

# 'A confused scientist'

International Symposium  
on Neuropsychiatry and HIV

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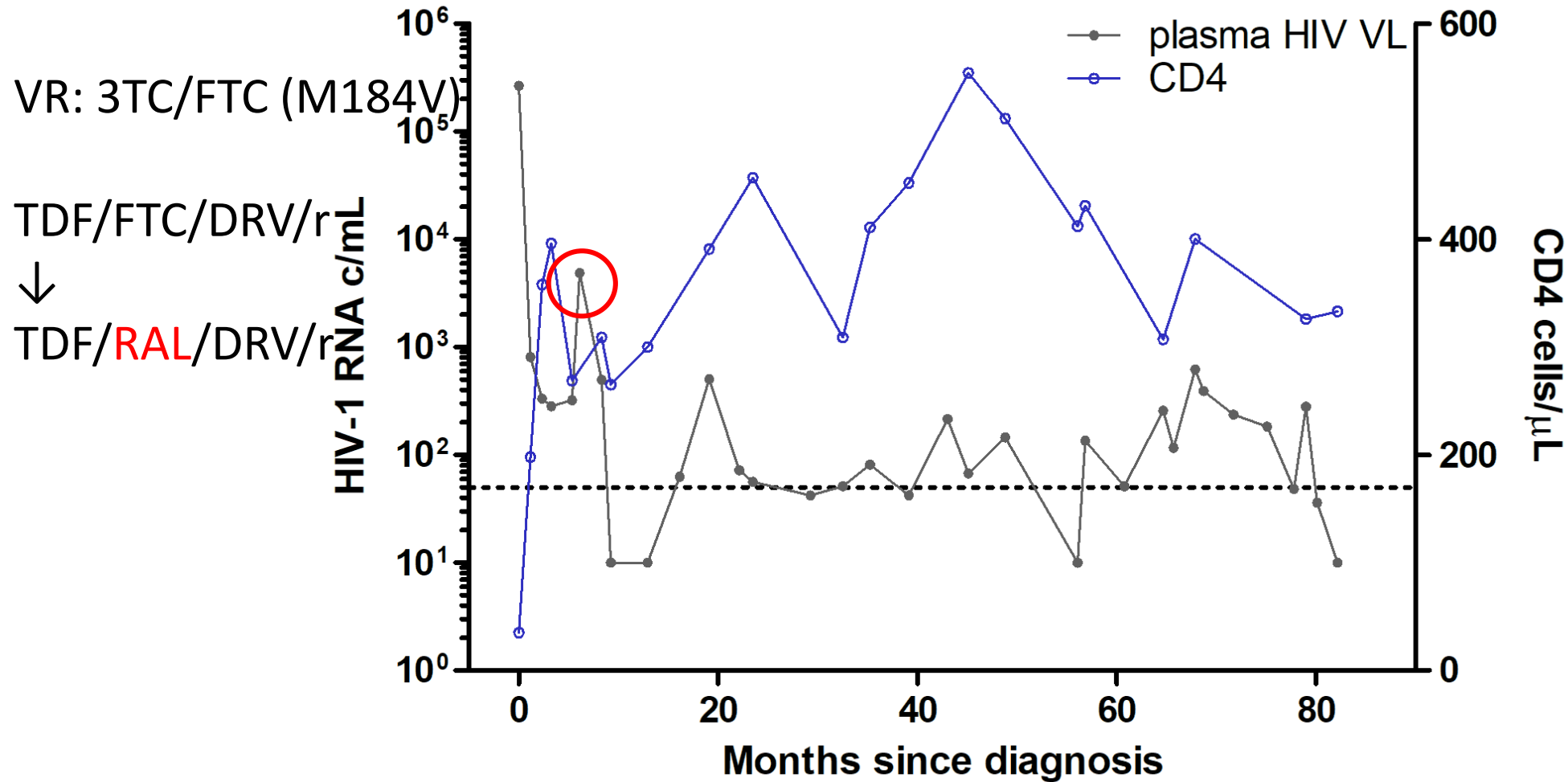
# Case history: Background

- 'M', 46F
- Born in Nigeria, in UK since 2001
- PhD (2006), works as Biomedical Scientist

# HIV history

- Diagnosed HIV+ 2012: collapse, pneumonia, ITU stay
- Severe microcytic anaemia, likely due to uterine fibroids
- Baseline bloods:
  - CD4 T-cell count 35 cells/ $\mu$ L
  - HIV viral load 200,000 copies/mL
- Possible undisclosed prior HIV diagnosis in Nigeria?
- Baseline HIV viral resistance: nevirapine (V108I)
- Commenced ART: TDF/FTC/DRV/r

# HIV treatment response



# Neuropsychiatric history

- At HIV diagnosis (2012, aged 40): confused
  - Feeling 'frightened', 'trapped'
- (non-contrast) MRI brain – mild atrophy only
- CSF: protein 0.61 g/L, glucose 3.1/5.5 , 0 WBC
- No pathogens identified:
  - CSF PCRs: toxoplasma / JC / HSV1&2, VZ, CMV – neg
  - Treponemal Ab neg (blood), CrAg neg (blood / CSF)

