

ORAL PRESENTATION

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# Liver fibrosis is strongly associated with an enhanced level of immunosuppressive tryptophan catabolism independently of HCV viremia in ART-treated HIV/HCV co-infected patients

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## Background

HCV infection induces hepatic and extra-hepatic damage that includes kidney and neurocognitive dysfunction. Tryptophan (Trp) is catabolized into immunosuppressive kynurenine (Kyn) by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3 dioxygenase (TDO). Increased Trp catabolism measured by Kyn/Trp ratio has been associated with neurocognitive impairment and immune dysfunction in HIV mono-infection. Here, we assessed the contribution of Trp catabolism in HCV/HIV co-infected patients.

## Methods

Plasma samples were collected from ART-treated (HIV RNA <40 copies/ml) HCV/HIV co-infected patients with or without liver fibrosis (n=20 per group), HBV/HIV co-infected patients (n=25), ART-treated and untreated HIV-mono-infected patients and 30 healthy subjects (HS), (n=30 per group). Furthermore, 17 additional HCV/HIV INF- $\alpha$ /ribavirin treated patients were longitudinally assessed before and 6 months after sustained virological response (SVR). IDO and TDO enzymatic activity (Kyn/Trp ratio) was measured by isotope dilution tandem mass spectrometry. Statistical analyses were performed using Anova, unpaired or paired t-tests and Spearman correlation tests.

## Results

Among HCV/HIV patients, those having fibrosis compared with non-fibrosis had higher APRI scores ( $2.48 \pm 0.23$  vs  $0.36 \pm 0.018$ ,  $p < 0.0001$ ) and elevated Kyn levels ( $2.6 \pm 0.24$  vs.  $1.97 \pm 0.15$   $\mu\text{mol/L}$ ,  $p = 0.038$ ). For HBV/HIV co-infected, Kyn level was also elevated ( $2.1 \pm 0.16$   $\mu\text{mol/L}$ ). The Kyn/Trp ratio was equally elevated in all HCV and HBV co-infected groups, similar to the untreated mono-infected HIV group. Importantly, HCV/HIV fibrotic and HBV/HIV groups but not the non-fibrotic group had higher Kyn/Trp ratios compared to the ART-treated and HS groups. Unlike HIV viremia, HCV viremia was not correlated with the Kyn/Trp ratio. However, in all HCV/HIV co-infected patients, Kyn/Trp ratio was correlated with the APRI score ( $p = 0.027$ ). Successful HCV treatment improved APRI score ( $0.89 \pm 0.13$  vs.  $0.4 \pm 0.04$ ,  $p = 0.001$ ), contrasting with unchanged elevated Kyn/Trp ratios six months after SVR.

## Conclusion

ART-treated HCV/HIV and HBV/HIV co-infected patients presented with elevated immunosuppressive Kyn/Trp ratios when compared to mono-infected HIV-treated patients and reached a ratio similar to the untreated HIV mono-infected patients. In ART-treated patients, liver fibrosis on its own, but not HCV viremia, was associated with an enhanced level of immunosuppressive Tryptophan catabolism. These findings suggest that a necrotic-inflammatory liver syndrome persists even after SVR, and subsequently induces a systemic immune activation by increasing tryptophan catabolism.

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