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Acquisition of acute HCV in HIV-infected subjects is associated with cerebral disturbances but not increased microglial cell activation: a PET study

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Background

Fatigue frequently reported in chronic HCV monoinfection[1]

Investigation of biological mechanism:

- *HCV RNA detected in CSF and brain tissue[2,3]*
- *increased microglial cell activation[4] and neuroinflammation[5,6]*
- *cognitive impairments[6,7]*

Now generally accepted despite potential confounders:

- *depression,'diagnosis effect', drug use, hepatic encephalopathy*
- *independent of drug-use or liver disease severity and reverse with SVR[8]*

[1] NEJM (1995) 332(22):1463-6 [2] J Virol 76(19): 10064-8 [3] J Neurovirol 14(1): 17-27 [4] J Hepatol 49(3): 316-22 [5] J Hepatol 41(5): 845-51 [6] J Hepatol (2002) 36(6):812-8 [7] Lancet 358(9275): 38-9 [8] HIV Med 9(8): 520-8

Acute HCV

Whether CNS disturbance occurs during acute phase of HCV infection is not yet known

Higher rates of SVR with early treatment[1] – due to shorter time for HCV to establish CNS reservoir?

Low efficacy of IFN monotherapy maybe due to its inability to cross the BBB[2]

Current epidemic of acute HCV in HIV-infected MSM gives unique opportunity for study

[1] J Viral Hepat 17(3): 201-7 [2] J Hepatol 31 S1: 152-9

Aim

To investigate the effect of acute HCV in HIV-infected subjects upon cerebral function:

-cognitive performance

-cerebral metabolites using MR-spectroscopy

-microglial cell activation using PET scans

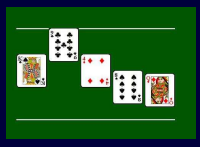
Methods

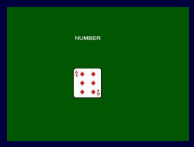
Case-control study performed at St Mary's and Hammersmith Hospitals, 2009-10

- **Inclusion criteria: acute HCV/HIV cases (*aHCV*)**
  - Acute HCV = confirmed positive plasma HCV RNA within 12 months of negative RNA
  - Chronic HIV infection, age >18 years
- **Inclusion criteria: HIV-monoinfected controls (*HIVmono*)**
  - HCV IgG/RNA negative within past 12 months and normal ALT thereafter
  - Matched by age, time since HIV diagnosis, current and nadir CD4+ count, current plasma HIV RNA and type of cART (naïve, NNRTI or PI-based)
- **Exclusion criteria (all) :**
  - No recreational drugs or BDZs for 4 weeks
  - Current ADI, any neurological disease, dementia, untreated syphilis, chronic HBV, **current receipt of IFN/RBV,** hepatic synthetic function impairment

Methods

1. Neurocognitive performance using computerised cognitive assessment *(Cogstate)*

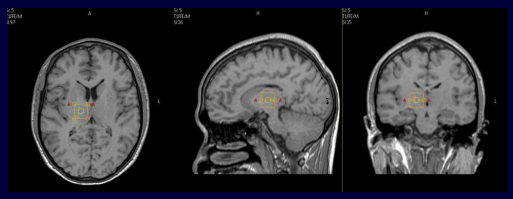


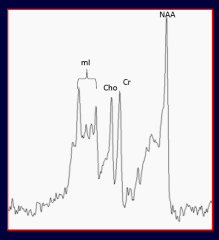


•Cognitive speed, performance accuracy, executive function and composite *Z*-score

Methods

2. MR proton spectroscopy – to investigate cerebral inflammation





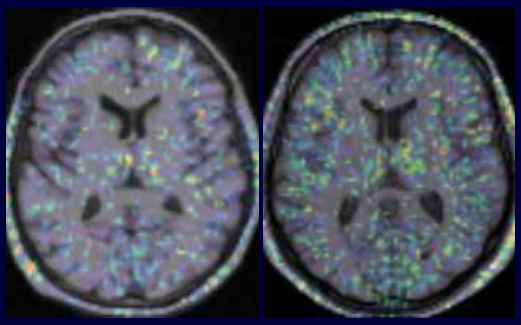
Spectra output from basal ganglia

Objectively quantifies chemical metabolites in brain tissue

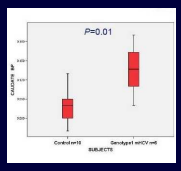
- N-acetyl aspartate (NAA)- *neuronal origin – reduced in dementia*
- myo-inositol (mI)- *increased in neuroinflammation, microglial activation and astrogliosis*
- Choline (Cho)- *increased in inflammatory CNS diseases*

