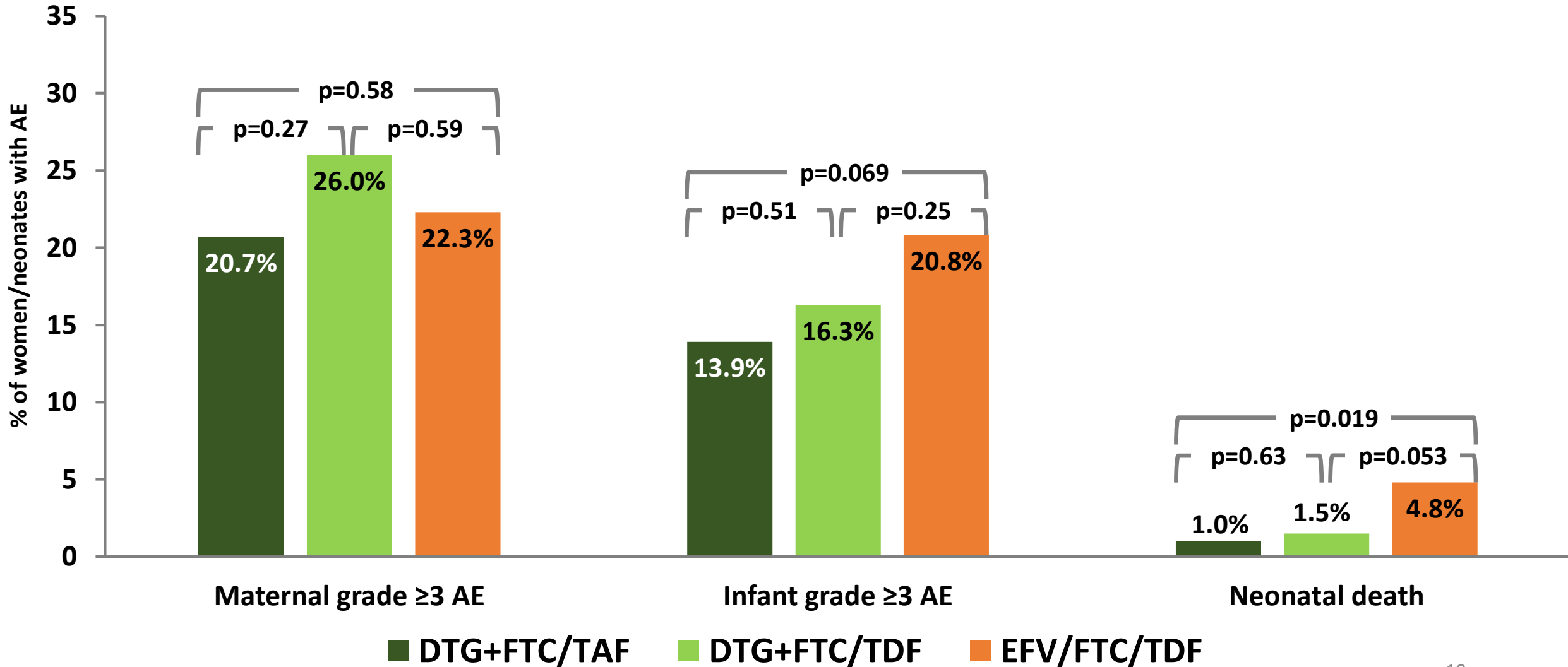
DTG arms had shorter time to viral suppression: log-rank p-value <0.001

