Co-infection with HIV adversely impacts every stage of hepatitis C (HCV) infection. Liver damage in HCV infection results from HCV-specific CD8+ T cell immune responses against HCV-infected hepatocytes rather than the direct cytopathic effects of the virus itself. Despite a depressed cellular immune response, HIV/HCV co-infected patients show accelerated rates of hepatic fibrosis compared with subjects with HCV mono-infection. This paradox has, as yet, not been fully explained. Furthermore, data suggest a likely benefit of HIV control on the liver in HIV/HCV co-infection. T-regulatory (Treg) cells (CD4+ and FOXP3+) down regulate immune response and are hypothesised to limit hepatic damage in HCV. Our hypothesis was that reduced frequency of Treg in HIV/HCV co-infection compared with HCV mono-infection may explain poorer clinical outcome and histological appearance in co-infected patients. Methods: We analysed the frequency of FOXP3+, CD4+, CD8+, and CD20+ cells in the liver biopsies of 35 male subjects, 12 HIV mono-infected, 12 HCV mono-infected, and 11 HIV/HCV co-infected. Subjects were matched by age (+/- 7 years) and ISHAK fibrosis score. Results: HIV/HCV co-infected subjects had significantly fewer hepatic FOXP3+ (p = 0.031) and CD4+ cells (p = 0.001) than HCV mono-infected subjects. Co-infected subjects had more hepatic CD8+ cells compared with HCV mono-infected (p = 0.01), and a significantly lower ratio of FOXP3+ to CD8+ cells (0.08 vs. 0.27, p <0.001). Multivariate analysis including FOXP3+ and CD4+ cells showed that the number of CD4+ cells controlled for the observed difference in numbers of FOXP3+ cells between groups. Conclusion: The numbers of hepatic FOXP3+ cells were significantly lower in HIV/HCV co-infected patients compared with HCV mono-infected patients, suggesting lower Treg activity. This difference was accompanied by proportionately fewer CD4+ cells, indicating that lower numbers of FOXP3+ cells reflect fewer hepatic CD4+ cells rather than specific Treg loss. We observed higher numbers of cytotoxic CD8+ cells in HIV/HCV co-infected patients. This picture of increased cytotoxic cells and decreased regulatory cells may provide an explanation as to why HIV/HCV co-infected patients have poorer outcomes than those with HCV mono-infection. It also suggests a potential mechanism by which control of HIV replication by HAART and maintenance of CD4 cell counts benefits HIV/HCV co-infected patients.