

Dr Sion Williams

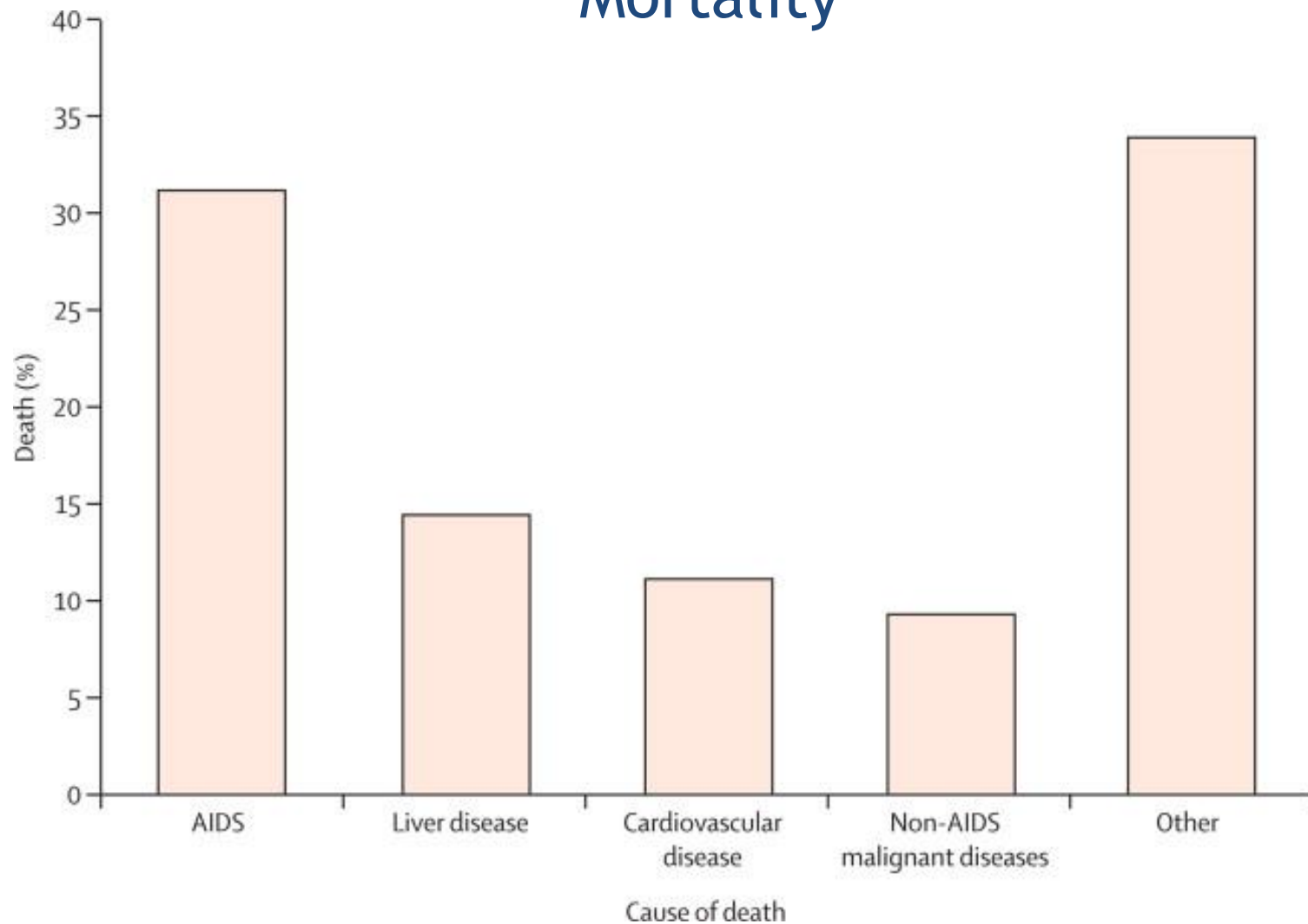
Brighton and Sussex University Hospitals

Quantification of hepatic FOXP3+ T-lymphocytes in HIV-hepatitis C co-infection - a mechanism for poor outcomes?

