Summary of the Symposium and Discussion

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Acknowledgements & Conflicts

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- Igor Grant
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26-27 May 2017

Barcelona, Catalonia, Spain

Measuring Cognitive Changes in HIV Infection: Size Really Matters

Jose A. Muñoz-Moreno, Ph.D.

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Measuring Cognitive Change in HIV Population

Updated research nosology for HIV-associated neurocognitive disorders

Neurology 69 October 30, 2007

	Neuropsychological (NP) Testing is 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.
Mild Neurocognitive Disorder (MND)	At least mild NP impairment (>1 SD below a demographically appropriate normative mean), involving ≥2 cognitive domains.
HIV-Associated Dementia (HAD)	≥ Moderate NP impairment (>2SD below a demographically appropriate normative mean) on > 2 cognitive 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)

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Measuring Cognitive Change in Non-HIV Population

Neurocognitive Function in HIV-Infected Patients: Comparison of Two Methods to Define Impairment

Alejandro Arenas-Pinto[1,2*], Alan Winston[3,4], Wolfgang Stöhr[1], John Day[5], Rebecca Wiggins[6], Say Pheng Quah[7], Jonathan Ainsworth[8], Sue Fleck[1], David Dunn[1], Alex Accoroni[9] and Nicholas I. Paton[1,10] for the PIVOT Trial Team[¶]

July 2014 | Volume 9 | Issue 7 | e103498

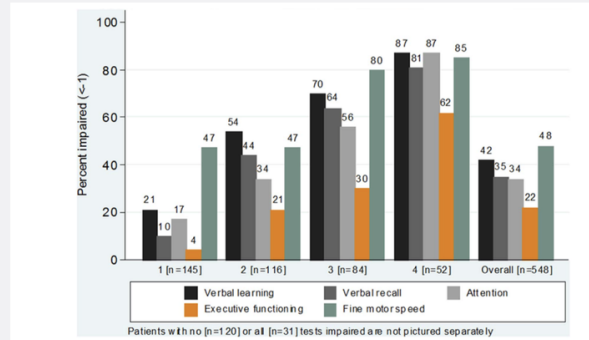

Figure 1. Proportion of patients with functional domains impaired (<−1SD), overall and by number of tests impaired.
doi:10.1371/journal.pone.0103498.g001

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Muñoz-Moreno / Barcelona / May 2017

Measuring Cognitive Change in Non-HIV Population

Assessment, Diagnosis, and Treatment of HIV-Associated Neurocognitive Disorder: A Consensus Report of the Mind Exchange Program

The Mind Exchange Working Group

HIV/AIDS • CID 2013:56 (1 April) • 1005

5. The use of normative data (to adjust for demographic/sociodemographic factors) is essential for the correct interpretation of standard neuropsychological tests with quantitative outcomes (See standard reference books: Heaton et al., 2004b; Lezak et al., 2004; Strauss et al, 2006). Note that the neuropsychologist will also use qualitative information (for example level of motivation, level of reading or writing proficiency, etc) to contextualise the quantitative results.

   a. In developing and developed countries the effects of age, education, and gender (as well as ethnicity in some countries) must be considered. See standard reference books Lezak et al., 2004; Strauss et al, 2006
   b. Geographic characteristics (such as coming from an urban versus rural environment) may need to be considered in addition to the traditional demographic factors in developing countries. See standard reference books Heaton et al., 2008; Lezak et al., 2004; Strauss et al, 2006
   c. Normative data should be selected to best represent the demographic references for a particular participant. In some instances, local norms based on a smaller sample size are recommended over non-local norms based on large sample sizes. See standard reference book Strauss et al, 2006

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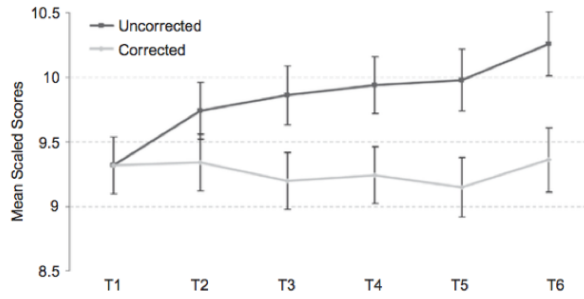
Muñoz-Moreno / Barcelona / May 2017

Practice Effect

Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change

Lucette A. Cysique[1,2], Donald Franklin, Jr[1], Ian Abramson[1], Ronald J. Ellis[1], Scott Letendre[1], Ann Collier[3], David Clifford[4], Benjamin Gelman[5], Justin McArthur[6], Susan Morgello[7], David Simpson[7], J. Allen McCutchan[1], Igor Grant[1], Robert K. Heaton[1], the CHARTER group, and the HNRC group

JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY
2011, 33 (5), 505–522



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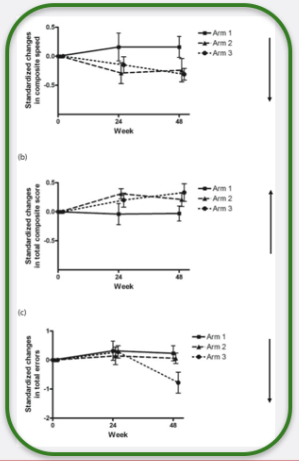
Examples of Studies (5)

Dynamics of cognitive change in HIV-infected individuals commencing three different initial antiretroviral regimens: a randomized, controlled study

A Winston,[1] R Puls,[2] SJ Kerr,[2,3] C Duncombe,[3] PCK Li,[4] JM Gill,[5] SD Taylor-Robinson,[1] S Emery[2] and DA Cooper[2] for the Altair Study Group
[1]*Imperial College London, London, UK,* [2]*National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, NSW, Australia,* [3]*HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand,* [4]*Queen Elizabeth Hospital, Kowloon, Hong Kong and* [5]*Calgary Regional Health Authority, Calgary, Canada*

Winston et al, HIV Medicine, 2012



	Characteristics
Autor / Year	Winston et al / 2012
Design / Sample	Randomized, Open-Label / N = 28
Intervention	cART: FTC + 1) EFV, 2) ATV/r, 3) AZT/ABC
Efficacy Endpoint	NPZ9 / 3 domains
Time	24 weeks + 48 weeks
Statistical Approach	t test, p values
Results	Significant improvements

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Examples of Studies (3)

Rivastigmine for HIV-associated neurocognitive disorders

A randomized crossover pilot study

Simioni et al, Neurology, 2013

	Mean combined outcome (SD)	F[b]	p Value
ADAS-Cog	−0.09 (1.14)	$F_{1,13} = 0.31$	0.589
RTI reaction time	−0.53 (2.94)	$F_{1,13} = 1.87$	0.195
RTI movement time	0.68 (2.62)	$F_{1,13} = 0.45$	0.512
RVIP	−0.12 (1.26)	$F_{1,13} = 0.03$	0.858
SWM errors	0.19 (1.24)	$F_{1,13} = 0.08$	0.786
SWM strategy	0.44 (0.88)	$F_{1,13} = 3.94$	0.068
Trail Making Test A	1.20 (1.89)	$F_{1,13} = 5.57$	0.034[c]
Trail Making Test B	0.22 (3.28)	$F_{1,13} = 0.06$	0.816
SOC correct problems	0.26 (0.95)	$F_{1,12} = 1.17$	0.301
Symbol Digit test	0.11 (0.66)	$F_{1,13} = 0.27$	0.613
Digit span backward	0.08 (2.17)	$F_{1,13} = 0.00$	0.946
Digit span forward	−0.03 (2.21)	$F_{1,13} = 0.03$	0.867
MOS-HIV perceived health[d]	0.20 (21.18)	$F_{1,13} = 0.06$	0.804
MOS-HIV social function[d]	−9.53 (56.09)	$F_{1,13} = 0.70$	0.418
MOS-HIV cognitive function[d]	16.87 (34.76)	$F_{1,13} = 2.71$	0.124
MOS-HIV mental health[d]	4.67 (31.24)	$F_{1,13} = 0.12$	0.730
MOS-HIV global quality of life[d]	14.73 (43.58)	$F_{1,13} = 1.45$	0.249

