EFAVIRENZ PHARMACOKINETICS IN HIV/TB COINFECTED PERSONS INITIATING ART WHILE RECEIVING HIGH DOSE RIFAPENTINE

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On behalf of the TBTC S31 and ACTG A5349 Study Teams

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Disclosures

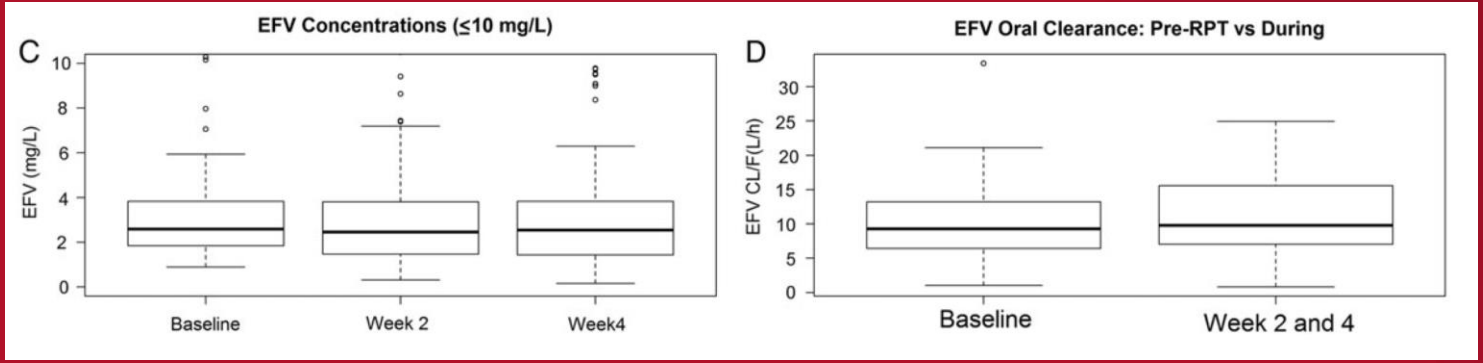
Anthony T. Podany has no financial relationships with commercial entities to disclose.

Pharmacology Background

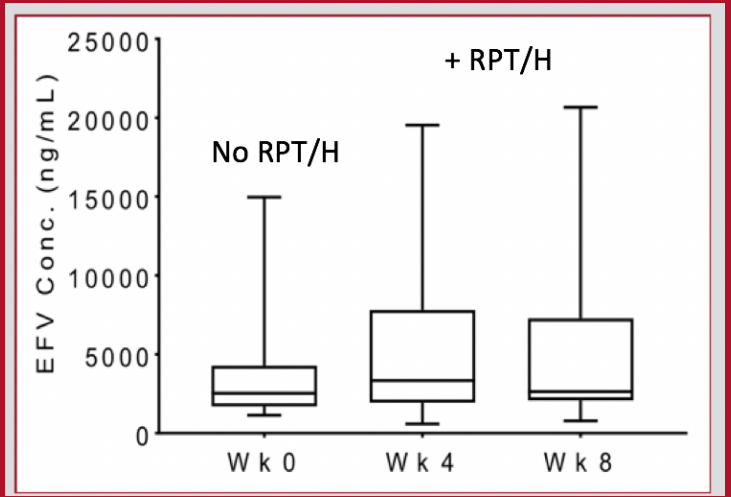
- Rifamycins Background:
  - all have phase 1 and 2 enzyme inducing properties
  - Rifapentine (RPT) a semisynthetic rifamycin derivative
    - Used in 3HP, 1HP and TB tx shortening
- Midazolam as a substrate
    - RPT reduced AUCs by >90%
    - RIF reduced AUCs by 75%
      - Dooley et. al. *Clin Pharm & Ther* 2012 91(5) 881-888.
- Efavirenz Metabolism:
  - Major CYP2B6, Minor CYP2A6, CYP3A4
- Daily RPT (15mg/kg; no INH) + EFV based ART
    - 37% & 33% reduction in EFV AUC & Cmin

