# Nevirapine Pharmacokinetics in HIV Infected Persons Receiving Rifapentine and Isoniazid for TB Prevention in ACTG 5279/BRIEF TB

Anthony T. Podany

For the A5279 Study Team

# Disclosures

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

# ACTG 5279/BRIEF TB Study Overview

- ACTG A5279 multicenter, open label, phase III clinical trial (N=3000) of preventive therapy for TB in HIV infected individuals.
- HIV-infected men and women ≥13 yrs with positive TST or IGRA, or living in high burden area of TB prevalence
  - ≥60 cases / 100,000 population / year
- Participants randomized to:
  - 4 weeks of daily weight based rifapentine + isoniazid 300mg (1HP)
  - 9 months of daily isoniazid 300mg (9H)
- No significant difference in incidence rates of TB & TB death by arm 1HP vs. 9H (0.65/100 PY and 0.67/100 PY)
- Treatment completion was higher in 1HP than 9H (97%vs 90% P<0.01)

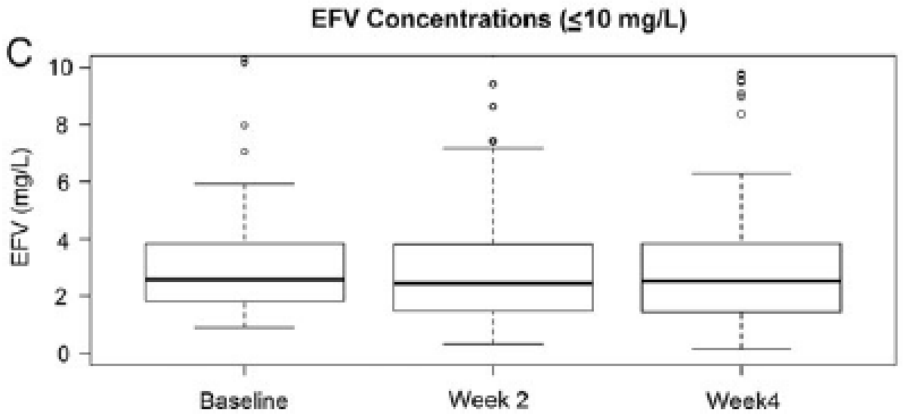
# Pharmacology Background

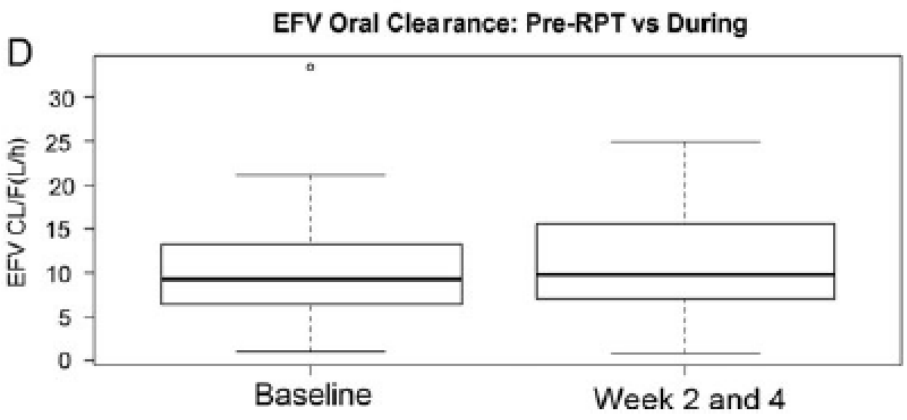
- PK Objectives:  to assess the effects of concomitant rifapentine (RPT) & isoniazid (INH) on nevirapine (NVP) pharmacokinetics.
- Rifamycins Background:
  - all have CYP inducing properties
  - using midazolam as a substrate
    - RPT reduced AUCs by >90%
    - RIF reduced AUCs by 75%
      - Dooley et. al. *Clin Pharm & Ther* 2012 91(5) 881-888.
- Nevirapine Metabolism:
  - Major CYP3A, Minor CYP2B6

