Effect of *CYP2B6* Metabolizer Status on Levonorgestrel Pharmacokinetics When Combined with Efavirenz-based Antiretroviral Therapy

Michelle Pham, Olive Mbabazi, Megan Neary, Shadia Nakalema, Kayla Campbell, Lauren Cirrincione, Anthony T. Podany, Marco Siccardi, Courtney V. Fletcher, Andrew Owen, Mohammed Lamorde, Kimberly K, Scarsi

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Background

- Progestin-releasing implants are an important contraceptive option
- Significant drug-drug interactions (DDIs) exist between levonorgestrel (LNG) and efavirenz (EFV)-containing antiretroviral therapy (ART):
  - LNG subdermal implant (150mg) plus EFV-based ART resulted in 45-57% lower LNG concentrations[1]
  - Doubling the LNG implant dose (300mg) still resulted in 34% lower LNG concentrations[2]
  - The mechanism of this interaction is proposed to be CYP3A4 mediated
- EFV metabolism is influenced by *CYP2B6* single nucleotide polymorphisms (SNPs)
  - *CYP2B6* SNPs associated with slow metabolism and high EFV concentrations resulted in lower LNG exposure[3]

[1.] Scarsi et al. CID 2016. [2.] Scarsi et al. CROI 2019. [3.] Neary et al. Clin Pharm Ther 2017.

Objective

To evaluate the impact of *CYP2B6* genotype on double dose (300 mg) levonorgestrel pharmacokinetics (PK) when combined with EFV-based ART

Methods

- Participants
  - EFV-based ART ≥ 30 days with HIV-1 RNA ≤400 copies/mL
  - EFV 600mg daily + 2 NRTIs
  - Copper IUD as a second form of contraception
- Pharmacokinetic (PK) Sample Collection
  - LNG implants were inserted, one in each arm, on Day 0
  - Plasma samples were collected on Day 0 and Weeks 1, 4, 12, and 24 for LNG PK analysis
  - Validated LC-MS/MS method; assay calibration 50-1500 pg/mL
  - Area under the concentration time curve from entry to 24 weeks ($AUC_{(0-24weeks)}$) was calculated using the trapezoidal rule

Methods

- Genotyping
  - Real-time PCR based allelic discrimination assays for selected candidate SNPs
  - 3 *CYP2B6* SNPs defined EFV normal, intermediate, and slow metabolizer phenotype[1]
- Statistical Analysis
  - SNPs tested for Hardy-Weinberg equilibrium
  - Univariate and multivariate linear regression ($P < 0.05$) used to assess impact of genotype on LNG PK
  - Univariate linear regression ($P < 0.05$) to investigate correlations between EFV and LNG PK

Normal
516GG – 983TT – 15582CC
516GG – 983TT – 15582CT
Intermediate
516GG – 983TT – 15582TT
516GG – 983CT – 15582CC
516GG – 983CT – 15582CT
516GT – 983TT – 15582CC
516GT – 983TT – 15582CT
Slow
516TT – 983TT – 15582CC
516GT – 983CT – 15582CC
516GG – 983CC – 15582CC

[1] Haas et al. CROI 2019

Demographics

Characteristic	**N = 28**
Age in years, median (IQR)	33.0 (28.0 – 40.5)
Weight in kg, median (IQR)	58.0 (48.5 – 66.0)
SHBG* in nmol/L, median (IQR)	148.9 (98.4 – 185.5)
CYP2B6 Metabolizer Status	
Normal, n (%)	8 (29%)
Intermediate, n (%)	15 (54%)
Slow, n (%)	5 (18%)

CYP2B6 rs4803419 15582C→T was not in Hardy-Weinberg equilibrium ($\chi 2=11.75$), which may compromise its interpretation.