# Neuropsychiatric progress

- Initial confusion appeared to resolve with treatment of HIV and pneumonia
- Followed up by specialist HIV psychology service (2012):
  - Reported previous consultations with GP for depression (no current anti-depressant medication)
  - Reports 'hearing voices' during childhood / adolescence, but these were always pleasant and/or 'fortune-telling' in nature
  - No prior diagnosis of psychosis
- Voices became more persecutory
  - Referred to community psychiatric service
- 2013: 'no psychiatric issues', 'not on medication', back at work'

# Neuropsychiatric progress

- 2014-2016: no contact with mental health services
- 1/2017-5/2017 (aged 44): detained under MHA
  - Acute psychotic episode: diagnosed paranoid schizophrenia
    - paranoid persecutory beliefs
    - 3<sup>rd</sup> person hallucinations
    - elementary hallucinations (knocking)
  - Confused at initial presentation; MMSE 26/30 (2/2017)
    - Normal EEG
    - no MRI or CSF examination performed as felt to be low risk for HIV encephalitis
- Rx: aripiprazole, procycline

# Neuropsychiatric progress

- 8/2017: 'no psychotic features'; aripiprazole switched to quetiapine (EPSE)
- 10/2017: reports not taking quetiapine
  - 'a little disorientated'
  - Planning to move away from area, therefore discharged back to GP
- 5/2018 (HIV clinic): 'tearful', 'odd affect'
  - Admits occasional missed doses of ART (always claimed 100% adherence previously)



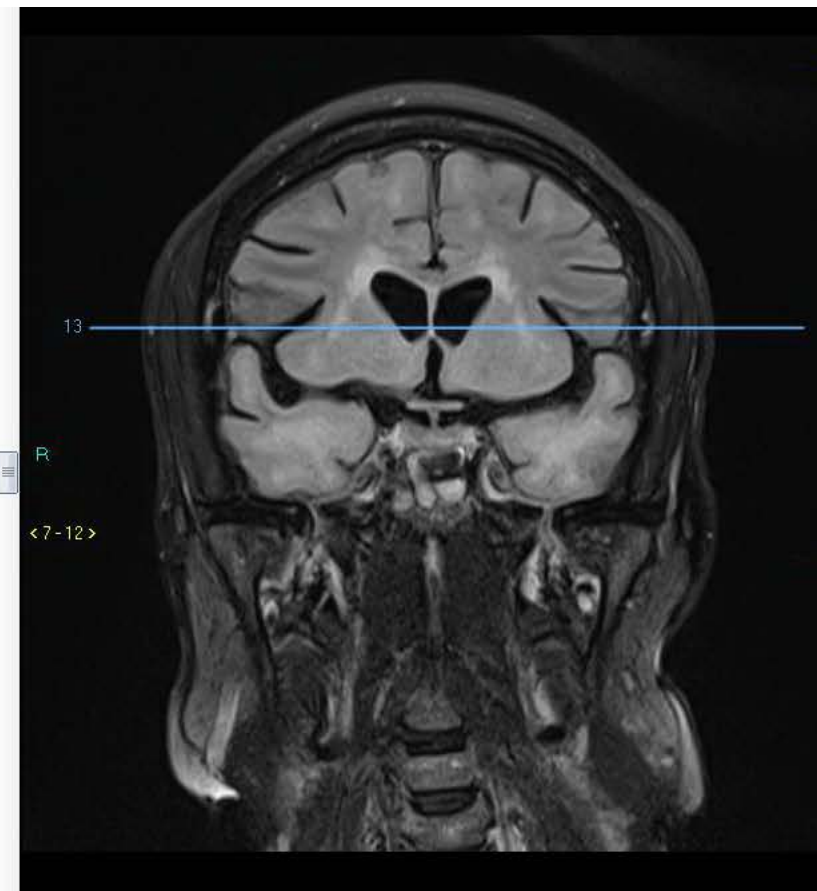
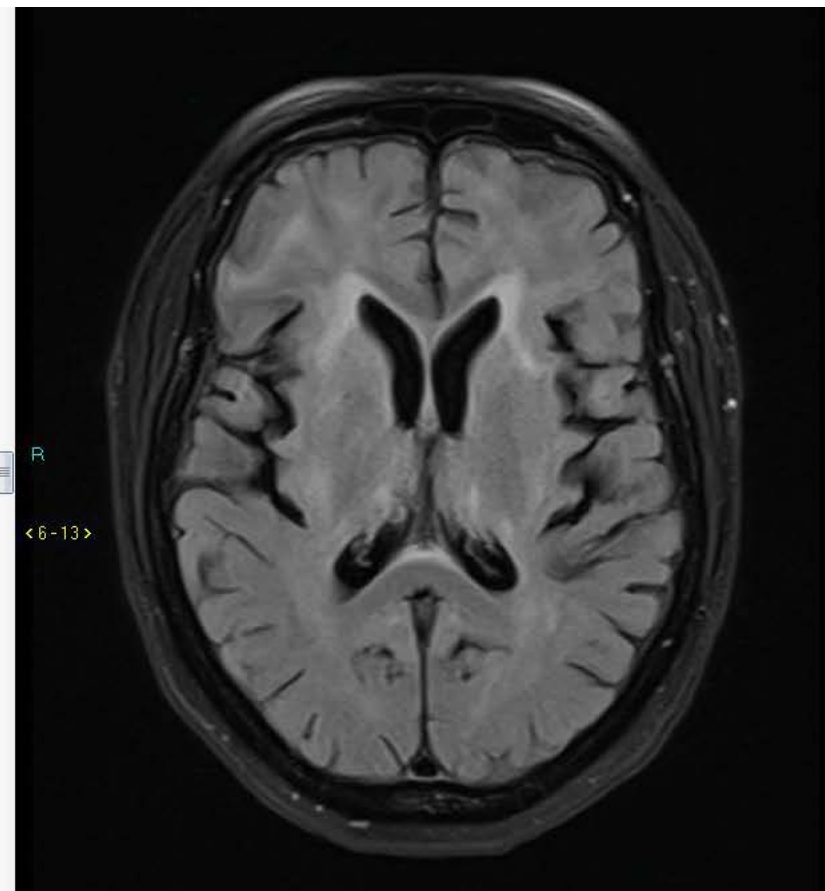
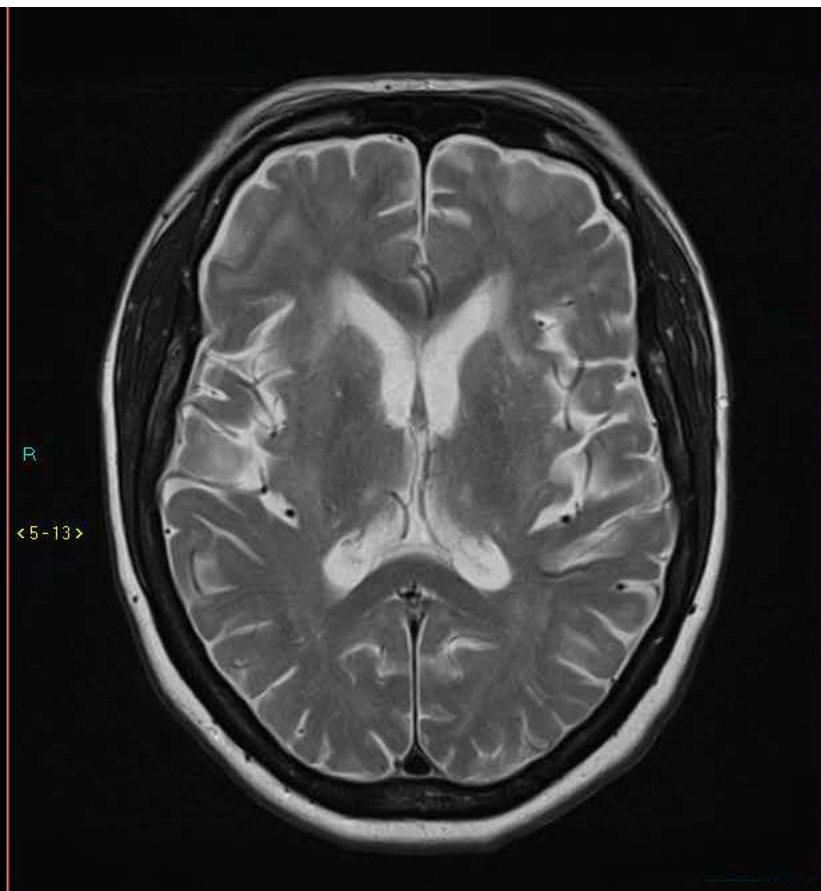
# Current episode