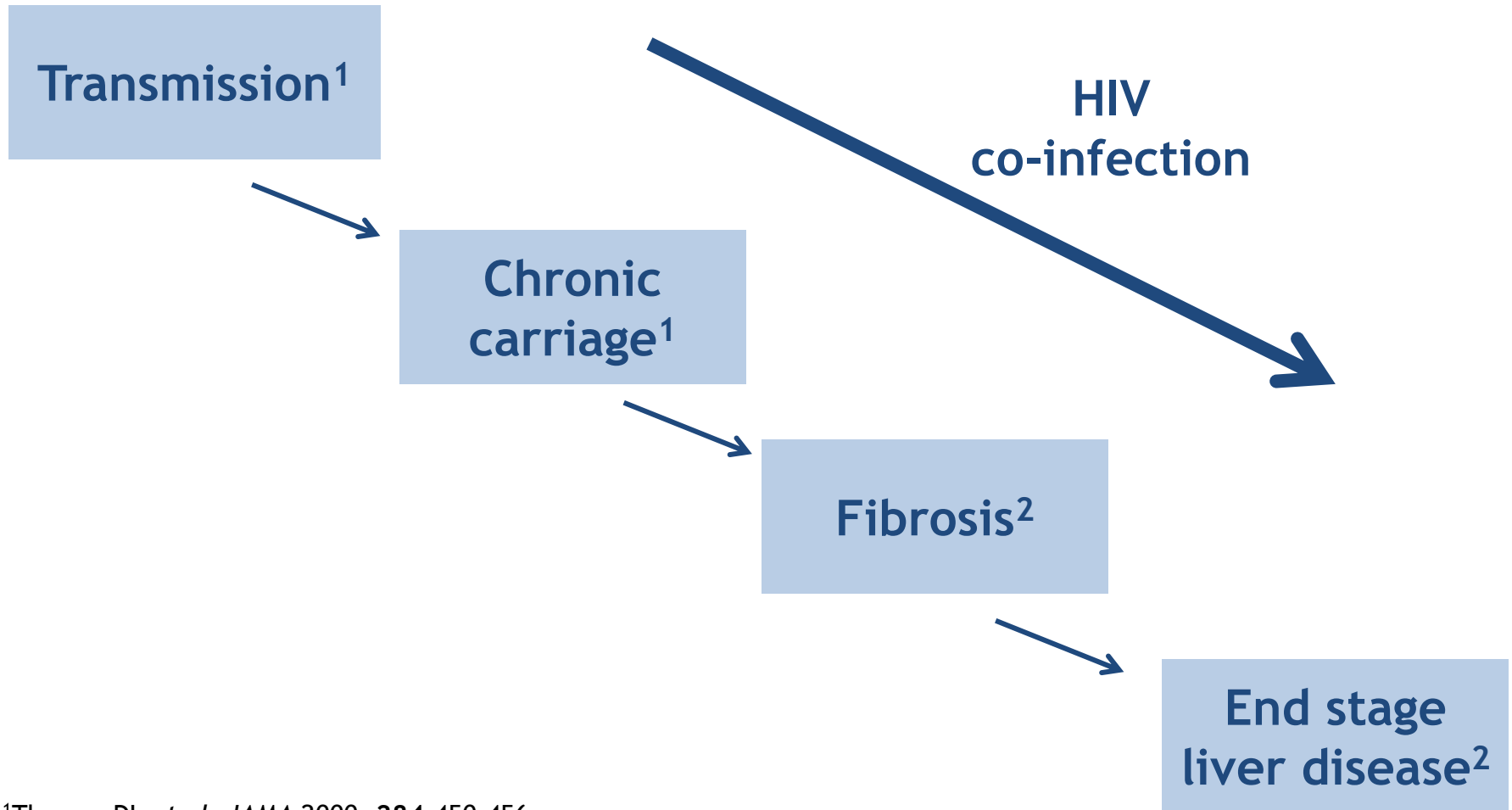
SK Williams, E Donaldson, T Van der Kleij,
L Dixon, M Fisher, J Tibble, Y Gilleece,
P Klenerman, AH Banham, M Howard,
DP Webster

Liver disease in HIV

Mortality



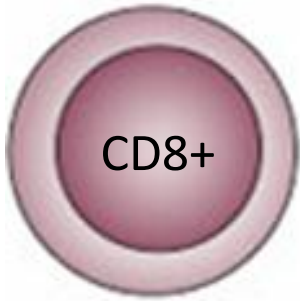
History of HCV infection



¹Thomas DL *et al.* *JAMA* 2000; **284**:450-456.