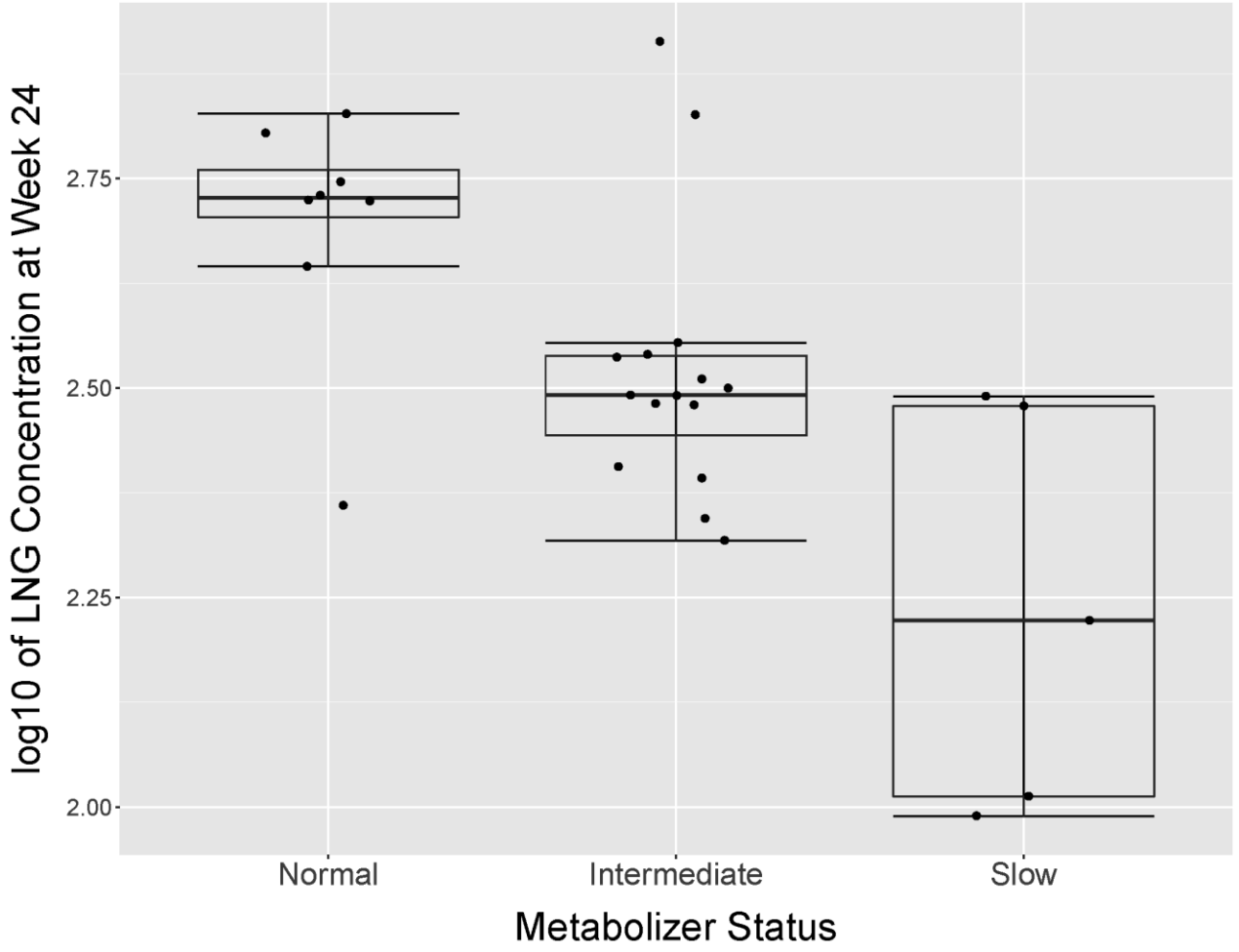
*Sex Hormone Binding Globulin

LNG Week 24 Concentrations and *CYP2B6* Metabolizer Status

- Compared to normal *CYP2B6* metabolizers at week 24:
  - Intermediate metabolizers: LNG ↓ 42%
  - Slow metabolizers: LNG ↓ 69%

Status	Median pg/mL (IQR)	β-coefficient	P-value
Normal	534 (507 – 577)		
Intermediate	310 (279 – 346)	-0.21	5.16×10^{-5}
Slow	167 (103 – 301)		

