Impact of Endotoxin Exposure on the Hepatic Expression of Drug Transporters in HIV-1 Transgenic (HIV-Tg) Rats
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Purpose
As infection-induced inflammation alters the expression of many drug transporters and metabolizing enzymes, it is plausible that this may be potentiated in HIV infected individuals due to augmented inflammatory responses. Similar to humans the HIV-1 transgenic rat develops immune disorders and AIDS associated conditions. Therefore, our objective was to examine the impact of endotoxin administration on hepatic gene expression of drug transporters in HIV-Tg rats.

Methods
Three month old HIV-Tg male and female rats or wild-type littermates (WT) were treated with 5 mg/kg endotoxin or saline (n=4-9/group), animals sacrificed and tissues collected 18 hr later. Gene expression was measured in liver samples using qRT-PCR and cytokine levels were measured in serum using ELISA.

Results
In the saline groups, only the basal expression of Abcb11 was significantly different between HIV-Tg and WT. As compared to the saline-treated groups, TNF-α, IL-6, IL-1β mRNA and serum protein levels were elevated in the endotoxin-treated WT and HIV-Tg rats which was associated with significant downregulation in the hepatic expression of Abcb1a, Abcb11, Abcg2, Abcc2, Slco1a4, Slco1a2, Slco1b2, Slc10a1, Slc22a1 in addition to Cyp3a2 and Cyp7a1 (p<0.05). We saw an augmented endotoxin-mediated induction of cytokines in the serum and liver of HIV-Tg. As compared to WT, there were pronounced trends towards a greater downregulation of transporters and enzymes in endotoxin-treated HIV-Tg, which reached significance for Abcg2, Abcc2, Cyp3a and Slc22a1 in females and Abcc2 and Slco1a2 in males. Significantly higher total bile acid concentrations were seen the serum of endotoxin-treated HIV-Tg (male 118±28; female 252±40 μmol/L) as compared to endotoxin-treated WT (male 49±6, female 103±48 μmol/L).

Conclusion
Our results indicate that the inflammatory response and endotoxin-mediated downregulation of drug transporters is potentiated in HIV-Tg rats. This indicates an increased possibility that heptobiliary clearances may be altered in the HIV population due to co-existing infections or inflammatory conditions. This may be important in identifying potential drug-disease interactions.