

**Project Title:****Non-alcoholic fatty liver disease in HIV-infected individuals in Hong Kong****(Project Code: MSS 228R)****Executive Summary:****Objectives**

We hypothesize that non-alcoholic fatty liver disease (NAFLD) is prevalent in HIV mono-infected individuals in Asian population, causes higher degree of advanced fibrosis than in the general population, and is related to higher cardiovascular risk and microbial translocation. This study aims to evaluate the:

1. prevalence of hepatic steatosis (HS) and advanced fibrosis in HIV-infected individuals (without HBV and HCV co-infection) in Hong Kong,
2. risk of fibrosis in patients with HS as compared to non-HIV-infected individuals,
3. correlation of HS with cardiovascular risk and markers of microbial translocation.

**Design**

A cross-sectional case-control study was performed. HIV-infected patients were recruited for measurement of HS and liver fibrosis. Age- and gender-matched controls were selected from a previously published population-based study of NAFLD in Hong Kong.

**Setting**

HIV-infected individuals were recruited from patients followed up in the Infectious Diseases clinic in a university-affiliated hospital in Hong Kong.

**Participants**

Eighty HIV-infected individuals aged  $\geq 18$  years and of Asian ethnicity (94% Chinese, 93% male) completed the study. 160 controls were randomly selected from a cohort of patients previously evaluated for HS, by matching gender, age and drinking status. All recruited participants had negative HBsAg and HCV antibody.

**Main outcome measures**

Clinical and demographic data was collected using a structured standardized research tool for HIV/AIDS studies. Anthropometric measurements were performed by trained research nurses. Fasting blood samples were collected to measure liver function, metabolic markers, immunoglobulin M endotoxin core (EndoCab IgM) and intestinal fatty acid-binding protein (I-FABP). The 10-year coronary heart disease risk was calculated by Framingham risk score. HS was measured by proton-magnetic resonance spectroscopy. An intra-hepatic triglyceride (IHTG) content of 5% was used to distinguish between patients with and without HS. Two HIV-infected patients with cirrhosis underwent liver biopsy, and their diagnosis of NAFLD was supported by histological findings. Transient elastography was used to measure liver stiffness (LS). LS  $>11.5$ kPa was considered as

cirrhosis.

## Results

Among the 80 HIV-infected individuals, 93% were male, mean±SD age was 54±11 years, 16% drank alcohol with alcohol consumption 36(IQR 29,87)g/week; duration of HIV infection was 8(IQR 4,13)years, 49% had history of AIDS, CD4 count was 503±248 cells/mm<sup>3</sup>, 95% had undetectable viral load, and all were receiving combination anti-retroviral therapy. Compared to controls, more HIV-infected individuals had diabetes (49% vs 4%, p<0.001), dyslipidemia (49% vs 12%, p<0.001), coronary artery disease (6.3% vs 0.6%, p=0.017), and metabolic syndrome (63% vs 22%, p<0.001). HIV-infected individuals also had higher body mass index (BMI), waist-hip ratio (WHR), alkaline phosphatase, aspartate aminotransferase, fasting glucose, HbA1c, triglyceride; and lower total cholesterol, HDL cholesterol, LDL cholesterol, and ferritin.

HIV-infected individuals had similar proportion of HS as controls (IHTG ×5%: 29% vs 28%, p=0.839), but significantly higher degree of LS [4.9(IQR 4.1,6.2)kPa vs 4.2(IQR 3.6,5.0)kPa, p<0.001], and more HIV-infected individuals had cirrhosis (5.2% vs 0%, p=0.011). Among the 25 HIV-infected individuals and 44 controls with HS, LS was 6.0(IQR 4.8,8.1)kPa and 4.6(4.0, 5.4)kPa respectively (p=0.001), and cirrhosis was detected in 17% vs 0% respectively (p=0.013). Liver fibrosis estimated by AST/ALT ratio, FIB-4, NAFLD fibrosis score, and BARD score also demonstrated higher level of advanced fibrosis in HIV-infected individuals with HS.

Among HIV-infected individuals, HS was associated with higher AMI, WHR, HbA1c, triglyceride, and ferritin levels, and lower HDL cholesterol level (all p<0.05). Those with HS had a trend of higher 10-year coronary artery disease risk (high risk 56% vs 40%, p=0.175). HS was not associated with duration of HIV infection, history of AIDS, CD4 count or individual anti-retroviral drugs. HS was also not associated with markers of microbial translocation: EndoCab IgM levels were 21(IQR 13,28) and 23(IQR 17,32)MMU/mL respectively (p=0.264); and I-FABP levels were 612 (IQR 336,1272) and 865 (IQR 373,1486)pg/mL respectively (p=0.369). On multivariate analysis, HS is associated with BMI [aHR 1.5 (95% CI 1.2-1.9), p=0.001] and triglyceride level [aHR 1.4 (95% CI 1.0-2.1), p=0.072].

## Conclusion

HIV mono-infected individuals have similar rates of hepatic steatosis, but significantly higher risk of cirrhosis, compared to the general population. Mechanisms leading to more rapid progression of advanced fibrosis/cirrhosis need to be further evaluated.