

# Dr Lucy Garvey

Imperial College Healthcare NHS Trust, London

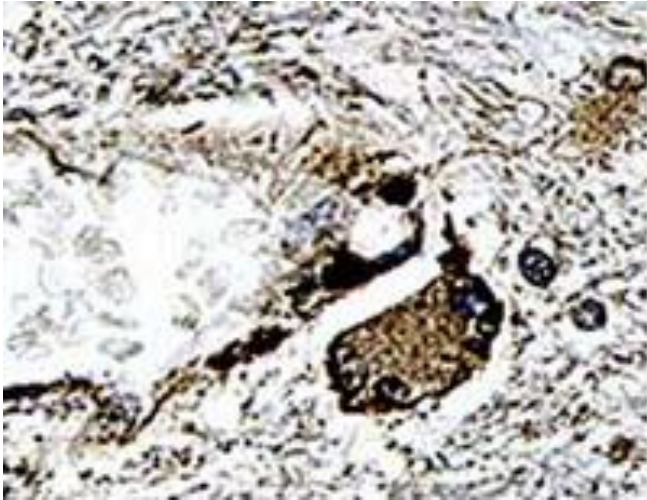
**Microglial cell activation is visualised with  
11C-[R]-PK11195-PET scans in  
neuro-asymptomatic HIV infected subjects on  
effective antiretroviral therapy**

**Lucy Garvey, Nicola Pavese, Marios Politis, Anil Ramlackhansingh,  
Simon D Taylor-Robinson, David Brooks and Alan Winston**

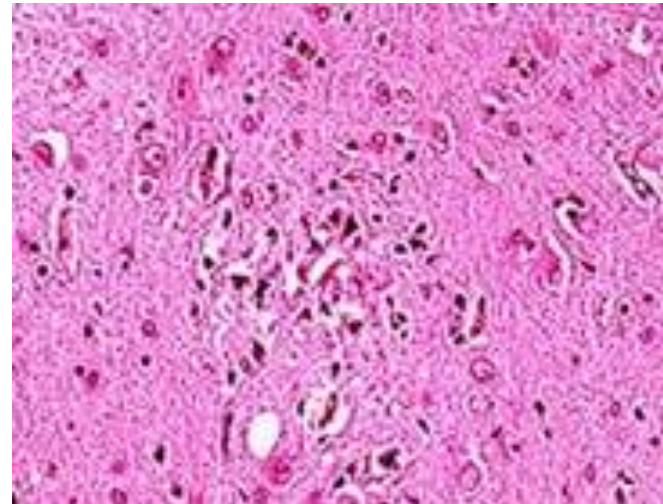
# Pathogenic mechanisms

Pathogenesis	Clinical risk factor
Persistent immune activation	Nadir CD4 count Late treatment
CNS viral replication	Late treatment Poor adherence Inadequate exposure of cART
Antiretroviral toxicity	Antiretroviral therapy
Immune restoration	Nadir CD4 count
Accelerated brain ageing	Age
Co-morbidities	Cardiovascular HCV Lifestyle Others as yet unidentified?