²Macías J *et al.* *Hepatology* 2009; **50**:1056-1063.

Effector
T-lymphocytes



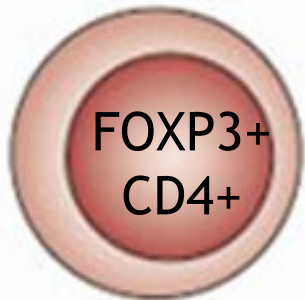
Damage



HCV-infected liver



Inhibition



Regulatory
T-lymphocytes

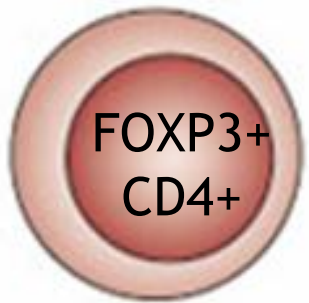
Effector
T-lymphocytes



Damage

HCV-infected liver

Inhibition



Regulatory
T-lymphocytes

- FOXP3 is a transcription factor in Treg¹
- Treg marker²
- Protective against cytotoxic T-cells³
- Significant role in HCV²
- Inversely proportional to fibrosis in HCV²
- No studies in co-infected patients

¹Hori, S. *et al. Science* **299**, 1057-1061 (2003).

²Ward, SM. *et al. J Hepatol* 2007; **47**:316-324.

³Sakaguchi, S. *et al. Annual Review of Immunology* **22**, 531-562 (2004).

Hypothesis

Fewer hepatic FOXP3+ Treg cells in subjects with HIV/HCV co-infection compared with HCV mono-infection may explain the poorer clinical outcome

FOXP3 cells in HIV-HCV co-infection study

- Retrospective, cross-sectional
- Archived liver biopsies from Sussex patients
- 35 participants
 - HCV mono-infected (11)
 - HIV/HCV co-infected (12)*†
 - HIV mono-infected (12)*
- Male, non-African, no HepB
- Matched
 - Age (+/- 7 yrs)
 - Fibrosis (ISHAK)

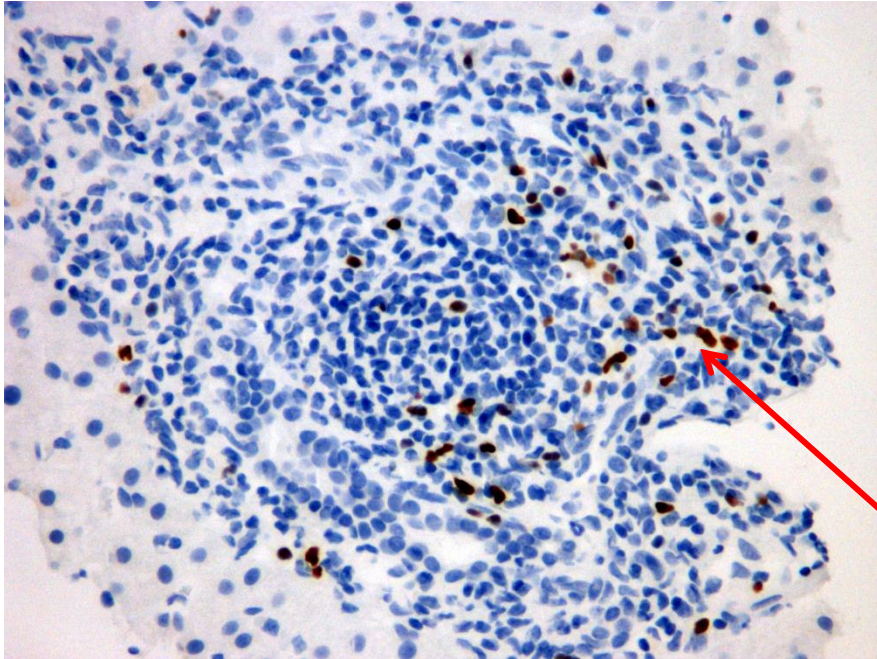
	Mean (range)
Age (years)	47 (34-61)
ISHAK score (/6)	2 (0-6)
Blood CD4 [‡] (x10 ⁶ /L)	570 (230-950)

