Intrahepatic CXCR3 and CXCL10 are associated with liver disease in HIV-HBV co-infection

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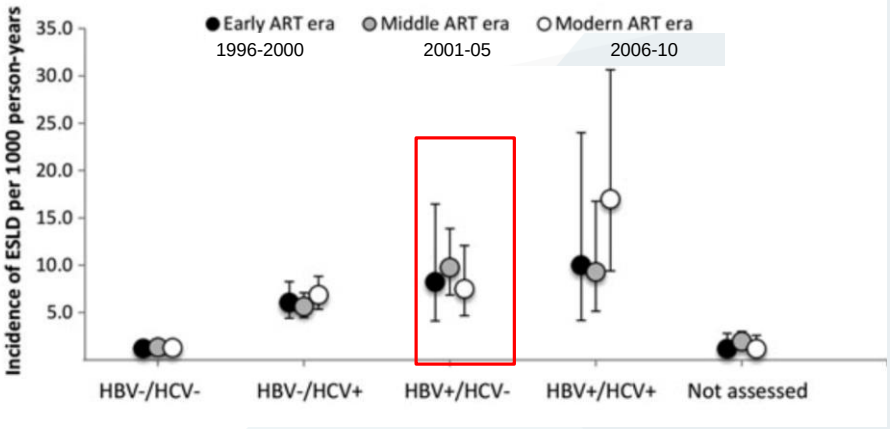
THE UNIVERSITY OF MELBOURNE
The Royal Melbourne Hospital
A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Background – accelerated progression of liver disease persists on HBV-active antiretroviral therapy



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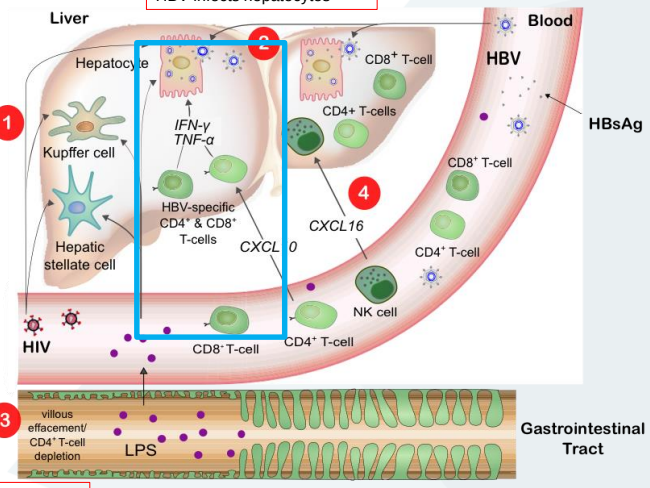
Klein et al, Risk of ESLD in HIV-Viral Hepatitis Coinfected Persons in North America from the early to Modern ART Eras, CID 2016

Background - Effects of HIV and HBV on the liver and circulating HBV-specific immune cells



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Hypothesis

In HIV-HBV co-infection, increased immune activation (IA) & microbial translocation (MT) drive liver apoptosis and fibrosis.

Accelerated progression of liver disease is a consequence of elevated CXCL-10 and not directly related to circulating levels of LPS

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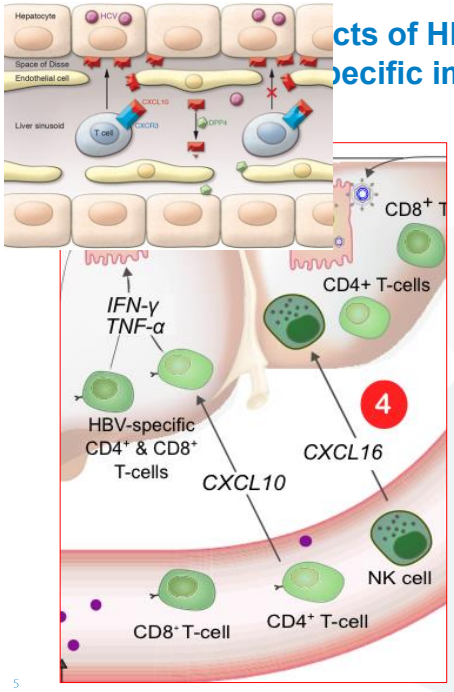
cts of HIV and HBV on the liver and pecific immune cells



In HBV, liver disease can be mediated by migration to the liver of HBV specific and non-HBV specific T cells, CXCR6+ NK cells and monocytes

