Presentation of Clinical Case

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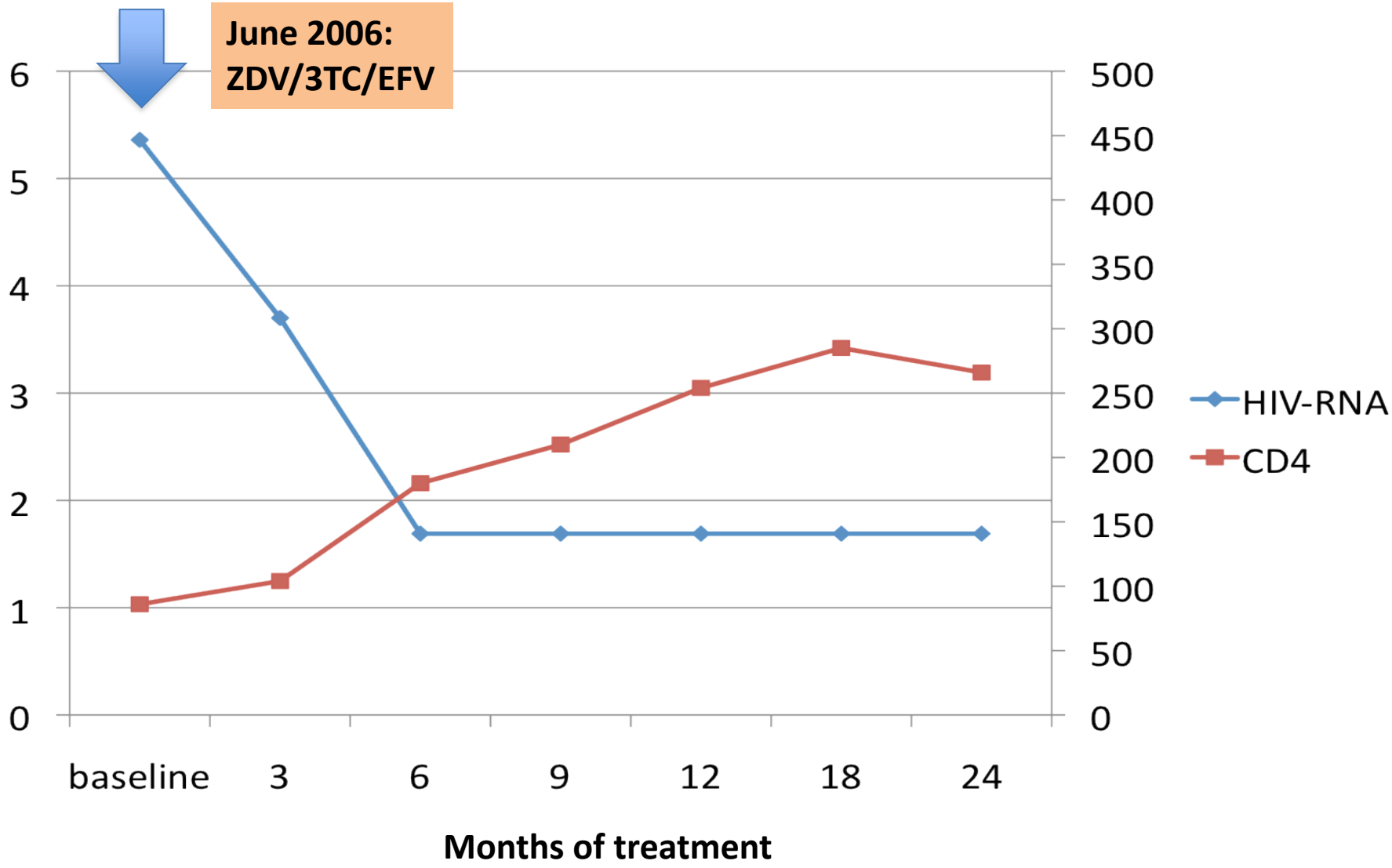
Case history – Background I

- V.A. male, caucasian, 58 yrs, HCV+, strong smoker
- High scholarity (academic degree). Musician
- In 2006 HIV diagnosis during cinical assessment for myelodisplasia (leukopenia, anemia and trombocytopenia)
- Heterosexual intercourse
- At diagnosis: CD4+ 86 cell/mmc, HIV-RNA 230.000 copies/mL
- Genotypic HIV resistance test: WT. B subtype
- HCV genotype 1b; HCV-RNA 2.370.000 UI/mL; normal ALT

Case history – Background II

- **June 2006**: ART started by a combination of ZDV/3TC/EFV
- Rapid HIV-RNA decline (<50 copies/mL after 4 months)
- Not completed CD4 recovery (after 1 year count between 200 and 300 cell/mmc)
- EFV-associated neuropsychiatric effects in the first 12 weeks (dizziness, abnormal dreams, insommnia; no mood disorders). After 3 months, effects resolved
- Adherence >95% (self-reported questionnaire)

Case history – Background III

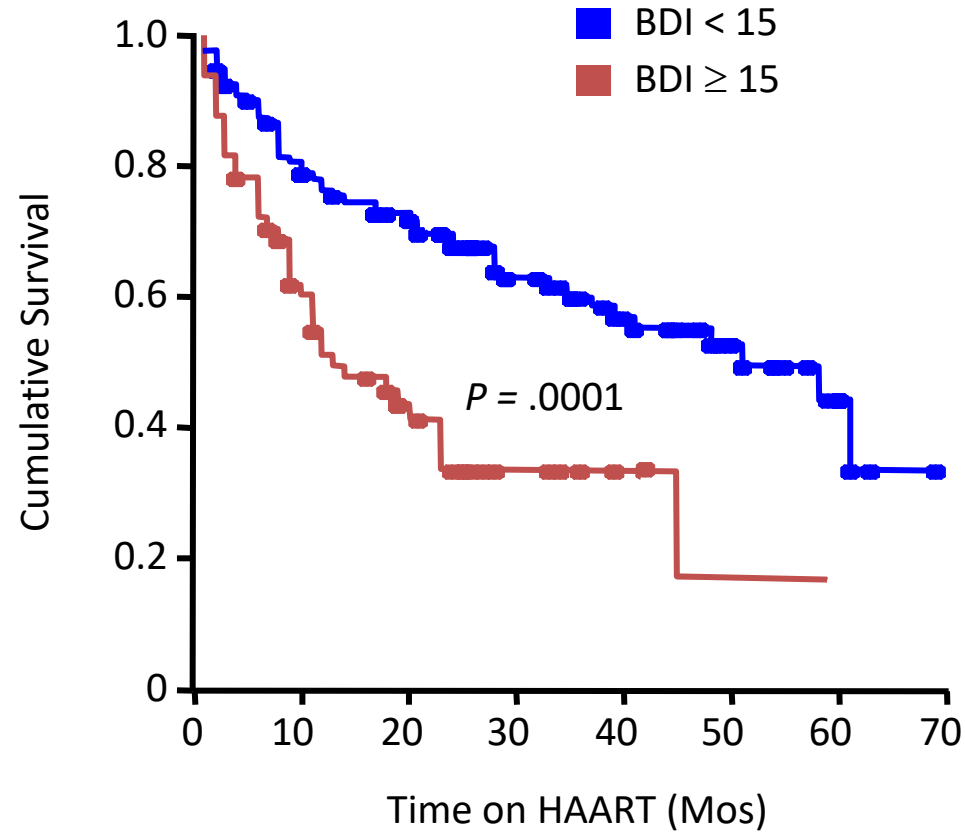


Case history - I

- **April 2008**: 2-year treatment by ZDV/3TC/EFV
- HIV-RNA persistently <50 copies/mL; CD4 count between 200 and 300 cell/mmc
- Mild localized central cheek lipoatrophy
- Depressed mood. Beck Depression Inventory=20.
- No neurological signs or symtoms
- Reduced adherence (80-95%)

More Rapid Discontinuation of ART in Depressed Persons

- Depressive symptoms measured in HIV-positive patients (N = 83) by BDI
- Less depressive: BDI < 15 (n = 50); more depressive: BDI ≥ 15 (n = 33)
- Adherence by MEMS caps and pill counts
- Patients with BDI ≥ 15 on HAART for longer period of time (35 months) vs those with BDI < 15 (*P* = .01) but had more periods of unstructured TI (*P* = .01)
- HIV-1 RNA < 400 copies/mL in 40% of patients with BDI < 15 vs 15% of patients with BDI ≥ 15
- Adherence significantly greater by MEMS data (79% vs 53%; *P* = .02) and pill counts (66% vs 44%; *P* = .02) in patients with BDI < 15



Bangsberg DR, et al. ICAAC 2001. Abstract 1721.

What intervention would have you made?

Intervention	Comments
1. NRTI switch (substitution of ZDV/3TC with TDF/FTC or ABV/3TC)	Effect on lipoatrophy and eventually on poor CD4 recovery
2. HCV treatment	Limited fibrosis Negative effect of IFN on depression
3. Anti-depressive treatment	BDI >15
4. EFV substitution with a PI/r	Late mood disorders (controversial)

Case history - II

- May 2008:
- Fibroscan: 6.2 kpa (METAVIR=F1)
- No HCV treatment (IFN controindication)

- Antidepressive therapy with citalopram (8 mg/die increased to 16 mg/die)