‡where applicable

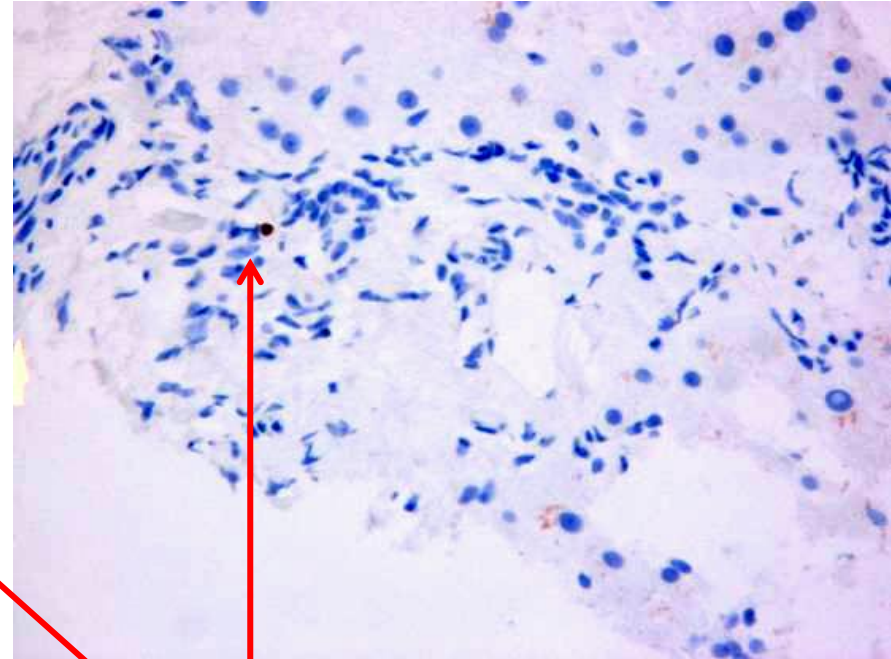
*HIV-1 infected

†11 of 12 on HAART

HCV mono-infected patient