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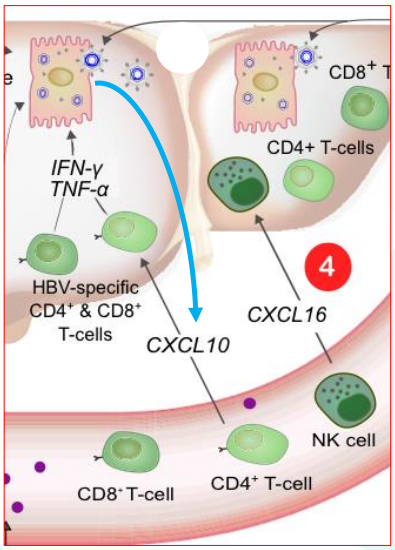

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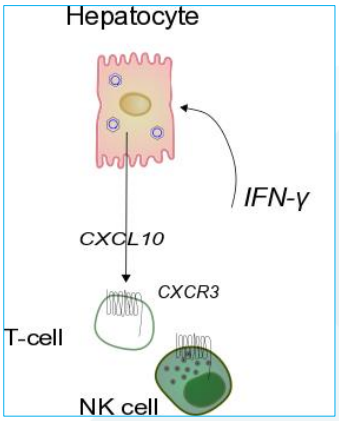
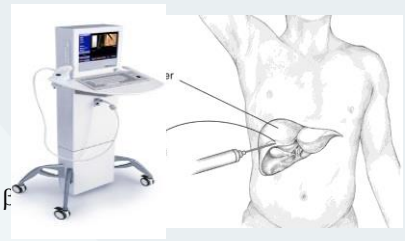
Background – CXCL10 in the liver



Methods (1) cross sectional clinical study

X-sectional (off ART) **Thailand (n=37)**

Inclusion criteria
≥ 18 years, HIV Ab positive, HBV surface antigen (HBsAg) positive for >6 months, HBV DNA > 2 × 10^3 IU/mL, HCV antibody negative



- Transient elastography
- Plasma (LPS, sCD14, CCL2, CXCL10)
- PBMC
- Biopsy (HIV RNA, CXCL 10, CXCR3, IFN α, β

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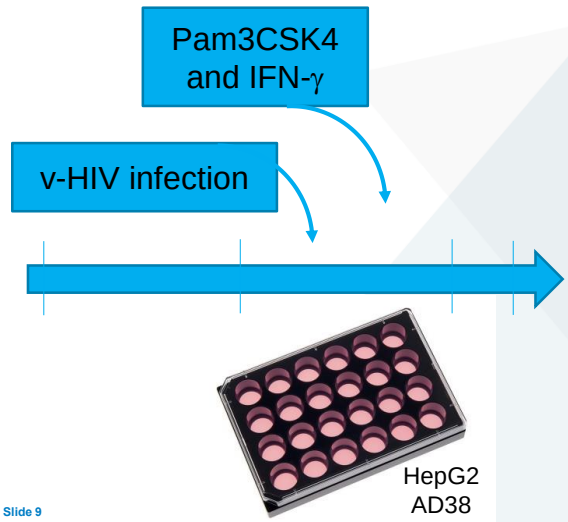
Methods (2) In vitro model of hepatocyte response to IFN -γ



- **CXCL10** (ELISA)
- **eGFP (HIV), viability**

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Demographic, clinical, fibrosis and immune activation characteristics (n=37)

Characteristics	median (IQR)
Age, years	32.2 (25.3-36.2)
Sex, % male (n)	89.2 (33)
Alcohol intake-Never	43.2% (n=16)
Known duration HIV +	0.7 (0.2-3.3) years
Nadir CD4, cells/ul	320 (205.0-430.5)
HBV DNA, $\log_{10}$ (IU/L)	7.4 (2.5-8.1)
HBeAg positive	64.9% (n=24)
Liver fibrosis <F3	81.1% (n=30)

