HIV/HBV VIRAEMIA AND NOT IMMUNE DYSREGULATION IS ASSOCIATED WITH LIVER INFLAMMATION IN SOUTH AFRICAN PATIENTS

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Background
HIV and HBV co-infection are highly prevalent in South Africa due to shared transmission routes. HIV infection negatively affects the natural progression of HBV infection resulting in rapid progression of fibrosis and early development of hepatocellular carcinoma. However, the effect of HBV on HIV progression is not completely understood. HIV infection is characterized by increased systemic immune activation, attributed to multiple factors including the "leaky gut" phenomenon. Increased systemic levels of microbial products and immune dysregulation may have a profound effect in the liver environment. In this study we investigated the role of immune dysregulation and microbial translocation towards the pathogenesis of liver fibrosis.

Methods
Ethics approval was obtained to recruit 46 HBV/HIV co-infected; 47 HBV mono-infected and 39 HIV mono-infected age-matched patients attending the Infectious Diseases Clinic and Gastroenterology Clinic at Tygerberg Hospital, Cape Town. All HIV-infected patients were on HAART for ≥3 months. Liver stiffness measurements were taken using the Fibroscan 402 (Echosens, Paris). Cell-based immune markers of activation and exhaustion (including CD38, HLA-DR, PD-1, CTLA-4) were measured using multi-parameter flow cytometry of fresh whole blood (Navios, Beckman Coulter, MI, USA). Soluble serum/plasma immune biomarkers were measured using ELISA and Luminex technology on the Bio Plex 200 platform (Bio Rad Laboratories). Statistical analysis was performed using Statistica version 12 (StatSoft, Oklahoma, USA).

Results
There was significantly increased expression of HLA-DR/CD38 and PD-1 on CD8 T lymphocytes in co-infected subjects compared to the other two groups ($p<0.05$), Table 1. Soluble CD14 and Interferon-γ-Inducible Protein-10 (IP-10) were also significantly elevated in the plasma of co-infected patients. Co-infected subjects had significantly lower CD4/CD8 T cell ratio and CD4 cell counts and more frequent HIV viremia (28% vs 18%) compared to HIV monoinfected participants. The HBV mono-infected group had the highest proportion of participants with moderate/advanced liver fibrosis together with increased IL-1b, IL-1ra and basic-FGF compared to the other groups ($p<0.05$).

Conclusion
We report persistent T-lymphocyte dysregulation punctuated by continued immune activation and exhaustion in HAART-experienced HBV/HIV co-infected patients. However, this dysregulation does not appear directly associated with severity of liver fibrosis in the South African setting. Moderate/advanced liver fibrosis in HBV mono-infection may be indicative of inadequate access to screening and treatment of HBV.

Table 1: Virological and immunological characteristics of study patients.

	HIV/HBV co-infected	HBV Mono-infected	HIV mono-infected
Female %	53%	50%	66%
Age, mean (IQR)	38 (32-45)	37 (31-44)	37 (31-44)
HAART, months Median, (IQR)	36 (23– 63)	n/a	36 (12- 63)
HBeAg n (%)	13/46 (28%)	6/46 (13%)	n/a
HIV viral load >1000 copies/ml	6/36 (17 %)	n/a	3/33 (9.1%)
Plasma HBV DNA >2000 IU/ml	12/45 (26%)	15/44 (32%)	n/a
CD4 count	328 (242- 562)	922 (647- 1297)	528 (367- 657)
CD4/CD8 ratio	0.5 (0.3-0.7)	1.5 (1.1- 2.1)	0.7 (0.6-1.0)
%CD8/CD38+/HLA-DR+	30 (17-53)	17 (14-22)	23 (16-33)
IL-1β	1.3 (0.9- 2.8)	2 (1.5- 3.1)	1.2 (0.9- 1.9)
IL-1ra	59 (40.4- 100.8)	110.8 (85.1- 376.7)	62.2 (40.4- 85.8)
IP-10	1.5 (1.0- 2.8)	0.9 (0.7- 1.5)	1.1 (0.8- 1.5)
IFN-γ	88.7 (57.5- 145.3)	121.2 (80.1- 182.0)	66.7 (48- 125.7)
Basic-FGF	43.1 (21.8- 66.9)	65.7 (46.2- 92.3)	44.8 (24.2- 61.3)
sCD14	3.6 (2.4-6.2)	1.8 (1.1-2.4);	2.4 (1.8-4.3)
LBP	12.4 (10.2-15.6)	10.8 (8.4-13.4)	9.9 (7.8-16.0)