# A5279 EFV PK Outcomes

## Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention

**Anthony T. Podany,[1] Yajing Bao,[2] Susan Swindells,[3] Richard E. Chaisson,[4] Janet W. Andersen,[2] Thando Mwelase,[5] Khuanchai Supparatpinyo,[6] Lerato Mohapi,[7] Amita Gupta,[8] Constance A. Benson,[9] Peter Kim,[10] and Courtney V. Fletcher[1,3]; for the AIDS Clinical Trials Group A5279 Study Team**



# ACTG 5279 Key PK Study Characteristics

- Participants at study entry already receiving NVP-containing ART.
- Convenient and minimally invasive PK sampling: single sample at weeks 0 (pre-RPT/INH), 2 and 4 (on-RPT/INH).
  - Targeted trough (12 hr) post dose sample.
  - NVP Threshold set to 3mg/L.
- Pharmacokinetic analysis: Bayesian estimation of apparent oral clearance (CL/F) at week 0 (for pre RPT/INH value) and using combined weeks 2 and 4 (for during RPT/INH therapy).
- Statistical analysis: summary statistics, and geometric mean ratio (90% CI) of wk 2-4 CL/F to wk 0.

# Participants Baseline Demographics - 1

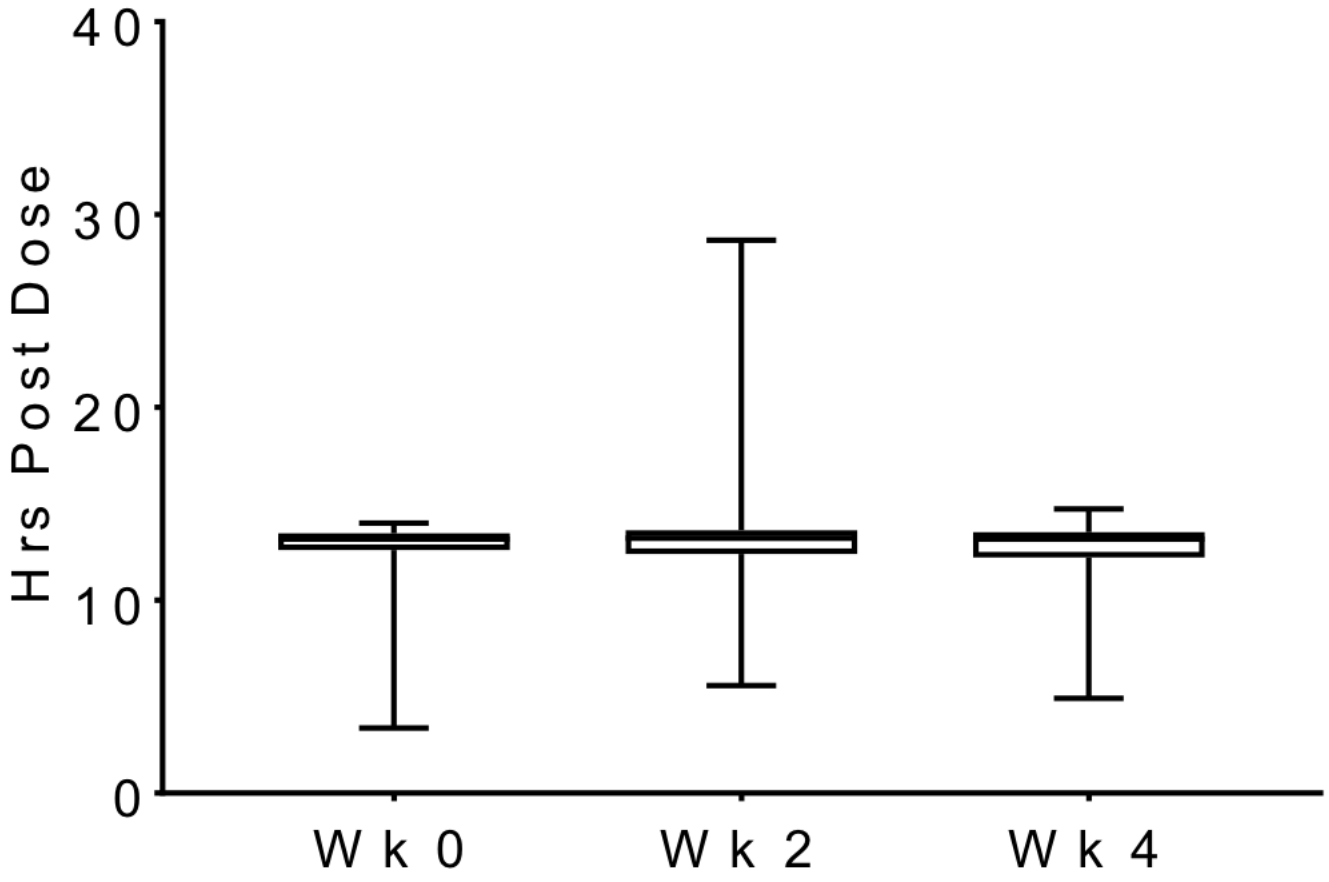
| Characteristic | Metric | Total (N=78) |
|---|---|---|
| Age | Median | 40 |
| | Min, Max | 13, 66 |
| Gender | F | 61 (78%) |
| Race/Ethnicity | Black Non Hispanic | 51 (65%) |
| Weight | Median Kg (IQR) | 57.9 (47.1 - 66.8) |
| Sites | Zimbabwe | 33 (42%) |
| | Thailand | 25 (32%) |
| | Botswana | 7 (9%) |
| | Kenya | 5 (6%) |
| | Malawi | 3 (4%) |
| | South Africa | 3 (4%) |