	Characteristics
Autor / Year	Simioni et al / 2013
Design / Sample	Cross-over, Pilot/ N = 17
Intervention	Rivastigmine
Efficacy Endpoint	Specific scores / 5 domains
Time	20 weeks
Statistical Approach	ANOVA, p values
Results	No significant improvement

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Neurological Soft signs in HIV associated neurocognitive disorder (HAND):
an easy clinical examination for screening and early recognition

Johannes Schröder, Christina Herold and Pablo Toro
Section for Geriatric Psychiatry, Rupprecht- Karls Universität Heidelberg
Dept. of Psychiatry, Pontificia Universidad Católica de Chile

Neurological soft signs

- comprise both, minor motor and sensory abnormalities
- are frequently found in major psychiatric disorders
- vary in the clinical course
- can be reliable assessed by using rating scales, such as the Heidelberg scale as part of the routine work up

Schröder et al., 1992

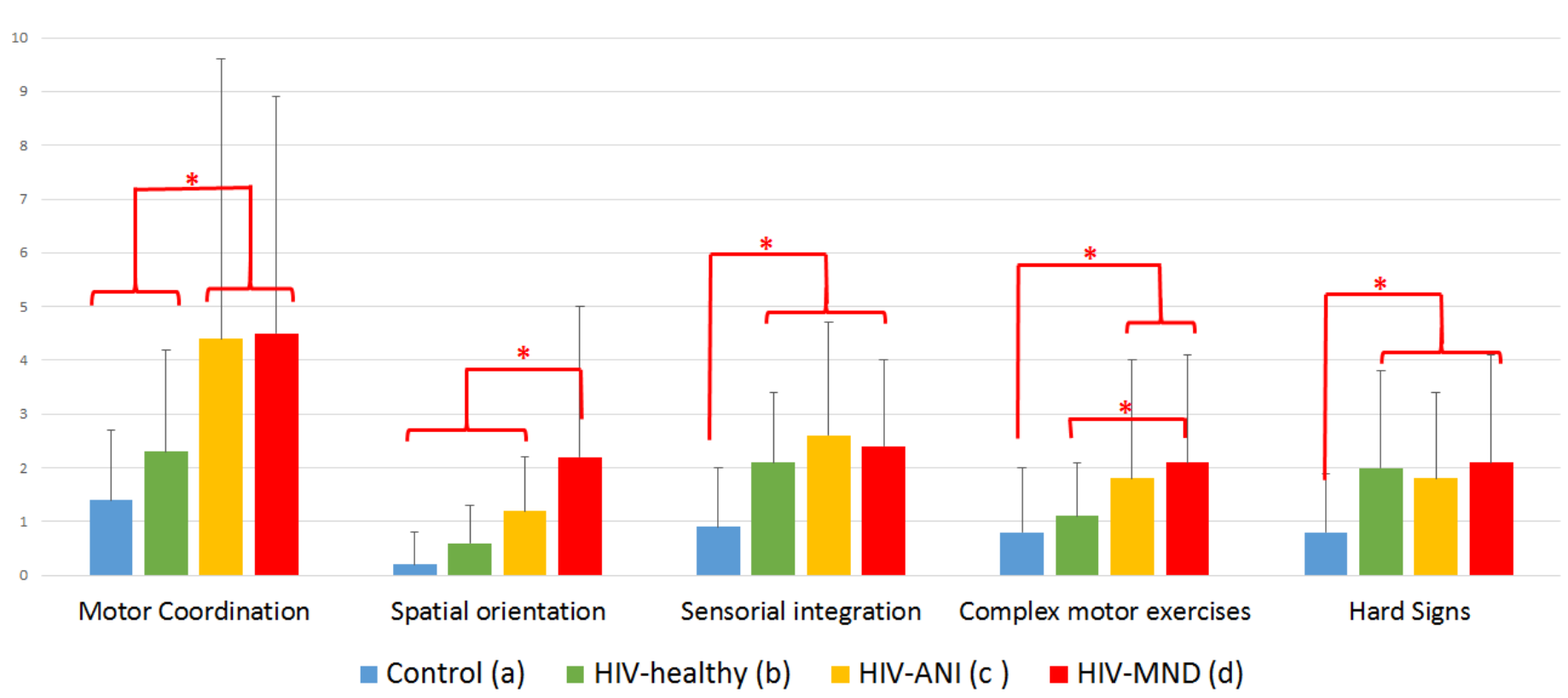
Heidelberg Scale Subscale and Test
1. Motor coordination
Ozeretzki's test
Diadochokinesis
Pronation/supination
Finger/thumb opposition
Articulation
2. Sensory integration
Gait
Tandem gait
2-point discrimination
3. Complex motor tasks
Finger-to-nose test
Fist-edge-palm test
4. Right/left and spatial orientation
Right/left orientation
Graphesthesia
Face/hand sensory test
Stereognosis
5. Hard signs
Arm-holding test
Mirror movements

Heidelberg NSS-Scale

- **Three point rating scale**
  (max. 81 points)
- **High internal consistency**
  Cronbach's α: 0.85/0.89
- **test-retest reliability**
  rtt=0.80, p<0.001
- **interrater reliability**
  r=0.88, p<0.005

Schröder et al., 1992
Bachmann et al., 2005
Valenzuela et al., 2014

NSS subscales



* p < 0.05

Preliminary study of a novel cognitive assessment device for the evaluation of HIV-associated neurocognitive impairment

Albert M. Anderson[1] · Jeffrey L. Lennox[1] · Minh L. Nguyen[1] · Drenna Waldrop-Valverde[1] · William R. Tyor[1] · David W. Loring[1]

J. Neurovirol. (2016) 22:816–822
DOI 10.1007/s13365-016-0458-z

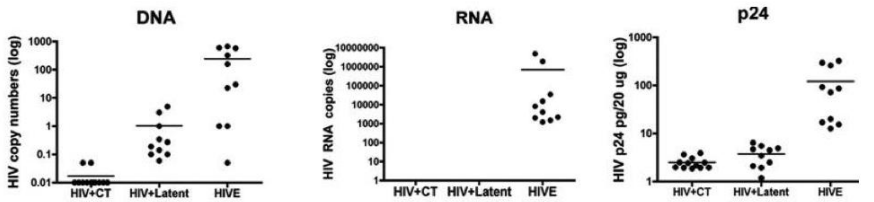
Questions for Consideration

- **What standardized methods should be used to ensure comparability between trials?**
  - **Neuropsychological testing, NSS, imaging, biomarkers**
  - **How often should participants be assessed?**
  - **For how long should participants be followed?**
- **The Frascati guidelines are a decade old. Should they be updated considering 10 years of progress?**
- **What are the most promising interventions now?**
  - **Changing "habits": Exercise, diet**
  - **Treating comorbid disease: depression, substance use, sleep disorders, metabolic and vascular disease**
  - **Adjunctive therapies: rivastigmine, paroxetine**

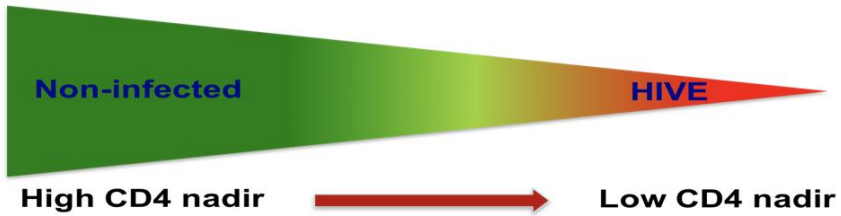
Pros and Cos of antiretroviral treatment on CNS

Ignacio Pérez Valero
Hospital U. La Paz

Intensity of CNS disease is not always the same



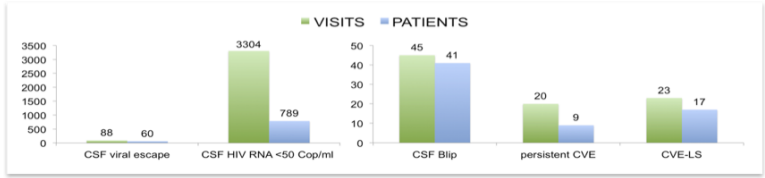
HIV+ CT
HIV+ Latent



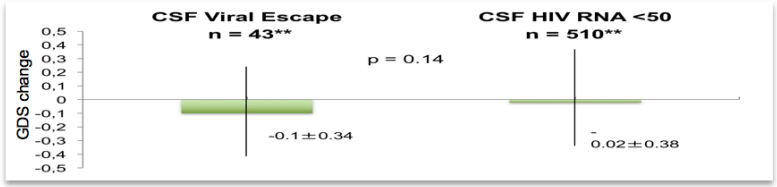
Desplats P et al. Neurology 2013;80(15):1415-23.