- 8/2018: detained again under MHA
  - Agitated, easily distressed, delusional
  - Home squalid, in state of disrepair
- Noted to have poor level of functioning, needing prompting for ADLs
- No focal neurological signs (has EPSE)
  
- Rx: flupenthixol

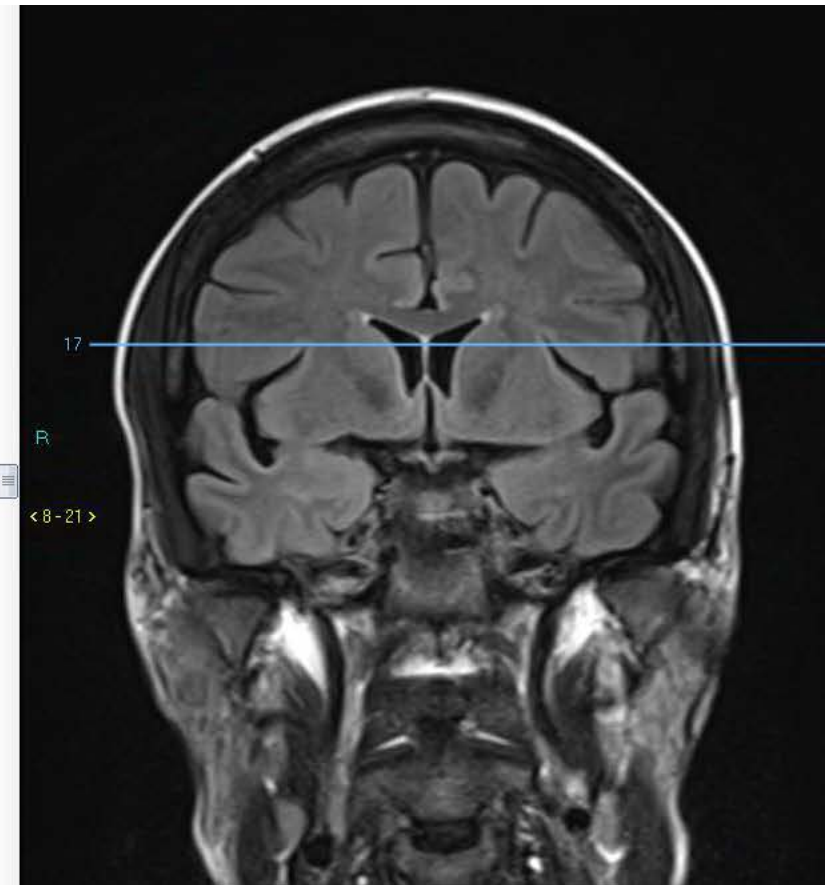
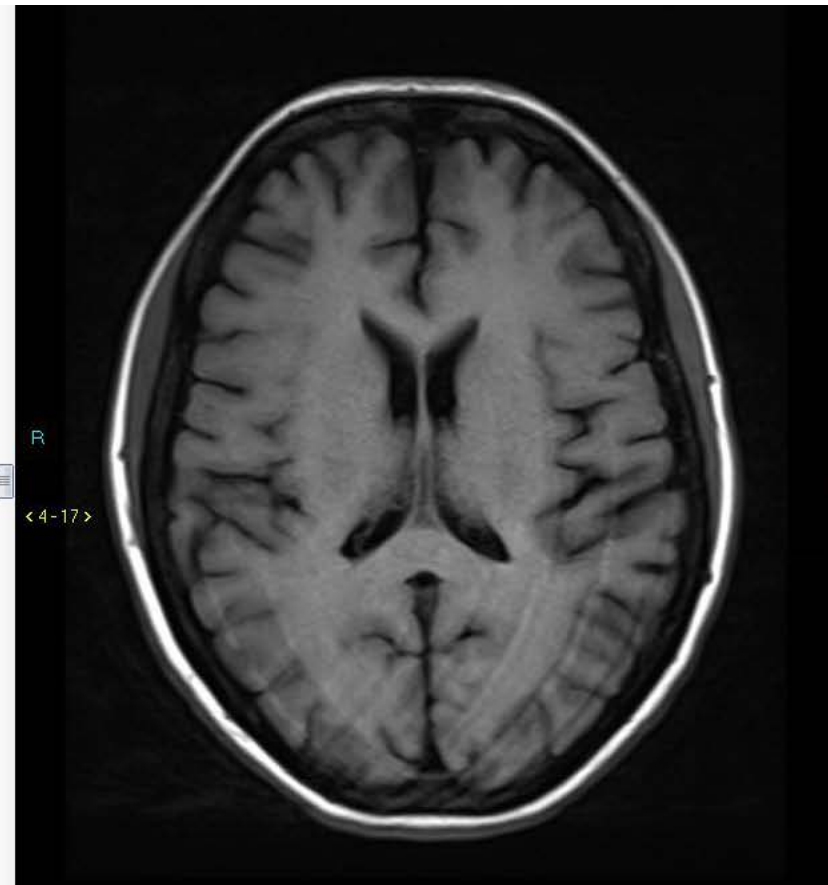
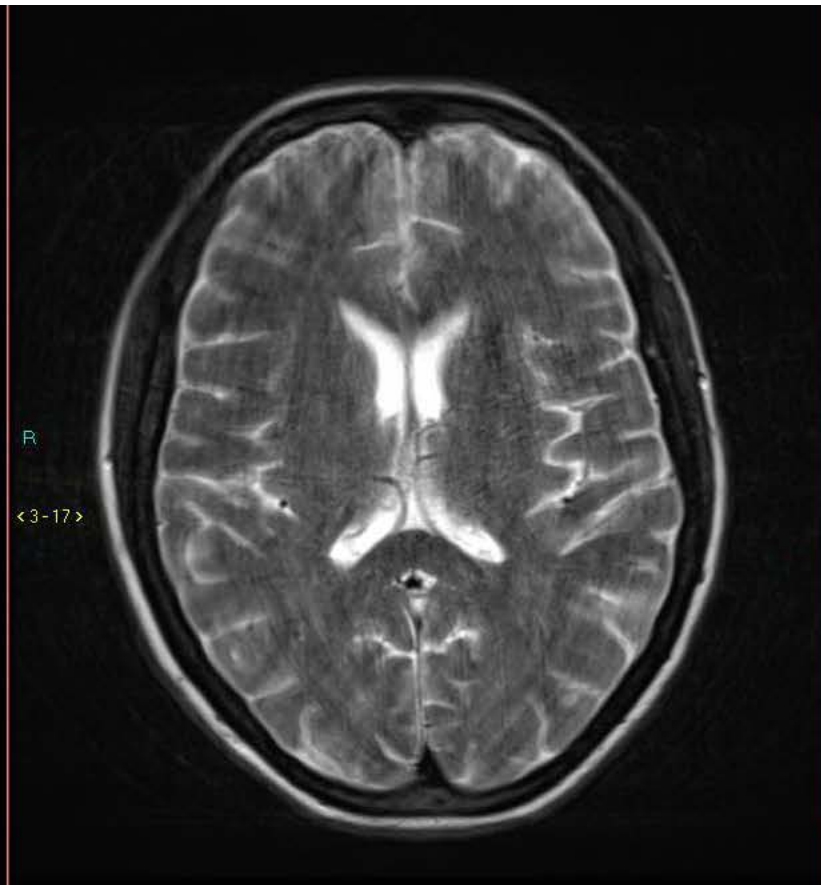
# Neurocognitive testing (11/2018)

