Pharmacokinetics of Dolutegravir After Switching to Abacavir/Dolutegravir/ Lamivudine From an Efavirenz-Based Regimen: A PK Sub-Study From STRIIVING

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Introduction

- Triumeq® (ABC/DTG/3TC) is the first single-tablet regimen that contains DTG and is tenofovir (TDF)–free
- Triumeq was approved in North America in August 2014 and in Europe in September 2014
- The STRIIVING study (NCT02105987) was conducted to evaluate the efficacy, safety, tolerability, and treatment satisfaction of switching to Triumeq in subjects stable and suppressed on a variety of regimens
- The study enrolled April 2014 to October 2014

de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

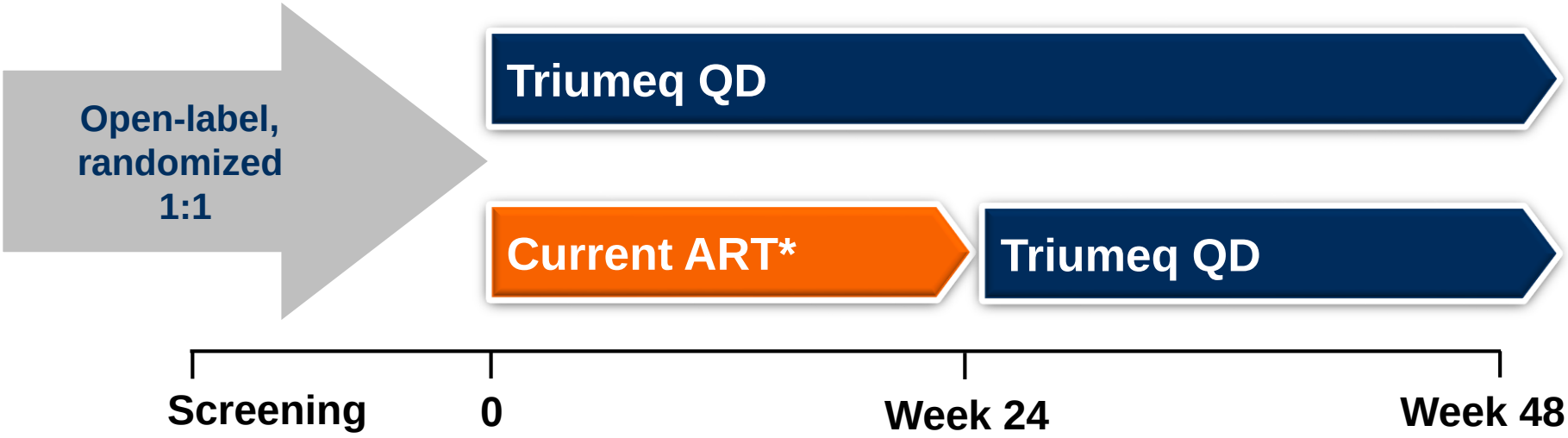
Introduction

- DTG is metabolized primarily by UGT1A1 and is a minor substrate for CYP3A4
- Co-administration of DTG 50 mg once daily with efavirenz (EFV), a CYP3A4 and UGT1A1 inducer, 600 mg once daily decreased DTG AUC and $C\tau$ by 57% and 75%, respectively,[1] necessitating BID dosing of DTG upon co-administration of EFV
- Generaux et al, in a SimCYP simulation, predicted there would be no time when both drugs would fall below target concentrations[2] and justified conducting the study post-EFV
- This sub-study of the STRIIVING study evaluated the duration of EFV induction effect on the PK properties of DTG when virologically suppressed patients were switched from an EFV-based regimen to a DTG-based regimen

1. Song et al. *Eur J Clin Pharmacol.* 2014;70:1173-1179. **2.** Generaux et al. Clin Pharm 2014; Washington, DC. Poster P_36.
de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

STRIIVING Study Design

Countries: US, Canada, Puerto Rico



Inclusion criteria

- Virologically suppressed (confirmed HIV-1 RNA <50 c/mL)
- HLA-B*5701 negative

Primary endpoint at 24 weeks: VL <50 c/mL (Snapshot)

Assessments

- CD4 cell count changes
- Clinical and laboratory safety
- Lipids, renal, bone, and cardiovascular changes
- Development of resistance
- Treatment satisfaction

*Stable suppressive current ART with 2 NRTIs plus either a PI, an NNRTI, or an INI. ≥40% PIs, at least 25% INIs.