Current regimens have enough CNS penetration

Uncommon & transient

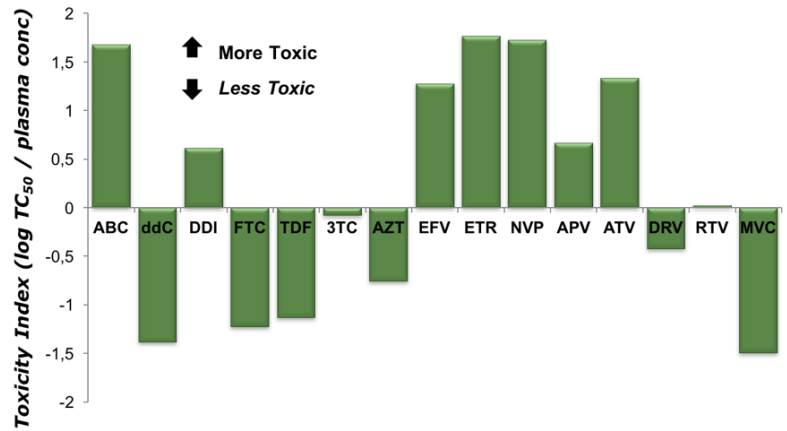


And it is not associated with NP decline



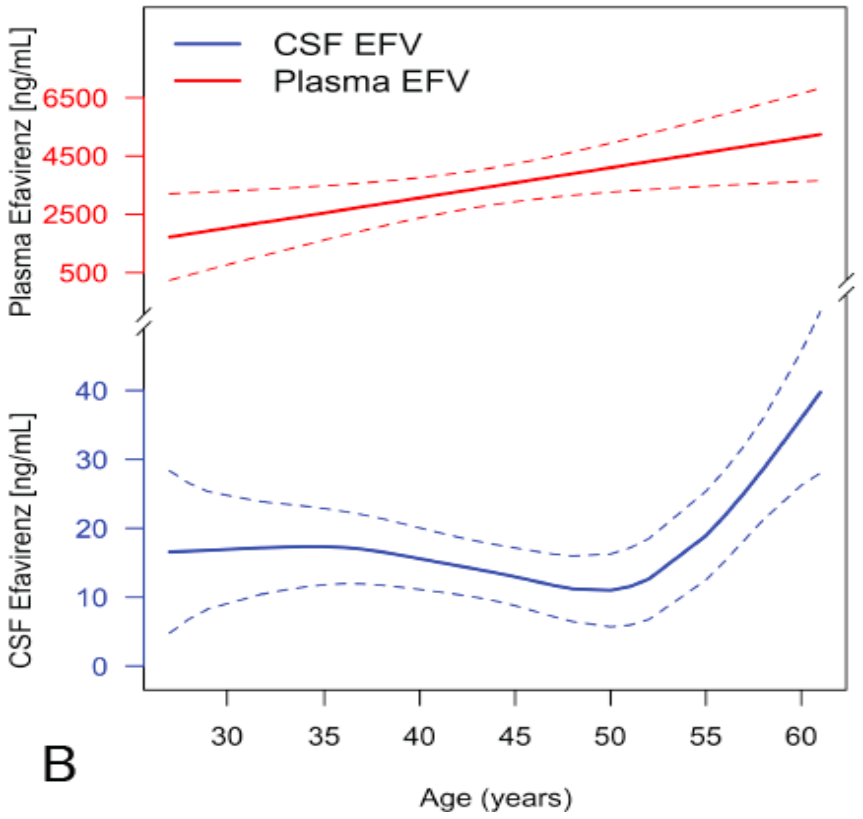
Perez Valero I et al. CROI 2013. Abstract 119

In-vitro neurotoxicity is associated to drug levels

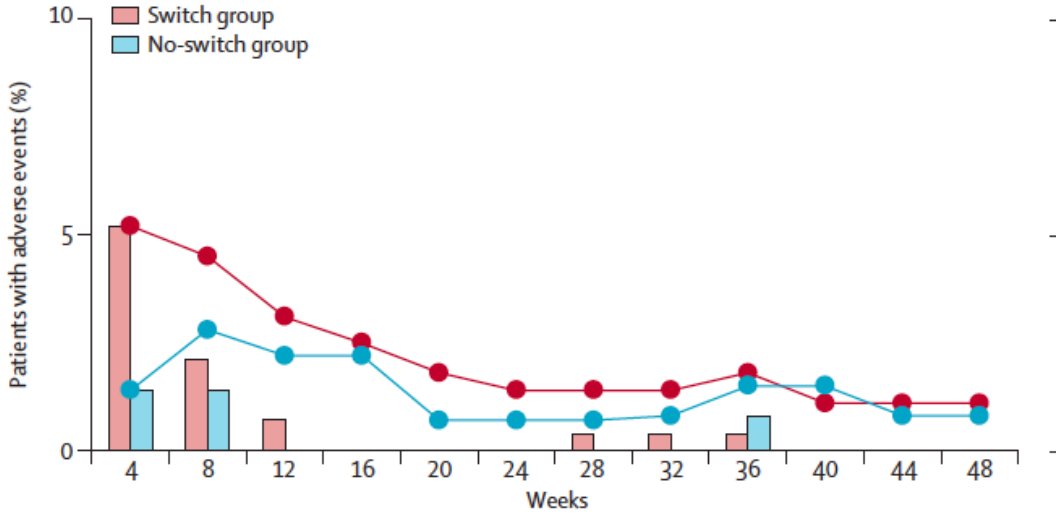


Robertson K et al. J Neurovirol 2012;18(5):388-99.

Does Changing CSF Pharmacology Over Time Influence CNS Adverse Events?



Croteau D. et al. CROI 2012, abstract 592.