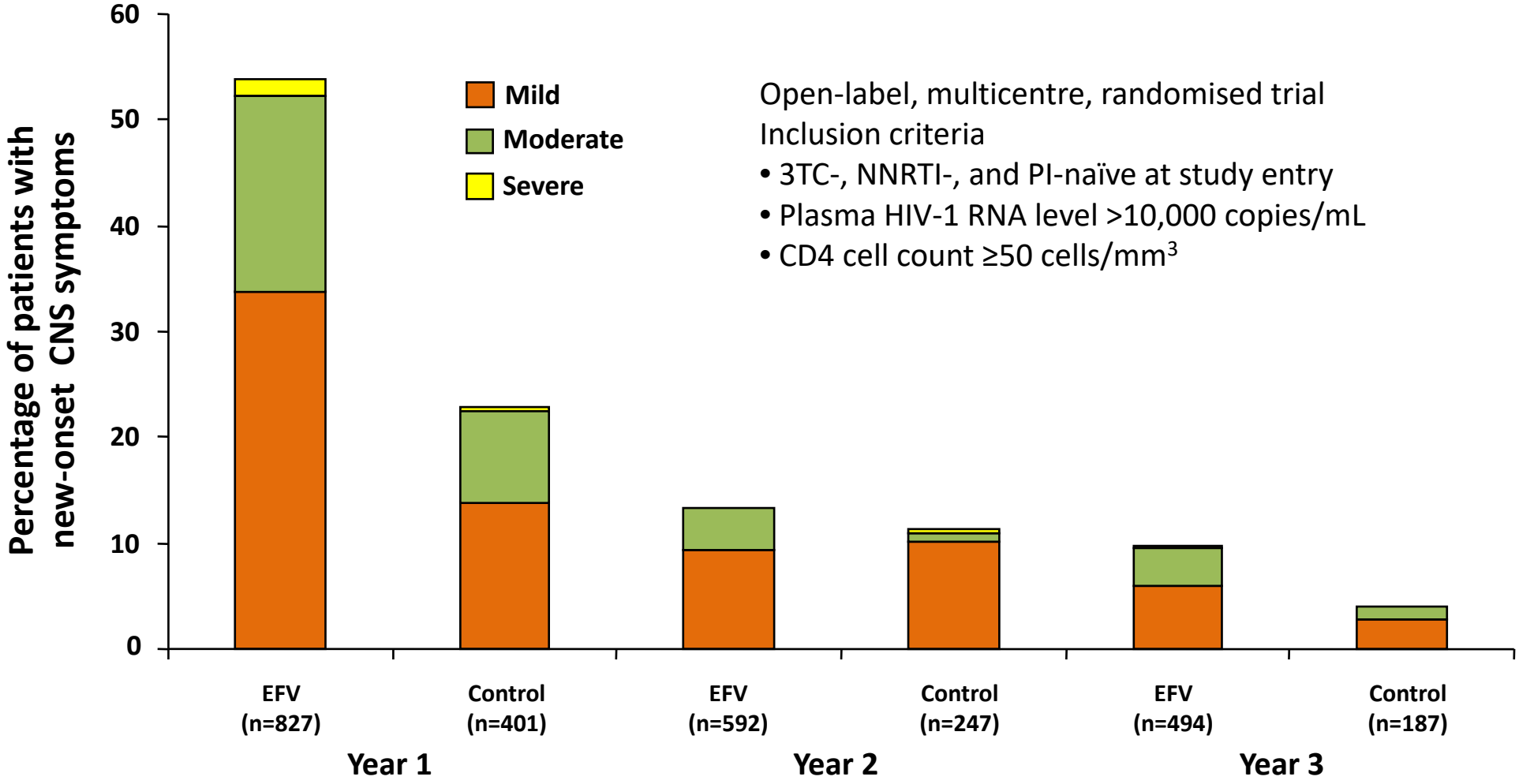
- ART change from ZDV/3TC/EFV to TDF/FTC/ATV-RTV (lipoatrophy, protection from eventually late EFV effect)

Relationship Between Antidepressant Use and Adherence to ART

- 1997-2001, retrospective review
- 1713 HIV-positive patients in an urban healthcare setting
  - 57% of patients were depressed
    - 46% of depressed patients received antidepressant treatment
    - 52% of depressed patients received ART
- **Antiretroviral adherence lower among depressed patients not on antidepressants (*P* <.005) vs patients on antidepressants**
- Nonadherence to ART more likely in patients nonadherent to antidepressants (*P* = .0019) and in patients who used alcohol (*P* = .01)

Yun LW, et al. J Aquir Immune Defic Syndr. 2005;38:432-438.

Long-term incidence of CNS symptoms is low and mainly mild-to-moderate with EFV

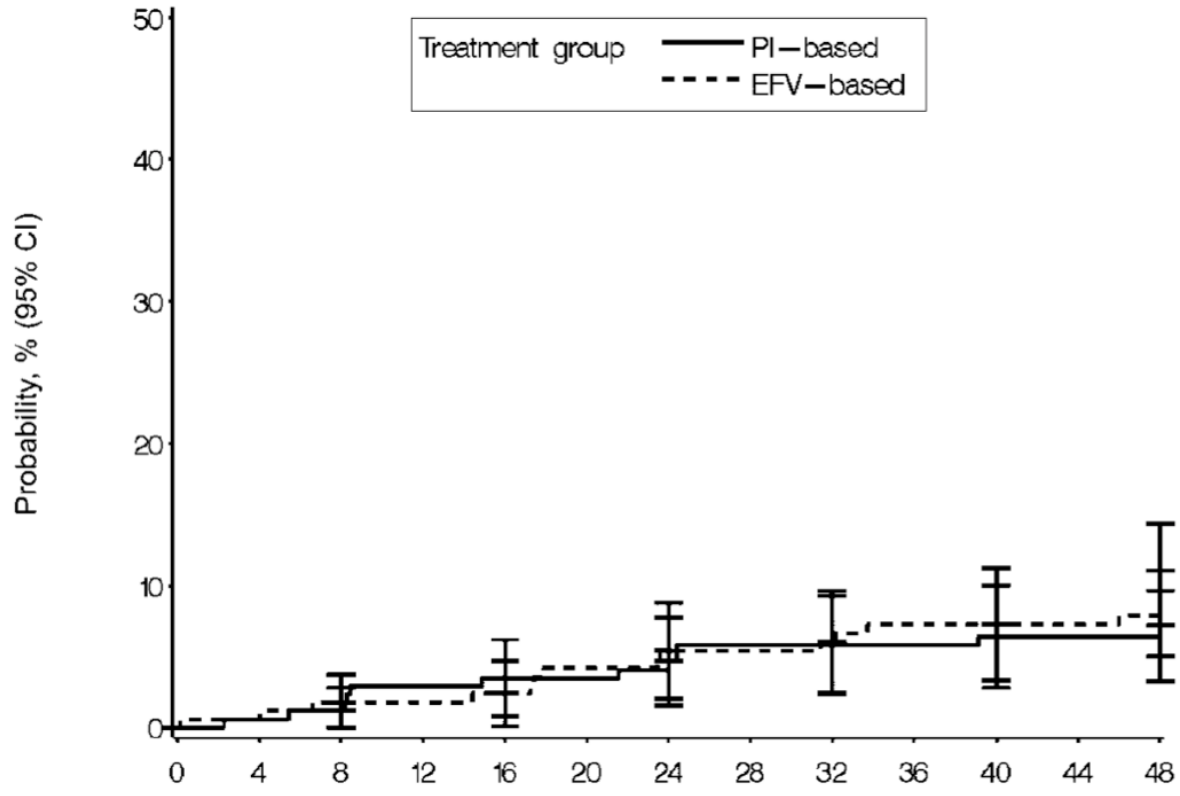


Control=IDV 800 mg TD+ZDV 300 mg BD+3TC 150 mg BD

Adapted from: Johnson M, et al. 8th European Conference on Clinical Aspects and Treatment of HIV infection 2001:Abstract 22

Probability of first depressive disorder on treatment, by KM method, according to treatment group

Use of Efavirenz was not associated with a higher risk of depressive disorders. A Substudy of the Randomized Clinical Trial ALIZE-ANRS 099



Treatment group	No. of patients at risk						
PI–based	175	172	167	164	160	158	122
EFV–based	175	166	163	155	151	145	104

Journot V, et al. Clin Infect Dis, 2006

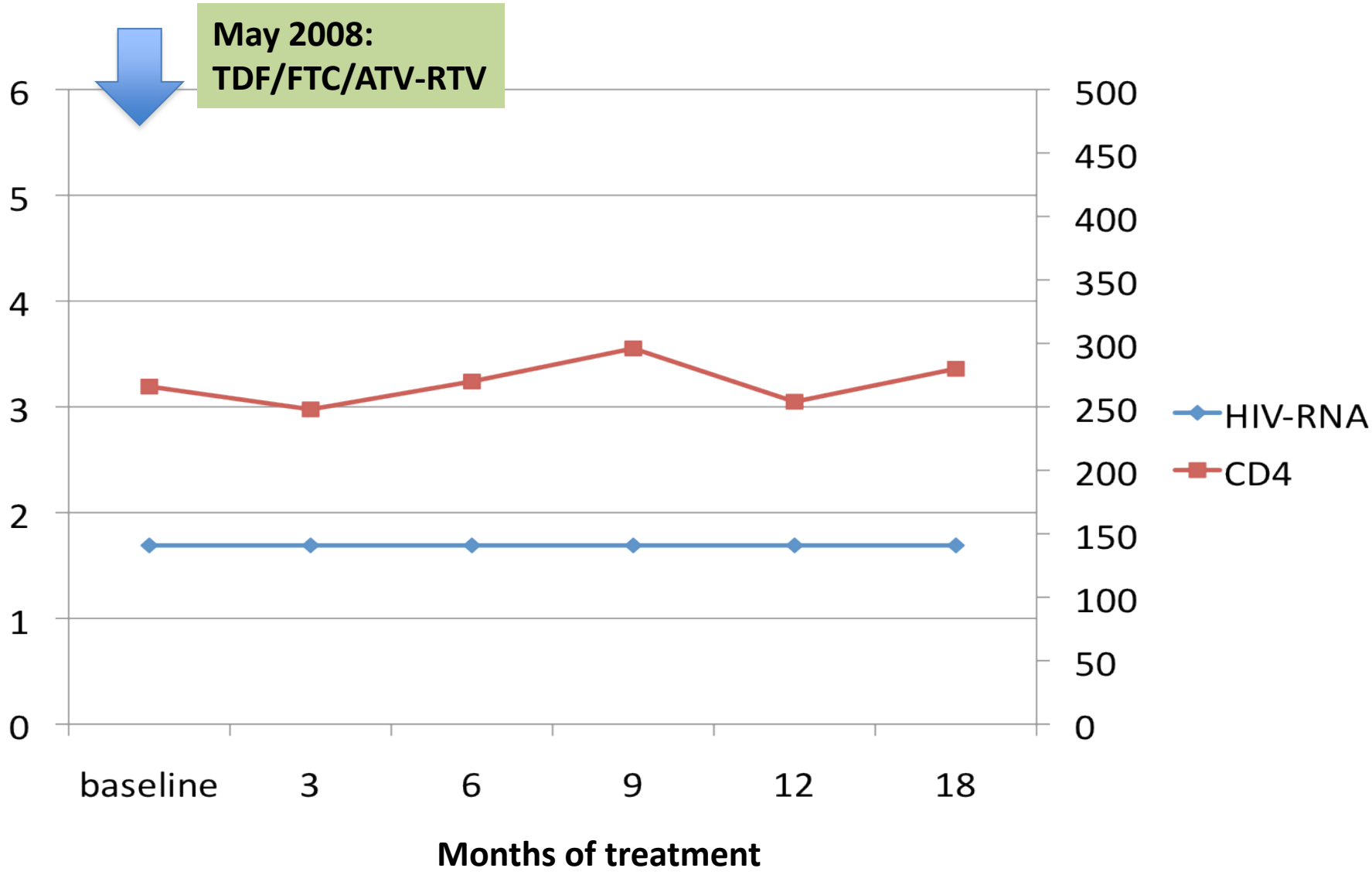
Mild, clinically tolerable CNS symptoms may persist after a mean of 2 years

- Cross-sectional study comparing 60 patients treated with EFV and 60 patients treated with a PI regimen for ≥1 year