90% power based on 10% non-inferiority margin (estimated response rate = 85%).

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PK Sub-Study Design

- 24 patients on an EFV-based regimen were enrolled in the PK sub-study
  - Early switchers (ES) were subjects randomized to switch to Triumeq and start treatment on Day 1
  - Late switchers (LS) were subjects randomized to continue their current regimen until Week 24 when they switched to Triumeq
- Blood samples for evaluation of DTG and EFV plasma PK were collected prior to the DTG dose on Day 1 and at Weeks 1, 2, 4, 8, and 24 (ES) and Weeks 24, 25, 26, 28, 32, and 48 (LS)
- DTG and EFV plasma concentrations were measured by validated LC/MS/MS methods with LOQ of 20 and 0.1 ng/mL, respectively

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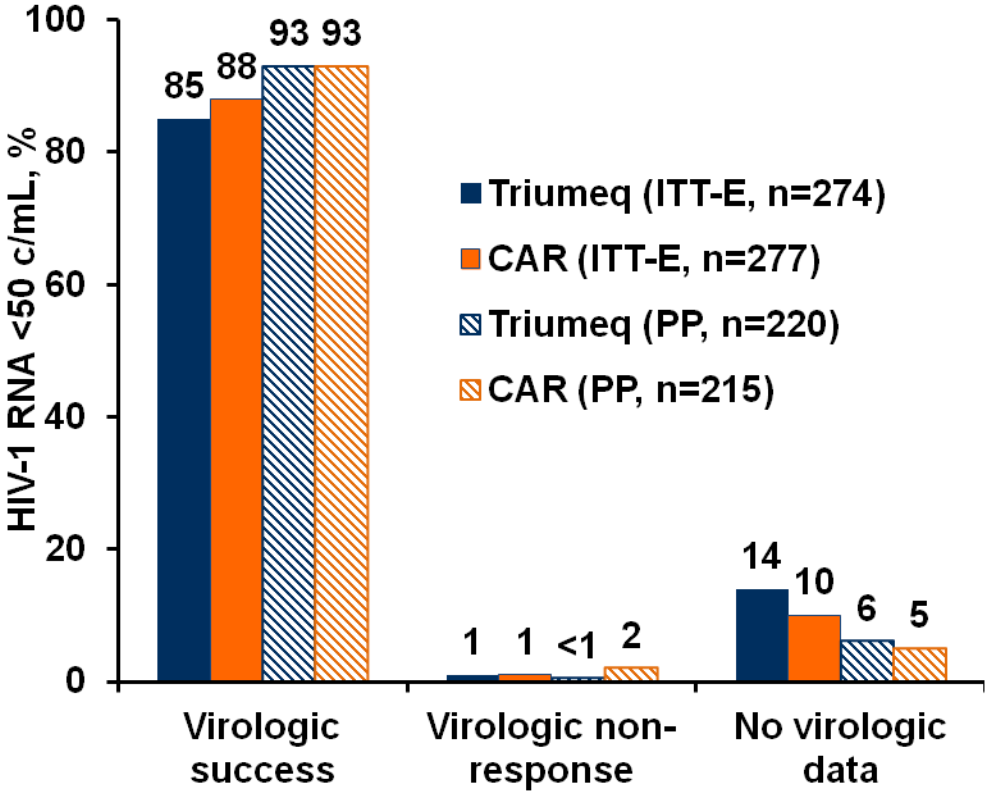
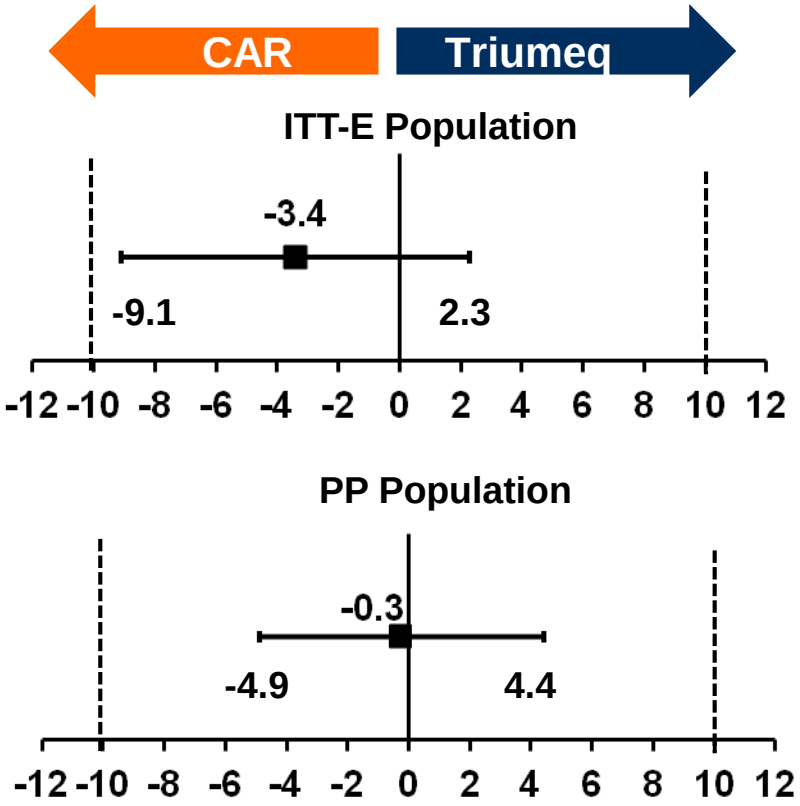
Overall Snapshot Outcomes at Week 24: ITT-E and PP Populations