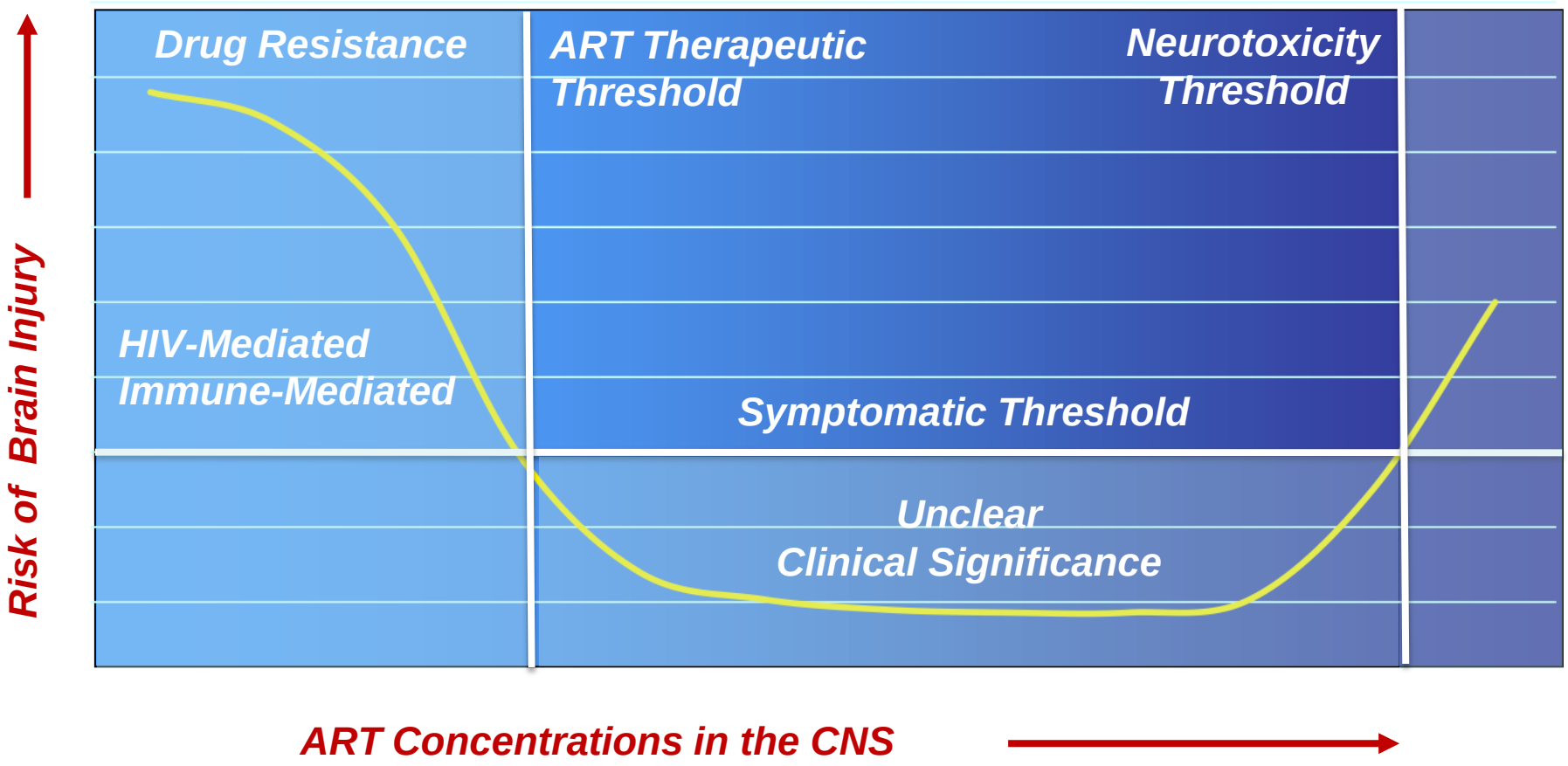
Pozniak et al, Lancet Infectious Disease 2014; 14: 590–99

	Week 2	Week 16	Change (%)
DTG Plasma, total*	3360	3210	-4.5%
DTG Plasma, unbound*	17.1	23.9	+39.8%
DTG CSF, total*	18.2	13.2	-27.5%
CSF–total plasma ratio, %	0.516	0.412	-20.2%

*ng/mL
All values are medians

Letendre et al, Clin Infect Dis 2014;59(7):1032–7

We need ART to be balanced



Personal Slide Courtesy of S. Letendre

Questions for Consideration

- Do current ART regimens have sufficient potency outside and inside the CNS to minimize the effects of HIV replication?
  - Will we continue to see CSF viral escape?
- How will the clinical environment shift over the next 5 years (long-acting ART, new classes of drugs)
- How will we control inflammation from low-level replication and production of neurotoxic HIV proteins?
- How do we implement neurotoxicity data into the clinic?
- Will we need different treatment strategies for patients with different characteristics (e.g., aged)?

Imperial College London

Integrase inhibitors and the brain

Professor Alan Winston

St. Mary's Hospital London

May 2017

Disclaimer:

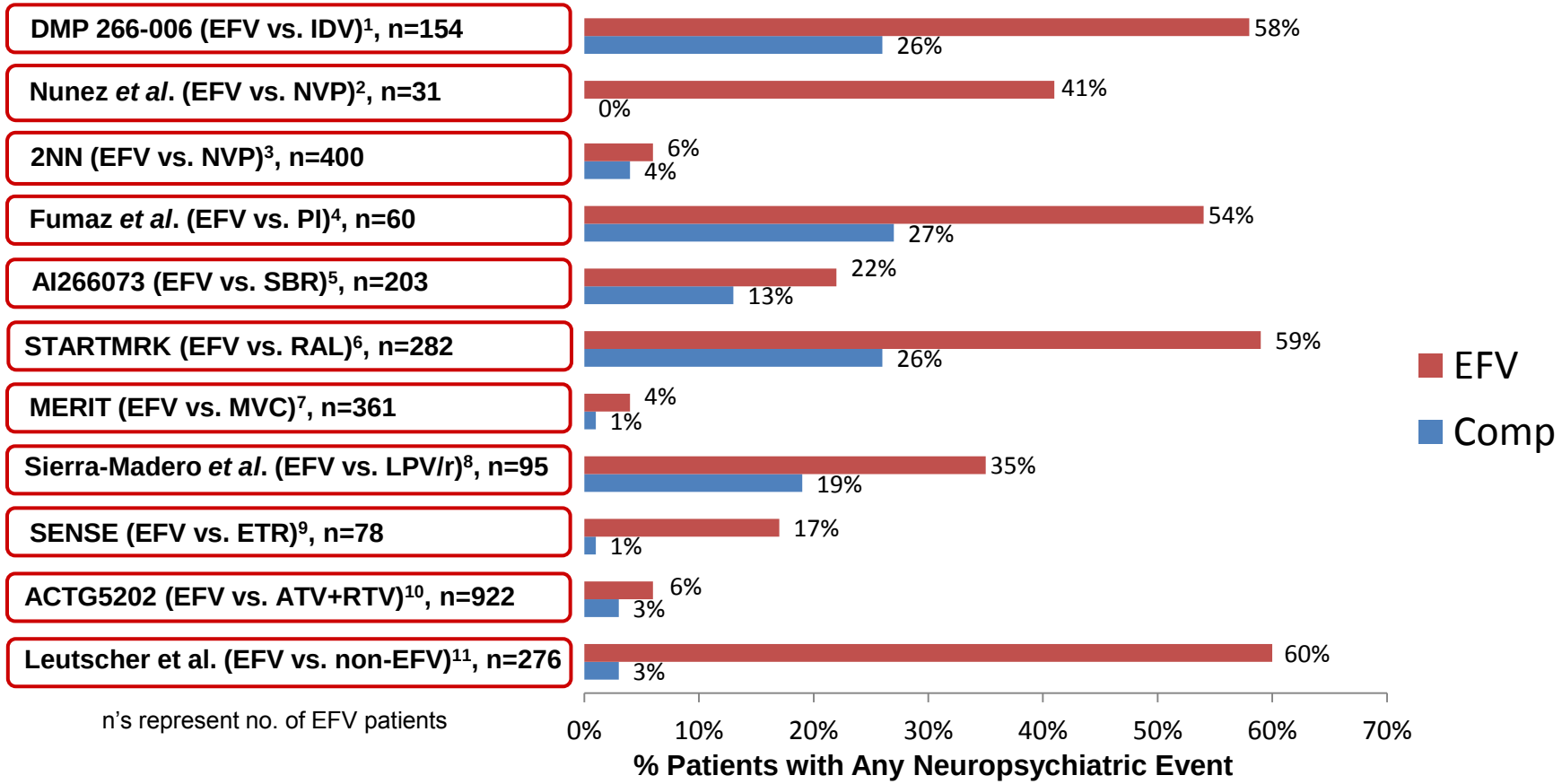
Gilead Sciences Europe Ltd has provided the funding for this session

The presentation express the views and opinion of the presenter which are based on information and data available at the time

HIV/IHQ/17-05//1539a Date of Preparation: May 2017

The history of EFV-associated CNS toxicities

Imperial College London



IDV, indinavir; NVP, Nevirapine, PI, protease inhibitor; SBR, stable baseline regimen; RAL, raltegravir; MVC, maraviroc; LPV, lopinavir; ATV, atazanavir; ETR, etravirine; RTV, ritonavir; EFV, efavirenz; Comp, comparator

1. Staszewski S, et al. NEJM 1999;341:1865–1873; 2. Nunez M, et al. HIV Clin Trials 2002;3:186–194; 3. Van Leth, F et al. Lancet 2004;363:1253–1263; 4. Fumaz C, et al. JAIDS 2005;38:560–565; 5. DeJesus E, et al. JAIDS 2009;51:163–174; 6. Lennox J, et al. Lancet 2009;374:796–806; 7. Cooper D, et al. JID 2010;201:803–813; 8. Sierra-Madero, et al. JAIDS 2010;53:582–588; 9. Gazzard B, et al. AIDS 2011;25:2249–2258; 10.Daar E, et al. Ann Intern Med 2011;154:445–456; 11. Leutscher PDC, et al. Scan J Inf Dis 2013; Early Online.