# Histopathological studies HIV Encephalopathy



Expression of p24 HIV proteins



Parenchymal microglial nodules

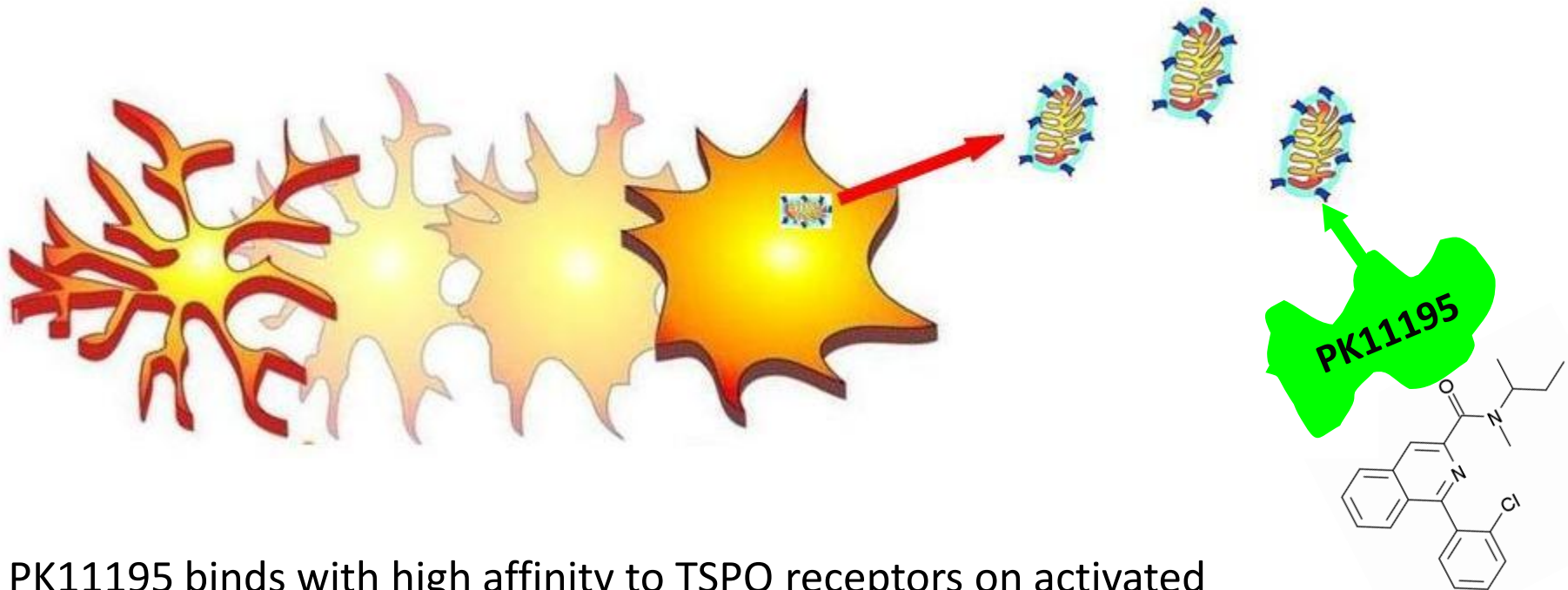
Role of neuroinflammation in milder forms of HIV associated brain disease remains unclear

# Neuroinflammation

Microglia in resting state  
'healthy brain'