# Participants Baseline Demographics - 2

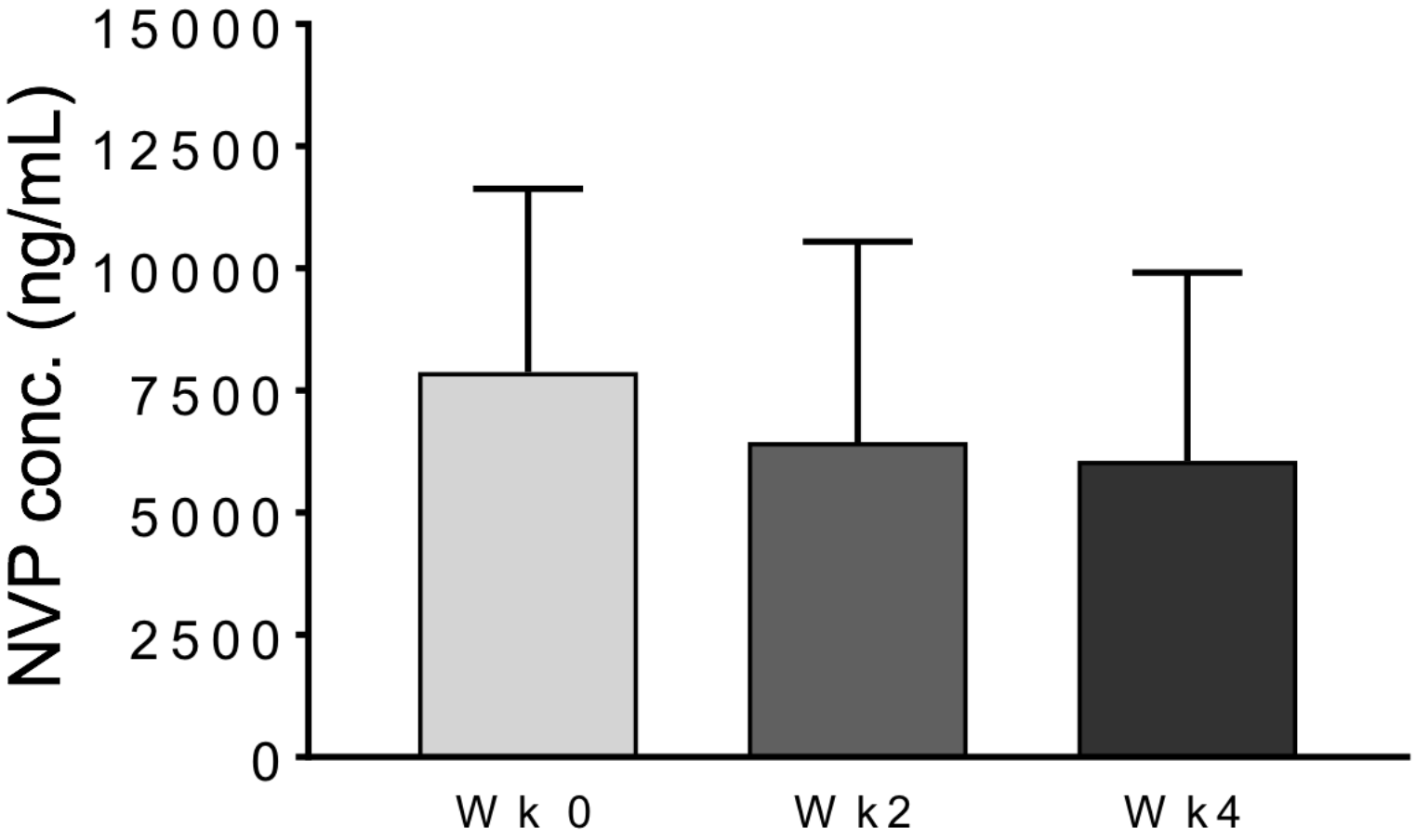
| Characteristic | Metric | Total (N=78) |
|---|---|---|
| HIV-1 RNA (log10 cpm) | Mean (SD) | 1.6 (0.2) |
| | Min, Max | 1.6, 3.0 |
| | Undetectable (<40cpm) | 70 (90%) |
| | Detectable | 8 (10%) |