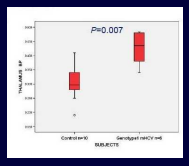
Methods

3. PET scans with injectable ligand (*PK-11195*) specific for activated receptors on microglial cells



[A] healthy volunteer [B] mild chronic HCV

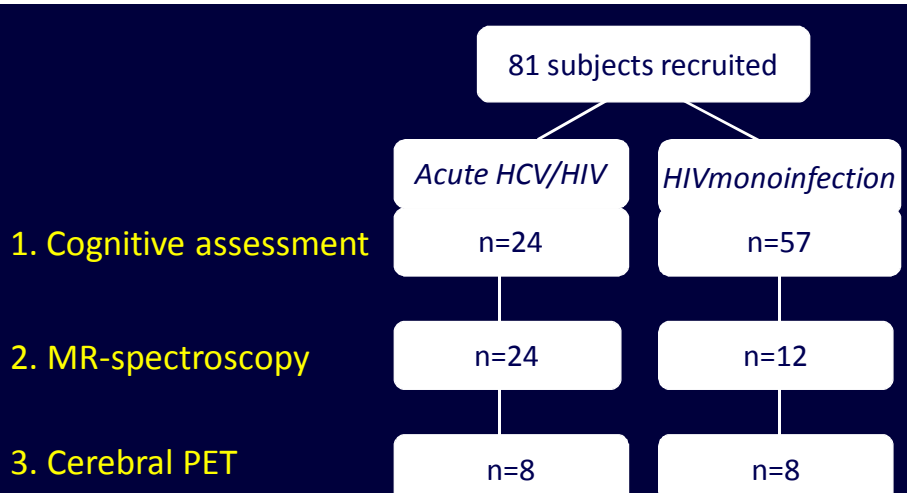




Results

	Number, n	*Acute HCV/HIV* 24	*HIVmonoinfection* 57
Patient demographics	**Age (years)**, *median [IQR]*	41 [36, 44]	47 [39, 56]
	Male gender, *n(%)*	24 (100)	50 (89)
	Time-elapsed since HIV diagnosis (years), *median [IQR]*	6 [3, 12]	11 [5, 16]
HIV disease parameters	**Current CD4+(cells/µL)**, *median [IQR]*	590 [458, 745]	505 [382, 783]
	Nadir CD4+(cells/µL), *median [IQR]*	200 [215, 395]	205 [88, 283]
	Receiving antiretroviral therapy, *n (%)*	17 (71)	54 (95)
	Current plasma HIV RNA <50 c/mL, *n (%)*	16 (67)	54 (95)
	HIV VL of remaining subjects (c/mL), *median*	17099	14182
Acute HCV parameters	**Time elapsed since negative HCV RNA (weeks)**, *median [IQR]*	24 [20, 32]	-
	Current ALT (IU), *median [IQR]*	213 [78, 237]	-
	Peak ALT (IU), *median [IQR]*	237 [180, 820]	-
	HCV genotype, n (%)		
	1	21 (88)	-
	2	0	-
	3	1 (4)	-
	4	2 (8)	-
	Most recent HCV PCR, copies/mL, *median*	3 849 936	-

Results



Results – Cognitive Assessment

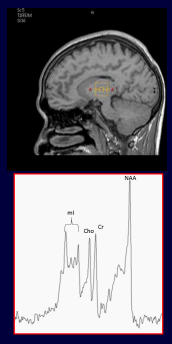
	Acute HCV versus *HIV monoinfection* study group	
	***p*-value**	**95% CI**
Composite Z-score	0.68	[-1.38, 0.90]
Cognitive speed score	0.05	[-0.99, 0.01]
Accuracy score	0.20	[-0.18, 0.83]
Executive function	**0.02**	**[0.09, 1.07]**

