IMPAACT 2014 24-week PK and Safety of Doravirine/3TC/TDF in Adolescents with HIV-1

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Introduction

Background

- Doravirine (DOR) is a novel NNRTI approved for treatment in ARV-naïve or suppressed adults with HIV
- Pharmacokinetics of the 100mg single tablet DOR was previously confirmed in adolescents ages 12- <18 years and ≥ 45kg

Study Objective

- Evaluate the pharmacokinetics and 24-week safety and tolerability of a fixed dose combination tablet (FDC) with DOR (100mg)/3TC (300mg)/TDF(300mg)in adolescents living with HIV-1 infection

Methods

- Adolescents aged 12- <18 and weighing ≥ 45kg either virologically-suppressed on stable ART or ART-naive
- Open label trial of once daily FDC of DOR/3TC/TDF

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Results

Participants

- 43 virologically-suppressed and 2 ART-naïve
- Mean age15 yrs (12-17)
- Mean weight 53.8 kgs (45.1-79.8)
- 58% female
- 78% Asian, 22% Black

Study Sites

- Thailand
- South Africa
- United States

Safety

- 1 drug-related AE – grade 1 dizziness
- No drug-related SAEs
- 9 participants with Grade 3 AEs:
  - increased ALT (1)
  - increased creatinine with decreased eGFR (2)
  - decreased eGFR (1)
  - gastroenteritis (1)
  - diarrhea (1)
  - increased blood pressure (4)
- No grade 4 AEs
- No premature discontinuations due to AEs

Virologic efficacy

- 42/45 (93.3%; 95% CI 81.7,98.6) achieved or maintained HIV-1 RNA < 40 c/ml (FDA snapshot algorithm)

- 42/43 (97.7%; 95%CI 87.7,99.9) achieved or maintained HIV-1 RNA < 40 c/ml (observed failure approach)

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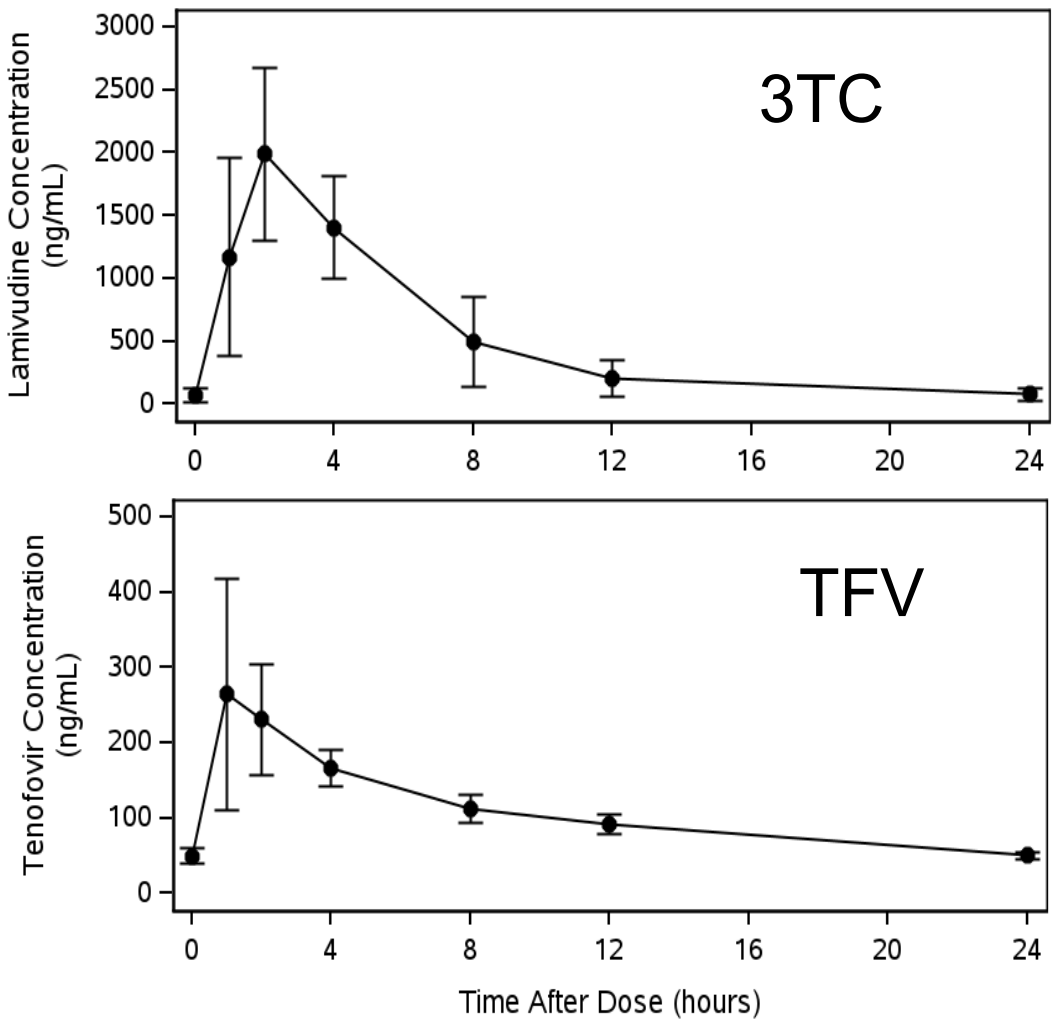
Arithmetic mean (SD) PK for 3TC and TFV at week 1, n=10