Multivariate adjusted model with Age, Weight, and SHBG

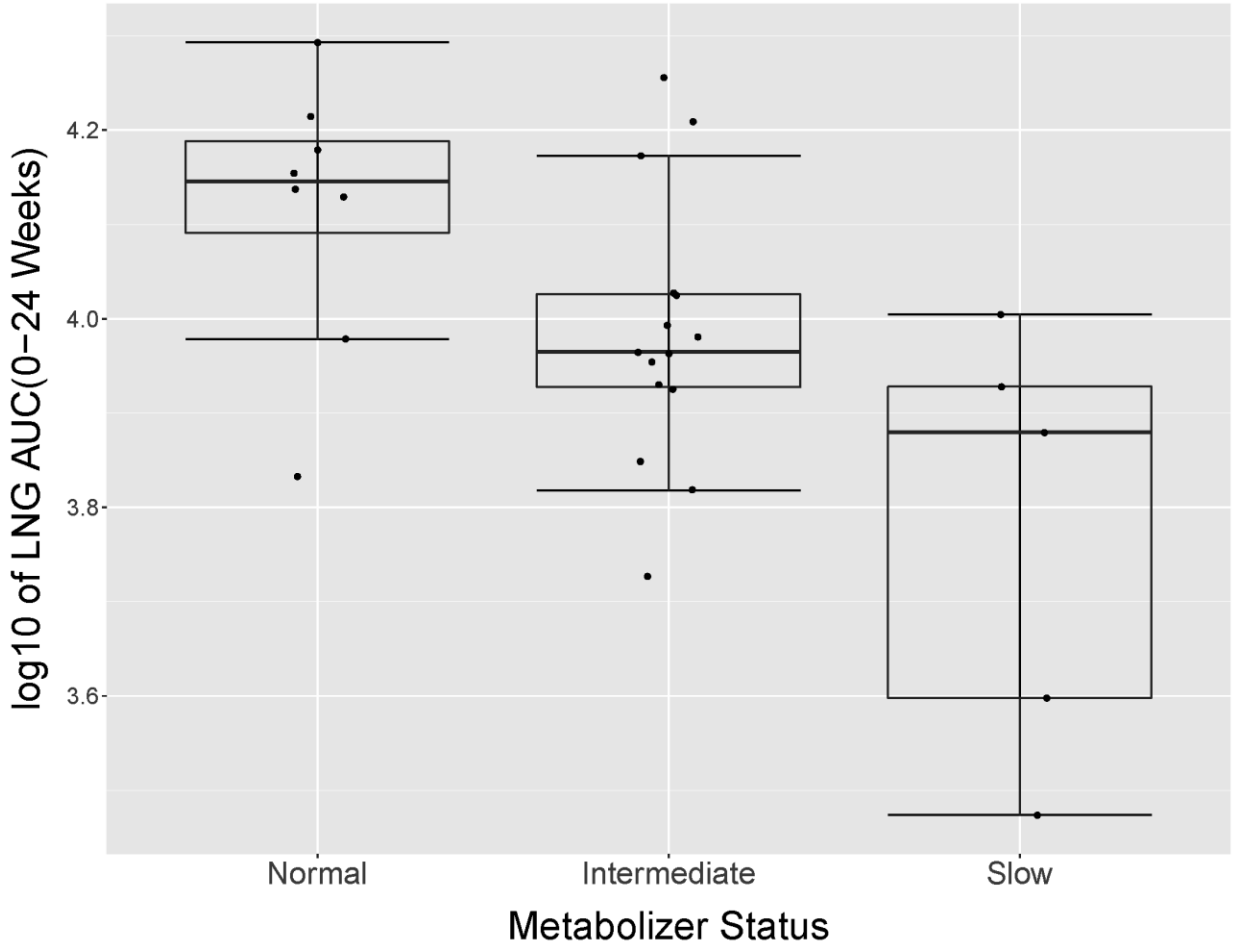


LNG $AUC_{(0\text{-}24weeks)}$ and *CYP2B6* Metabolizer Status

- Compared to normal *CYP2B6* metabolizers LNG $AUC_{(0\text{-}24weeks)}$:
  - Intermediate metabolizers: LNG ↓ 34%
  - Slow metabolizers: LNG ↓ 46%

Status	Median pg*week/mL (IQR)	β-coefficient	P-value
Normal	13989 (12470 - 15432)		
Intermediate	9221 (8466-10617)	-0.15	2.26×10^{-4}
Slow	7576 (3963-8474)		