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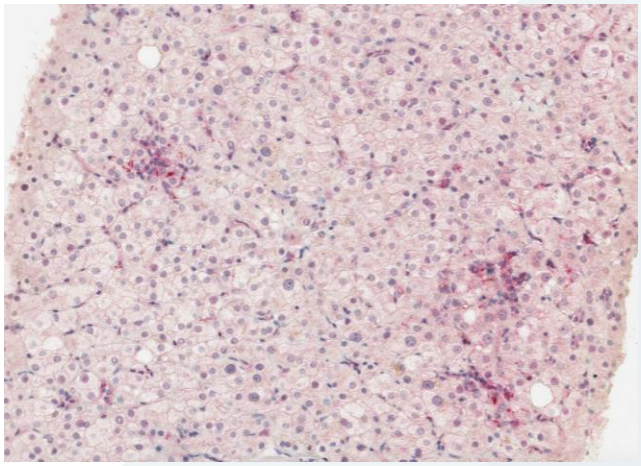
Liver biopsy - Intrahepatic CXCL10



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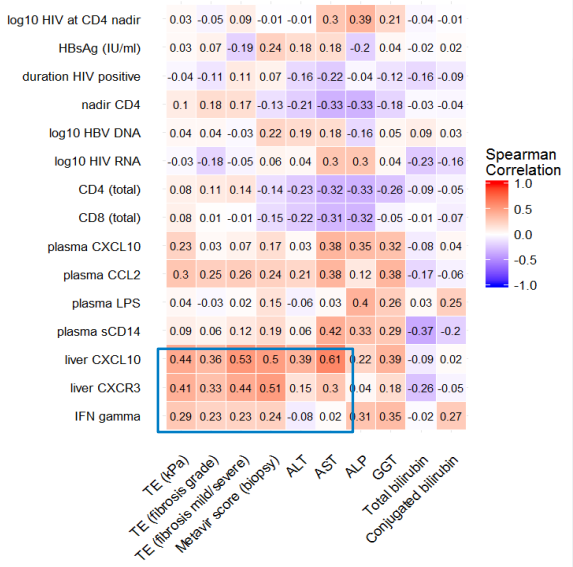
Intrahepatic CXCL10 covered a median of 0.44% of liver sections, with the majority found associated with inflammatory infiltrates of the portal regions of the liver biopsies.

Intrahepatic CXCL10, CXCR3 significantly associated with liver fibrosis and liver enzyme elevation



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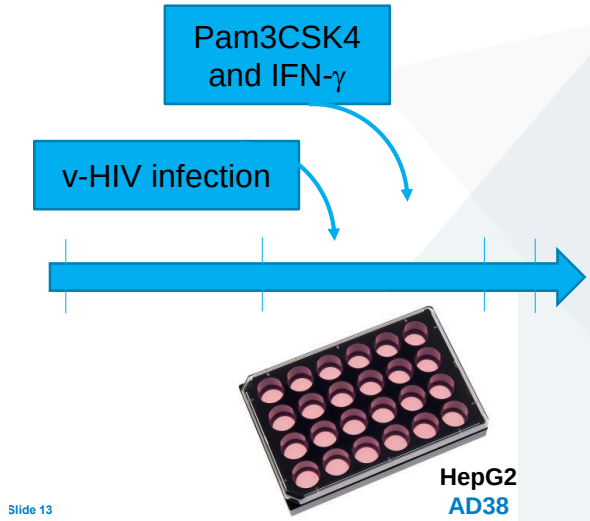
Methods (2) In vitro model of hepatocyte response to IFN -γ