HIV/IHQ/17-05//1539a Date of Preparation: May 2017

How long does it take to identify a problem?

Drug/class	FDA approval	Toxicity	Signal	Delay (years)	Risk (95%CI)
stavudine[1]	1994[14]	Lipoatrophy	1999[7]	5	RR 1.95 (1.18-3.22)
nevirapine[2]	1996[14]	Toxicity at high CD4	2005[8]	9	Female 12 x higher risk Male 5 x higher risk
PIs	1996[14]	Heart attack	2003[9]	7	RH 2.56 (1.03-6.34)
efavirenz[3]	1998[14]	Suicidality	2013[10]	15	HR 2.28 (1.27,4.10)
abacavir[4]	1998[14]	Heart attack	2008[11]	10	RR 1.14 (1.08–1.21)
tenofovir[5]	2001[14]	Fracture	2012[12]	11	HR 1.080 (1.02,1.15)
Raltegravir[6]	2007[14]	Myopathy	2013[13]	5	OR 2.64 (1.57-4.45)

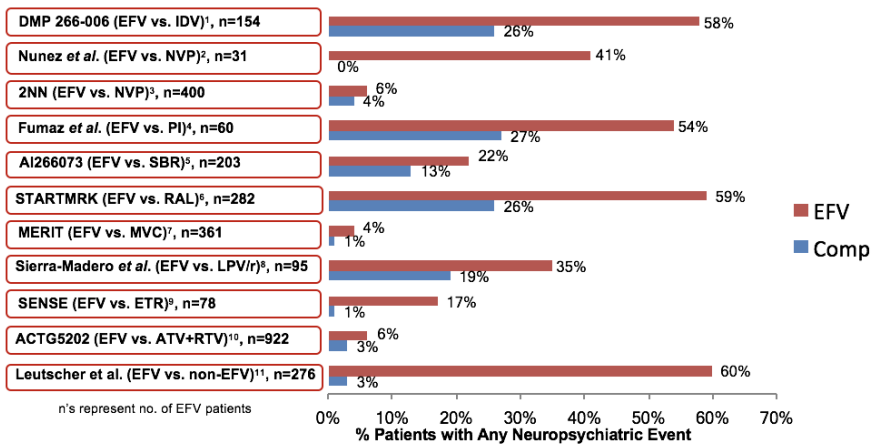
PIs, Protease Inhibitors; RR , Relative risk; RH , Relative hazard; HR , Hazard ratio; OR, overall risk

1.Stavudine SPC https://www.medicines.org.uk/emc/medicine/21122, 2.Nevirapine SPC https://www.medicines.org.uk/emc/medicine/322, 3. Efavirenz SPC https://www.medicines.org.uk/emc/medicine/11284, 4. Abacavir SPC https://www.medicines.org.uk/emc/medicine/2476, 5.Tenofovir SPC https://www.medicines.org.uk/emc/medicine/9008, 6. Raltegravir SPC https://www.medicines.org.uk/emc/medicine/20484, 7. Sain-Marc et al, AIDS 1999; 8. FDA Public Health Advisory for Nevirapine, 2005, 9. Mary-Krause M et al, AIDS. 2003 Nov 21;17(17):2479-86 10. Mollan et al, IDSA 2013; 11.DAD Study Group, Lancet 2008; 12. Bedimo et al , AIDS 2012; 13. Lee et al, JAIDS 2013; 14. FDA Antiretroviral drugs used in the treatment of HIV infection, https://www.fda.gov/forpatients/illness/hivaids/treatment/ucm118915.htm Last accessed May 2017

HIV/IHQ/17-05//1539a Date of Preparation: May 2017

The history of EFV-associated CNS toxicities

Imperial College London



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PIs, Protease Inhibitors; RR , Relative risk; RH , Relative hazard; HR , Hazard ratio; OR, overall risk

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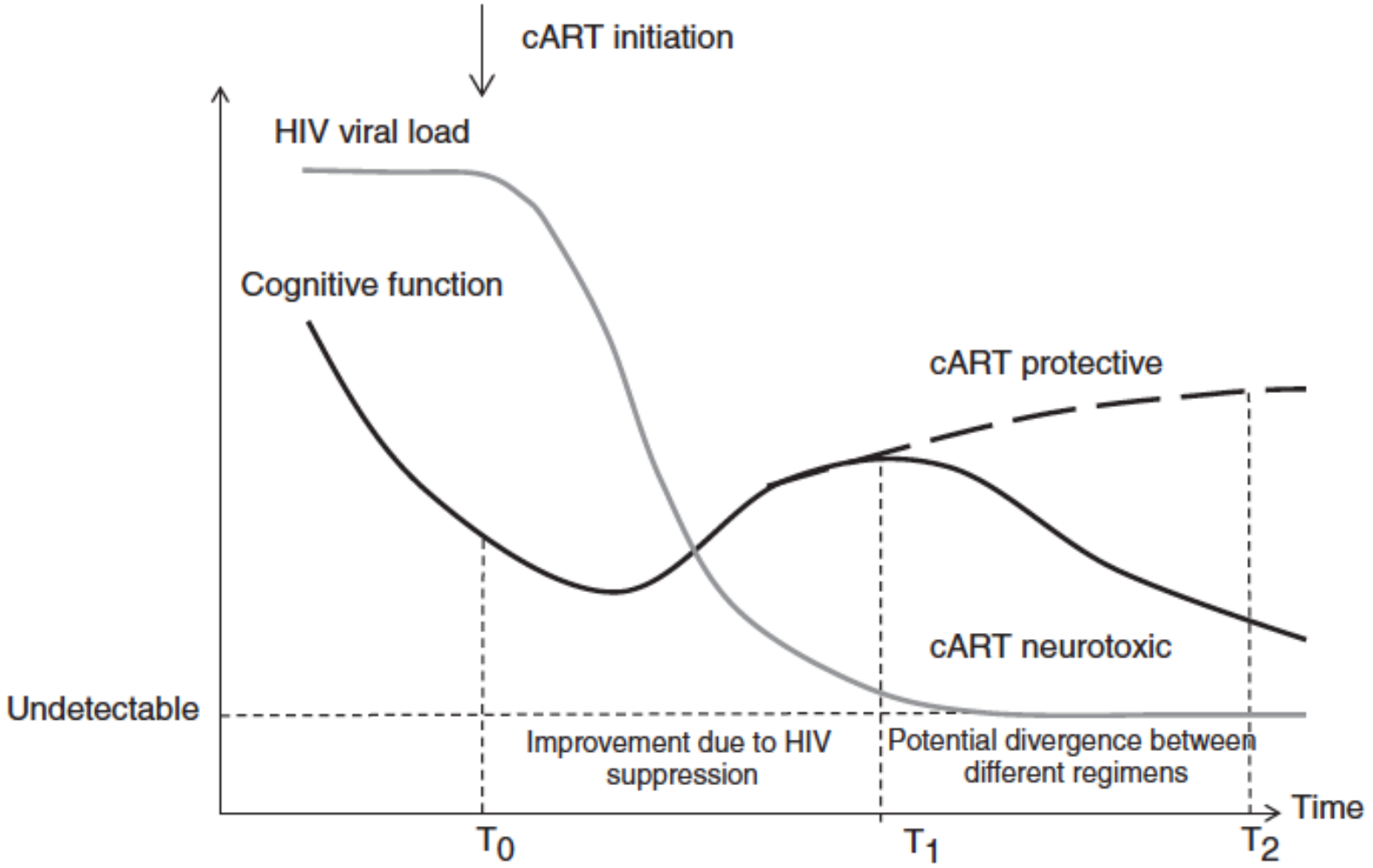
Neurotoxicity May Be Masked in the Early Treatment Period