Adverse event with p value <0.05, n (%)	EFV	PI	p value
Dizziness	13 (21.7)	3 (5)	0.008
Sadness	22 (36.7)	9 (15)	0.008
Mood changes	16 (26.7)	7 (11.7)	0.041
Irritability	18 (30)	6 (10)	0.007
Lightheadedness	17 (28.3)	5 (8.3)	0.005
Nervousness	18 (30)	7 (11.7)	0.015
Impaired concentration	16 (26.7)	7 (11.7)	0.041
Abnormal dreams	29 (48.3)	1 (1.7)	<0.001

Fumaz CR, et al. J Acquir Immune Defic Syndr 2005;38:560–5

Case history - III

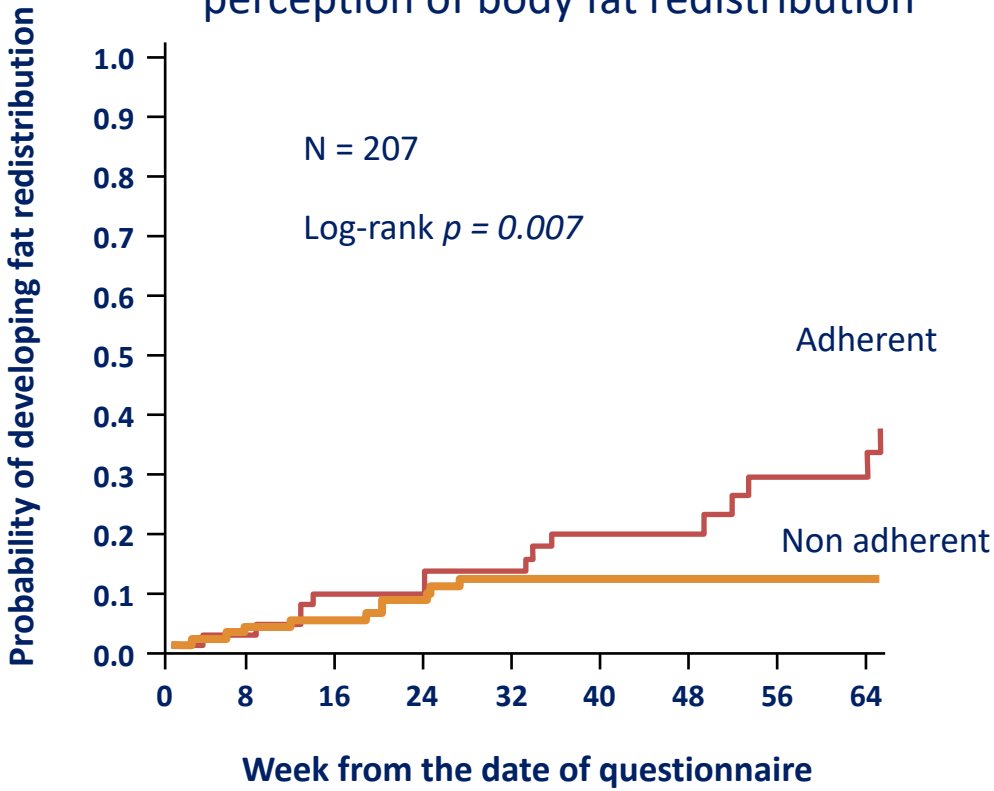


Case history - IV

- November 2009:
  - On TDF/FTC/ATV-RTV from 18 months
  - Persistently undetectable (<50 copies/mL) HIV-RNA
  - CD4 not fully recovered (280 cell/mmc)
  - Improvement of depression
  - Stable mild facial lipoatrophy (no reversion)
  - Suboptimal adherence (memory deficits)

Patient perceptions of fat redistribution may impact future adherence

- AdICoNA & LipoICoNA Cohort
- A self-report questionnaire was administered to measure adherence and patient perception of body fat redistribution

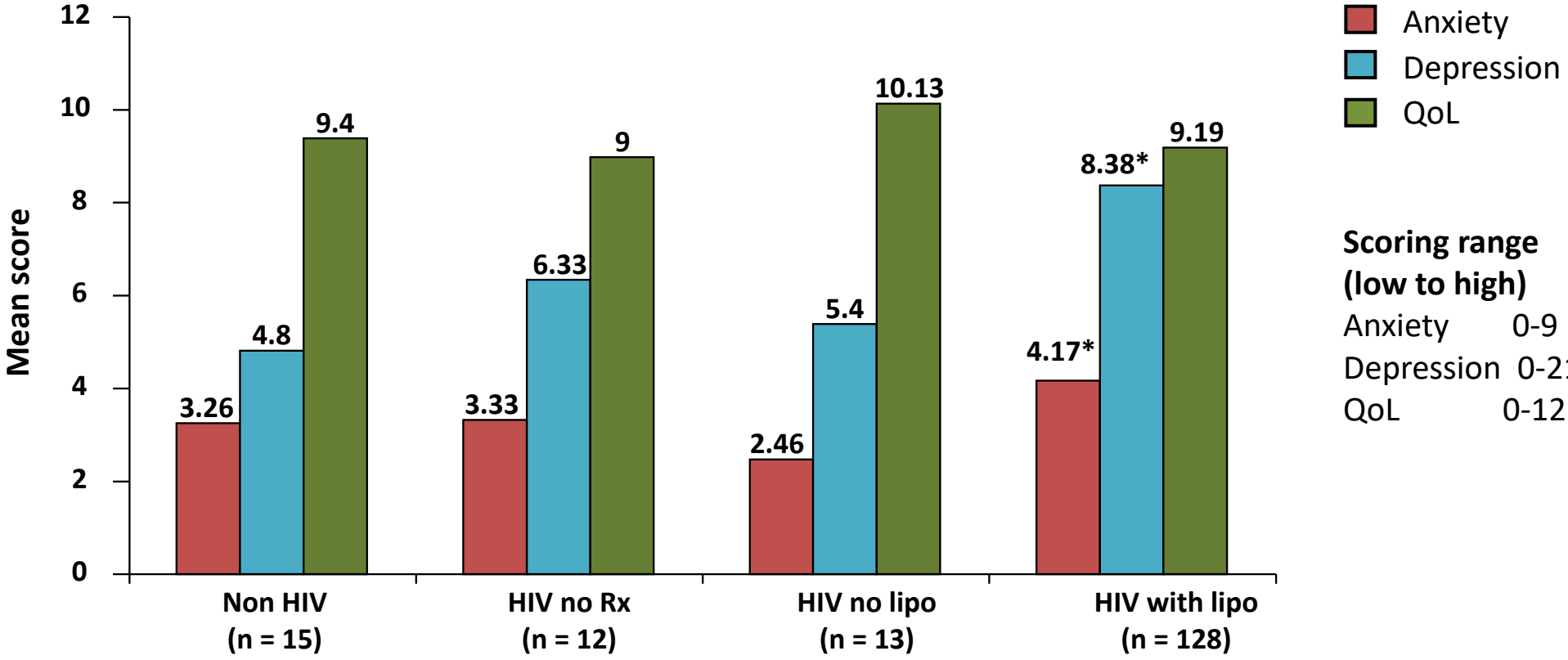


Risk of future non adherence	OR* (95% CI)	*p*
Patient perceived fat accumulation	4.67 (1.01-22.4)	*0.05*
Duration on ARV therapy per additional year	1.84 (1.08-3.15)	*0.03*

*Adjusted for patient demographics, mode of HIV transmission, prior ARV use, total duration ARV therapy

Ammassari A et al. *J Acquir Immune Defic Syndr* 2002

Impact of body fat redistribution on patient anxiety, depression and QoL



*$p < 0.01$ between HIV+ with and without LD
HIV no Rx = HIV infected naive patients
HIV no lipo = HIV patient on therapy without LD
HIV with lipo = HIV patient with LD

Marin A et al. Qual Life Res 2006

Nov. 08 - Neuropsychological assessment

- The patient refers to have trouble with his memory. Recently, he was unable to remember a few important engagements, some people who know him well made him notice this (his) defaillances. Some interests (of pleasure), such as night reading of a good book were reduced: the patient is unable to concentrate, “he cannot keep his train of thought”. At times, he must read an already read page in order to continue his reading. He refers to have become less tolerant to sounds, such as “excessive noise”. If he enters an environment where there are many people speaking, he has a hard time following a specific conversation, he feels uncomfortable, bothered and feels forced to leave the environment (cocktail party phenomenon). In addition, he has also lost interest for playing the piano “he does not like it like before”. When asked to clarify this statement, he refers that he feels as if his fingers are “plastered” (the fluidity of the automatic movement is reduced): he has already tried to play something for his friends, however he had to interrupt the performance (experience of failure). The relationship with his partner demonstrates some moments of crisis: she holds that he is “withdrawn”, not reacting.

HIV-associated Neurocognitive Impairment

	Neuropsychological (NP) Testing is available	NP Testing not available
Asymptomatic Neurocognitive Impairment (ANI)	NP impairment in ≥ 2 cognitive domains that cannot be explained by opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects. No reported or demonstrated functional decline.	Mental Status Exam (MSE) impairment involving ≥2 cognitive domains, that cannot be explained by opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects. No reported or demonstrated functional decline.
Mild Neurocognitive Disorder (MND)	At least mild NP impairment (>1 SD below a demographically appropriate normative mean), involving ≥2 cognitive domains that cannot be explained by confounding conditions. AND Reported or demonstrated mild functional decline that cannot be explained by confounding conditions.	At least mild MSE impairment (>1SD below a demographically appropriate normative mean), involving ≥2 cognitive domains, that cannot be explained by confounding conditions. AND Reported or demonstrated mild functional decline that cannot be explained by confounding conditions.
HIV-Associated Dementia (HAD) Note: Severity of NP impairment and functional decline must both meet these standards in order to diagnose the person as having HAD. If either NP impairment or functional decline is mild, the condition should be classified as MND.	≥ Moderate NP impairment (>2SD below a demographically appropriate normative mean) on > 2 cognitive domains.* Impairment cannot be explained by confounding conditions (see Table 2). AND Reported or demonstrated major functional decline that cannot be explained by confounding conditions. *Alternatively, one domain could be more severely impaired (>2.5 SD below the mean) and another less severely impaired (>1 SD below the mean) -–see Woods et al., 2004 (7).	≥ Moderate MSE impairment (>2SD below a demographically appropriate normative mean), involving ≥2 cognitive domains, that cannot be explained by confounding conditions. AND Reported or demonstrated major functional decline that cannot be explained by confounding conditions.