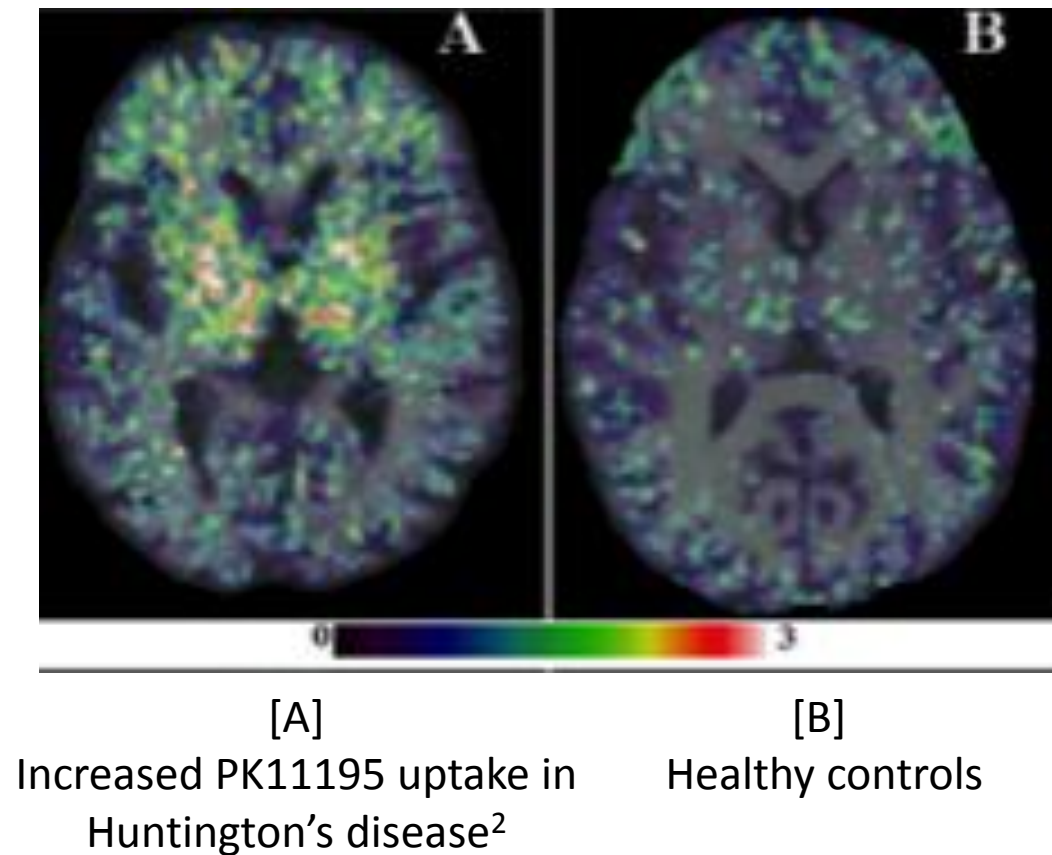
Activation = Increased expression of  
translocator proteins  
(TSPO) 18kDa receptors<sup>1</sup>



PK11195 binds with high affinity to TSPO receptors on activated microglial cells<sup>2</sup>

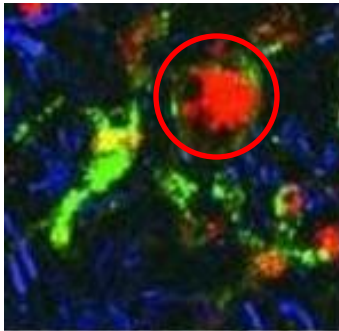
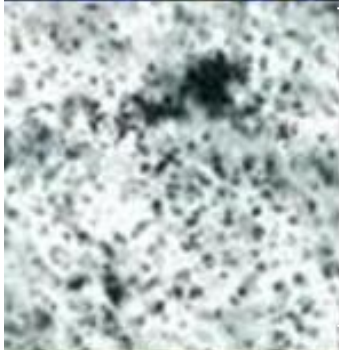
# Imaging microglial activation *in vivo*

PK11195 can be radiolabeled with  $^{11}\text{C}$  and used as a tracer with PET imaging to identify and quantify microglial activation<sup>1</sup>





# Imaging microglial activation

	<b>1. Immunostaining</b> <ul style="list-style-type: none"> <li>• Microglial cells</li> <li>• HIV virus</li> <li>• Reactive astrocytes</li> </ul>	Study population	Observation with PK 11195 and PET
		SIV-encephalitis <sup>1</sup> HIV-associated dementia <sup>1,2</sup>	Increased binding
	<b>2. PK 11195 binding</b>	SIV without encephalitis <sup>1</sup> HIV with mild cognitive deficits <sup>2</sup> Asymptomatic HIV <sup>3</sup>	No increase
	<b>3. Merged image showing areas of increased PK 11195 binding and microglial cell activation</b>	Healthy brain <sup>4</sup>	No increase

Post-mortem cortex in HIV Encephalitis<sup>1</sup>

# PK11195 clinical studies

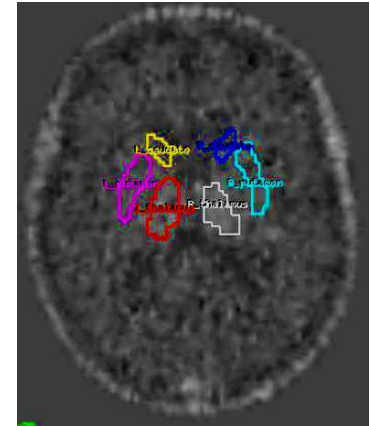
*Two analysis methods used in studies to date:*

