

CROI 2020 Review: Antiretroviral Therapy Safety and Side Effects

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Disclosures

No conflicts of interests or relationships to disclose.

Outline

- IMPAACT 2010: DTG + FTC/TAF During Pregnancy
 - ADVANCE: EFV Metabolism and Weight Gain
 - ADVANCE: CVD and Diabetes with EFV vs. DTG
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- GEMINI1/2: DTG/3TC Initial ART Update
- ATLAS-2M/FLAIR: Long-acting CAB + RPV Update
- G6207 and other long-acting ARV's in development

IMPAACT 2010: DTG + FTC/TAF or FTC/TDF vs EFV/FTC/TDF During Pregnancy

DTG + FTC/TAF or FTC/TDF vs EFV/FTC/TDF During Pregnancy

IMPAACT 2010: Background

Study Design: IMPAACT 2010

- **Background:**
 - Randomized, open-label, international, phase III noninferiority trial (22 sites in 9 countries)
- **Enrollment Criteria:**
 - ART-naïve pregnant adults (<14 days ART during pregnancy permitted)
 - 14-28 weeks gestation
- **Endpoints:**
 - Primary: delivery HIV RNA <200 copies/mL
 - Secondary: adverse pregnancy outcomes, maternal and fetal adverse effects

DTG + FTC/TAF
n = 217

DTG + FTC/TDF
n = 215

EFV/FTC/TDF
n = 211

DTG + FTC/TAF or FTC/TDF vs EFV/FTC/TDF During Pregnancy

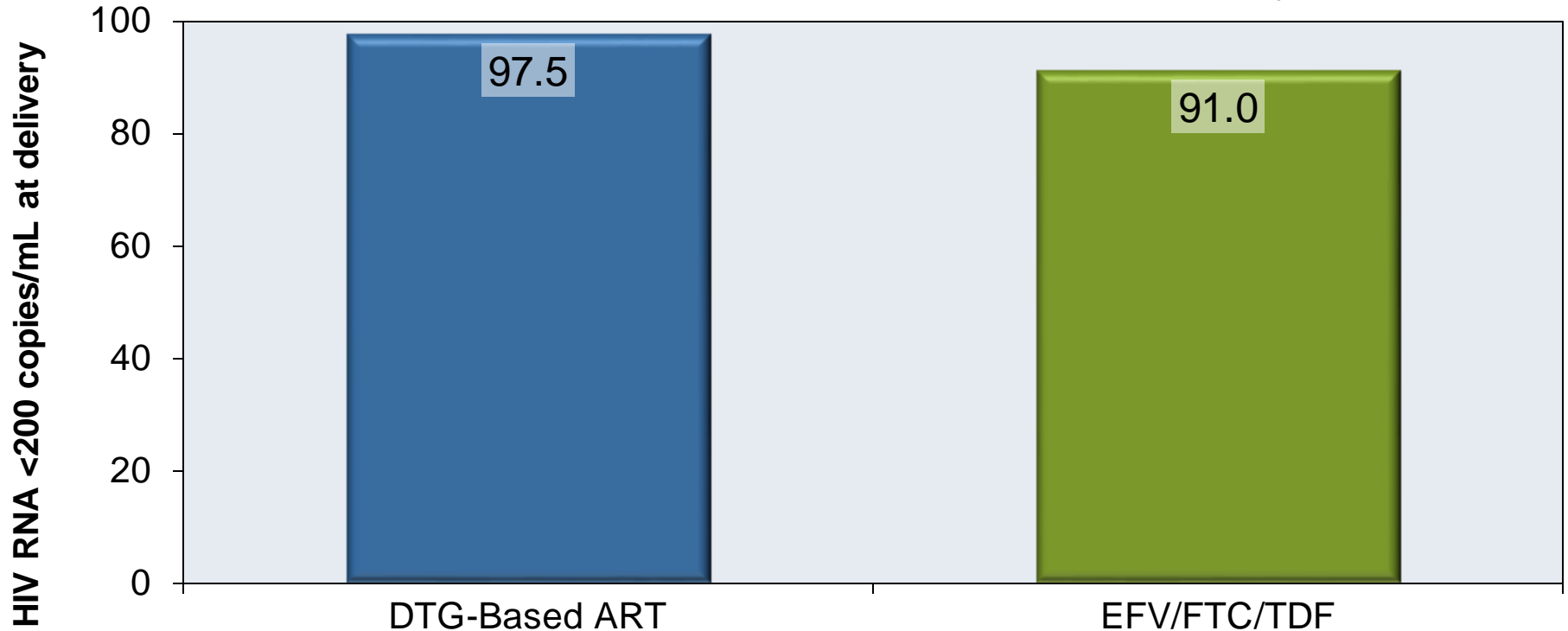
IMPAACT 2010: Baseline Characteristics

IMPAACT 2010: Baseline Characteristics			
Characteristic	DTG + FTC/TAF (n = 217)	DTG + FTC/TDF (n = 215)	EFV/FTC/TDF (n=211)
Age, years, median	26.8	26.0	26.6
Enrolled in Africa, n, %	187 (86)	189 (88)	188 (89)
Median gestational age, weeks	22.1	21.3	22.1
Median CD4 count, cells/mm ³	467	481	439
Median HIV RNA, copies/mL	781	715	1,357
HIV RNA <50 copies/mL, n, %	36 (17%)	37 (17%)	27 (13%)
ART prior to entry, n, %	176 (81%)	180 (84%)	176 (83%)