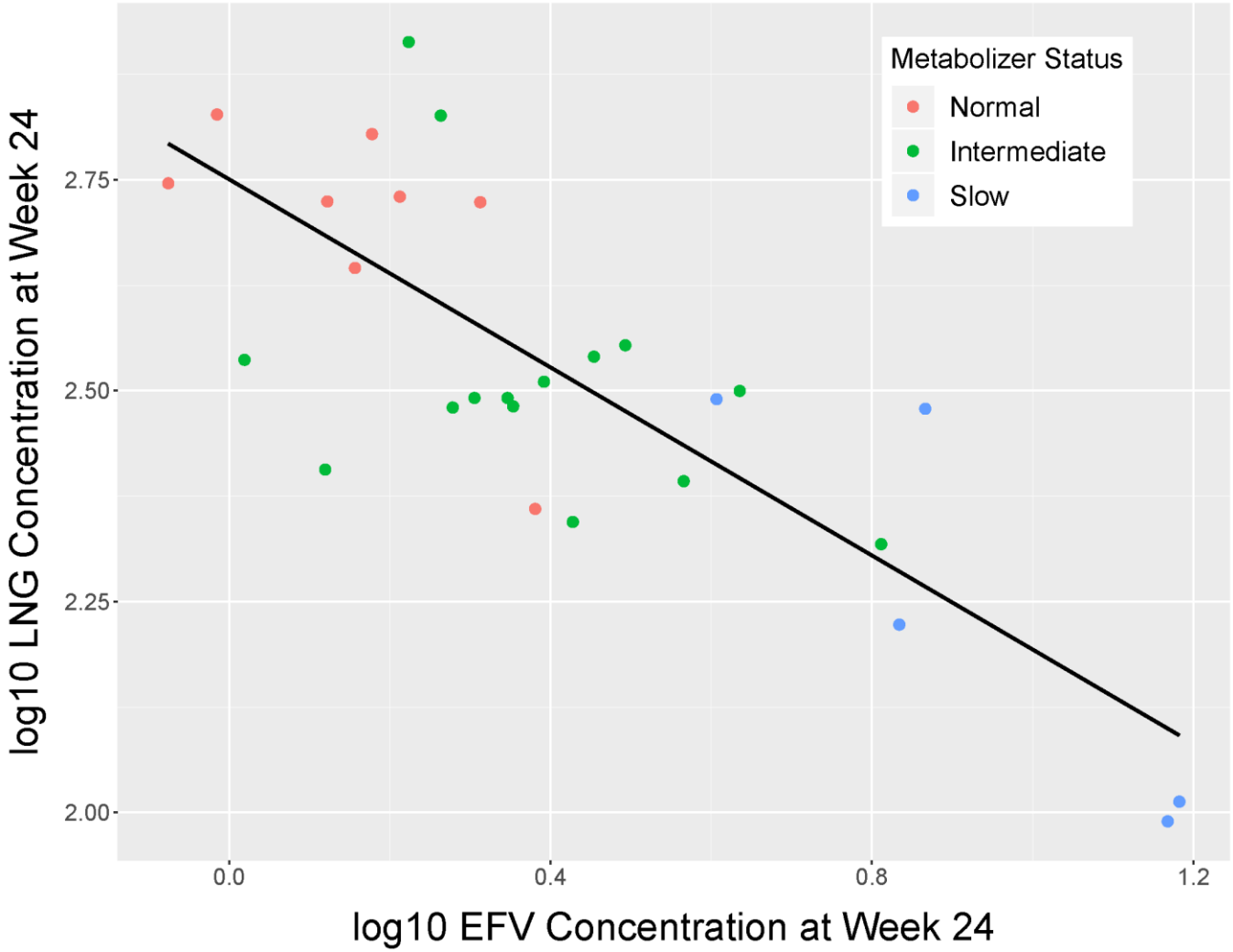
Multivariate adjusted model with Age, Weight, and SHBG