Underwood et al, AIDS 2015, 29:253–261

Imperial College London

Dolutegravir cohort data

Clinic	No. of patients	d/c due to AEs n (%)	Main reasons for d/c
OLVG[1]	387	62 (16%)	Sleeping, gastro-intestinal, neurological
Brighton[2]	128	16 (13%)	Sleep
Foch[3]	105	11 (10.4%)	Vertigo, headache, insomnia, malaise
Cardiff[4]	63	6 (10%)	Sleep
Manchester[5]	178	15 (8.4%)	CNS, malaise and joint pain
Cologne[11]	985	67 (6.8%)	Neuropsychiatric (5.0%), gastro-intestinal (0.7%), skin (0.3%), renal (0.2%), hepatic (0.1%)
St Thomas [6]	181	9 (5%)	Insomnia, malaise/myalgia
DOL-ART[10]	411	18 (4,4%)	Depression (1.2%), GI symptoms (1%)
Ramòn Y Cajal[9]	827	36 (4,3%)	Headache, dyslipidemia, insomnia, dizziness, mood disorders
Cruser Kobler AIDS centre[8]	73	3 (4.1%)	CNS (2), gastro-intestinal (1) 19% patients had AEs, and 11% CNS AEs
Liverpool[12]	178	8 (4%)	n/a, 33% have AEs of whom 20% CNS, 10% gastrointestinal, 7% neurological, 3% musculoskeletal, 3% lethargy
Llibre[14]	873	25 (3%)	Neuropsychiatric toxicity definition included anxiety, depression, insomnia, dizziness, nightmares, paresthesia, somnolence, tremor and vertigo (adjusted HR of 3.18 DTG vs RAL & 4.93 DTG vs EVG/COBI)
Imperial[7]	138	3 (2%)	Sleep dizziness
Osaka[13]	101	n/a	20.8% reported CNS AEs: headache (7.9%), insomnia (5.9%)

d/c, discontinuation; AE, adverse events; CNS, central nervous system

1. Brinkman K, et al. CROI 2016, Boston, MA. #948; 2. Kirby, et al. BHIVA 2016, Manchester UK. P26; 3. Zucman D, et al. AFRAVIH 2016, Brussels, Belgium. P1405; 4. Cunningham, et al, BHIVA 2016, Manchester, UK. P36; 5. Jewsbury S, et al. BHIVA, Manchester, UK. 2016. P20; 6. Simons R, et al. Guy's and St Thomas' NHS Foundation Trust, P9; 7. Negedu, et al. BHIVA, Manchester UK. April 2016. p 28; 8. Tau L, et al. HIV Drug Therapy, Glasgow, UK. 2016. P108; 9. Vivancos-Gallego M, et al. HIV Drug Therapy, Glasgow, UK, 2016. P116; 10. Postel N, et al. HIV Drug Therapy, Glasgow, UK, 2016. P133; 11. Sabranski M, et al. HIV Drug Therapy, Glasgow, UK, 2016. O214; 12. Fernandez C, et al. HIV Drug Therapy, Glasgow, UK, 2016. P212; 13. Yagura H, et al. HIV Drug Therapy, Glasgow, UK, 2016. P312; 14. Llibre JM et al. CROI 2017. Seattle, WA. P651.

HIV/IHQ/17-05//1539a Date of Preparation: May 2017

CNS Safety Data from Dolutegravir Clinical Trials

	SPRING-1[1]		SPRING-2[2]		FLAMINGO[3]		SINGLE[4]	
	DTG n=51	EFV n=50	DTG n=411	RTG n=411	DTG n=242	DRV/r n=242	DTG n=357	EFV n=362
Headache	10%	4%	14%	13%	17%	11%	6%	7%
Dizziness	6%	18%	6%	6%	6%	5%	7%	33%
Insomnia	6%	10%	6%	5%	8%	7%	10%	6%
Depression	*	*	6%	5%	6%	4%	**	**
Anxiety	*	*	4%	5%	5%	4%	**	**
Abnormal Dreams	*	*	**	**	**	**	7%	16%

* < 3%
** < 5%

All data are from 96 weeks

[1]*Stellbrink et al, AIDS 2013, 27:1771–1778*
[2]*Raffi et al, Lancet 2013, 13: 927–35*
[3]*Molina et al, Lancet HIV 2015; 2: e127–36*
[4]*Walmsley et al, JAIDS 2015, 70:515–519*

CNS Safety Data from Elvitegravir Clinical Trials

	Study 102[1]		Study 103[2]		STRATEGY-NNRTI[3]		STRATEGY-PI[4]	
	EVG/c n=348	EFV n=352	EVG/c n=353	ATV/r n=355	EVG/c n=291	NNRTI n=143	EVG/c n=293	PI/r n=140
Headache	16%	11%	17%	15%	10%	3%	6%	6%
Dizziness	7%	26%	*	*	**	**	**	**
Insomnia	11%	16%	*	*	6%	5%	3%	5%
Depression	12%	14%	10%	12%	**	**	4%	6%
Anxiety	*	*	*	*	**	**	6%	4%
Abnormal Dreams	15%	28%	*	*	**	**	**	**
Back Pain	*	*	12%	5%	**	**	**	**

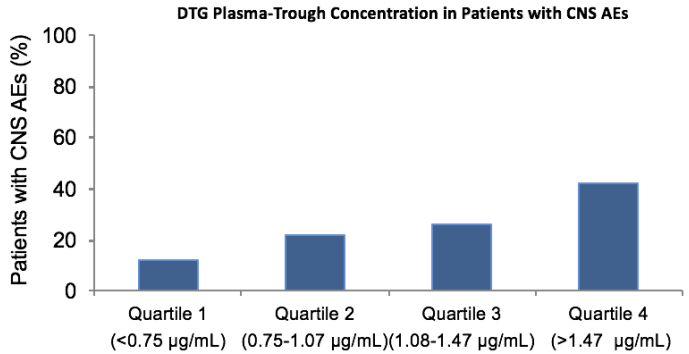
* < 10%
** < 5%

[1]*Zolopa et al, JAIDS 2013, 63: 96–100*
[2]*Rockstroh et al, JAIDS 2013, 62: 483–486*
[3]*Pozniak et al, Lancet Inf Dis 2014; 14: 590–99*
[4]*Arribas et al, Lancet Inf Dis 2014, 14: 581–89*

Imperial College London

Pharmacokinetic considerations

Evaluation of association of DTG concentration and CNS side effects in 162 HIV-infected patients on DTG in Osaka, Japan, Apr 2014 to Mar 2016



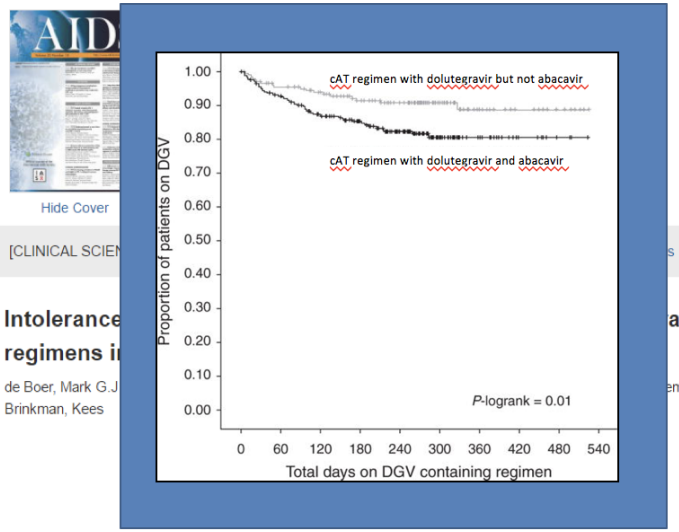
"A positive correlation between DTG plasma trough concentration and CNS side effects was identified in a Japanese population."