	Parameter	IMPAACT 2014 DOR/3TC/TDF Mean (SD)	Adult* 300 mg 3TC 300 mg TDF Mean (SD)
3TC	AUC (ng/mL hr)	11,700 (3310)	11,000 (1700)
	Cmax (ng/mL)	2160 (513)	2600 (500)
TFV	AUC (ng/mL hr)	2570 (362)	2290 (690)
	Cmax (ng/mL)	310 (114)	300 (90)

* Based on EPIVIR and VIREAD USPI

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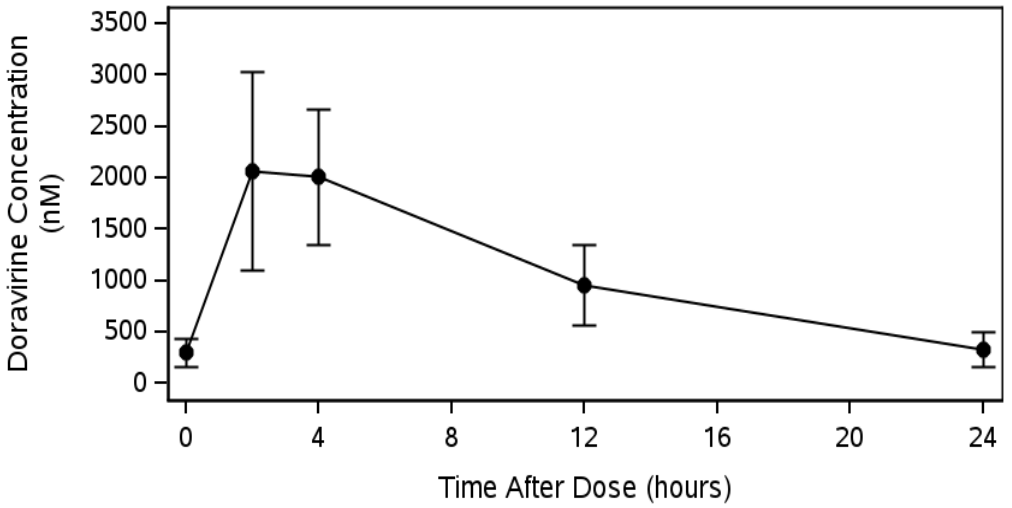
DOR PK at Week 1 to Week 24



Study Visit	DOR PK at Week 1 GM (%CV)	N	IMPAACT 2014 DOR/3TC/TDF	Adult* 100 mg QD
Week 1 (Semi-intensive)	AUC (uM hr)	10	22.9 (47%)	37.8 (29%)
	Cmax (uM)	10	2.13 (43%)	2.26 (19%)
	C24 (nM)	10	282 (74%)	930 (65%)
Week 4 (Sparse)	Pre-dose	45	747 (109%)	
Week 24 (Sparse)	Pre-dose	43	1090 (63%)	

* Yee KL, Ouerdani A, Claussen A, de Greef R, Wenning L. Population Pharmacokinetics of Doravirine and Exposure-Response Analysis in Individuals with HIV-1. Antimicrob Agents Chemother. 2019;63:e02502-18 GM-geometric mean; CV- coefficient of variance

- DOR PK at Week 1 were lower than steady-state values for 100 mg QD in adults
- 8/10 participants switched from efavirenz-based regimen, resulting in decreased DOR concentrations due to CYP3A induction
- By Week 4, DOR plasma concentrations approached adult steady-state levels for 100 mg QD

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Conclusions

- Doravirine when taken as an FDC of DOR/3TC/TDF by adolescents had excellent safety and tolerability
- Pharmacokinetics of doravirine in adolescents ages 12-<18 years and ≥45 kg was comparable to data reported in adults
- Overall virologic efficacy was comparable to data reported in adults
- Doravirine provides another alternative effective therapy for adolescents living with HIV

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