Antinori A, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007; 69: 1789-99

Examples of NP tests that may be used to document impairments in ability domains

Fluency

Controlled Oral Word Association Test (FAS) (1, 2)
Thurstone Word Fluency Test (3)
Category Fluency (4)
Action Fluency (5)
Design Fluency Tests (6, 7)

Executive Functions

Stroop Color and Word Test (8)
Trailmaking Test – Part B (3, 9)
Color Trails –II (10)
Wisconsin Card Sorting Test (11)
Halstead Category Test (3, 9)
Odd Man Out Test (12-14)
Tower Tests (15-17)
Delis-Kaplan Executive Function System (7)

Speed of Information Processing

WAIS-III Digit Symbol Subtest (18)
WAIS-III Symbol Search Subtest (18)
Symbol Digit Modalities Test (19)
Trailmaking Test – Part A (3, 9)
Color Trails – I (10)
Digit Vigilance Test (3, 20)
Stroop Color Naming (8)
Reaction Time Tests, e.g., California Computerized Assessment Battery (21)

Attention/Working Memory

WAIS-III Digit Span Subtest (18)
WAIS-III Letter-Number Sequencing Subtest (18)
WMS-III Spatial Span Subtest (22)
Paced Auditory Serial Addition Test (23)
Digit Vigilance Test (error component) (3, 20)

Verbal and Visual Learning

Verbal:

California Verbal Learning Test (Original and Revised; Total Learning) (24)
Rey Auditory Verbal Learning Test (Total Learning) (25)
Story Memory Test (Learning component) (3)
Hopkins Verbal Learning Test- Revised (Total Learning) (26)
Buschke Selective Reminding Test (27)
WMS-III Logical Memory I (22)
WMS-III Paired Associates I (22)

Visual:

WMS-III Visual Reproduction-I (22)
WMS-III Family Pictures-I (22)
Brief Visuospatial Memory Test – Revised (Total Learning) (28)
Figure Memory Test (Learning component) (3)
Rey-Osterreith Complex Figure Test (Immediate Recall) (29, 30)

Verbal and Visual Memory

Delayed recall scores of the 12 learning/memory tests listed above, with interpretation also guided by results on any normed, forgetting/savings scores and delayed recognition scores.

Motor Skills

Grooved Pegboard Test (3, 31)
Purdue Pegboard Test (32, 33)
Arendt Central Motor Test Battery (34, 35)
Finger Tapping Test (3)
Timed Gait (36)

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Nov. 08 - Neuropsychological examination

Attention

A sustained attention test (**trail making A**) that includes psychomotor speed and visual spatial skills research shows execution time slightly higher than normal .

A divided attention test (**trail making B/executive function)** that includes psychomotor speed, visual spatial skills research and working memory shows execution time higher than normal and some missing of (problems in keeping) the target of attention.

A selective attention test (**Stroop Test word/color interference**) shows execution time higher than normal and 2 mistakes.

Memory

Digit span memory for direct repetition: 6 chunks. **Digit span memory for reverse repetition** is slightly reduced: 4 chunks. Visual span memory, evaluated with the **Corsi's Cube test**: 5 chunks.

A memory task that includes learning and spontaneous recalling of 15 semantically non-related words (**Rey's test AVLT**) shows some difficulties in the learning phase; during the first repetition session he can recall 5 words; during the second 5; during the third 6; during the fourth 8; during the fifth 7.

After 15 minutes he spontaneously recall 6 words. During a multiple recognition task recognises 8 words (previously not recalled) and gives 2 false recognitions.

A memory test that includes learning of 5 verbal elements logically connected to each other (learning, immediate recall and delayed recall of a short street address), needs 1 additional repetition in order to be properly executed. After 15 minutes he can remember 4 of the 5 elements previously learned.

The performance is poor in a non-verbal memory task, such as the delayed recall (after 45 minutes) of the **Ray Complex Figure**.

Nov. 08 - Neuropsychological examination

Manual dexterity, visual-constructional skills and praxis

A task which assesses constructive practice (copy of **Rey Complex Figure**) shows a good performance. A task that requires manual dexterity, visual exploration, eye-hand coordination (**Grooved Pegboard test**) shows execution time slightly higher than normal.

Language

Sufficient **verbal fluency** for phonemic categories. Spontaneous speech carries a normal amount of information.

Abstraction and generalization of concepts

Good preservation of cognitive abilities of **logical thinking**. Good conservation of abilities of **abstraction** and **generalization of complex concepts**.

Functional status

Good preservation of autonomy in daily living activities (**ADL**). Good preservation of autonomy in instrumental day living activities (**IADL**).

Mood evaluation

The scale for the assessment of depression **BDI-II** does not highlight specific changes of mood.

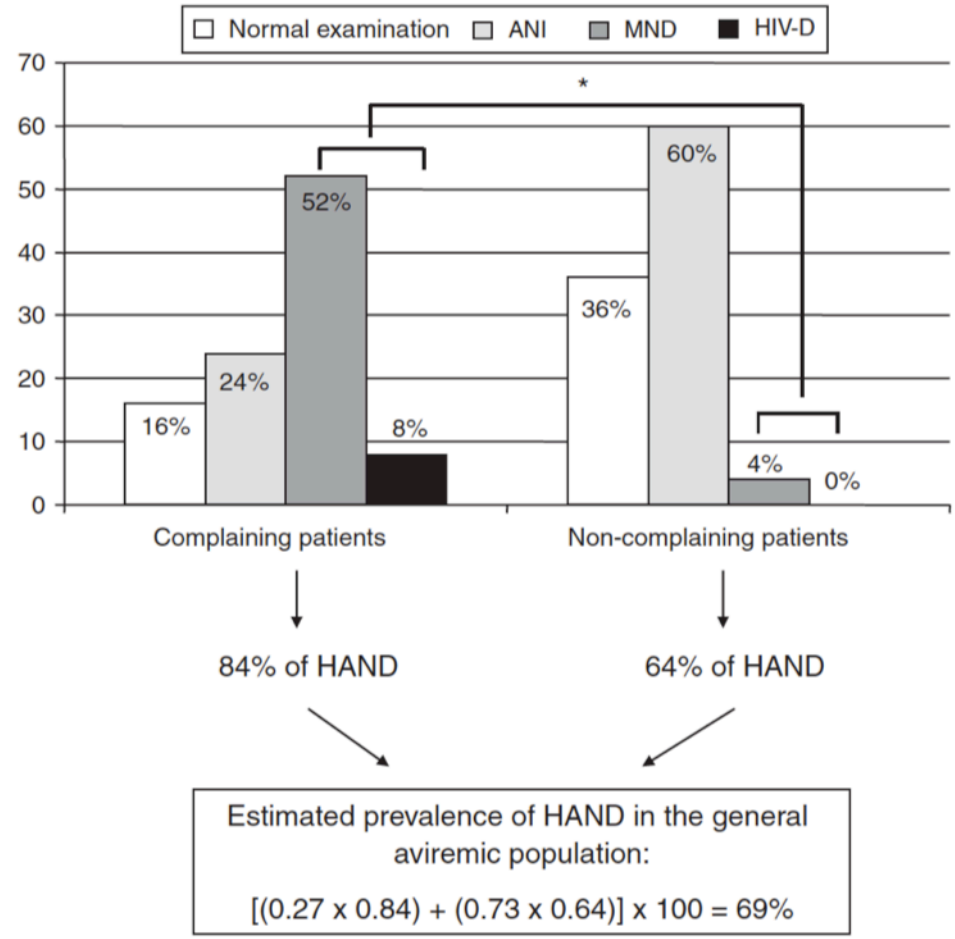
Guidelines for classifying confounds to HIV-associated cognitive disorders

	Secondary Condition: compatible with HIV related neuro-cognitive disorder	**Contributing condition: HIV-related neurocognitive disorder**	**Confounding condition: unable to attribute abnormalities to direct effects of HIV**
Depression*	Depressed mood and/or major depressive disorder but without psychotic features, and no clinical indication of inadequate effort/motivation on cognitive testing (NP or MSE). Normal performance on ≥1 effort-demanding NP test (e.g., Trails B, WAIS-III Processing Speed or Letter-Number Sequencing, PASAT).	Major depressive disorder with psychotic features or some clinical evidence of fluctuating or suboptimal effort on cognitive testing. Nevertheless, impairment is present on non-speeded tests or on tests on which patient appeared to put forth good effort. Patient responds well to task demands with some examiner encouragement.	Major depressive disorder with psychotic features and/or persisting clinical evidence of suboptimal effort in the cognitive testing process. Patient does not respond well to examiner prompting or encouragement, OR Major depression with functional complaints but normal cognitive results and normal performance on any objective tests of functional abilities.

*Other classifying confounds for history of remote traumatic brain injury, history of developmental disability, history of alcohol or other substance use disorder, HIV-related CNS opportunistic disease, non-HIV-related neurologic condition, systemic disease, co-infection with HCV.

Antinori A., et al. Neurology 2007; 69: 1789-99

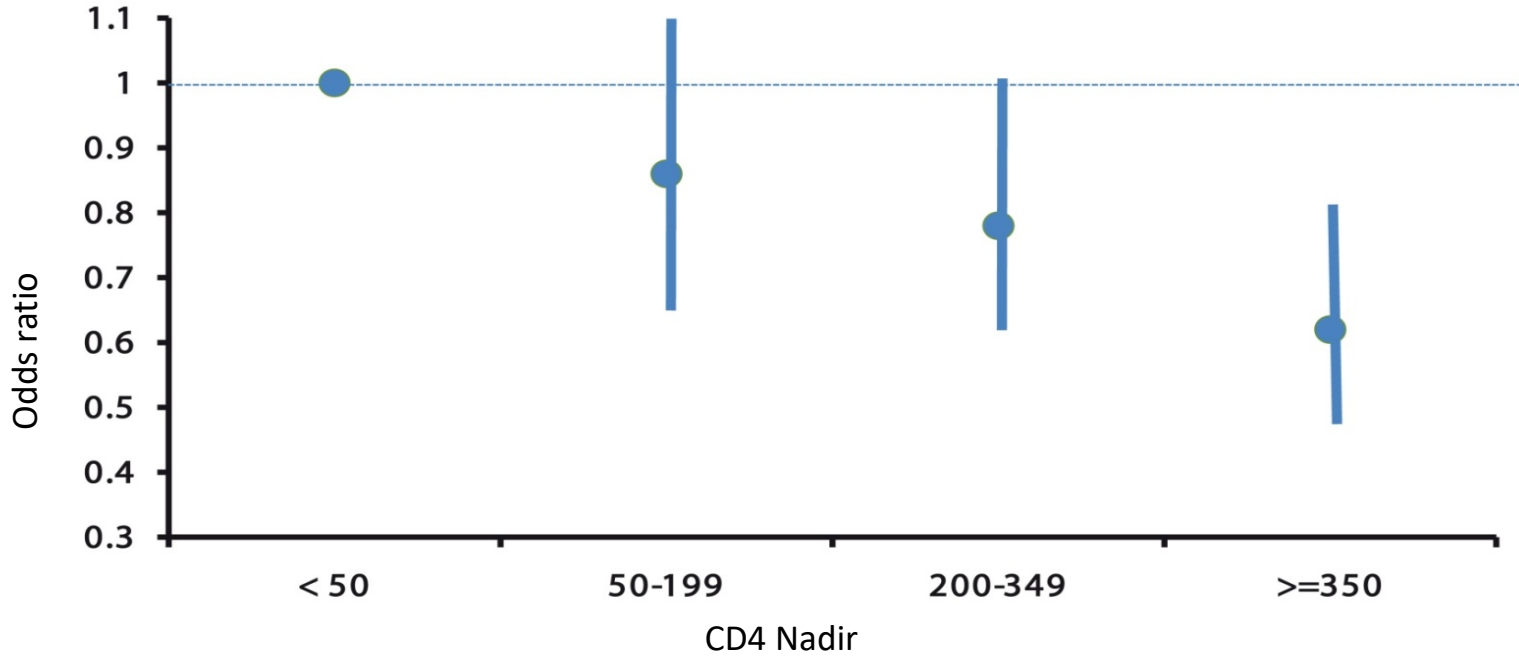
High prevalence of HAND despite long-standing suppression of viremia