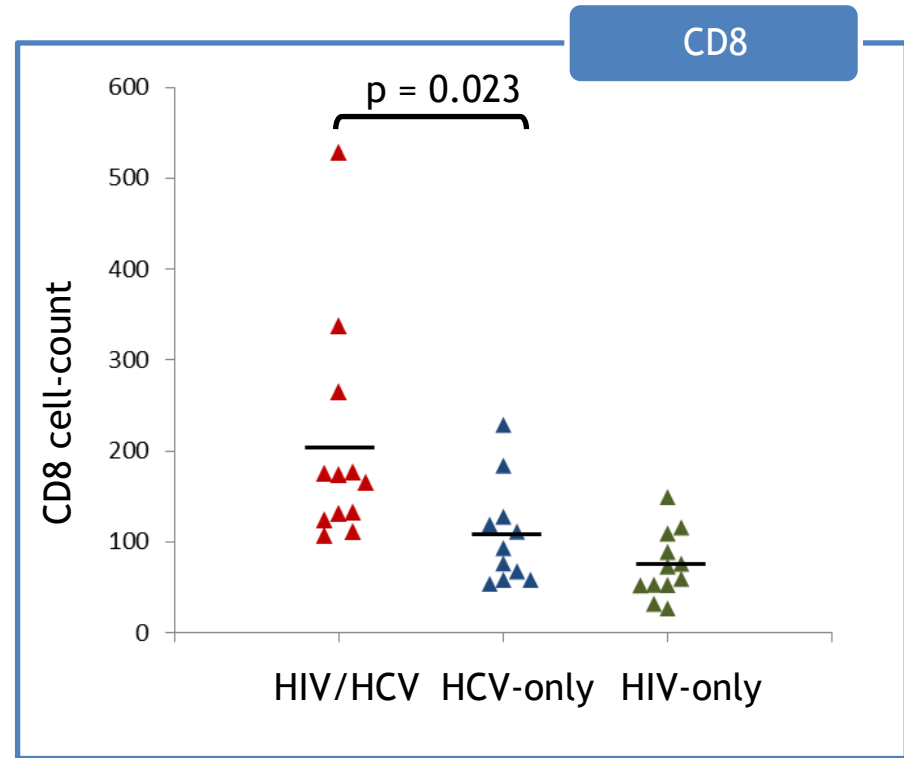
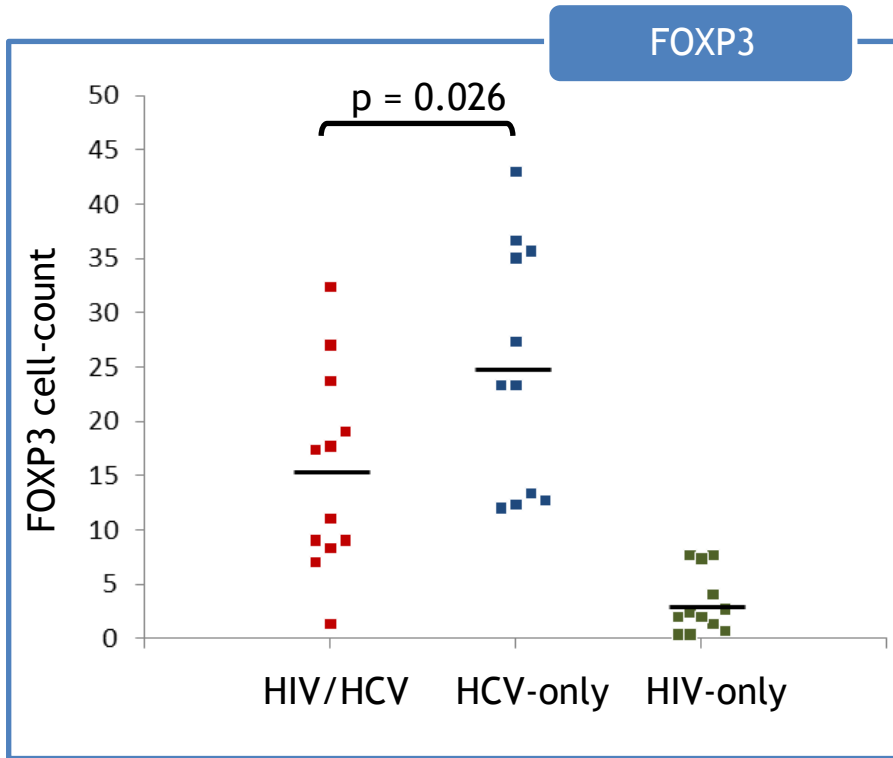
HIV/HCV co-infected patient