## Regions of interest (ROI) analysis

Targeted technique using template maps

Calculates PK11195 binding in each location eg frontal, temporal, occipital, caudate, putamen, thalamus

Subtle areas of increased binding maybe missed

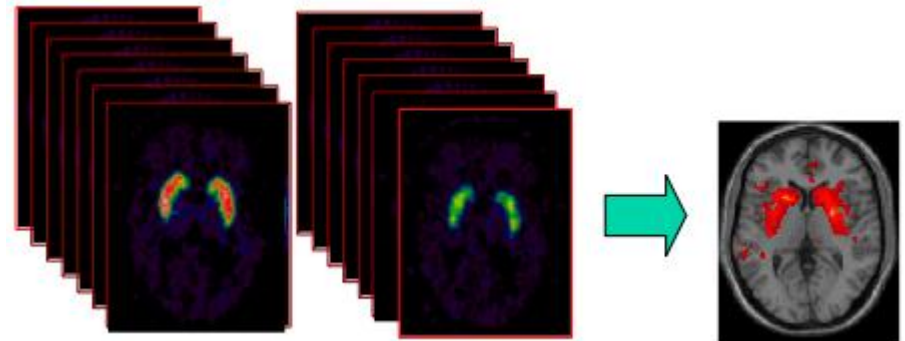


## Whole brain analysis

Voxel-based technique using Statistical Parametric Mapping (SPM) software

Detects subtle differences between groups

Little data in HIV/SIV





## Aims of study

Investigate for *in vivo* evidence of microglial activation via PK11195 ligand binding and PET scans in neuro-asymptomatic HIV infected subjects on cART

Use both targeted ROI and whole brain analysis techniques

Correlate findings with HIV disease parameters and cognitive performance

Cross-sectional study conducted at Imperial College Healthcare NHS Trust and Imperial College London, 2009-2011

### Inclusion criteria

#### Cases:

Adults over 18 years  
Chronic HIV infection  
On cART containing 3 drugs  
Plasma VL<50 for at least 6 months

#### Healthy Controls:

HIV negative adult volunteers  
Not receiving any medication

### Exclusion criteria (all) :

Any neurological symptoms or known neurological/cognitive disease  
Untreated syphilis  
Hepatitis B or C infection  
Use of recreational drugs or BDZs within the past month  
Alcohol consumption exceeds recommended weekly limits

## Assessments undertaken on same study day:

1. Cerebral T1 and T2-weighted MR scan
2. CT/PET scan  
30 seconds after scan started, iv  $^{11}\text{C}$ -[R]-PK11195 ligand  
Target quantity of PK11195 was 296 MBq (8.00mCi, approx 1.7mSv)
3. Computerised neurocognitive test (*Cogstate*<sup>TM</sup>)  
Cognitive speed, performance accuracy and executive function

## Statistics:

1. Between group comparison of PK11195 binding using ROI and voxel-based techniques
2. Association between PK11195 binding and clinical parameters and cognitive performance using SPM software