Test	Percentile (Score)	Range
<b>Test of Premorbid Functioning (TOPF)</b>	---	Average
<b>Wechsler Adult Intelligence Scale- IV (WAIS-IV)</b>		
Verbal comprehension index overall • Similarities • Vocabulary	9 <sup>th</sup> 37 <sup>th</sup>	Low Average Average
Perceptual Reasoning index overall • Block Design • Matrix Reasoning	16 <sup>th</sup> 1 <sup>st</sup>	Low Average Impaired
Working Memory index overall • Digit Span	5 <sup>th</sup>	Borderline
Processing speed index overall • Coding	1 <sup>st</sup>	Impaired
<b>BIRT Memory and Information Processing Battery (BMIPB)</b>		
Story recall (verbal memory) • Immediate • Delayed • Retained	<2 <sup>nd</sup> <2 <sup>nd</sup> <2 <sup>nd</sup>	Impaired Impaired Impaired
Figure recall (visual memory) • Immediate • Delayed • Retained	2 <sup>nd</sup> 10-25 <sup>th</sup> 10-25 <sup>th</sup>	Impaired Low Average Low Average
List Learning • Total A1-A5 • Post distraction • Distraction • Total word recognition • Total list recognition	<2 <sup>nd</sup> 5 <sup>th</sup> 5 <sup>th</sup> <2 <sup>nd</sup> 2 <sup>nd</sup>	Impaired Borderline Borderline Impaired Impaired
<b>Delis-Kaplan Executive Function System (DKEFS)</b>		
Verbal fluency • Letter fluency • Category fluency • Category switching responses • Category switching accuracy	2 <sup>nd</sup> 0.1 <sup>st</sup> 0.1 <sup>st</sup> 0.1 <sup>st</sup>	Borderline Impaired Impaired Impaired Impaired
<b>Behavioural Assessment of Dysexecutive Syndrome (BADS)</b>		
Key Search	---	Impaired
Zoo map • Version 1 • Version 2	--- ---	Impaired Impaired

12/2018



5/2012



ID and  
Neurology  
consults  
(12/2018)

# CSF (12/12/2018)

- Prot 1.68 g/L
- 0 WBC
- PCRs neg: JC, HSV, VZ, enterovirus, CMV
- CSF CrAg neg
- Serum treponemal Ab neg
- HIV-1 RNA: 3840 c/mL

# CSF (12/12/2018)

**HIV-1 RNA: 3870 c/mL (plasma = 281)**

ART class	5/2012	1/2013	12/2018
NRTI	TDF/FTC	TDF	ABC/3TC/AZT
NNRTI			
PI	DRV/r	DRV/r	DRV/r (bd)
INSTI		RAL	DTG

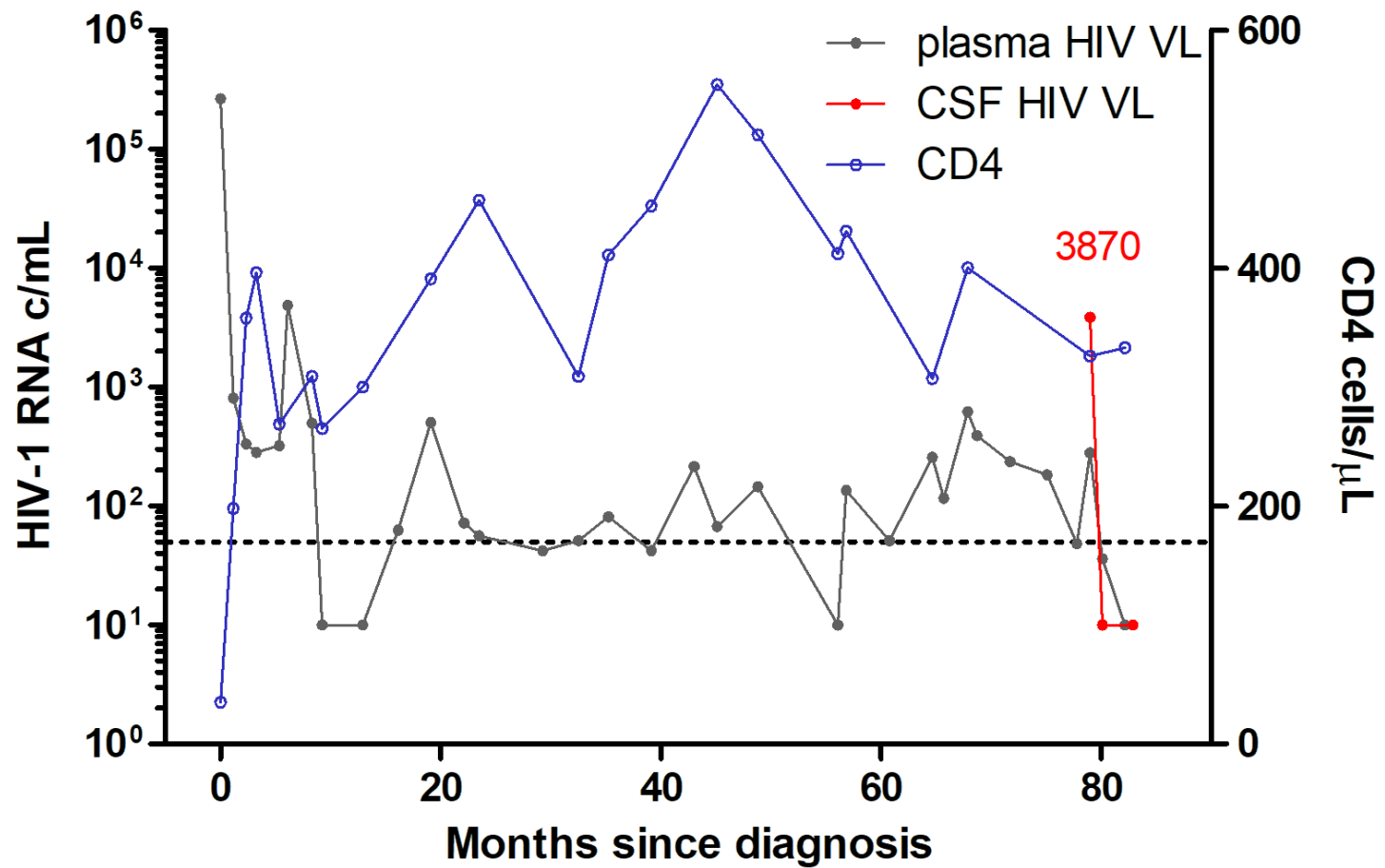
# CSF (12/12/2018)

