HIV-1 Infection Alters Intestinal Expression of Antiretroviral Drug Transporters and Enzymes

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Background: HIV-1 infection is associated with intestinal tissue pathology and inflammation, which may alter the functional expression of drug transporters and metabolic enzymes known to be involved in antiretroviral drug disposition and intestinal absorption. This study investigated the effect of HIV-1 infection and/or chronic antiretroviral therapy on the expression of intestinal drug transporters and metabolic enzymes.

Methodology: Human intestinal biopsy tissues were obtained from i) HIV+ patients receiving atazanavir-based antiretroviral treatment (viral load < 50 copies/mL), N=7; ii) HIV+ patients, therapy-naïve (VL > 10,000 copies/mL, CD4+ < 500 cells/μL), N=7; and iii) age-matched healthy individuals, N=7. Expression of intestinal drug transporters, such as P-glycoprotein (Pgp), multidrug-resistance associated proteins (MRPs), breast cancer resistance protein (BCRP), and organic anion transporting polypeptides (OATPs), as well as cytochrome P450 enzymes (CYP3A4, CYP2B6) was examined by real-time qPCR, immunoblotting, and immunohistochemistry analysis.

Results: Compared to uninfected subjects, antiretroviral-naïve HIV+ patients had significantly lower mRNA expression (2-4 fold) of CYP3A4, MRP2 (ABCC2), and OATP2B1 (SLCO2B1) genes. Several other genes (e.g., Pgp (ABCB1), BCRP (ABCG2)) also showed a trend towards downregulation. In antiretroviral-treated group, CYP3A4, Pgp, MRP2, and BCRP expression was partially restored to healthy levels; however, high inter-individual variability in expression was observed in this group. Immunohistochemistry analysis of CYP3A4 and MRP2 expression in paraffin-embedded tissue slices confirmed downregulation of these genes in HIV-1-infected patients.

Conclusions: Expression of drug-metabolizing enzymes and drug transporters differs between antiretroviral-naïve HIV+ patients and uninfected subjects. These findings are in agreement with studies reporting regulation of these drug transporters and drug-metabolizing enzymes by HIV-1 associated pathogenesis and inflammation in other organs and blood-tissue barriers. Since many antiretroviral drugs are substrates of CYP3A4 (PIs, NNRTIs, maraviroc), Pgp (PIs, NRTIs, integrase inhibitors, maraviroc), MRPs (Pis, NRTIs), and BCRP (NRTIs, raltegravir), these data suggest that the pharmacokinetics of these drugs may differ in HIV-infected patients when compared to healthy volunteers. Overall, antiretroviral pharmacokinetics data and drug-drug interactions assessed in healthy volunteers should be interpreted with caution as they may not reflect antiretroviral drug disposition in HIV-1 infected patients. This study is supported by the Canadian Foundation for AIDS Research.