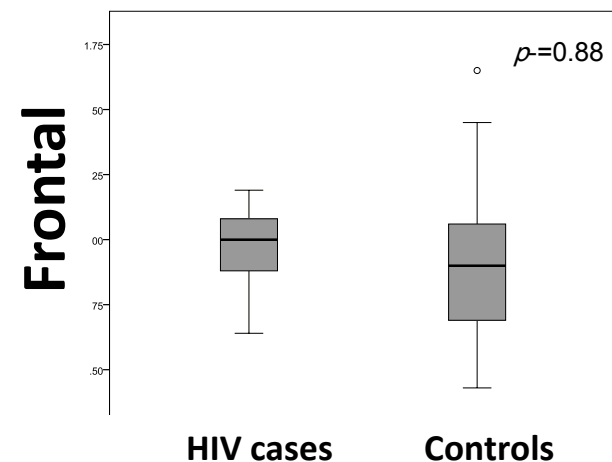
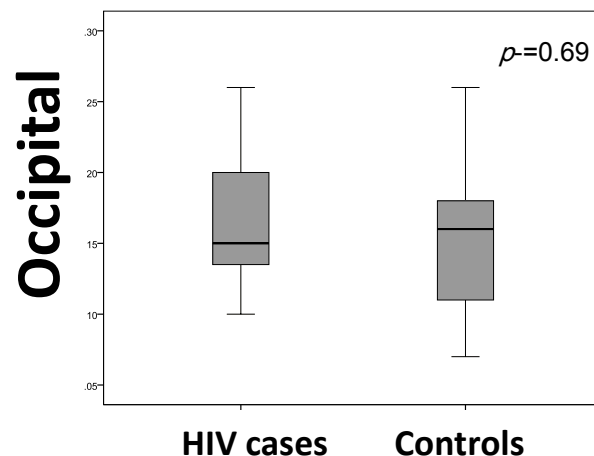
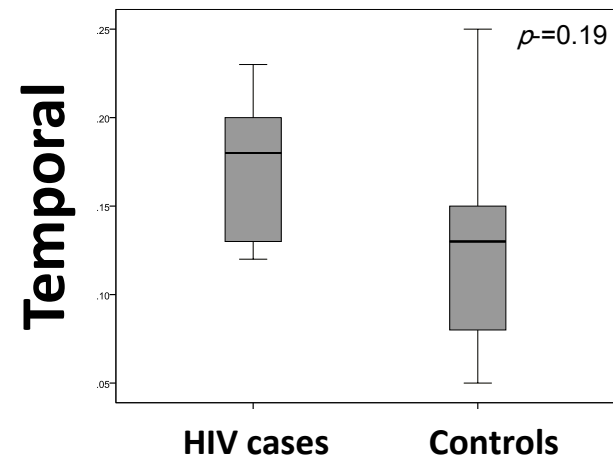
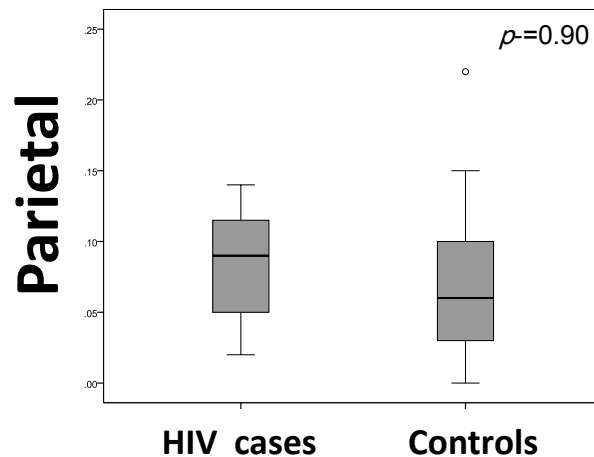
# Results – clinical parameters and cognitive assessment

Parameter, mean (SD) unless stated	Cases	Controls	Age-matched population data <sup>1</sup>
Number of cases, <i>n</i>	7	9	879
Age (years)	48 (11)	31 (5)	
White ethnicity, <i>n</i> (%)	7 (100)	9 (100)	
Current CD4+ (cells/uL)	490 (141)		
Nadir CD4+ (cells/uL)	275 (168)		
Years since HIV diagnosis, <i>mean [range]</i>	8.8 [3-22]		
Years since VL<50 copies/mL, <i>mean [range]</i>	3.6 [0.5-11]		
cART received at time of study, <i>n</i>			
<i>TDF FTC NVP</i>	1		
<i>ABC 3TC NVP</i>	1		
<i>TDF FTC EFV</i>	3		
<i>TDF FTC DRV/r</i>	2		
Cognitive assessment			
<i>Cognitive speed (ms)</i>	10.69 (0.41 )		10.74 (0.16)
<i>Accuracy (arc.proportion correct)</i>	2.33 (0.74)		1.91 (0.06)
<i>Executive function (error rate)</i>	21.28 (15.85)		-