Simioni S, et al. AIDS, 2010

Early initiation of ART may reduce HAND risk and associated disability

Odds ratio for cognitive impairment according to CD4 nadir strata

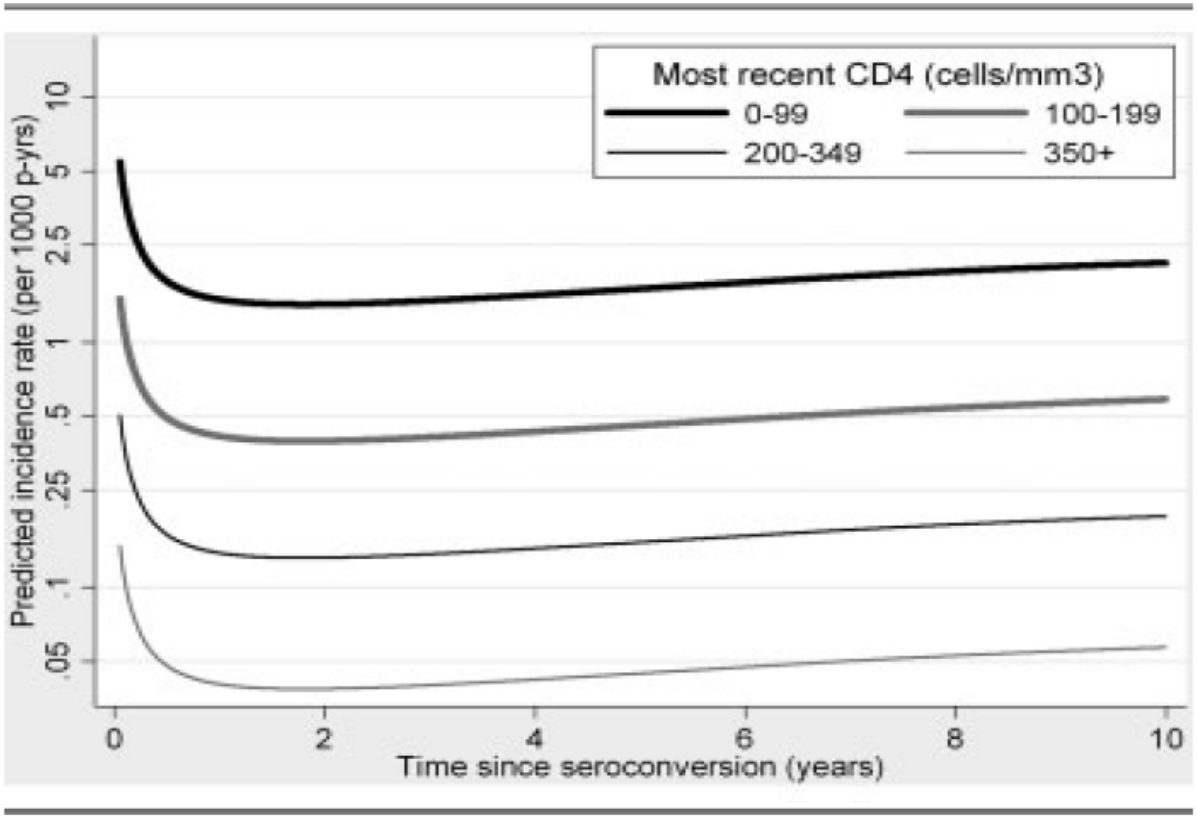


- Risk of HIV-Associated Neurocognitive Disorders (HAND) is associated with nadir, rather than current CD4; higher CD4 nadir confers a reduced risk of HAND
- This supports initiating ART in patients with CD4>350 cells/mm^3. Preventing lower CD4 by early initiation of ART may reduce the likely hood of HAND and associated disability

Adapted from Ellis R, et al. 17th CROI San Francisco, 2010. Poster 429.

Changes in the Incidence and Predictors of Human Immunodeficiency Virus–Associated Dementia in the Era of Highly Active Antiretroviral Therapy

Krishnan Bhaskaran, MSc,[1] Cristina Mussini, MD,[2] Andrea Antinori, MD,[3] Ann Sarah Walker, PhD,[1] Maria Dorrucci, PhD,[4] Caroline Sabin, PhD,[5] Andrew Phillips, PhD,[5] and Kholoud Porter, PhD,[1] on behalf of CASCADE Collaboration



CD4 rank	Adjusted relative risk
0-99	39.03 (22.96-66.36)
100-199	10.19 (5.72-18.15)
200-349	3.47 (1.91-6.28)
>350	1.00

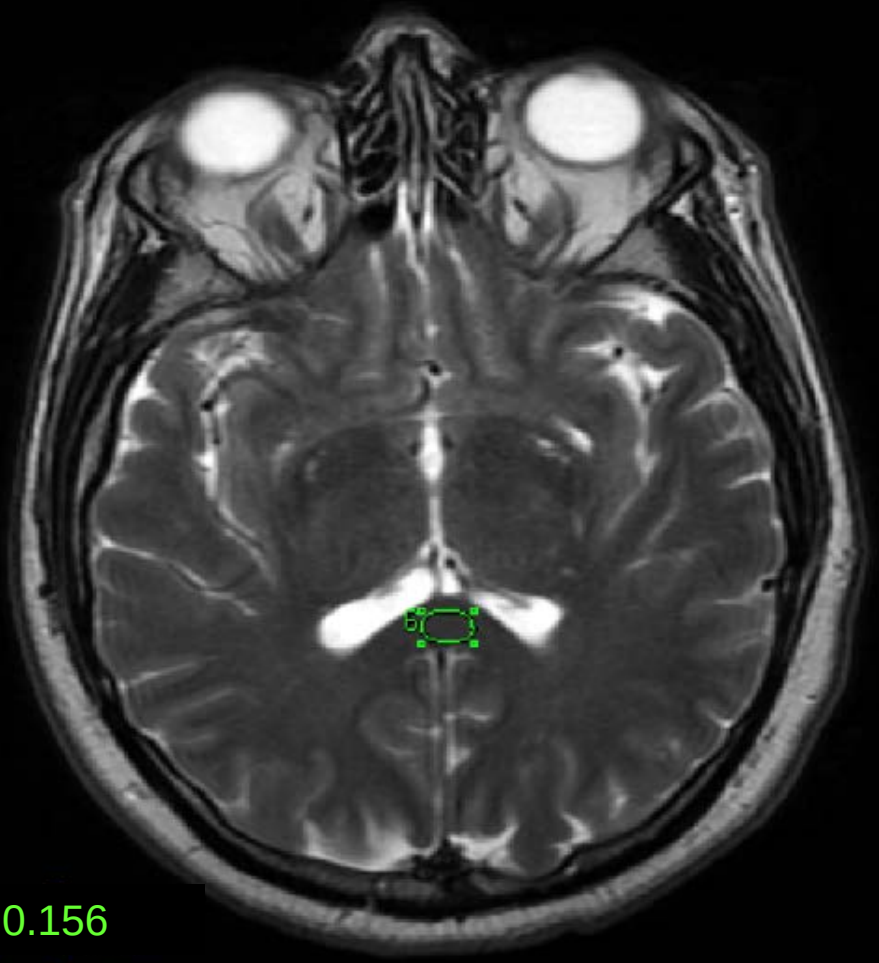
What intervention would have you made at this time (November 2009)?

Intervention	Comments
1. Morphological MRI	Excluding WML (PML o HIV encephalopathy)
2. DTI and/or MR Spectroscopy	Early NCI
3. Lumbar puncture	HIV CSF replication
4. Cerebrovascular doppler ultrasound	CV risk factors (ageing, smoking)

Clinical history - DT and MR spectroscopy (November 2009)

- DTI: increased Apparent Diffusion Coefficient in Corpus Callosum
- MR spectroscopy: increased mio-inositol (mI) and (Cho) cholin (glial markers), associated with slow reduction of N-acetylaspartate (NAA) (neuronal marker)
- Morphological MRI: no WMLs, no brain atrophy

•V.A. male, 61 yrs, HIV+



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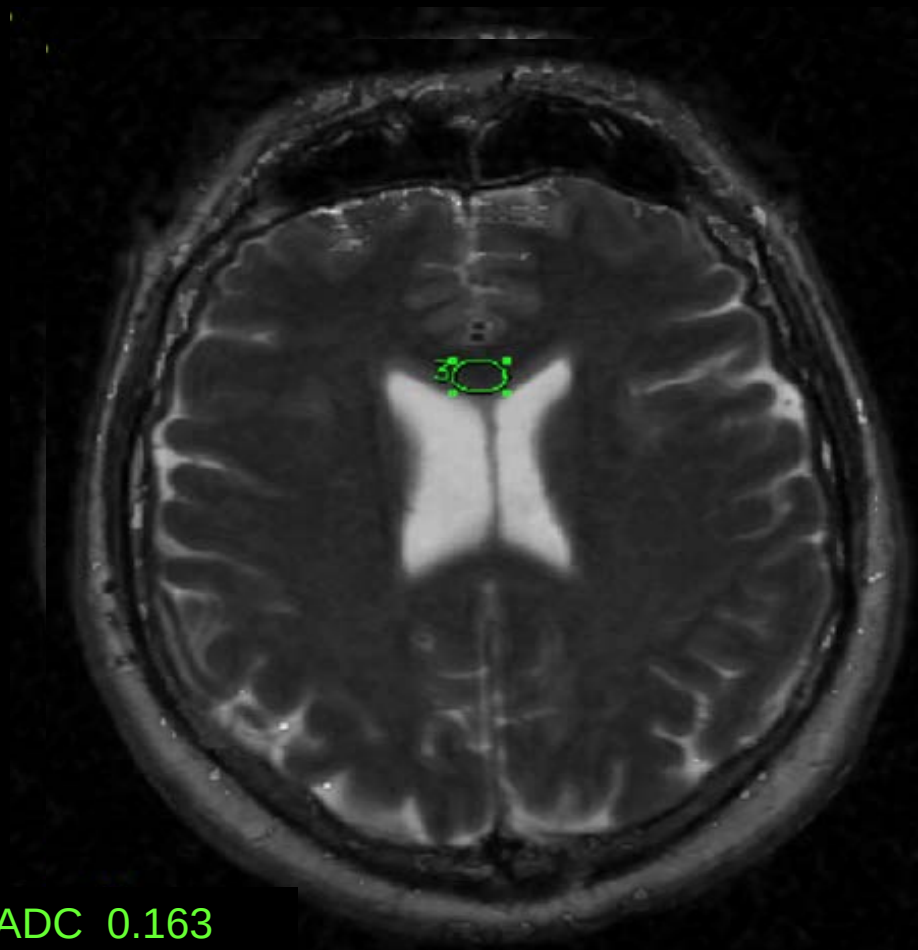