| | | (N=78) |
|---|---|---|
| CD4 cells/$mm^3$ at Entry | Mean | 548 |
| | Q1, Q3 | 91, 1233 |
| ARV Treatment at Entry | NVP | 78 (100%) |

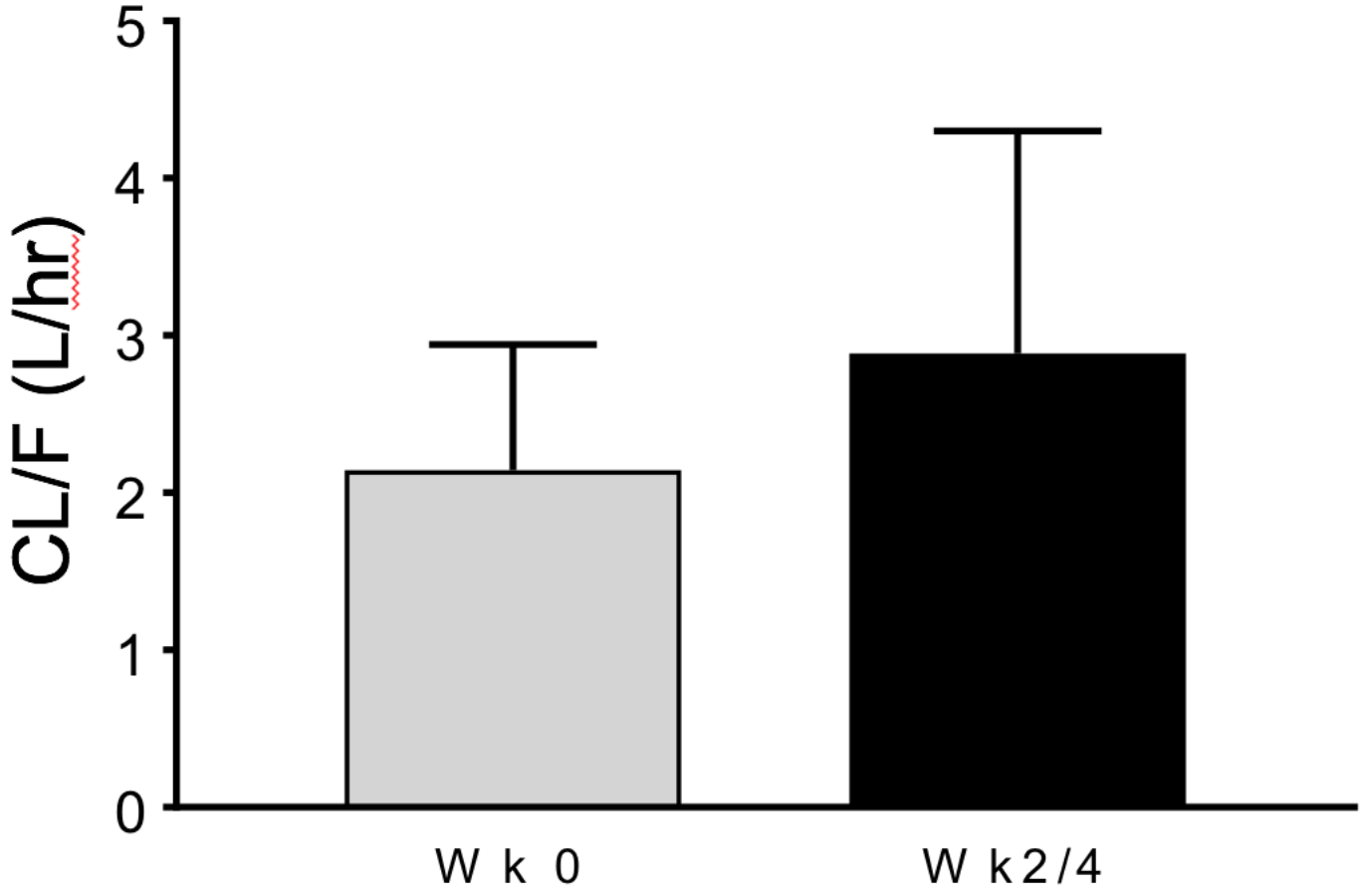
# NVP Sampling – Hours Post Dose



# NVP Concentrations



# NVP Oral Clearance: Pre-RPT vs During



# NVP Pharmacokinetic Characteristics

| Metric | Wk 0 (ng/mL) | Wk 2 (ng/mL) | Wk 4 (ng/mL) | Wk 0 CL/F (L/hr) | Wk 2-4 CL/F (L/hr) |
|---|---|---|---|---|---|
| Median | 7322 | 5537 | 5388 | 2.03 | 2.62 |
| Q1 | 5266 | 3552 | 3516 | 1.58 | 1.81 |
| Q3 | 9302 | 8462 | 8243 | 2.58 | 3.42 |
| N=<3mg/L | 0 | 14 (18%) | 15 (19%) | - | - |

| Metric | Ratio CL/F (Wk 2-4 / Wk 0) |
|---|---|
| Geo Mean Ratio | 1.30 |
| Lower 90% CI | 1.26 |
| Upper 90% CI | 1.33 |

# Observations and Conclusions

- Criteria: lower bound of 90% CI of % of participants with week 2 and 4 NVP concentrations > 3 mg/L had to remain above 80%.
- Results:
  - Week 2: 82% (73.2 – 88.6%)
  - Week 4: 81% (71.7 – 87.6%)
  - Weeks 2 & 4: 77% (67.6 – 84.3%)
- The CL/F of NVP significantly increased with RPT/INH, as judged by the GMR (1.3) and 90% CI (1.26-1.33).
- Assessments of plasma HIV-RNA pre and post RPT/INH are ongoing.
- These data suggest 1HP should not be co-administered with NVP-containing ART.

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