LIVER DISEASE PROGRESSION IN HIV-HBV COINFECTION ON ART IS ASSOCIATED WITH HMGB1

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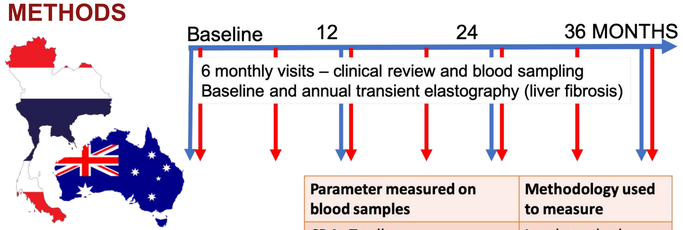
BACKGROUND

We investigated liver disease progression in HIV-HBV co-infected individuals on ART, and its relationship with inflammatory cytokines and products of microbial translocation.

In HIV-HBV co-infection, liver disease progression is accelerated, and liver related mortality increased, including in those on antiretroviral therapy (ART). Systemic inflammation and gut permeability are increased in HIV infection and may drive accelerated liver disease.

METHODS



Parameter measured on blood samples	Methodology used to measure
CD4+ T cells	Local standard
Viral load (HIV, HBV)	PCR (local standard)
Cytokines (IL10, IL18, CXCL9 (MIG) ,10 (IP10) ,11 (I-TAC), MCP-1 (CCL2) CC3 (MIP1a), CCL4 (MIP1b), tnf-α, CCL5 (RANTES))	Multiplex bead array
HMGB1, sCD14, LPS	ELISA

INCLUSION:
HIV+ AND HBsAg+ (>=6m)
ART ≥ 12m
Last HIV RNA <50 AND
HBV DNA ≤ 357 IU/mL
(Excluded +HCV)



Liver disease progression was defined as (1) an increase in Metavir grade (defined by kPa grade equivalent ranges defined in HIV-HBV infected individuals) (Table 1) and (2) at least 20% or a 2kPa increase in kPa with at least one value > 5.9kPa.

Table 1 Metavir grade equivalent transient elastography (TE) scores in HIV-HBV

	TE equivalent	
Metavir stage	**HIV-HBV**[1]	HBV
F1	**<5.9**	<7.1
F2	**5.9-7.5**	7.1-9.4
F3	**7.6-9.3**	9.5-14.1
F4	**>9.3**	>14

[1] Miailhes P, et al, J Viral Hepatitis 2011

Comparisons were made using Wilcoxon rank-sum test for continuous data and chi-square test or Fisher's exact test for categorical data at baseline and subsequent timepoints.

More than 15% of HIV-HBV co-infected individuals on suppressive antiretroviral therapy have **progressive liver fibrosis**. Liver disease progression was associated with higher **HMGB1** and lower **CD4 count.**

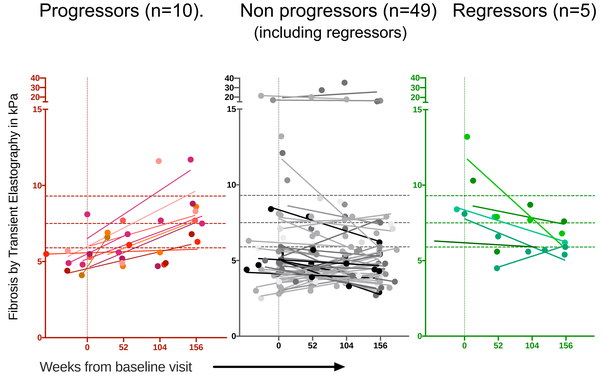
RESULTS

67 participants (57 male) were enrolled (Table 2 – Demographics). Median nadir CD4+ T cell count was 25 (IQR 35-225) cells/μL and 21/69 were HBeAg+. 59 were assessable for progression status. 10 participants were classified as progressors by fibrosis grade (Fig.2) and 10 by kPa. 8 were progressors by both definitions.

Table 2 Demographics

		Baseline
Site	HIV-NAT, Bangkok (n,%)	31/67 (46%)
	Australia	36/67 (54%)
Demog.	Age, years (mean, SD)	51 (44, 58)
	Female	9 (13%)
	BMI (mean, SD)	22.7 (20.9, 26.2)
	Excess alcohol (n=62)	8 (13%)
HBV	HBeAg positive (n,%)	21/67 (31%)
Liver fibrosis (TE)	Fibrosis – TE, kPa (median, IQR), n=63	5 (4.4, 5.9)
	- F1 (<5.9kPa) (n, %)	47/60 (75%)
	- F2 (5.9-7.5kPa) (n, %)	6/60 (10%)
	- F3 (7.6-9.3 kPa) (n, %)	4/60 (6%)
	- F4 (>9.3kPa) (n, %)	6/60 (10%)

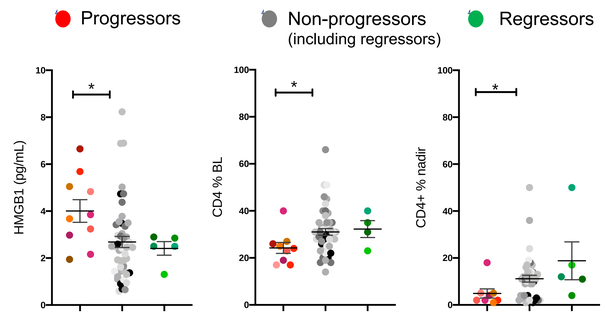
Fig1 Fibrosis progression by transient elastography (TE) by progressor status, classified by Metavir Grade (TE equivalent); Symbols of the same shade represent TE readings for the same individual



RESULTS (continued)

Progressors had similar baseline characteristics to non-progressors but progressors had significantly higher levels of high mobility group box 1 protein (HGMB1), a marker of cell death, using either definition (by fibrosis grade (p=0.011) and kPa (p=0.041)). CD4+ T cell count was significantly lower in progressors than non-progressors when defined by kPa change (27 and 145 cells/μL respectively; p=0.018).

Fig2. Progressors and non progressors had significantly different HMGB1 levels (far right) and CD4+ T cell % (both nadir (far left) and baseline (middle)); Each dot represents result for an individual patient. Comparisons by Mann-Whitney.



No significant differences were seen between the two groups in other parameters including lipopolysaccharide, soluble CD14 or inflammatory markers including CXCL-10, monocyte chemotactic protein-1 or tumour necrosis factor-α.

CONCLUSIONS

In the setting of ART, 10/59 (16%) of HIV-HBV co-infected individuals have progressive liver fibrosis. Liver disease progression was associated with higher HMGB1 and lower CD4+ T cell count. Interventions to prevent liver disease progression on ART require further investigation.

ADDITIONAL KEY INFORMATION

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