EFV and LNG Week 24 Concentrations

β-coefficient	P-value	Correlation Coefficient
-0.56	3.37×10^{-7}	-0.80

For every 3.6 µg/mL ↑ in EFV, LNG ↓ 1 pg/mL at Week 24



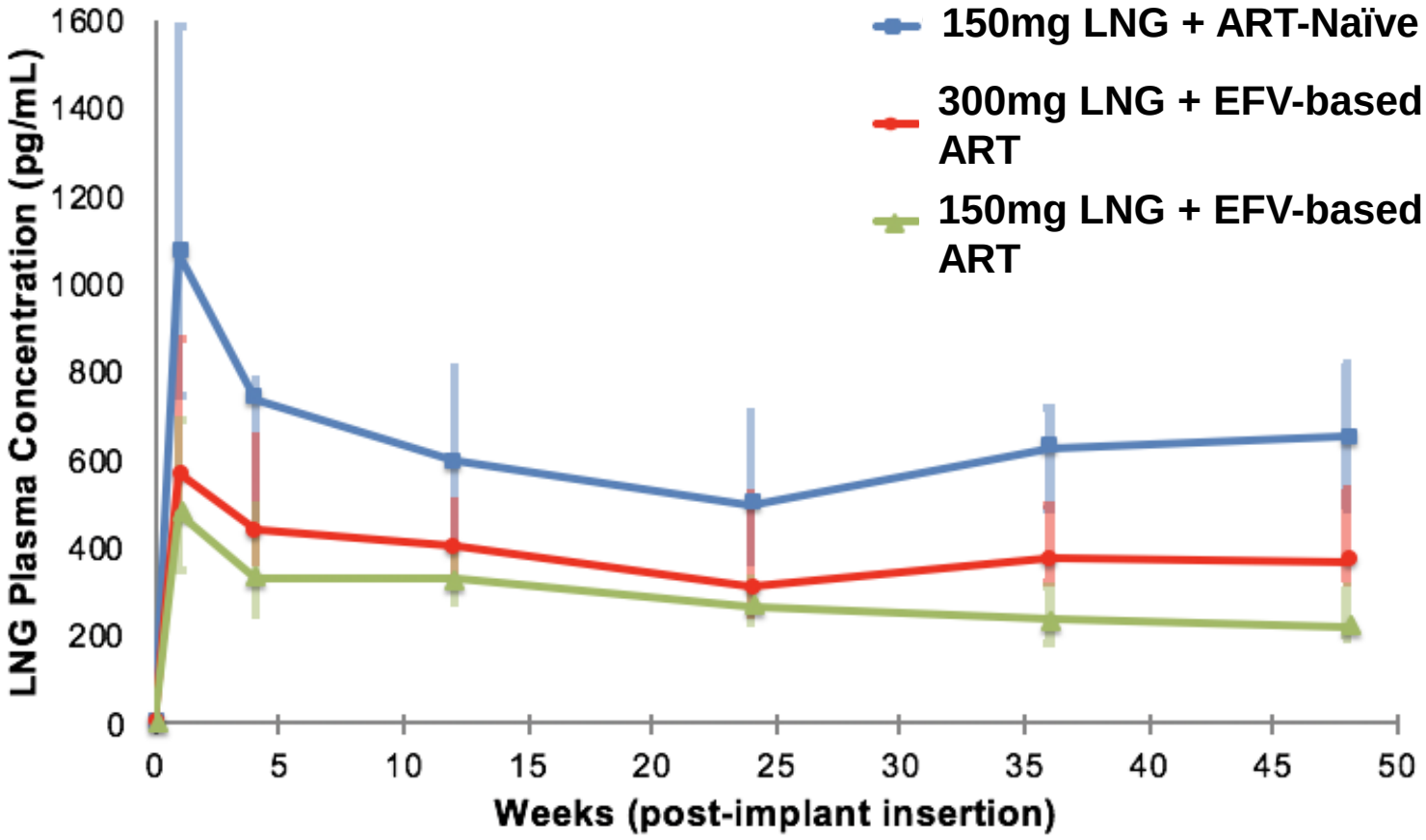
Comparing LNG Standard and Double dose regimens