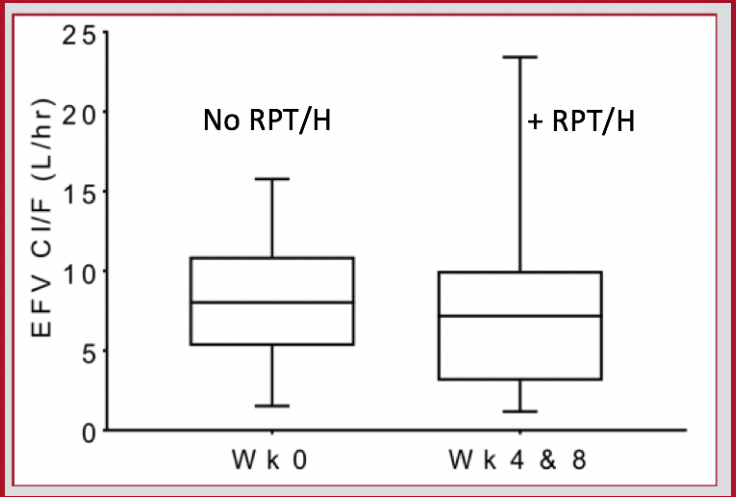
Previous EFV + RPT Data

EFV 600mg
+
RPT 600 mg
INH 300 mg



EFV 600mg
+
RPT 1200 mg
INH 300 mg





Podany et al CID 2015
Podany et al CROI 2018, #455

Gaps in RPT DDI Pharmacology

LTBI Regimen	Compatible ART	DDI Trial Status	Results Expected	Knowledge Gaps
3HP	EFV RAL 400 BID DTG	3HP w/ TAF in HV (Yoda) enrolling n=30, started 6/18	Final Results 2020	3HP + TAF in HIV
1HP	EFV	ACTG A5372	Initial PK 2020	DTG (what dose?) TAF

TB Treatment Regimen	Compatible ART	DDI Trial Status	Results Expected	Knowledge Gaps
RPT x 17 wks (S31)	EFV (tx exp)	S31 / A5349	Final PK results late 2019	DTG TAF

Slide adapted from S. Swindells & K. Dooley

Study 31 / ACTG 5349 Overview

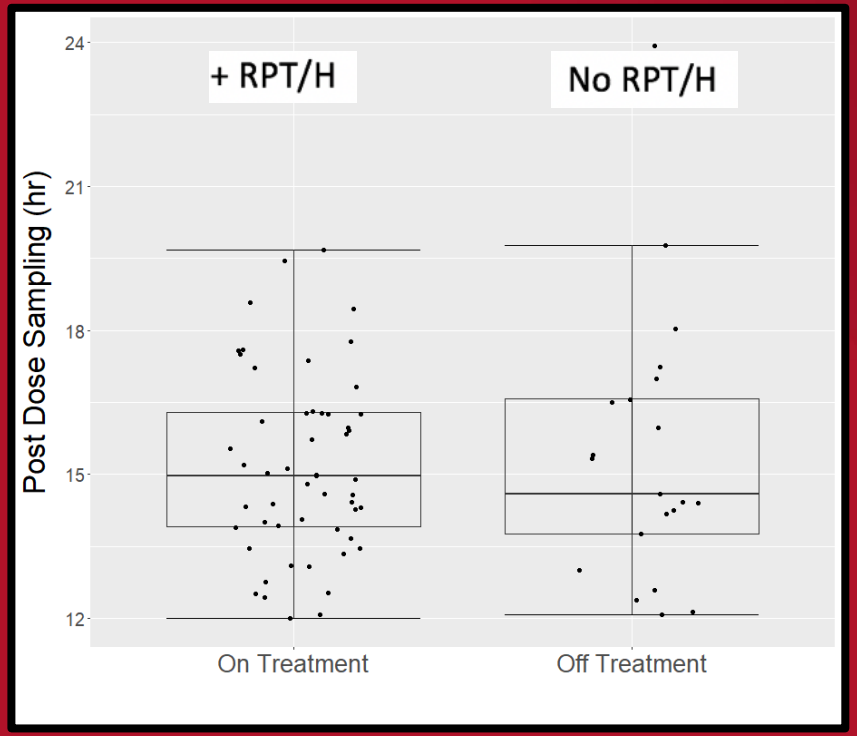
- International, multicenter, RCT, open-label 3 arm phase 3 non-inferiority trial (NCT#02410772)
- Co-conducted in the AIDS Clinical Trials Group (ACTG) and Tuberculosis Trials Consortium (TBTC)
- Patients with newly diagnosed, previously untreated pulmonary TB
- 17 weeks of daily RPT 1200mg based regimen (Investigational Arms 2 & 3)
- Males and females 12 yrs and older, target n=2500
- For HIV-infected, CD4+ > 100 cells/mm^3
    - Only EFV based ART allowed
        - Group 1: On EFV-based ART for >30d with HIV RNA <200 cpm
        - Group 2: Participants initiating EFV-based ART within first 12 weeks of TB tx