FOXP3+

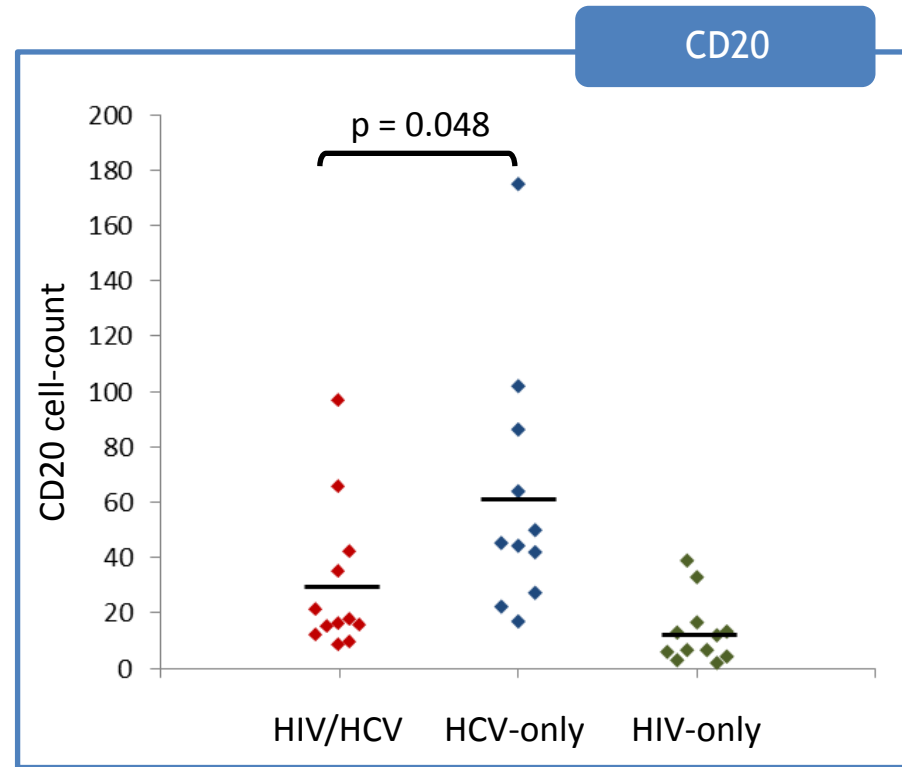
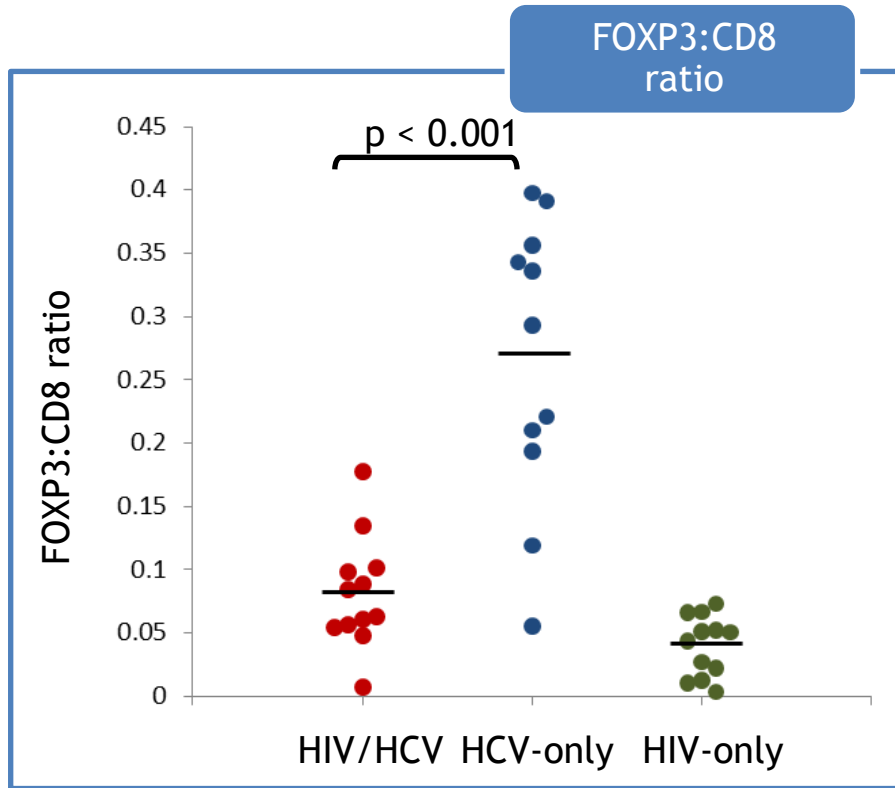
- Quantified FOXP3+, CD8+, CD4+ and CD20+ cells
- Indirect immunohistostaining and light microscopy

Results (1)



HIV/HCV co-infected patients have significantly fewer hepatic FOXP3+ cells and more CD8+ cells than HCV mono-infected patients

Results (2)



HIV/HCV co-infected patients have a significantly lower hepatic FOXP3:CD8 ratio than HCV mono-infected patients

HIV/HCV co-infected patients have a significantly fewer hepatic CD20+ cells than HCV mono-infected patients

Reduced regulatory activity dependent on hepatic CD4 count

Dependent variable (OR) of HCV mono-infected : HIV-HCV co-infected

Univariate

Variable	Odds ratio	P value
FOXP3	1.1	0.05
Variable	Odds ratio	P value
CD4 (liver)	1.1	0.02

Multivariate

Variable	Odds ratio	P value
CD4 (liver)	1.1	0.04
FOXP3	1.01	0.8

Discussion

- Fewer FOXP3+ cells in livers of co-infected patients suggests lower regulatory activity
- More CD8+ cells in co-infected patients suggests higher cytotoxic activity
- Fewer CD20+ cells suggests weakened humoral immunity
- This picture may explain why HCV/HIV co-infected patients have worse outcomes
- Rationale for starting HAART earlier in co-infected patients?

Thank you for listening.

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British HIV Association
BHIVA

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British HIV Association (BHIVA)**

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