Median time on ART, days	6	6	6

Median duration follow-up before delivery: 17.4 weeks

DTG + FTC/TAF or FTC/TDF vs EFV/FTC/TDF During Pregnancy IMPAACT 2010: Results

Proportion with HIV RNA <200 copies/mL at Delivery (ITT)



Virologic suppression at delivery superior with DTG ($p=0.005$)
Time to viral suppression also superior ($p=0.001$)

DTG + FTC/TAF or FTC/TDF vs EFV/FTC/TDF During Pregnancy

IMPAACT 2010: Results

IMPAACT 2010: Adverse Pregnancy Outcomes			
Adverse Outcomes, %	DTG + FTC/TAF (n = 217)	DTG + FTC/TDF (n = 215)	EFV/FTC/TDF (n=211)
Any adverse outcome	24.1	32.9	32.7
Preterm delivery	5.8	9.4	12.1
Small for gestational age	16.3	22.5	20.5
Stillbirth	3.7	5.2	1.9

Adverse pregnancy outcomes significantly less frequent with DTG + FTC/TAF vs DTG/FTC/TDF and EFV/FTC/TDF ($p < .05$)

Neonatal death significantly less frequent with DTG + FTC/TAF vs EFV/FTC/TDF ($p = .019$)

DTG + FTC/TAF or FTC/TDF vs EFV/FTC/TDF During Pregnancy

IMPAACT2010: Results

IMPAACT 2010: Maternal Weight Gain			
Maternal Weight Gain	DTG + FTC/TAF (n = 217)	DTG + FTC/TDF (n = 215)	EFV/FTC/TDF (n=211)
Average weekly weight gain, kg	0.378*	0.319	0.291

*More weight gain with DTG + FTC/TAF vs DTG + FTC/TDF (p=.011)
and vs EFV/FTC/TDF (p<.05) – clinical significance unknown

Investigator Conclusions

- For treatment-naive women initiating ART during pregnancy, VL suppression rate at delivery better with DTG-based ART vs EFV/FTC/TDF
- Adverse pregnancy outcomes less frequent with DTG + FTC/TAF vs DTG + FTC/TDF and EFV/FTC/TDF
- Maternal weekly weight gain greater with DTG + FTC/TAF vs DTG + FTC/TDF and EFV/FTC/TDF (significance unknown)
- *Overall, supports WHO rollout of DTG for all and suggests TAF may be preferred over TDF during pregnancy*