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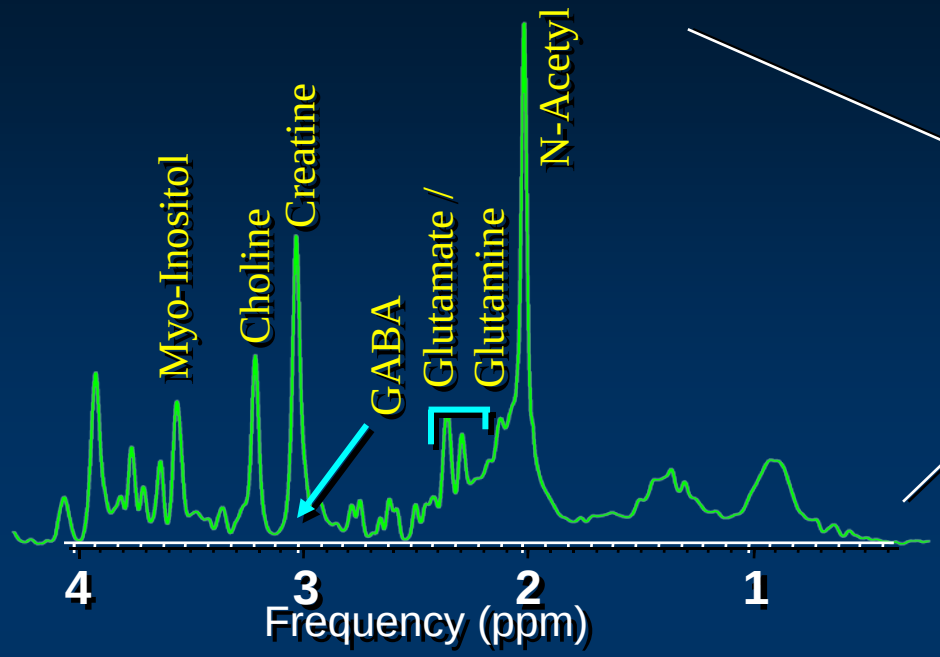
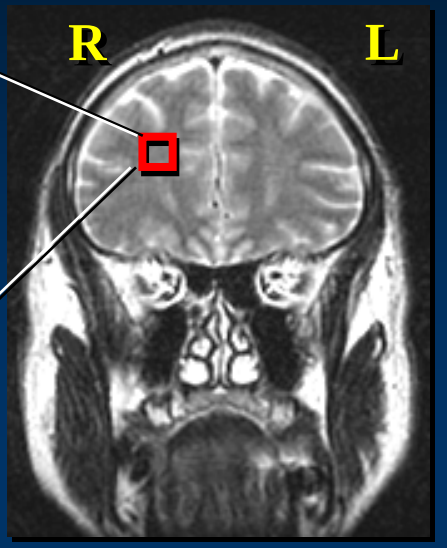
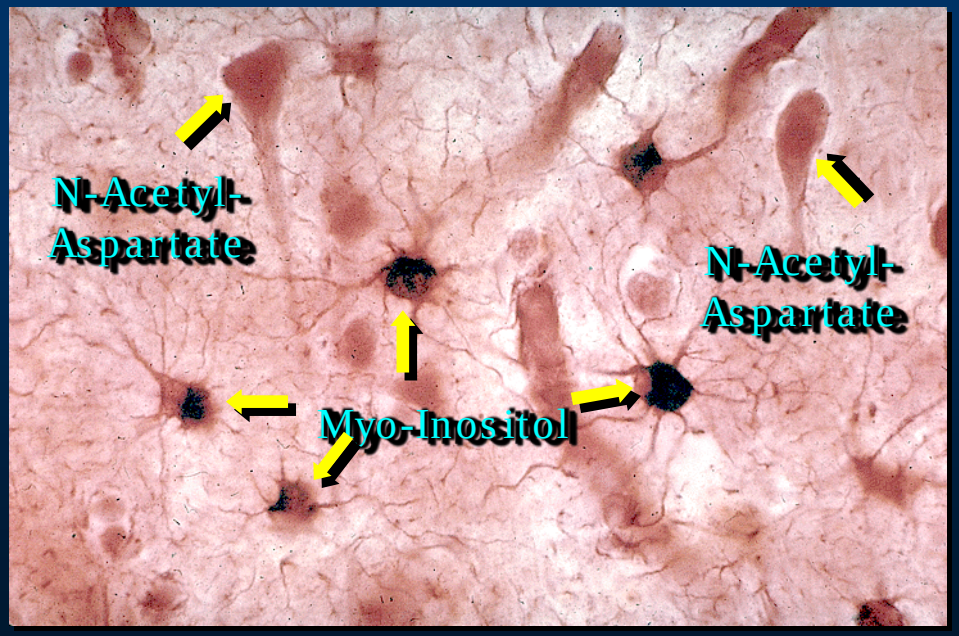
Proton MR Spectroscopy (^{1}H MRS)