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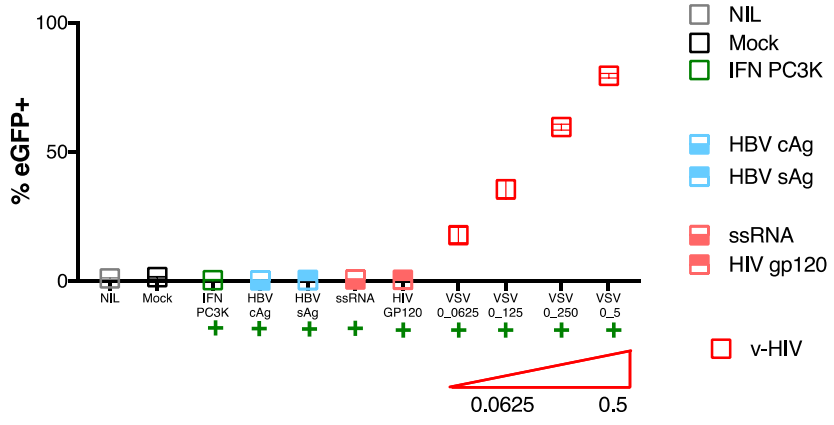
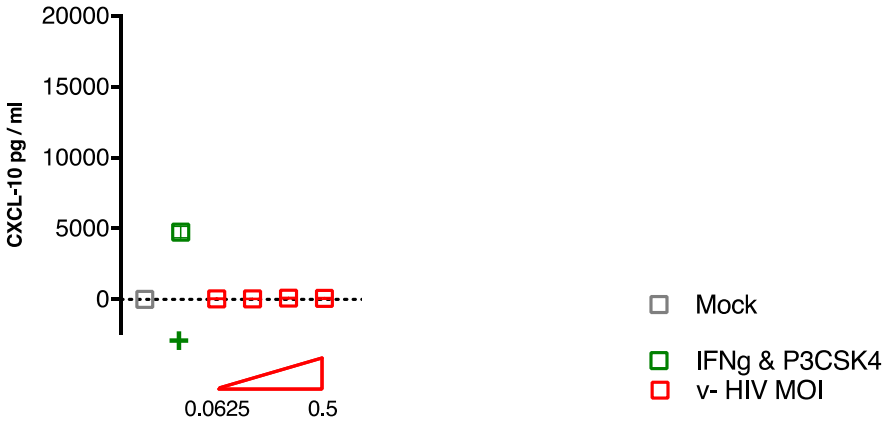
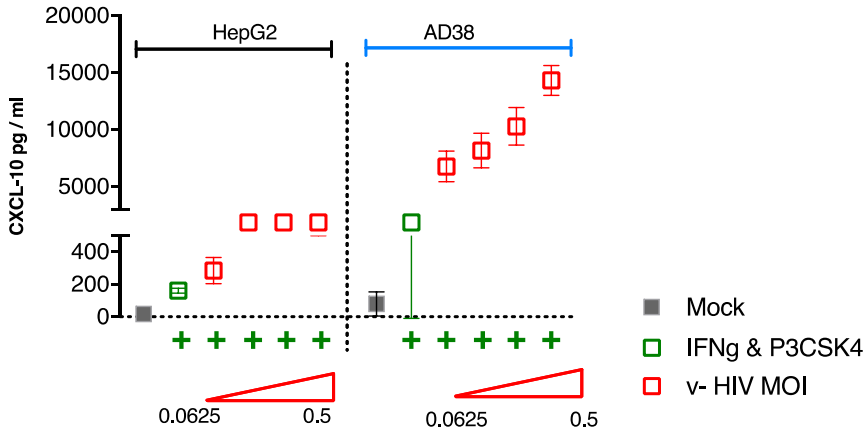
eGFP expression increased with increasing MOI – v-HIV (0.0625 to 0.5)



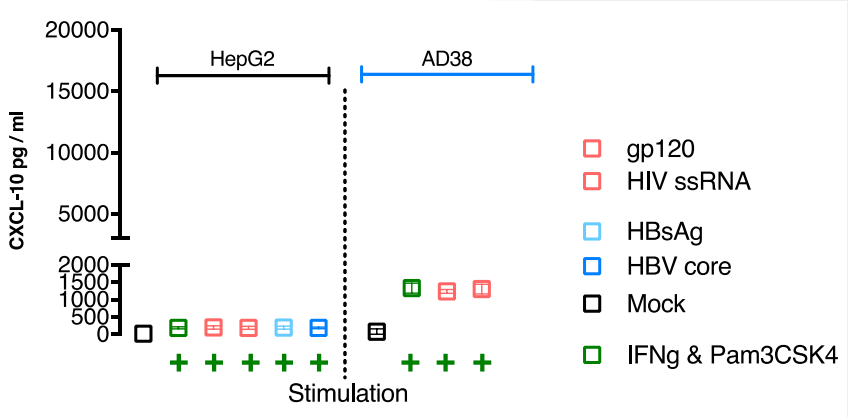
CXCL10 level increased with increasing MOI v-HIV in the presence of IFN-γ



CXCL10 production was higher in HBV transfected cell lines compared with the parent cell line with v-HIV infection



Hepatitis B / HIV proteins and ssRNA had little effect on CXCL10 production



Conclusions

- Markers of microbial translocation (LPS, sCD14) were not associated with liver disease in HIV-HBV infected individuals not on treatment
- CXCR3 and CXCL10 were significantly associated with fibrosis and liver enzyme elevation consistent with infiltration of CXC3+ cells (e.g. activated T-cells) driving liver disease
- CXCR3 and CXCL10 should be investigated as novel targets to minimize liver disease in HIV-HBV co-infection

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