- Viral resistance: **raltegravir** (Y143C/R), nevirapine (V108I)
- CSF viral tropism – failed to amplify
- Plasma VR – failed to amplify



# CSF

Date	protein	WBC	HIV-1 RNA
12/12/2018	1.68 g/L	0	3840 c/mL
15/1/2019	0.99 g/L	14 c/mm <sup>3</sup>	<20 c/mL
10/4/2019	0.43 g/L	0	<20 c/mL

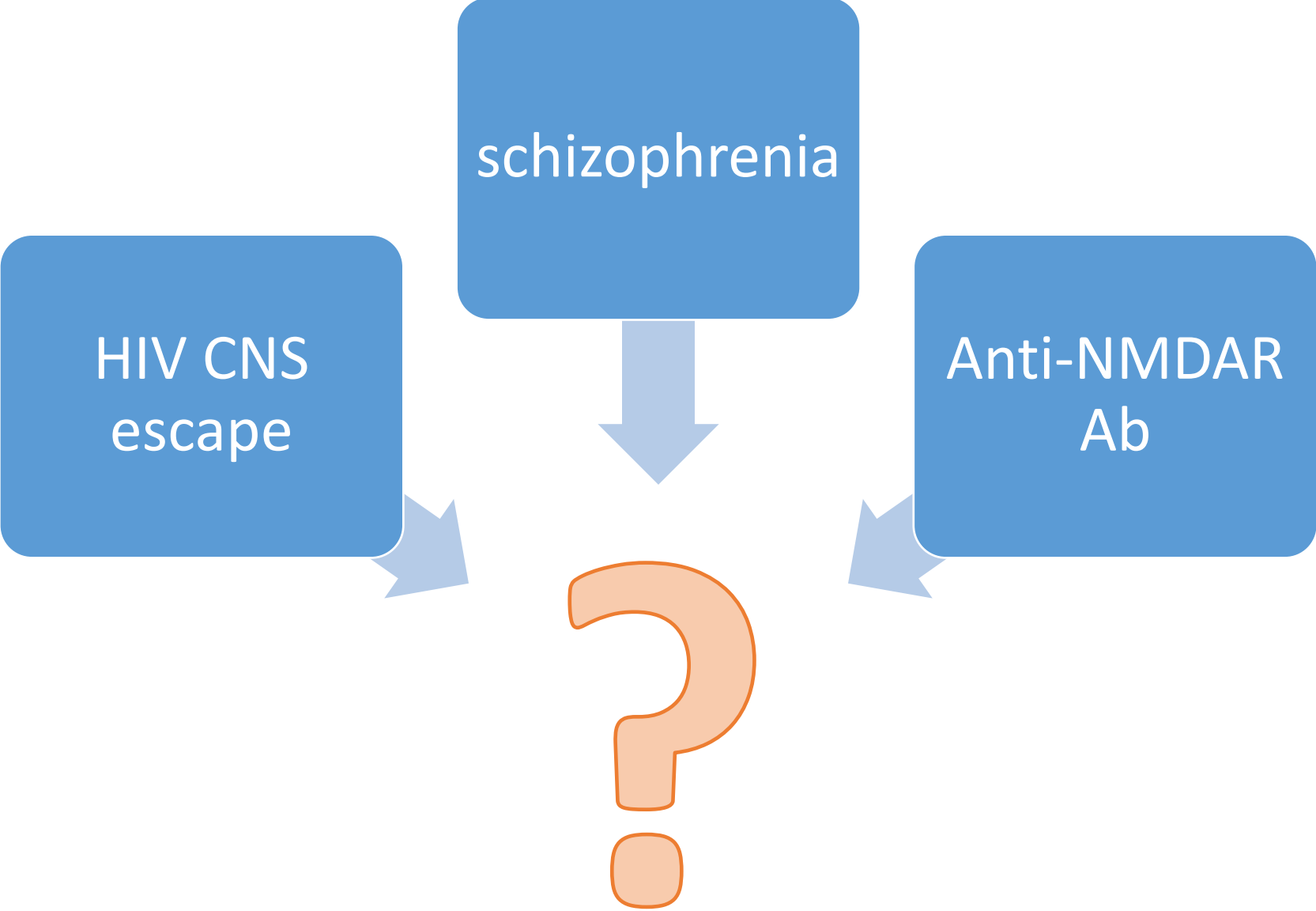


# CSF (12/12/2019)

- Prot 1.68 g/L
- 0 WBC
- PCRs neg: JC, HSV, VZ, enterovirus, CMV, (low-level EBV)
- CSF CrAg neg
- Serum treponemal Ab neg
- HIV-1 RNA: 3840 c/mL
- **Anti-NMDAR Ab positive** (serum/CSF, fixed/live cell assays)

# Clinical progress

- Currently in psychiatric rehabilitation unit
- Acute psychotic features resolved
  - Off anti-psychotic since 24/4/2019 ('thinking clearer since stopping')
- Still concern re. neurocognitive impairment – formal retest pending
- ADLs improving, but some weeks / months away from discharge



# HIV CNS viral escape

- Typical risk factors:
    - Previous VR
    - LLV
    - Suboptimal adherence
  - Typical neuroimaging
  - Typical CSF findings, VR
  - Plausible clinical features (trouble with ADLs, reduced cognition)
- **Definite CNS escape**
  - CSF escape definition (EACS):
    - either CSF HIV-VL detectable and plasma HIV-VL undetectable
    - or both CSF HIV-VL and plasma HIV-VL detectable, with CSF HIV-VL higher than plasma HIV-VL.
  - **Very likely symptomatic**

# Paranoid schizophrenia

- Fulfilled diagnostic criteria (DSM-5)
- Prior history of auditory hallucinations (specificity?)
- Responded to anti-psychotic medication
- Lack of other neurological findings
- Presence of confusion at each presentation (2012, 2017, 2018)
- Risk group for organic pathology
- Meets diagnostic criteria
- Organic element?

# Anti-NMDAR encephalitis

- Presence of anti-NMDAR Ab (blood / CSF, live / fixed cell assays)
- Association of anti-NMDAR Ab and psychosis
- Association of anti-NMDAR Ab and CNS infections
- No other neurological features typical of autoimmune encephalitis
- Response to anti-psychotic medication without immunotherapy
- Incidental finding?
- Causal / contributory?



# Anti-NMDAR encephalitis

Commonest autoimmune encephalitis associated with neuronal cell surface antibodies