Results – Cognitive assessment: executive function

Parameter	Univariate analysis		Multivariate analysis	
	p-value	95% CI	*p*-value	95% CI
Acute HCV	**0.02**	**[0.09, 1.07]**	**<0.001**	**[0.55, 1.60]**
Nadir CD4+ count, *per 100 cell/uL increase*	0.09	[-0.30, 0.02]	**0.001**	**[-0.42, -0.10]**
Current CD4+ count, *per 100 cell/uL increase*	0.70	[-0.12, 0.08]	-	
Age, *per 10 year increase*	0.68	[-0.28, 0.18]	-	
Receiving cART	0.70	[-0.95, 0.65	-	
Receiving NNRTI-based cART	0.38	[-0.65, 0.25]	-	
Time since HIV diagnosis, *per 10 year increase*	0.34	[-0.06, 0.02]	-	
CPE score	0.49	[-0.22, 0.45]	-	

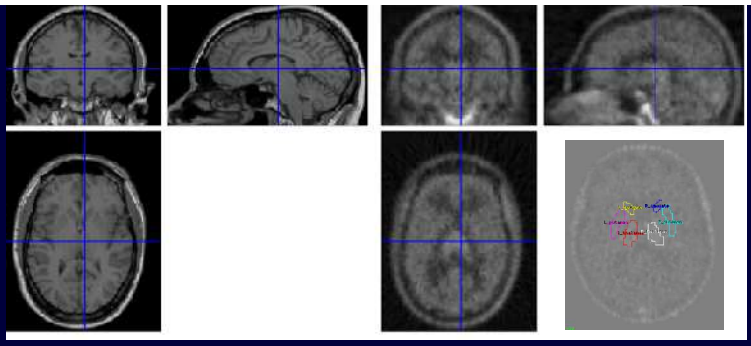
Results – MR Spectroscopy

Basal ganglia location	Acute HCV study group unadjusted analyses		Acute HCV study group adjusted analyses	
	p-value	95% CI	*p*-value	95% CI
Cerebral metabolite ratio				
N-acetyl aspartate/Cr	0.54	[-0.45, 0.84]	-	
Choline/Cr	0.36	[-2.27, 0.85]	-	
myo-Inositol/Cr	**0.06**	**[-0.03, 1.32]**	**0.03**	**[0.02, 0.35]**



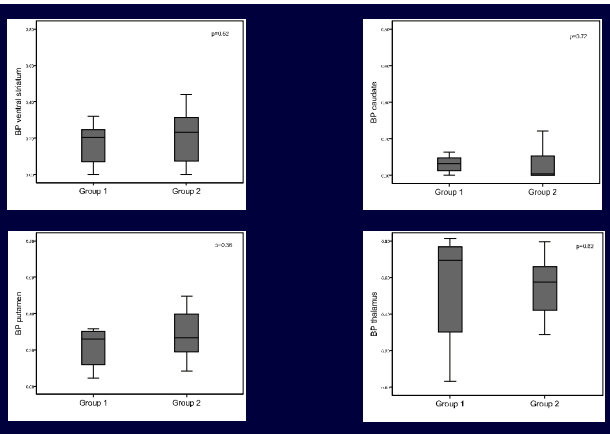
Elevated myo-inositol is objective marker of neuroinflammation

Results – PET scans



Binding potential (BP) of *PK-11195* calculated in selected cerebral locations:
Represents ratio of specifically-bound ligand to its maximum free concentration

Results – BP in ventral striatum, caudate, putamen and thalamus



No evidence of increased ligand-binding in either study group

Summary

Acute HCV coinfection associated with cerebral disturbances
- -poorer executive function
- -increased cerebral inflammatory metabolites

Similar changes previously described in chronic HCV monoinfection

Did not demonstrate increased *PK-11195* binding (differs from chronic HCV monoinfection)

Possible explanations

Microglial recruitment may occur more slowly or ligand not sensitive for acute changes (median 20 weeks since negative HCV RNA)

Microglial-cell activation may not be responsible and cerebral disturbances due to systemic circulating cytokines and fatigue

Future work to assess correlation of cerebral disturbances with Rx outcomes and longitudinal progression required

Acknowledgements

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