AEs, adverse events; DTG, Dolutegravir; CNS, Central Nervous System

Yagura H, et al. CROI 2017. Seattle, WA. Poster #426

Imperial College London

The contribution of abacavir



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Next Article >

Intolerance
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de Boer, Mark G.J
Brinkman, Kees

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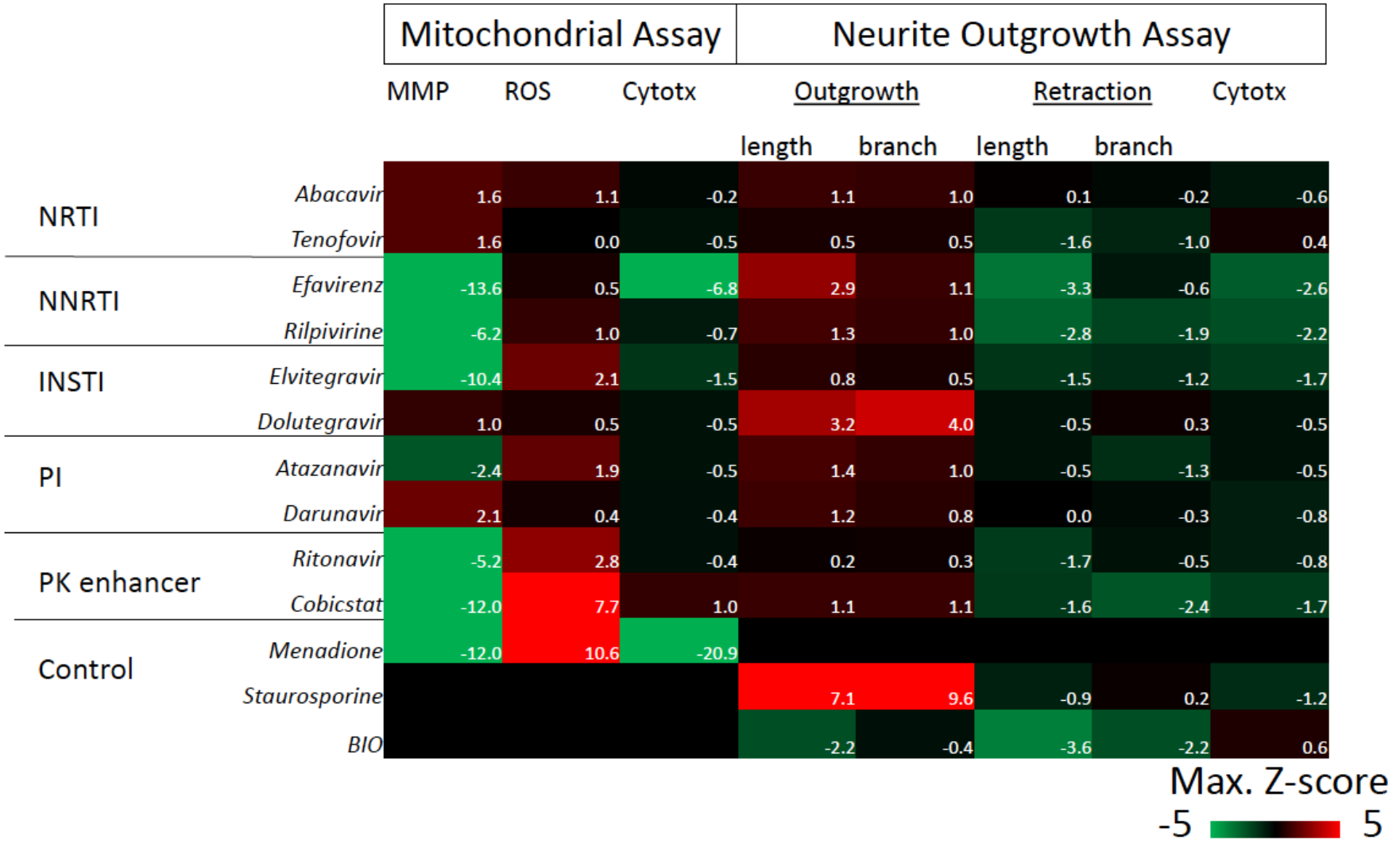
De Boer et al. (2016) AIDS 30(18): 2831-2834

Neurotoxicity Screening of ART Drugs With Human iPSC-Derived Neurons



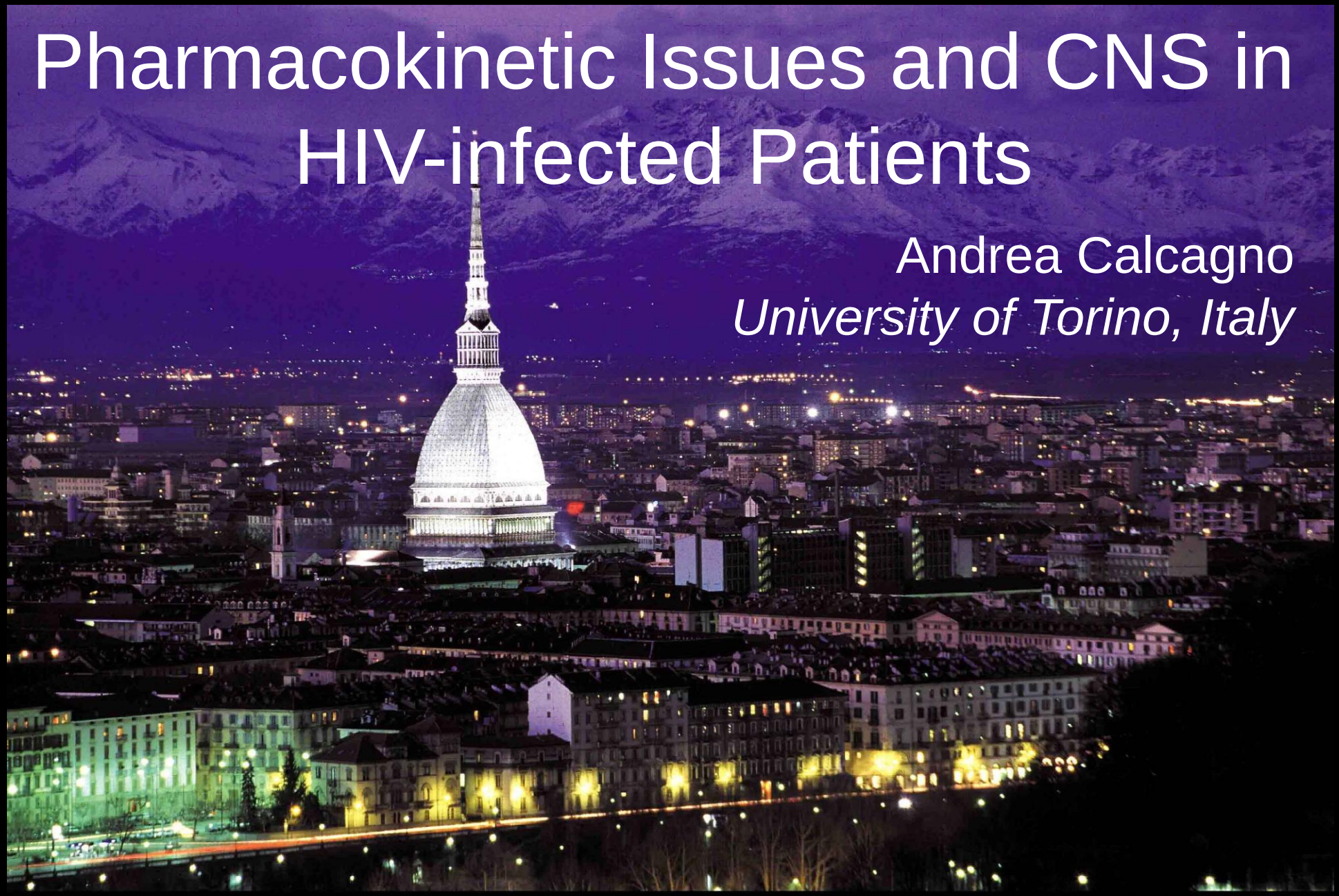
Hinckley et al, CROI 2016, Abstract 395

Questions for Consideration

- **Do neuropsychiatric adverse events occur with both dolutegravir and elvitegravir?**
  - **Will bictegravir also have neuropsychiatric side effects?**
  - **Is raltegravir an attractive alternative for initial therapy for patients with risk factors or for switching when AEs occur?**
- **What is the contribution of other risk factors (e.g., abacavir, age, sex)?**
- **If symptoms subside but drug is continued, will cumulative injury occur with resulting long-term cognitive or mood disorders?**
  - **If they do, will they be reversible?**