Background and Methods

- Secondary Objective: to evaluate the effect of rifapentine (RPT) on efavirenz (EFV) PK in ART naïve participants initiating EFV-containing ART while receiving RPT-containing TB treatment
- Patients initiated EFV-containing (600mg) ART within first 12 weeks of study
- 17 weeks of daily RPT 1200mg
- Sparse Plasma Samples Collected:
    - Twice during TB treatment (Week 4,8,12 or 17)
    - Once after TB treatment completion (Week 22)
- Mid-interval plasma EFV concentrations determined via LC/MS/MS
- EFV apparent oral clearance (CL/F) modeled using Bayesian estimation
- Patient characteristics summarized with descriptive statistics, PK data summarized as GMR (90% CI) of EFV CL during to post RPT/H completion
- Interim evaluations of number (%) of participants with EFV conc. > 1 mg/L at two time points during RPT treatment

Participant Baseline Demographics

Table 1. Participant Demographics		
Characteristic	**Metric**	**Total (n=28)**
Age	Median (IQR)	36 yrs (30-42)
Gender	F	7 (25%)
Race / Ethnicity	Black / African	27 (96%)
CD4 cells/mm^3 at entry	Mean (IQR)	252 (157 – 403)
HIV RNA Copies / mL	Median IQR	81,003 (27,171 – 343,245)