Virologic outcomes



Treatment differences (95% CI)



CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

- Virologic suppression was maintained through Week 48 in the ES arm. The proportion of LS subjects with HIV-1 RNA <50 c/mL at Week 48 was comparable to the proportion at Week 24 for the ES arm*

*Full 48-week results to be presented at a conference later this year.

Trottier et al. ICAAC 2015; San Diego, CA.

de Wet et al. Clin Pharm 2016; Washington, DC. Abstract O_23.

PK Results

Time since switch	Visit, early switcher/ late switcher	Pre-dose DTG, ng/mL mean (SD)	Residual EFV, μg/mL mean (SD)
Day 0	Day 1/Week 24	– (n=0)	1.83 (0.66) (n=24)
Week 1	Week 1/Week 25	938.20 (955.21) (n=24)	0.32 (0.23) (n=21)
Week 2	Week 2/Week 26	860.52 (627.49) (n=27)	0.14 (0.09) (n=23)
Week 4	Week 4/Week 28	1219.33 (709.65) (n=24)	0.090 (0.00) (n=20)
Week 8	Week 8/Week 32	1186.17 (713.95) (n=15)	– (n=0)
Week 24	Week 24/Week 48	1378.23 (1017.98) (n=23)	– (n=0)

DTG, dolutegravir; EFV, efavirenz; PK, pharmacokinetic; SD, standard deviation.