LNG PK Results with and without EFV-based ART

Historical Control Group:
LNG 150mg implant + ART-Naïve

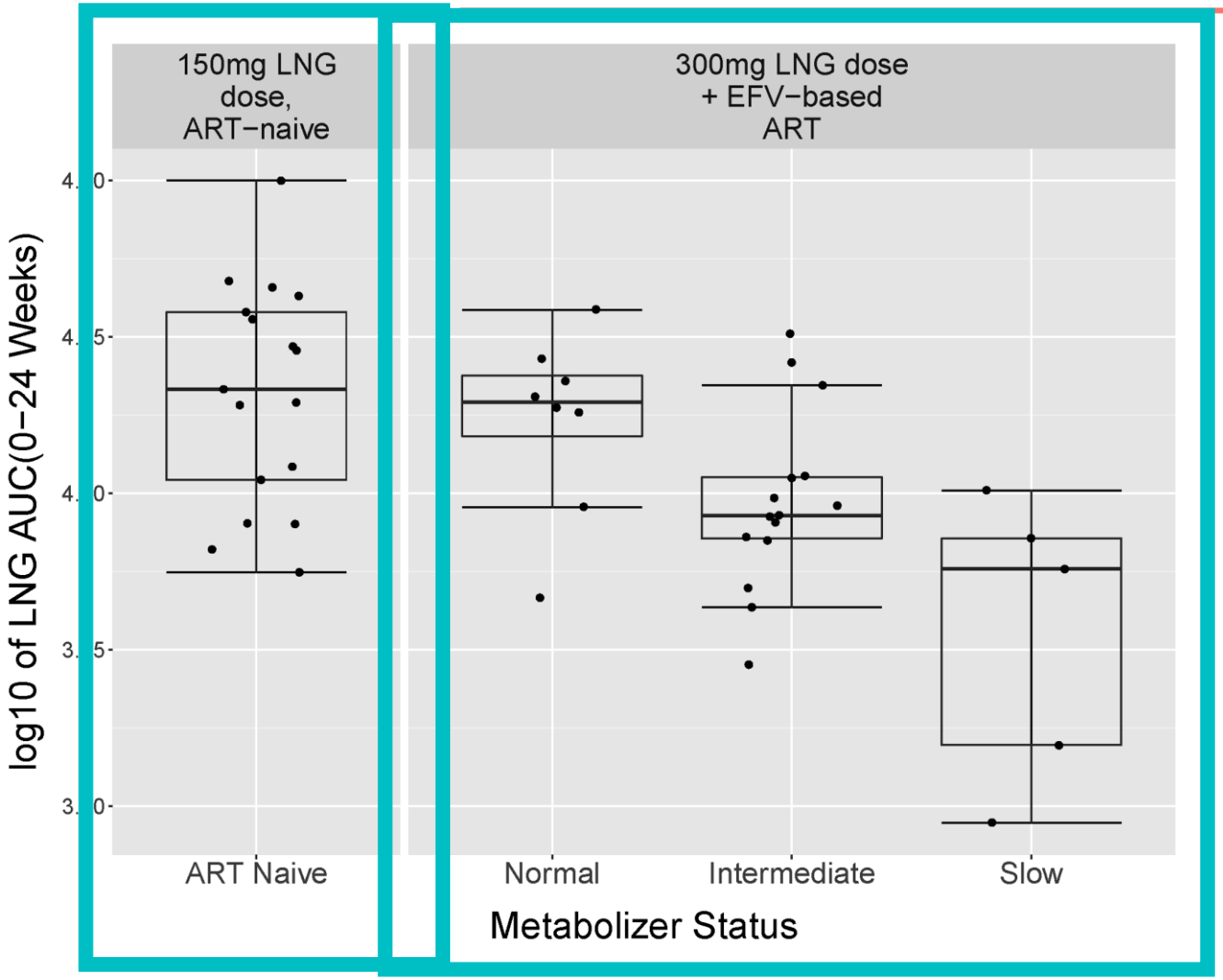
Historical LNG 150mg Group:
LNG 150mg implant + EFV-based ART[1]

- In women receiving EFV-based ART compared to the Control Group at week 48:
  - Double dose LNG ↓ 34%[2]
  - Standard dose LNG ↓ 57%