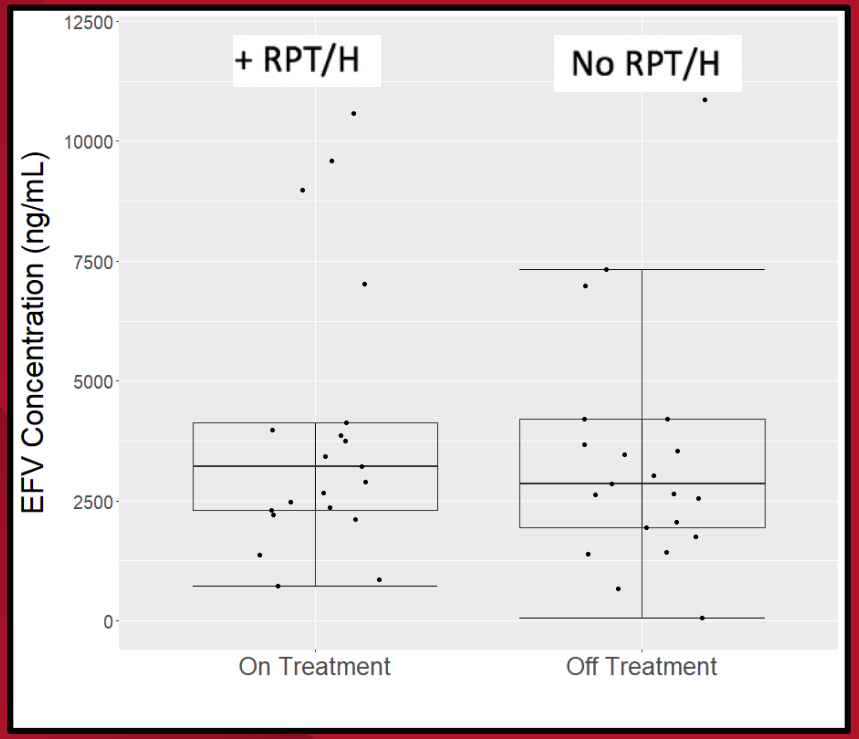


PK & HIV RNA Results

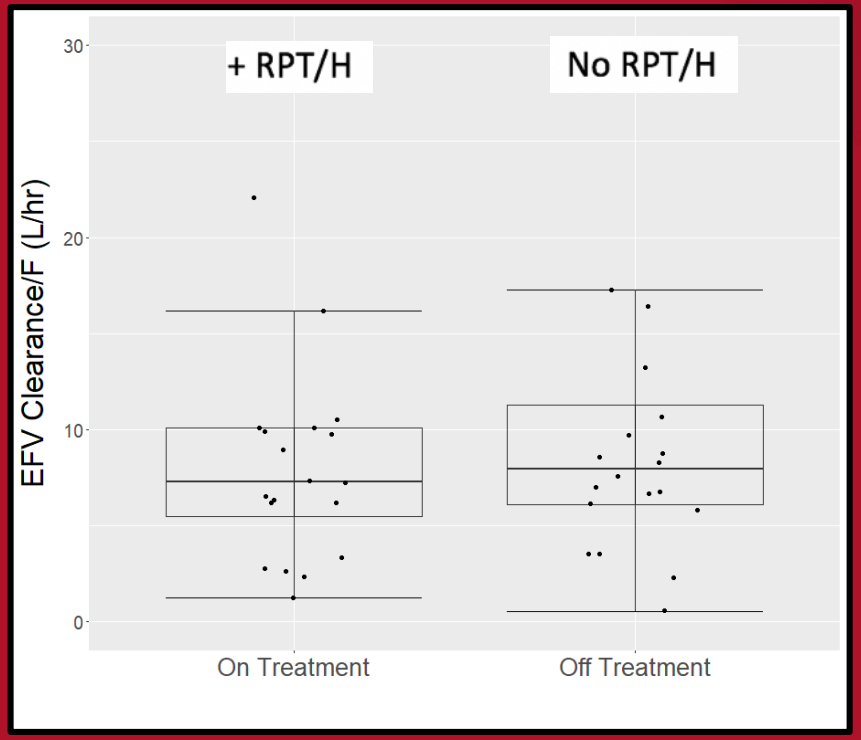
Table 2. Participant EFV PK Parameters					
Metric	EFV Concentrations ~ 4 weeks post initiation (mg/L)	EFV Concentrations ~ 8 weeks post initiation (mg/L)	EFV Concentrations Week 22 (mg/L)	EFV CL/F (L/hr) During TB Tx	EFV CL/F (L/hr) Post TB Tx
Median	2.76	2.86	2.86	7.28	8.3
Q1,Q3	2.12,4.67	2.19,4.88	1.93,4.21	5.47,10.08	6.17,10.66
N> 1mg/L	25/28 (89%)	26/28 (93%)	19/21 (90%)	-	-
GMR (90% CI) of during to post RPT/INH EFV CL/F was 0.89 (0.64-1.23)					
20 of 23 participants had undetectable HIV RNA at week 22					