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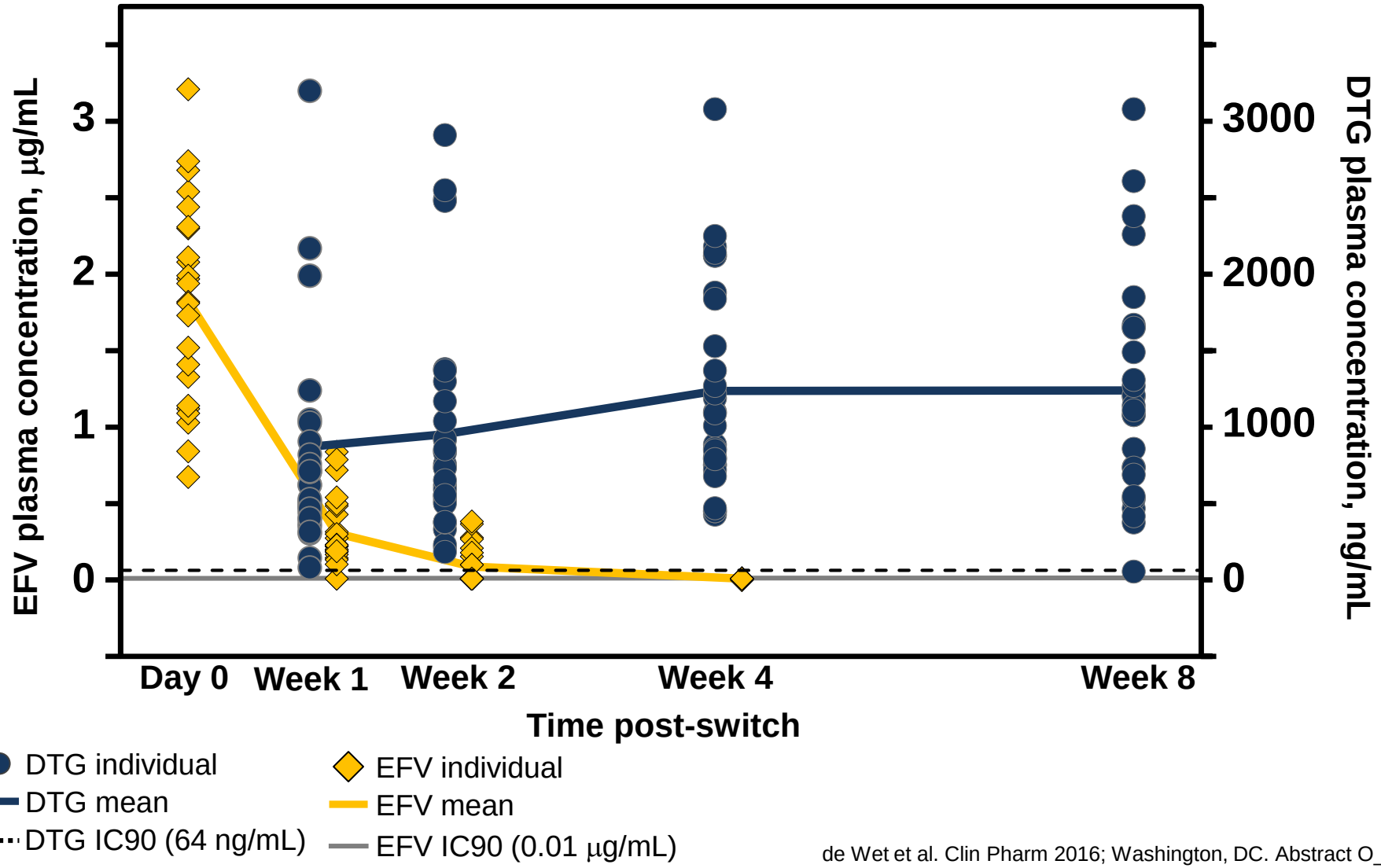
Pre-dose DTG and Residual EFV Plasma Concentration-Time Plot



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Maintenance of Viral Suppression

	HIV-1 RNA by subject, copies/mL																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Day 1	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 1	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 2	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 4	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 8	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50
Week 24	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50

Conclusions

- After switching to Triumeq, residual EFV plasma concentrations steadily decreased and DTG Cmin steadily increased reaching steady-state by 4 weeks post switch
- DTG mean concentrations were maintained above PA IC90 at all sample times and there was no time in the immediate post-switch period at which both EFV or DTG measured concentrations fell below their respective IC90 concentrations
- These PK data, along with the maintained virologic suppression, support switch to Triumeq from an EFV-containing regimen without need for DTG dosage adjustment

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  - PPD
  - The clinical investigators and their staffs

Canada

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