Classically affects young women, but can affect any age

Often paraneoplastic (esp. ovarian teratoma)

Some cases likely triggered by infection (usually 'viral' prodrome, association with herpes simplex encephalitis)

# Anti-NMDAR encephalitis

	Groups of symptoms
1	Psychiatric / behavioural (~80%, with ~60% as initial symptom)
2	Seizures (~70%)
3	Movement disorders (e.g. dyskinesias)
4	Memory loss
5	Speech disorder (reduced output, echolalia, perseveration etc., ~70%)
6	Reduced consciousness (>80% in first 3 weeks)
7	Autonomic dysfunction (~70%)
8	Central hypoventilation (~70%, may require ICU)

# Anti-NMDAR encephalitis

CSF typically: pleocytosis, mild increased protein, oligoclonal bands

MRI: may be normal in >50%; increased signals on T2 and FLAIR, commonly cortical and subcortical and hippocampus.

EEG: abnormal in 90%

Anti-NMDAR Ab testing (Oxford Diagnostic Immunology Service):

Fixed cell assay: 99% NPV, 100% PPV

Live cell assay: 100% NPV, 50% PPV

# ‘Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis’

	Titres	Patients with first-episode psychosis (n=228)	Controls (n=105)	Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
NMDAR antibodies	1:30–1:150	7 (3%)	0	5.4 (p=0.0204)†	..
LGI1 antibodies	1:20–1:100	3 (1%)	0	2.3 (p=0.1298)†	..
CASPR2 antibodies	1:100–1:250	2 (1%)	3 (3%)	0.3 (0.1–1.8)	2.2 (0.3–17.1)
GABA <sub>A</sub> R antibodies	1:50–1:100	8 (4%)	1 (1%)	3.8 (0.5–30.7)	0.4 (0.3–3.6)
AMPA antibodies	..	0	0	..	..
Any neuronal cell surface antibody	..	20 (9%)	4 (4%)	2.4 (0.8–7.3)	0.5 (0.1–1.7)
Other antibodies					
VGKC-complex antibodies >150 pM‡	..	11 (5%)	3 (3%)	1.7 (0.5–6.3)	0.8 (0.2–3.2)
Antinuclear antibodies >1/160	..	7 (3%)	9 (9%)	0.5 (0.2–1.4)	3.6 (1.0–13.6)

Not replicated in all studies

Lennox et al. *Lancet Psychiatry* 2017

# Psychosis of dual origin in HIV infection

## Viral escape syndrome and autoimmune encephalitis

David Anguizola-Tamayo, MD, Jone Bocos-Portillo, MD, Lara Pardina-Vilella, MD, Aida Rodriguez-Sainz, MD, Iñigo Vicente-Olabarria, MD, Eduardo Martínez, MD, Marian Gomez-Beldarrain, MD, and Juan Carlos Garcia-Monco, MD