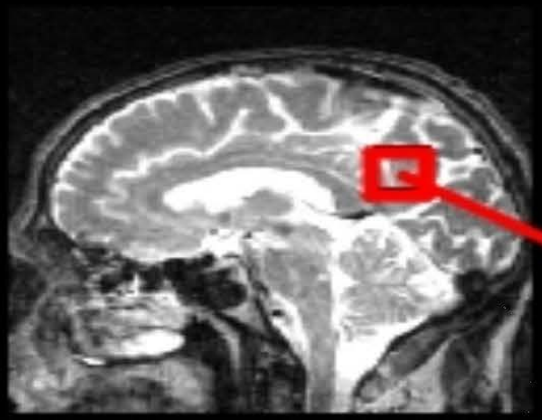


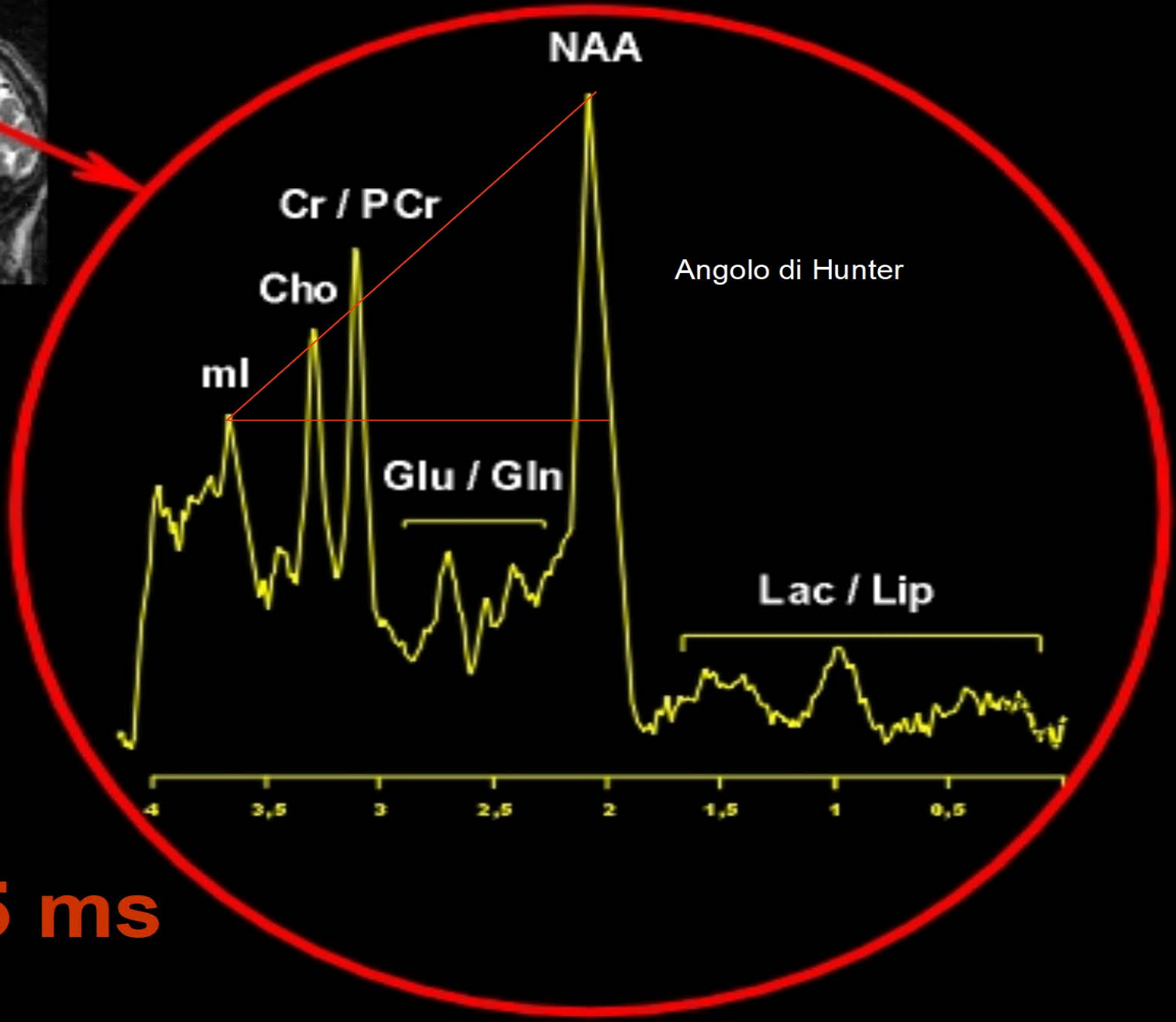


Neuronal Marker: NAA, Glu+Gln:
Glial Marker: Myo-inositol

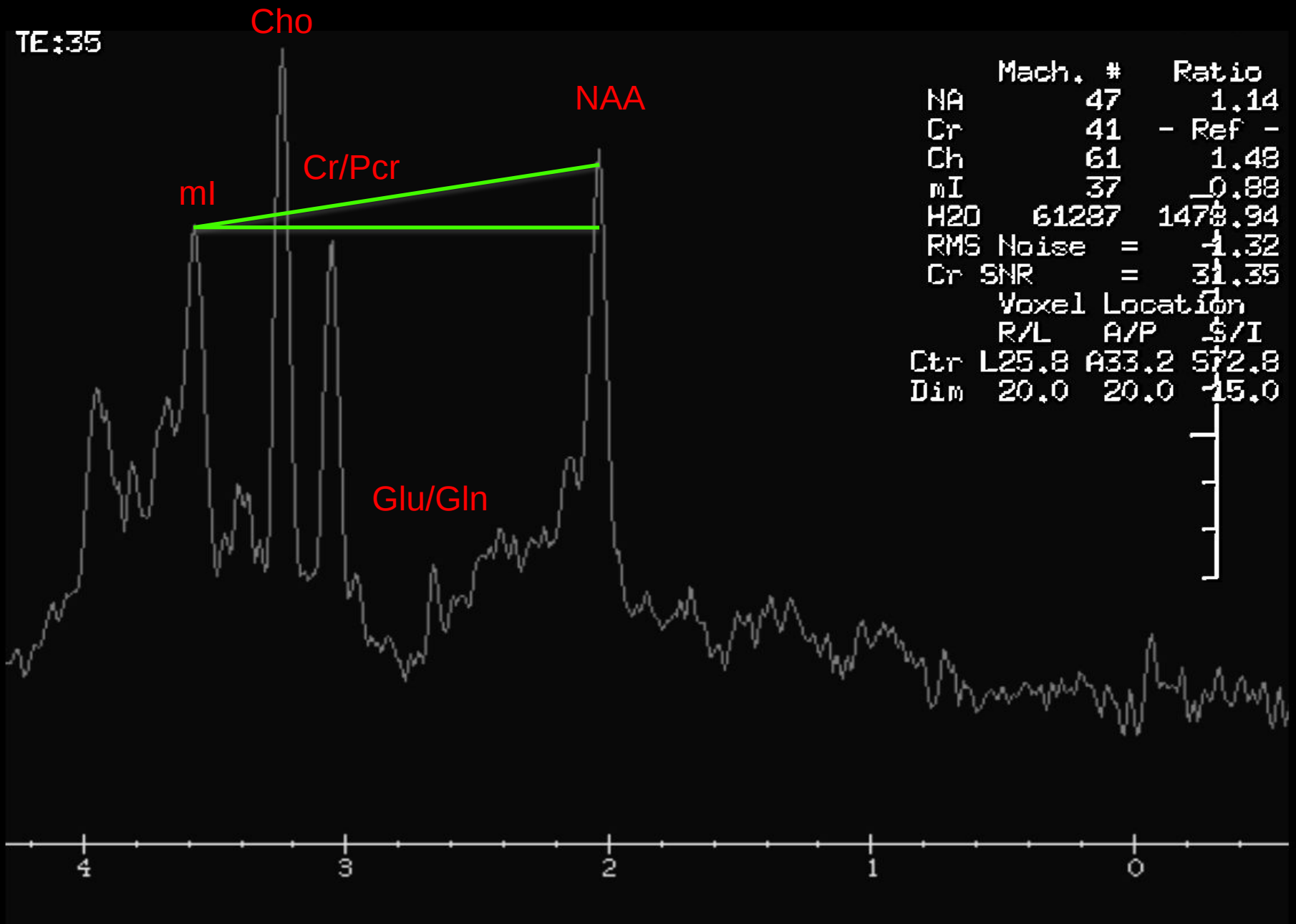
Total Creatine
Choline compounds

3x higher
in glia

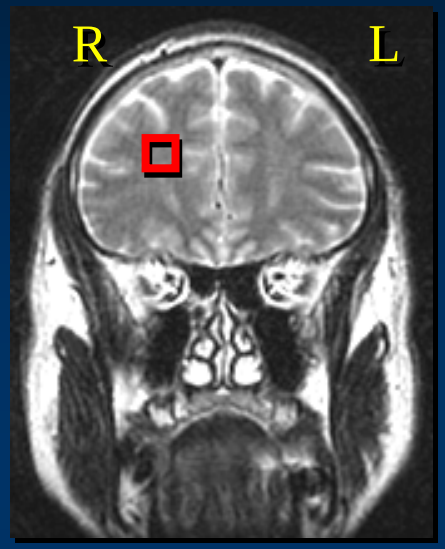



NAA
Cr / PCr
Cho
mI
Glu / Gln
Lac / Lip
Angolo di Hunter
4
3,5
3
2,5
2
1,5
1
0,5

SV TE 35 ms


TE:35
Cho
NAA
Cr/Pcr
mI
Glu/Gln
Mach. # Ratio
NA 47 1.14
Cr 41 - Ref -
Ch 61 1.48
mI 37 0.88
H2O 61287 1478.94
RMS Noise = 1.32
Cr SNR = 31.35
Voxel Location
R/L A/P S/I
Ctr L25.8 A33.2 S72.8
Dim 20.0 20.0 15.0
4
3
2
1
0
C 2060
W 25

Brain Metabolites in Adult HIV patients



Chang et al Neurology 1999

November 2009. Lumbar puncture

- Glucose, protein = normal range
- No pleiocytosis
- HIV-RNA: 540 copies/mL (<50 copies/mL in plasma)
- JCV-DNA, CMV-DNA, HSV-DNA, VZV-DNA, HHV-6 DNA, EBV-DNA, Mtb-DNA: all negative
- HIV genotype:
  - Plasma: WT
  - CSF: RT=M184V, Protease=WT
  - V3 sequencing=R5 (dual-tropic strain in plasma)

Discordance between CSF and plasma HIV replication in patients with neurological symptoms receiving suppressive ART

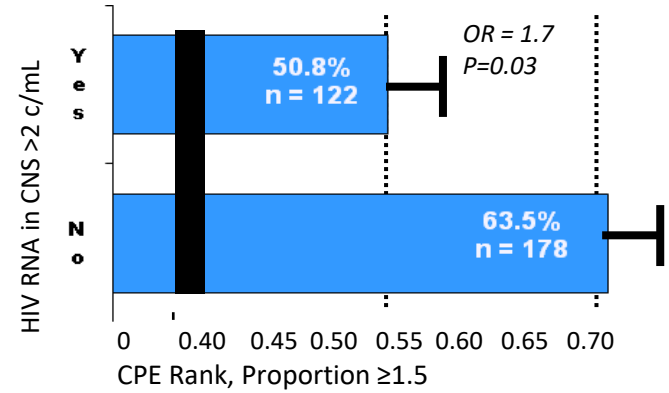
Patient	Age, years	Nadir CD4+ T cell count, cells/mm³	CD4+ T cell count, cells/mm³	Time with plasma HIV RNA level <50 copies/mL, months	Neurological symptoms	Treatment	CSF		Plasma	
							HIV RNA level, copies/mL	ART concentration trough, ng/mL	HIV RNA level, copies/mL	ART concentration trough, ng/mL
1	50	250	592	36	Persistent headache	TDF FTC ATVr	12,885	12 NA <30	147	52 19 538
2	49	4	190	11	Memory disorders, cerebellar ataxia	AZT 3TC IDVr T20	845	28 201 154 <50	<50	<10 244 565 1427
3	43	52	400	18	Cerebellar dysarthria, cerebellar ataxia	3TC ABC ATV IDVr	1190	NA 75 <30 97	<50	597 86 980 893
4	50	221	432	68	Tactile allodynia	TDF FTC fAPVr	870	NA NA 47	78	NA NA 1495
5	36	55	107	75	Glasgow Coma Score of 3	3TC ABC TDF DRVr	5035	<10 332 191 207	<50	<10 270 878 8992
6	47	64	631	64	Persistent headache	DRVr	580	<5	<50	3522
7	44	211	544	14	Memory disorders, cerebellar ataxia, pyramidal syndrome	FTC ABC ATVr	558	NA NA 18	<50	NA NA 194
8	53	25	360	12	Lower limb disesthesia and hypoesthesia	3TC AZT ABC EFV	1023	NA NA NA	<50	NA NA NA
9	68	110	147	12	Memory disorders, left lower limb disesthesia	3TC Ddl TDF NVP	586	NA NA NA	<50	388 NA 28 4864
10	68	25	534	18	Temporospatial disorientation, cerebellar ataxia	3TC AZT ATV	880	NA NA NA	<50	NA NA NA
11	55	2	593	10	Memory disorders, cerebellar dysarthria	LPVr	6999	NA	483	NA

Canestri A, et al. Clin Infect Dis, 2010

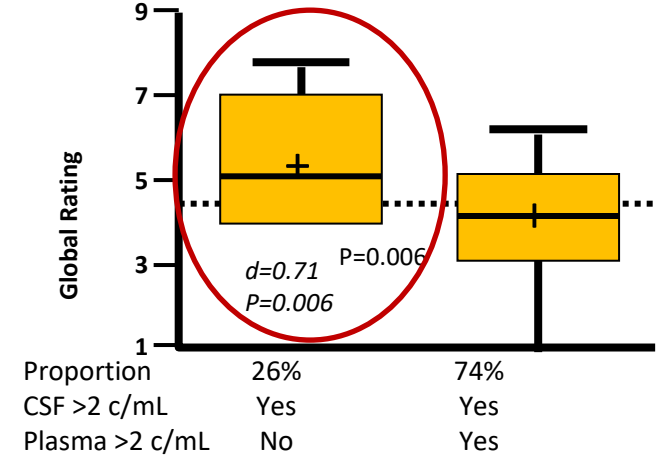
Even Low Levels of HIV RNA in CSF Associated with Neurocognitive Impairment

- Study to evaluate relationships between HIV RNA in CSF, ARV penetration in CSF and neuropsych performance
- Subjects with HIV RNA in CSF <50 c/mL (n=300)
- Test for HIV RNA with NucliSens EasyQ assay (sensitivity = 2 c/mL)
- Results
  - 26% of subjects had HIV RNA in CSF but not in plasma
  - Detection of low level HIV RNA in CSF associated with lower ARV CSF Penetration Effectiveness (CPE) score
  - Poorer neuropsych performance when HIV RNA detected in CSF but NOT plasma compared to subjects with HIV RNA in CSF and plasma