PK Results Con't

Efavirenz Concentrations +/- RPT



Efavirenz Clearance +/- RPT

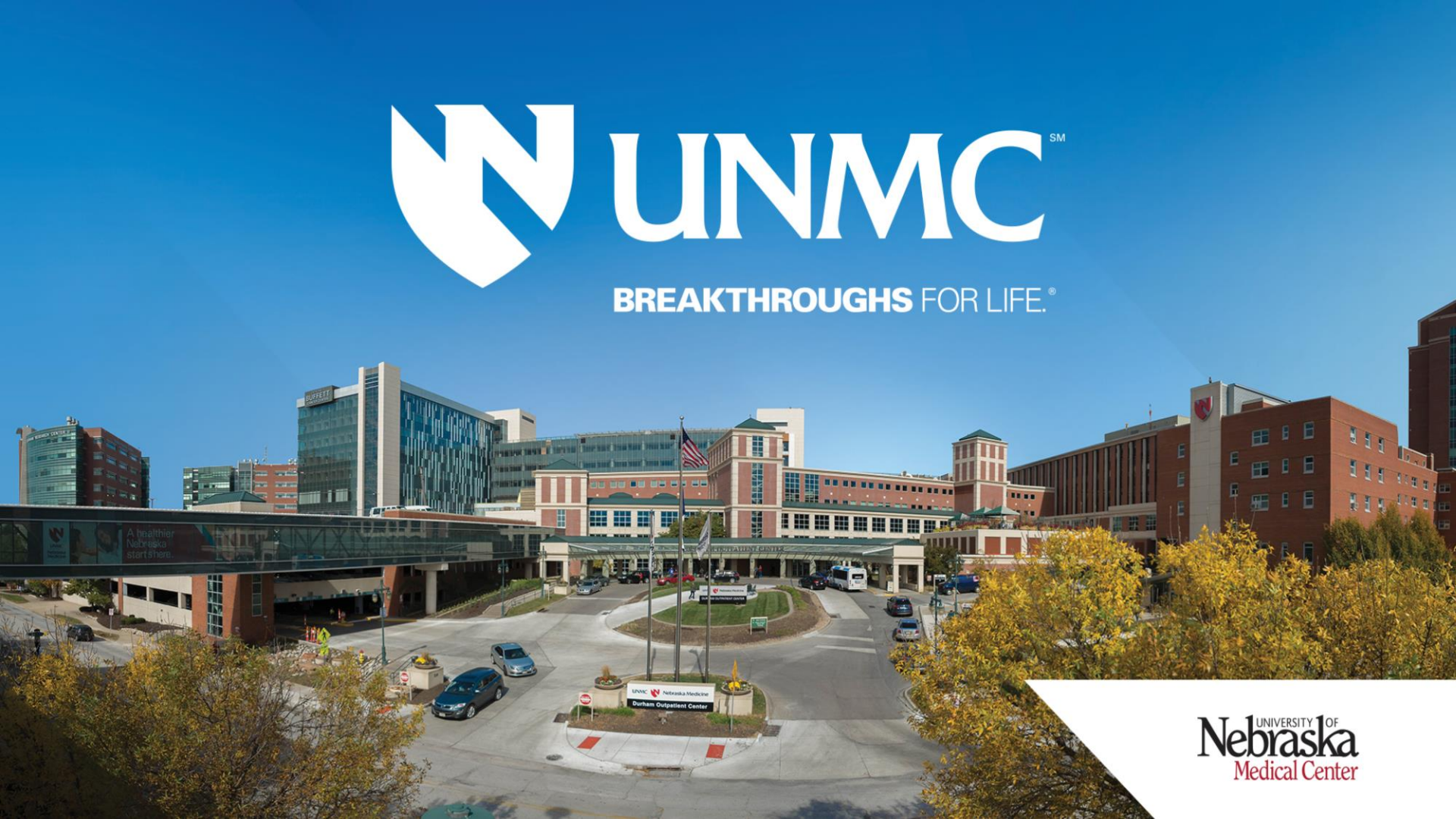


Conclusions

- For participants initiating EFV-based ART during RPT based TB tx:
- Median mid-dosing interval EFV concentrations were similar with and without RPT/H treatment (2.76, 2.86 and 2.86 mg/L at ~4, 8 weeks post EFV initiation and week 22)
- The CL/F of EFV decreased slightly with RPT/H (7.28 vs 8.3 L/hr; GMR 0.89).
- 87% of participants had suppressed viral load at study week 22
- These data provide preliminary support for initiating EFV-containing ART during co-administration of daily high-dose RPT for TB treatment.

Acknowledgements

- TBTC S31 / ACTG A5349 Study Participants
- TBTC S31 / ACTG A5349 Study Teams
- Antiviral Pharmacology Lab at UNMC
- Sanofi for pharmaceutical support
- Erin Sizemore
- Sue Swindells
- Kelly Dooley
- Kia Bryant
- E. Kurbatova
- Richard Chaisson
- Susan Dorman
- Payam Nahid
- W. Samaneka
- L. Mohapi
- J. Johnson
- H. Mayanja
- U. Lalloo
- S. Badal-Faesen
- Kayla Campbell
- Michelle Pham
- S. Miyahara
- Patrick Phillips
- Andrew Vernon
- Richard Hafner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