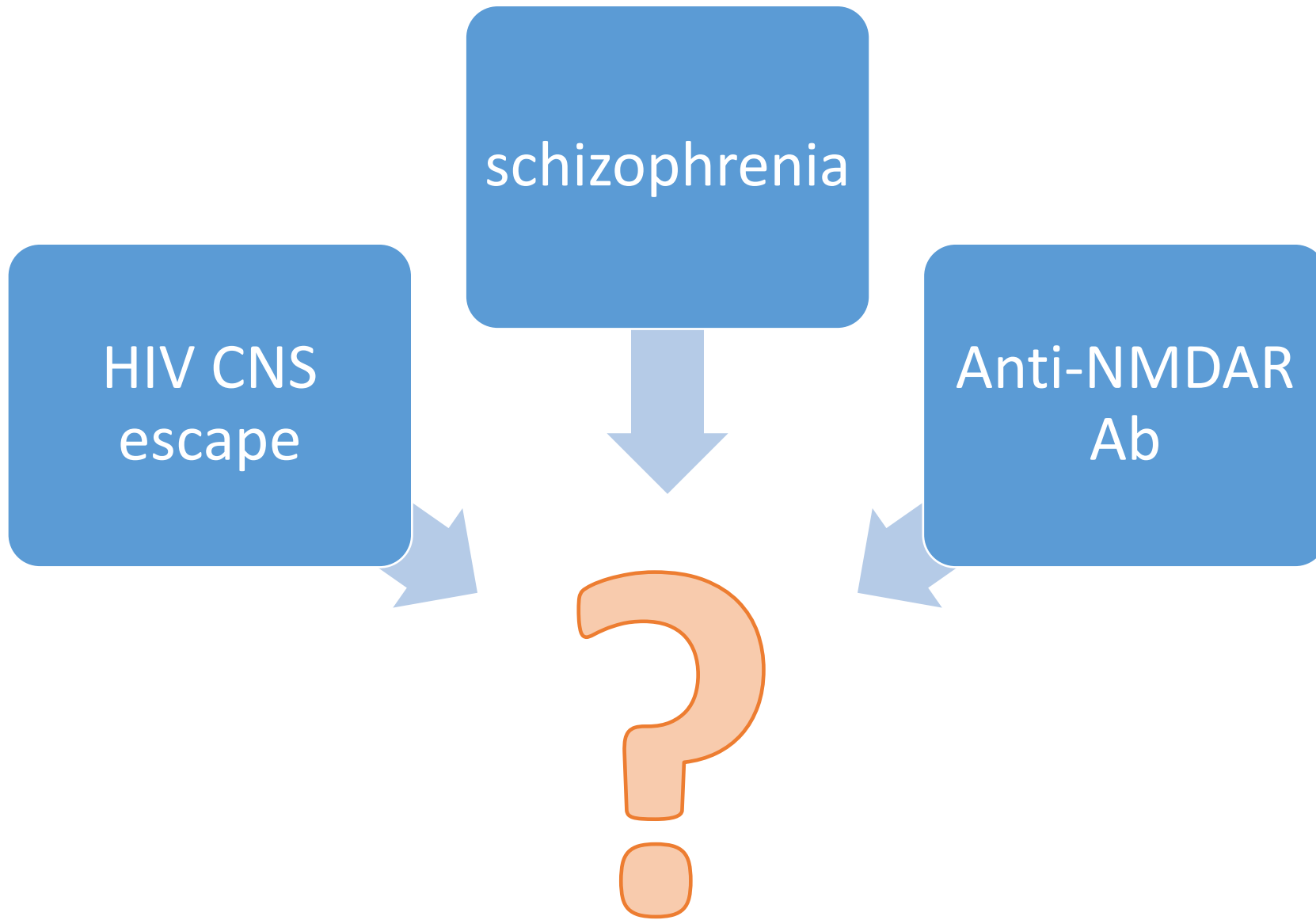
### Correspondence

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Small number of case reports of anti-NMDAR Ab in HIV.

Most reported features of autoimmune encephalitis, but I found 2 reports in new-onset psychosis.



schizophrenia



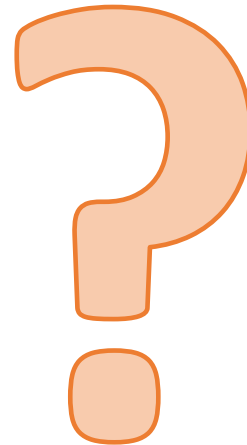
Suboptimal adherence to ART



CNS escape



Triggers anti-NMDAR Ab production



Advanced HIV / suboptimal adherence



CNS escape



Anti-NMDAR Ab



psychosis

For  
discussion:

Can psychotic symptoms be a prominent feature of HIVE?

Can anti-NMDAR Ab ever be considered as an 'incidental' finding?

Could the acute psychosis be anti-NMDAR Ab driven, and if so, should this be treated with immunotherapy?

Can HIV CNS escape trigger the production of anti-NMDAR Ab, and if so, what is the clinical significance?



Any suggestions very  
welcome!

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Thank you

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