Relationship Between ARV CNS penetration and HIV RNA in CSF



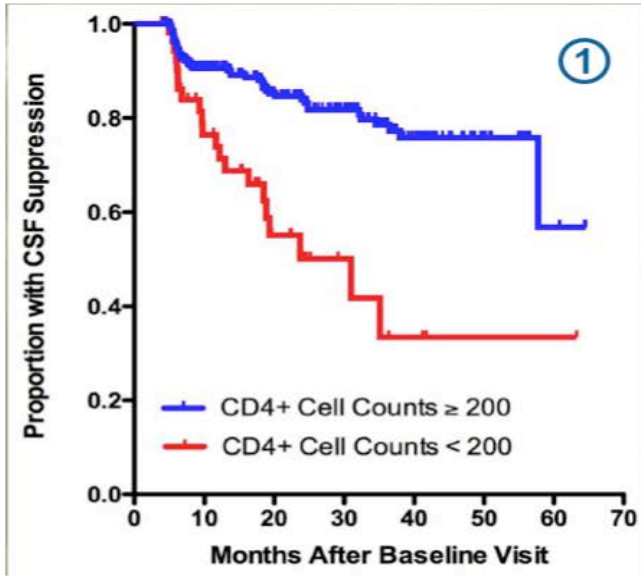
Neurocognitive Function and HIV RNA in CSF and Plasma

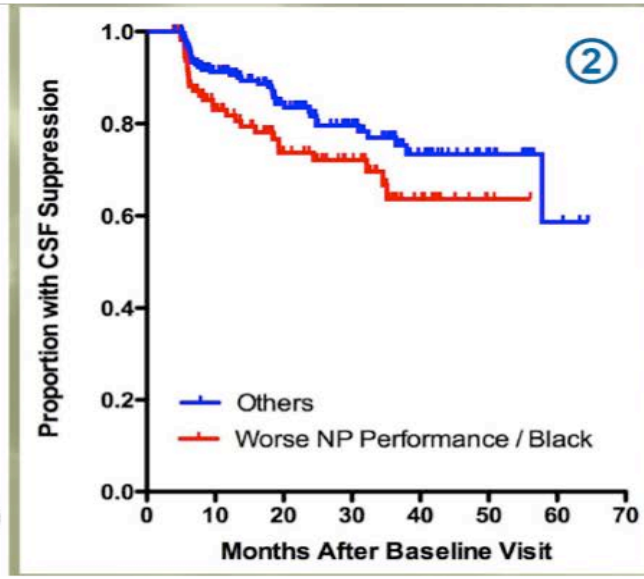


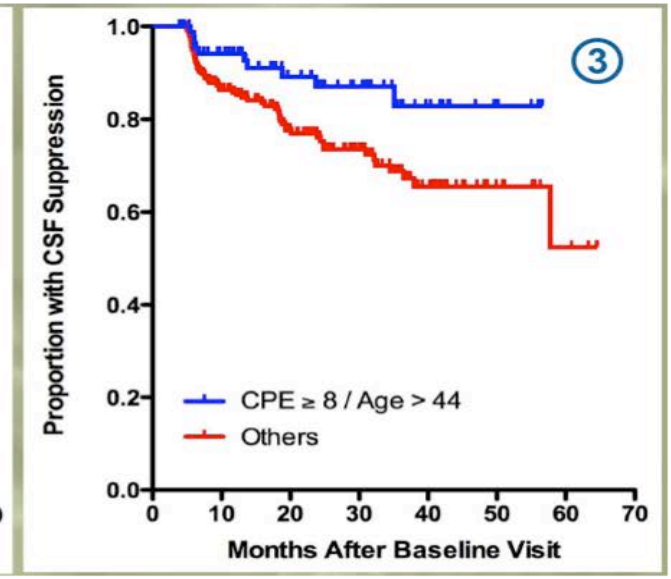
Letendre S, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 484b.

Correlates of TLOVR in CSF and plasma

Table 3.	Risk	CSF		Plasma	
		P	P (Cox)	P	P (Cox)
CD4+ Cell Count	< 200	< 0.001	< 0.001	< 0.001	< 0.001
Age	≤ 44	0.02	0.006	0.15	0.04
Ethnicity	Black	0.008	< 0.001	0.02	0.03
NP Global Rating	≥ 4	*	0.005	0.03	0.03
NNRTI- or PI-based Regimen	PI	0.06	0.06	> 0.15	-
CPE 2010 x Age	< 8, ≤ 44	0.01	0.07	> 0.15	-
Ethnicity x NP Global Rating	Black, ≥ 4	0.05	0.003	> 0.15	-
Plasma Viral Load	> 50 c/mL	0.04	-	-	-
Antidepressant Use	Non-Use	0.03	-	> 0.15	-





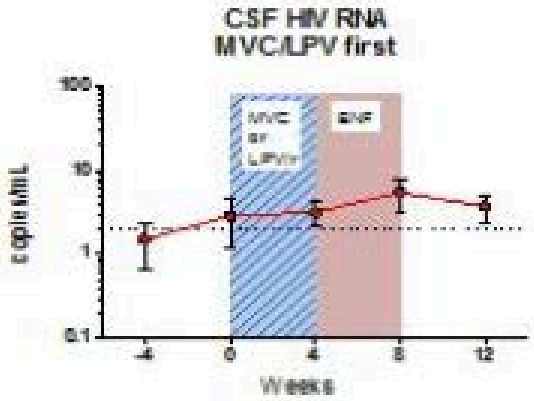


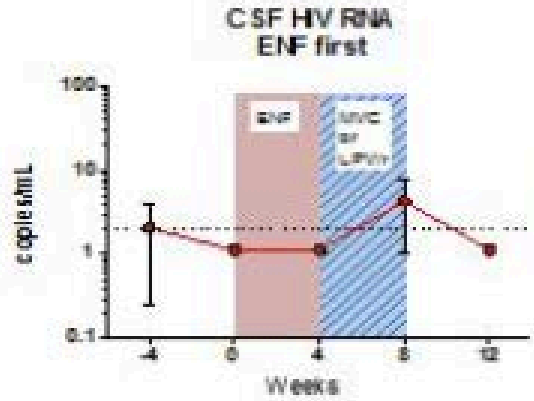
Letendre S, et al. 17° CROI, San Francisco (CA), 2010. Abst. #430

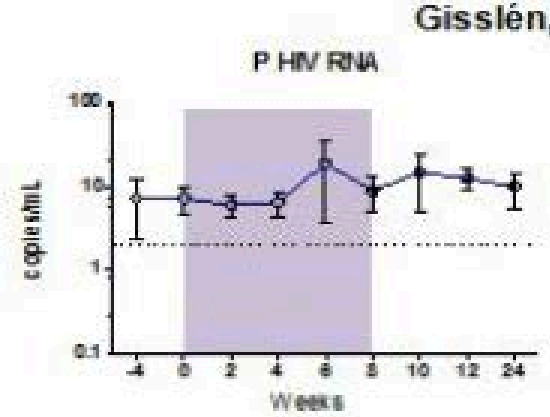
CNS Penetration-Effectiveness (CPE) Ranks (Revised 2010 Version)

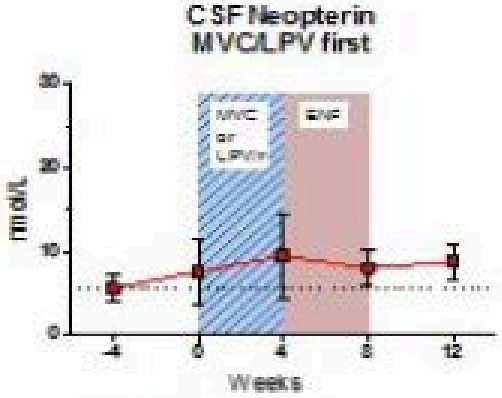
Table 1.	4	3	2	1
NRTIs	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PIs	Indinavir-r	Darunavir-r	Atazanavir-r	Nelfinavir
		Fosamprenavir-r	Atazanavir	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir-r
		Lopinavir-r		Saquinavir
				Tipranavir-r
Fusion/Entry Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

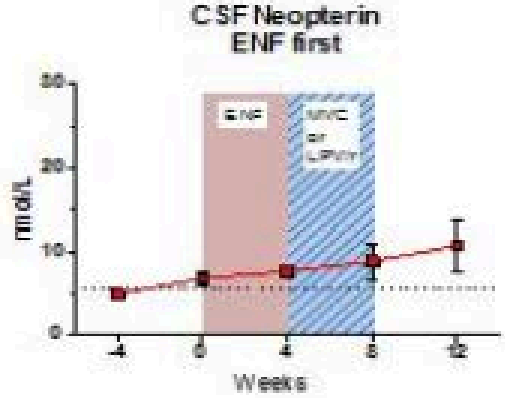
Letendre S, et al. 17th CROI, San Francisco (CA), 2010

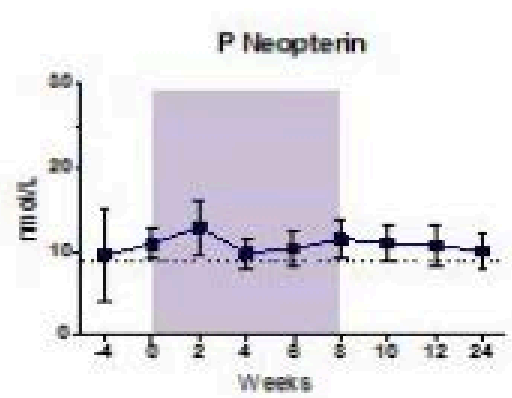












Conclusion

These findings do not support the hypothesis that ongoing viral replication is the main source of residual CSF viremia and intrathecal immune activation.

Would you modify ART regimen?

1. ZDV/3TC/EFV
2. ABV/3TC/EFV
3. ZDV/3TC/LPV-RTV
4. TDF/FTC/RAL
5. ZDV/3TC/DRV-RTV

Case history - V

- November 2009: changing ART to ZDV/3TC/LPV-RTV
- February 2010:
  - Plasma HIV-RNA <50 copies/mL; CD4 count 295 cell/mmc
  - CSF HIV-RNA <50 copies/mL
  - MR Spectroscopy: not changed
  - NCI stable

Key issues - I

- Older aging
- Low nadir CD4 count and current CD4 <350 cell/mmc
- Depression as confounding/contributing condition on NCI diagnosis (anti-depressive treatment impact on picture and adherence)
- Role of HCV-coinfection
- CSF HIV rebound during low CPE ART treatment (in older, with low CD4 nadir…)
- Discordant CSF/plasma HIV evolution
- Residual low-level viremia (not ongoing replication?)
- MR spectroscopy abnormalities before clinical expression of HIV dementia

Key issues – II. ART discussion

- ART changes as impact on case history (EFV removing, ATV/r and TDF combination, ZDV reintroduction, LPV/r)
- Long-term improvement of CNS damage (NCI, MR-spectroscopy)
- What choice of ART for long-term treatment and suppression (and CNS HIV control)
  - LPV/r: negatively affect CV risk (older aging, smoker)
  - ZDV: increasing LD, poor virological control, impaired CD4 recovery
  - What chances for new drugs (DRV/r, RAL, MRV – discordant V3 genotype)