Adverse Pregnancy Outcomes by Arm

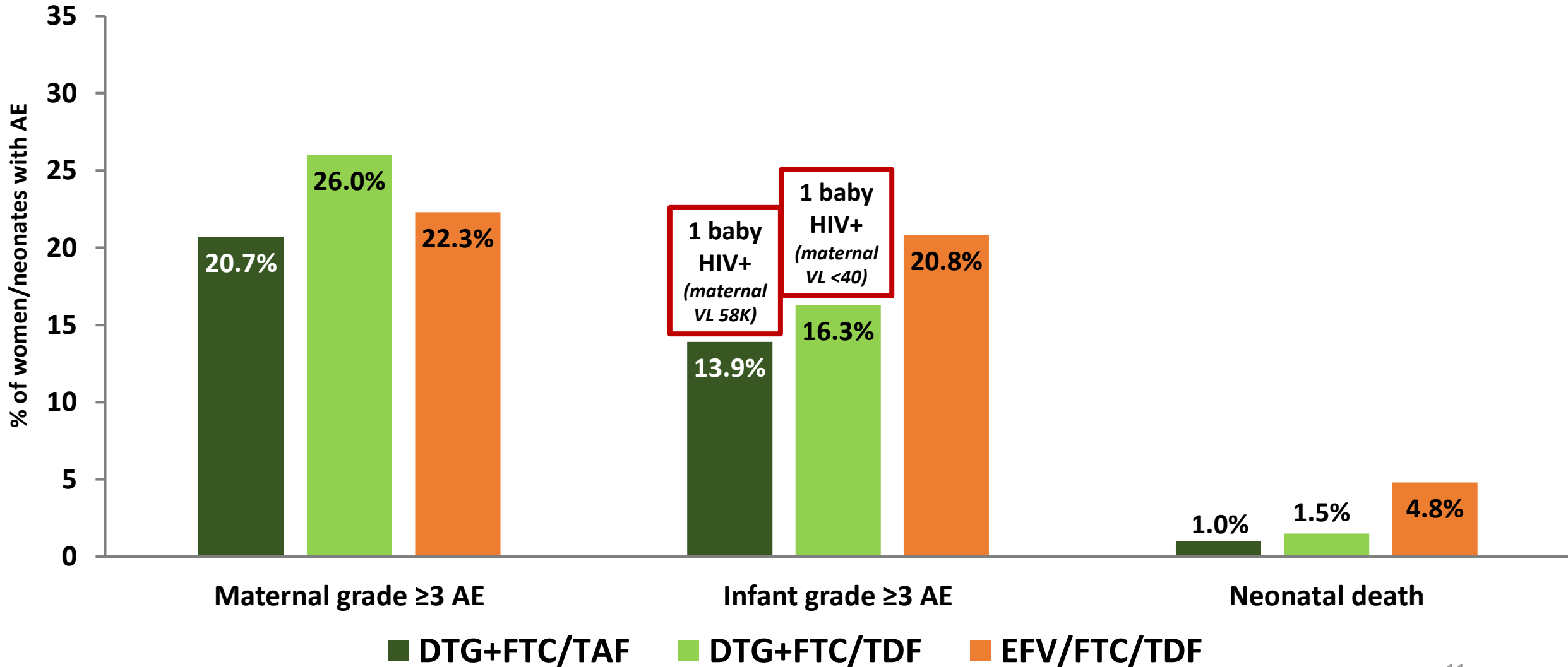


Notes: stillbirth was post-hoc analysis; and no spontaneous abortions occurred

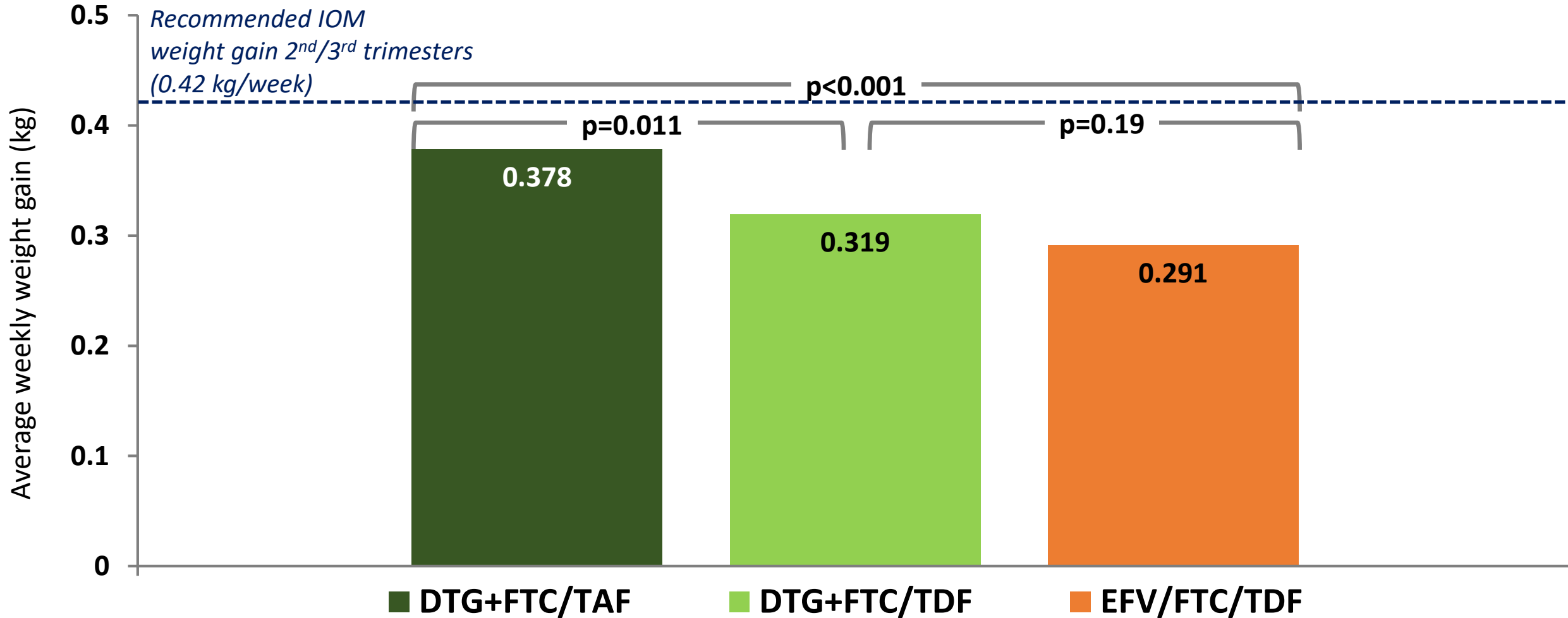
Maternal and Infant Grade 3 or Higher Adverse Events by Arm