**ADVANCE: *CYP2B6* Genotype Associated
with Differential Weight Gain in ART-Naïve
Persons Initiating Efavirenz**

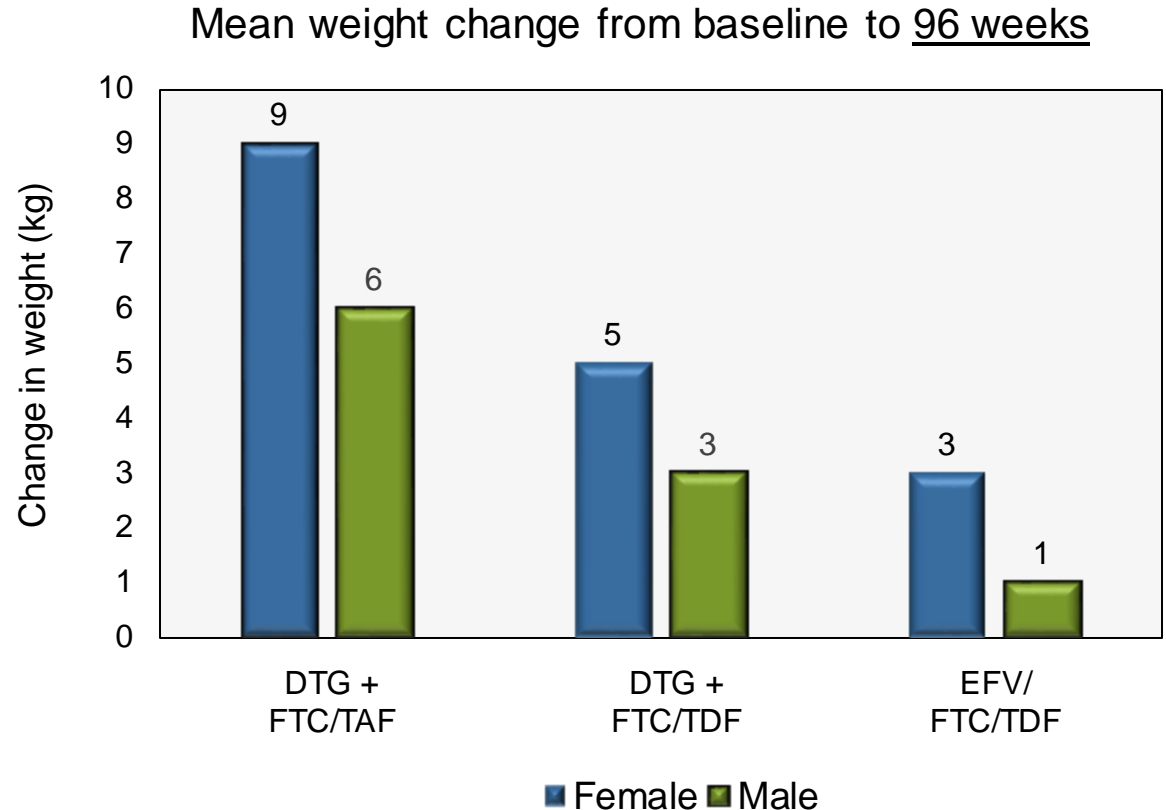
ADVANCE: *CYP2B6* Genotype Associated with Differential Weight Gain in ART-Naïve Persons Initiating Efavirenz (EFV)

- Prior RCTs in Africa (NAMSAL, ADVANCE) found treatment-emergent obesity more common with DTG vs EFV
- Loss of function SNPs in *CYP2B6* → higher EFV concentrations (slow metabolizers); ~20%-40% of African individuals
 - Prior study: more weight gain observed in *CYP2B6* slow metabolizers switching from EFV to INSTI-based ART
 - Maybe higher EFV means less lower weight before switch to INSTI? Due to mitochondria/adipocyte toxicity or impaired appetite?
- Current analysis: do loss of function SNPs in *CYP2B6* lead to lower weight/less weight gain in PWH who initiate EFV?