## Results – Imaging microglial activation, ROI technique

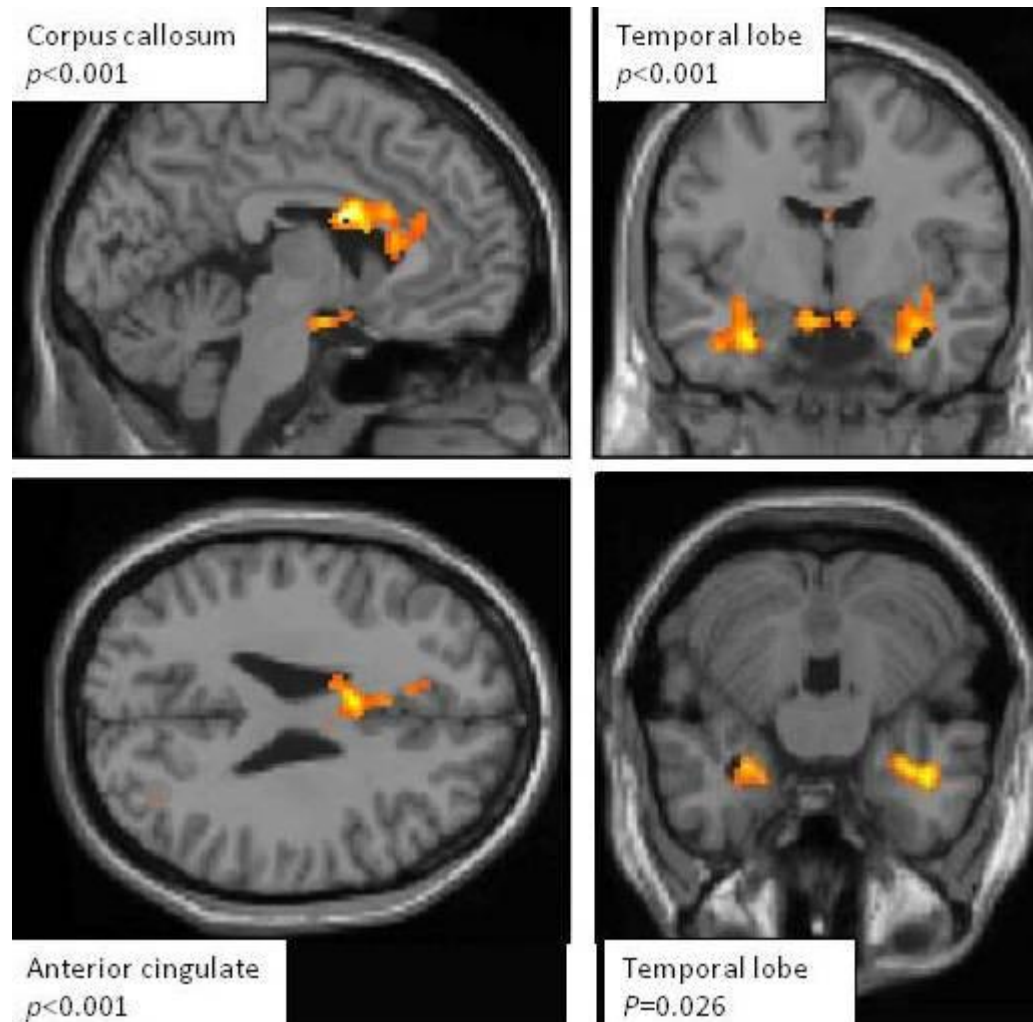
No significant difference in PK11195 ligand binding between HIV cases and controls

### PK11195 Binding



## Results – Imaging microglial activation, voxel technique

Significantly increased PK11195 ligand binding observed in HIV cases versus controls