Maternal and Infant Grade 3 or Higher Adverse Events by Arm



Average Weekly Maternal Weight Gain by Arm



Conclusions

- All three study regimens showed high efficacy, and safety that was similar to or better than that observed in other studies of ART in pregnancy
- DTG-containing ART had superior virologic efficacy at delivery compared to EFV/FTC/TDF
- DTG+FTC/TAF was associated with significantly fewer adverse pregnancy outcomes (driven by lower preterm and SGA rates) and fewer neonatal deaths than EFV/FTC/TDF
- Results affirm the WHO recommendation to use DTG in all populations, including during pregnancy, and showed that TAF may be preferable to TDF in pregnancy

Acknowledgements

The IMPAACT 2010/VESTED Protocol Team gratefully acknowledges the dedication and commitment of the 643 mother-infant pairs, their communities, and CAB representatives, without whom this study would not have been possible.

Sponsors:

US National Institutes of Health (Patrick Jean-Philippe, Renee Browning, Lynette Purdue, Nahida Chakhtoura)
Gilead Sciences, Mylan, ViiV Healthcare Ltd

Protocol Co-Chairs: Shahin Lockman and Lameck Chinula

Operations Center: Anne Coletti and Katie McCarthy

Statistical and Data Management Center: Sean Brummel, Lauren Ziemba, Benjamin Johnson, Chelsea Krotje, Kevin Knowles, Kyle Whitson

Laboratory Center: Frances Whalen, William Murtaugh, Sikhulile Moyo

Protocol Team Investigators: Rivet Amico, Judith Currier, Lee Fairlie, Lisa Frenkel, Risa Hoffman, Lew Holmes, Gaerolwe Masheto, Mark Mirochnick, Jeremiah Momper, Chelsea Morroni, Paul Sax, Roger Shapiro, Lynda Stranix-Chibanda, Jeffrey Stringer

Community: Nagawa Jaliaah, Cheryl Blanchette

Site Investigators of Record:

Botswana: *Gaborone and Molepolole:* Gaerolwe Masheto

Brazil: *Inst de Puericultura e Pediatria Martagao Gesteira:*

Elizabeth Machado; *Hosp Fed dos Servidores do Estado:*

Esau João; *SOM Fed Univ Minas Gerais:* Jorge Pinto; *Hosp Geral de Nova Iguacu:* Jose Pilotto

India: *BJMC:* Pradeep Sambarey

South Africa: *Umlazi:* Sherika Hanley; *FAMCRU:* Gerhard Theron;

Soweto: Haseena Cassim; *Wits RHI Shandukani:* Lee Fairlie

Tanzania: *KCMC:* James Ngocho

Thailand: *Siriraj:* Kulkanya Chokephaibulkit; *Chiang Rai:* Jullapong Achalapong; *Chiang Mai Univ:* Linda Aurbul

Uganda: *MUJHU:* Deo Wabwire; *Baylor-Uganda:* Violet Korutaro

United States: *Univ Miami:* Gwendolyn Scott; *Univ FI Jacksonville:* Mobeen Rathore

Zimbabwe: *St. Mary's:* Patricia Mandima; *Seke North:* Lynda Stranix-Chibanda; *Harare Family Care:* Tichaona Vhembo



Acknowledgements

IMPAACT 2010/VESTED is funded by the US National Institutes of Health (NIH).

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

The study products were provided by ViiV Healthcare Ltd, Gilead Sciences, Mylan.

