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Understanding How HIV and Hepatitis C Virus (HCV) Infection Affects *CYP2B6* Enzymatic Activity and Methadone Pharmacokinetics

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Background: Methadone is one of three essential medications approved for treatment of opioid use disorder. However, it's narrow therapeutic index and inter-individual variability in disposition create dosing challenges. While overdose can lead to toxicity and death, sub-therapeutic doses can potentiate withdrawal. We seek to develop safe, effective methadone dosing strategies. We initially sought to elucidate the association between *CYP2B6* genetic polymorphisms and methadone disposition in HIV and HCV patients.

Rationale/Significance: *CYP2B6* is a polymorphic, methadone metabolic enzyme with 38 variant alleles identified through single-nucleotide polymorphisms. Several loss-of-function alleles (*CYP2B6*5*, *CYP2B6*6*, *CYP2B6*7*, *CYP2B6*16, CYP2B6*18)* express low activity and CYP2B6.6 and CYP2B6.9 catalyze less methadone N-demethylation to metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) compared to wild-type (CYP2B6.1*1).

Hypothesis: We hypothesize that HIV and HCV infection affects *CYP2B6* enzymatic activity.

Results: Pre-dose (trough) plasma was collected from 98 adults on daily, oral methadone for measurement of (R&S)-methadone and (R&S)-EDDP concentrations. Participants were minority (61% African-American, 28% Caucasian) and non-Hispanic (68%). Exploratory data analysis revealed that mean (R&S)-methadone concentrations appear to be similar between wild-type and loss-of-function alleles. Analysis by infection status (HIV/HCV co-infected, HCV mono-infected, uninfected) revealed that *CYP2B6*7* activity was particularly diminished in co-infected participants as indicated by higher (R&S)-methadone concentrations compared to wild-type and lower EDDP/(R&S)-methadone ratios compared to mono-infected participants. Co-infected *CYP2B6*6* homozygotes (**6/*6*) also revealed numerically greater (R&S)-methadone concentrations compared to *CYP2B6*6* carriers (*1/*6) and wild-type (*1/*1).

Discussion: Co-infection particularly affects *CYP2B6*7* and **6/*6* enzymatic activity. Results suggest that infection status may affect *CYP2B6* enzymatic activity with regard to methadone pharmacokinetics.