## Results – Imaging microglial activation, voxel technique

Six cerebral locations with significantly increased PK11195 binding in HIV cases versus controls

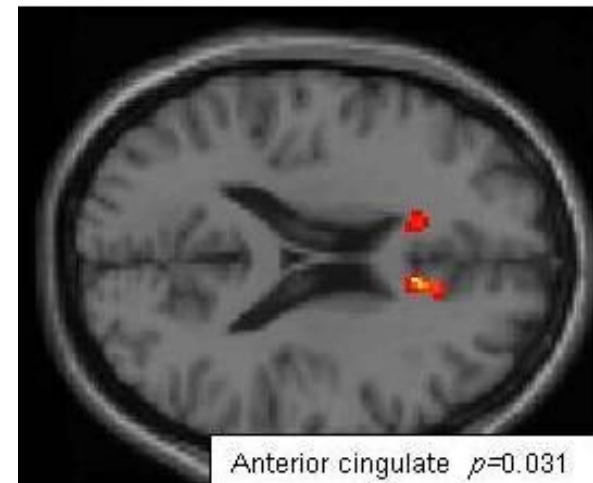
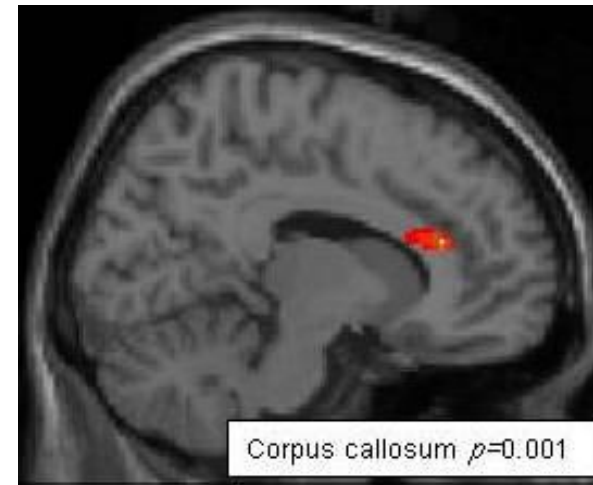
Location of increased PK11195 binding	Correlation coefficient	<i>p</i> -value
L corpus callosum	4.61	0.001
R anterior cingulate	3.28	0.001
R temporal lobe	5.60	0.001
Posterior corpus callosum/ L posterior cingulate	3.90	0.008
L temporal lobe	3.83	0.026
L frontal lobe	3.82	0.038

## Results – PK11195 and clinical/cognitive parameters

No correlation between PK11195 binding and age ( $p=0.21$ )

No correlation between PK11195 binding and cognitive speed, accuracy, nadir CD4+ count or time since HIV diagnosis ( $p>0.1$  all measures)

**Strong association between increased PK11195 binding in corpus callosum ( $p=0.001$ ,  $Z=3.04$ ) and anterior cingulate ( $p=0.031$ ,  $Z=4.66$ ) and poorer executive function in HIV cases**



## Conclusions

Using novel PET imaging and analysis techniques, this study demonstrates evidence of neuroinflammation via *in vivo* microglial cell activation in neuro-asymptomatic HIV-infected subjects on effective cART

Association between increased microglial cell activation and poorer cognitive performance but not other HIV clinical parameters

Size of study appropriate to ascertain differences in PK11195 binding, but limits secondary analysis therefore need to interpret cognitive findings with caution

We postulate persistent immune activation is a potential pathogenic mechanism which may be associated with ongoing HIV related brain disease in the cART era

# Acknowledgements

- Participants
- HIV Clinical Trials Unit, Imperial College, London UK
- Staff from the HIV Department, St Mary's Hospital, London UK
- Joanna Allsop and staff at the Robert Steiner Unit, MRC Clinical Sciences Centre, London UK
- Andy Blythe and staff at the Cyclotron Building, Hammersmith Hospital, London UK