1. Scarsi KK et al. CID 2016.
2. Scarsi et al. CROI 2019.

Comparing CYP2B6 genotypes to a control group

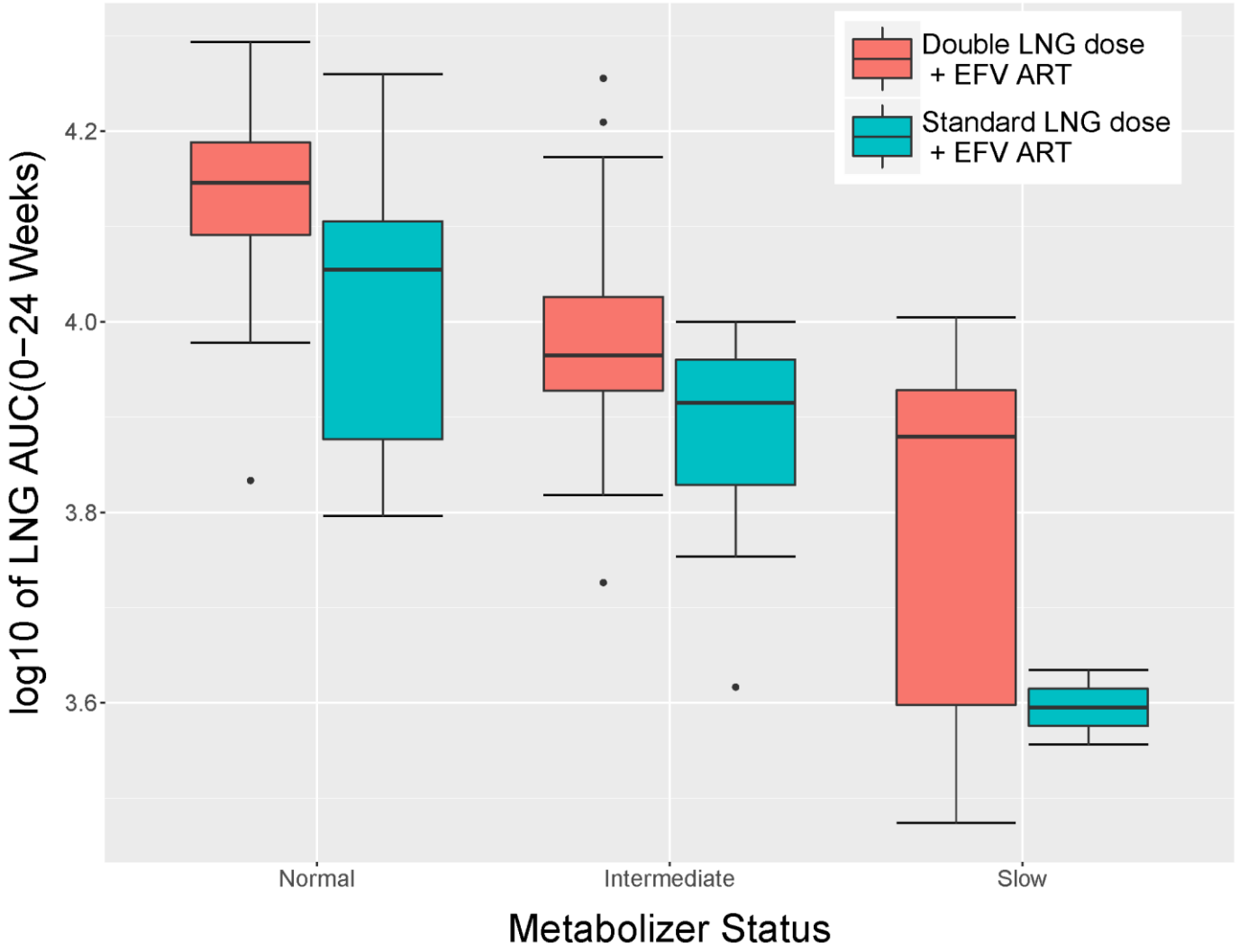


- Normal metabolizers receiving double dose had similar LNG exposure to historical controls
  - Less than 5% decrease in LNG exposure
- Intermediate and slow metabolizers had statistically lower LNG than historical controls

Comparison	P-value*
Normal to ART-Naïve	0.474
Intermediate to ART-Naïve	0.014
Slow to ART-Naïve	0.003

*Wilcoxon Rank Sum

Comparison of LNG Doses by Metabolizer Status



Parameter	β-coefficient	P-value
log_{10} $AUC_{(0\text{-}24\ weeks)}$		
Standard Dose	-0.18	1.65×10^{-3}
Doubled Dose	-0.16	1.04×10^{-3}
Comparison	**GMR* (300mg:150mg)**	
Normal	1.27	
Intermediate	1.29	
Slow	1.52	

*Geometric Mean Ratio

Conclusions

- In women receiving 600mg EFV-based ART plus LNG implants:
  - Double dose (300mg) of LNG in participants with normal *CYP2B6* metabolizer status result in comparable LNG exposure to standard dose LNG (150mg) in mixed-genotype ART-naïve controls
  - Intermediate and slow *CYP2B6* metabolizer status is associated with lower LNG concentrations, irrespective of LNG dose
- We propose that higher EFV exposure results in increased induction of *CYP3A4*[1,2]
- The potential for stratified LNG dosing based on *CYP2B6* genotype and EFV dose is worthy of further investigation

1. Mouly et al. Clin Pharmacol Ther 2002.
2. Hariparsad et al. J Clin Pharmacol 2004.

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Courtney Fletcher
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