ADVANCE

Comparison of Three First-Line Regimens

- Phase 3 RCT in South Africa
- Initial ART:
DTG + FTC/TDF,
DTG + FTC/TAF,
EFV/FTC/TDF
- DTG arms non-inferior with fewer discontinuations;
TAF led to fewer bone/renal AE's



48-week data: Ventner WDF et al. NEJM, August 2019.

96-week data: McCann K et al. 17th EAC, Nov. 6-9, 2019, Basel. Abstract 3/3



ADVANCE: *CYP2B6* Genotype Associated with Differential Weight Gain in ART-Naïve Persons Initiating Efavirenz (EFV)

- Participants treated with EFV and consented to *CYP2B6* genotype: n = 171
 - 51 extensive metabolizers, 74 intermediate, 46 slow
- Patients treated with DTG + FTC/TDF: n = 351
- Measured weight and limb/trunk fat (by DXA) at week 48

ADVANCE: *CYP2B6* Genotype Associated with Differential Weight Gain in ART-Naïve Persons Initiating Efavirenz (EFV)

- EFV/FTC/TDF arm: % change in weight significantly lower in slow vs extensive metabolizers ($p = .004$)
 - No difference for intermediate vs extensive metabolizers
 - On average, slow metabolizers lost weight; intermediate metabolizers remained at baseline weight or gained little weight; and extensive metabolizers gained weight from baseline
- Both slow and intermediate metabolizers had significantly lower % change in weight vs DTG + FTC/TDF
- No significant difference in % change in weight for extensive metabolizers treated vs DTG + FTC/TDF

ADVANCE: *CYP2B6* Genotype Associated with Differential Weight Gain in ART-Naïve Persons Initiating Efavirenz (EFV)

- Conclusion/interpretation:
 - Perhaps one of the reasons some individuals gain significant weight with switch from EFV to DTG is they are slow EFV metabolizers and high EFV levels suppress weight gain in some way

ADVANCE: Risk of CVD and Diabetes with DTG or EFV-Based Initial ART

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- Median % change in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) significantly greater at 96 weeks with DTG + FTC/TAF vs either comparator
- Significantly greater rise in certain metabolic parameters:
 - Total cholesterol comparing DTG + FTC/TAF to comparators
 - LDL comparing DTG + FTC/TAF to DTG + FTC/TDF
 - HDL comparing DTG + FTC/TAF to EFV/FTC/TDF
 - Fasting glucose comparing DTG + FTC/TAF to EFV/FTC/TDF
 - Systolic BP comparing DTG + FTC/TAF to DTG + FTC/TDF

ADVANCE: Risk of CVD and Diabetes with DTG or EFV-Based Initial ART

ADVANCE: 96-Week Metabolic Syndrome, CVD, and Diabetes Risk			
Outcome	DTG + FTC/TAF	DTG + FTC/TDF	EFV/ FTC/TDF
Metabolic syndrome (% persons)			
Baseline	5	6	4
Week 96	8*	6	3
10-year estimated MI risk (Framingham, % risk)			
Baseline	2.37	2.53	2.24
Week 96	+0.43	+0.22	+0.28
10-year estimated DM risk (Qdiabetes, % risk)			
Baseline	0.3	0.4	0.3
Week 96	+0.9**	+0.5	+0.7**

*DTG +FTC/TAF greater than both comparators

**DTG +FTC/TAF greater than DTG +FTC/TDF, and EFV/FTC/TDF greater than DTG +FTC/TDF

Source: Hill et al. CROI 2020. Abstr 81.



ADVANCE: Risk of CVD and Diabetes with DTG or EFV-Based Initial ART

- DTG + FTC/TAF resulted in:
 - Greater increases in incident obesity, VAT/SAT, 10-year DM risk, and metabolic syndrome
 - No differences in risk of MI or coronary death by Framingham estimation
- Limitations:
 - Median age 31 years
 - Weight gain among women has not plateaued
 - Models do not account for weight gain after week 96

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