Pharmacokinetic Issues and CNS in HIV-infected Patients

Andrea Calcagno
University of Torino, Italy



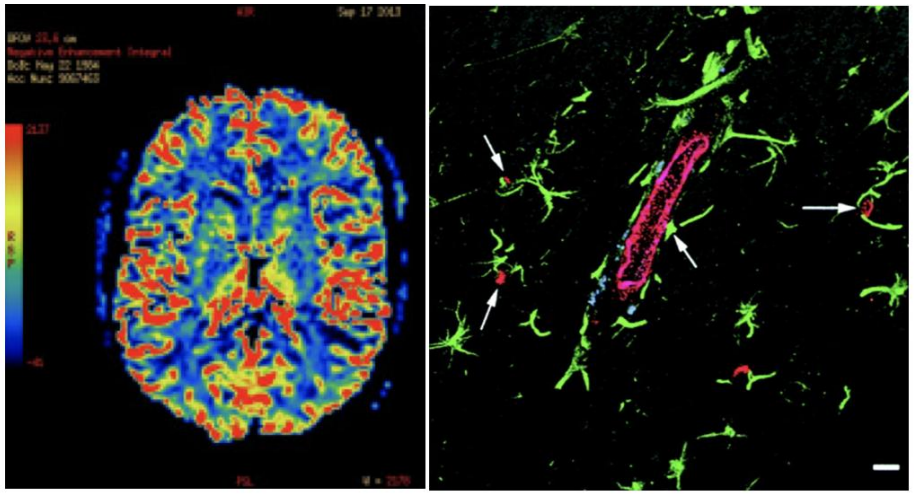
Fotografia di Michele D'Ottavio

10th Symposium on Neuropsychiatry and HIV – Barcelona 26-28 May 2017

Summary of PK and CSF/CNS outcomes

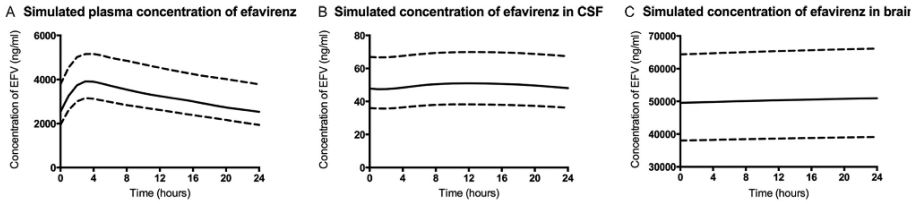
Neuropenetration/ Neuroeffectiveness	CSF HIV RNA < 50 copies/mL	Several cofactors
	CSF HIV RNA < 0.5-2 copies/mL	duration of treatment
	Asymptomatic CSF escape	LLV?
	Symptomatic CSF escape	Nadir CD4, RAMs!
	NC Function	Several cofactors

Penetrazione omogenea?



1. www.istockphoto.com 2. Williams K C et al. J Exp Med 2001.

Brain tissue concentrations



Predicted Cmax	Observed Cmax - rats
plasma 3184 ng/mL (2219 - 485)	plasma 69.7 ng/mL (44.9 – 130.6)
CSF 49.9 ng/mL (36.6 - 69.7)	
brainT 50343 ng/mL (38351 - 65799)	brainT 702.9 ng/mL (475.5 - 1018)
tissue to plasma ratio = 15.8	**tissue to plasma ratio = 9.5 (7-10.9)**

Curley P, et al. AAC 2016

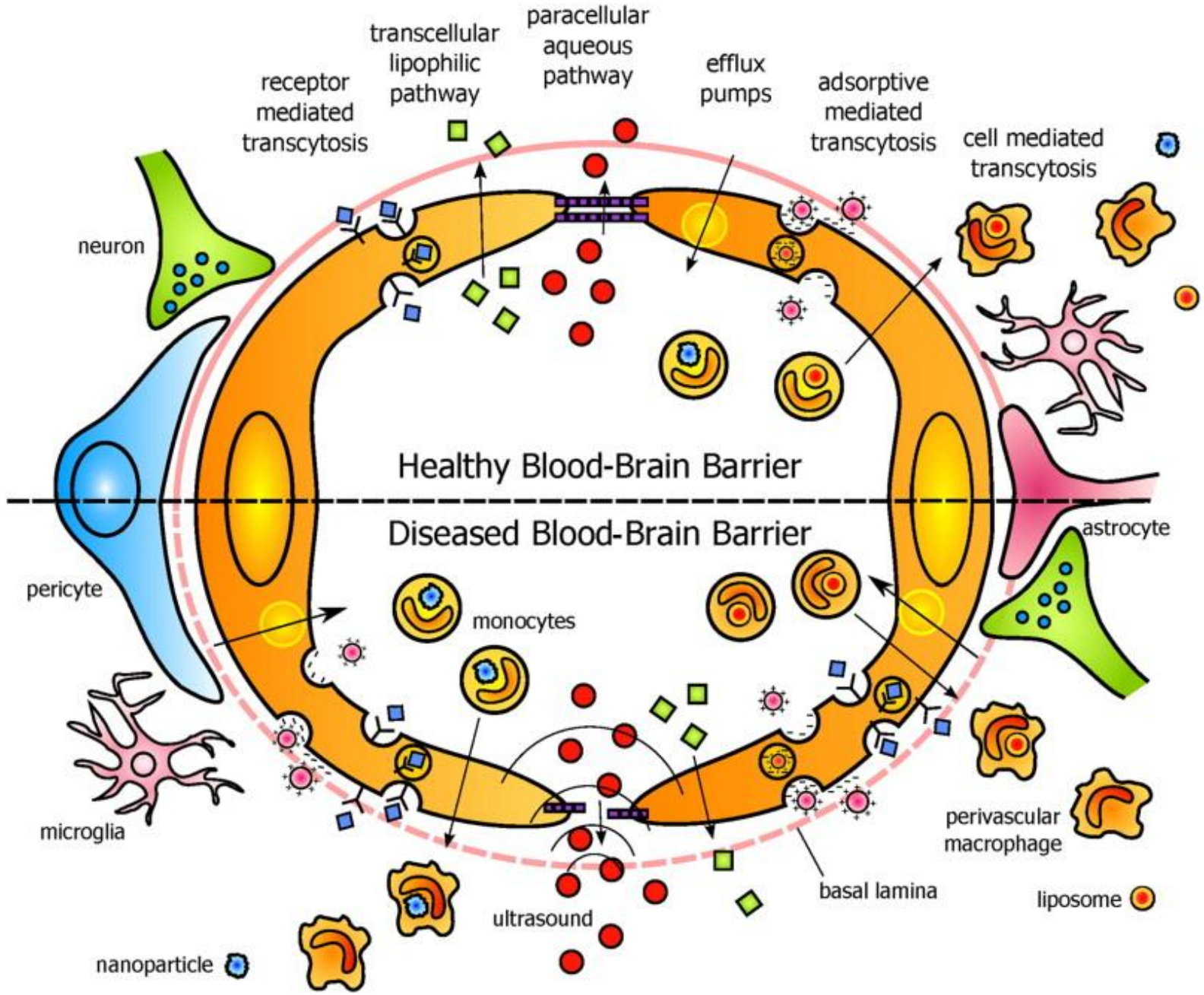
ART Drug Concentrations in Brain: Regional Variation, CSF Comparability

	n	Overall Mean	WM mean (ng/mL)	GP mean (ng/mL)	CGM mean (ng/mL)	CSF (ng/mL)
Concentrations Similar to Historical CSF Concentration						
Atazanavir (ATV)	2	< 25	< 25	< 25	< 25	10.3[1]
Efavirenz (EFV)	2	38.6	45.2	34.8	35.9	15.6[2]
Emtricitabine (FTC)	4	181.3	230.4	173.2	140.3	109.0[3]
Lamivudine (3TC)	3	196.9	205.5	209.8	175.4	107.8[4]
Concentrations in White Matter Higher than Historical CSF Concentration						
Lopinavir (LPV)	4	153.3	410.6	< 25	< 25	16.8[5]
Concentrations Higher than Historical CSF Concentration						
Tenofovir (TDF)	6	206.0	220.0	212.1	185.8	5.5[6]

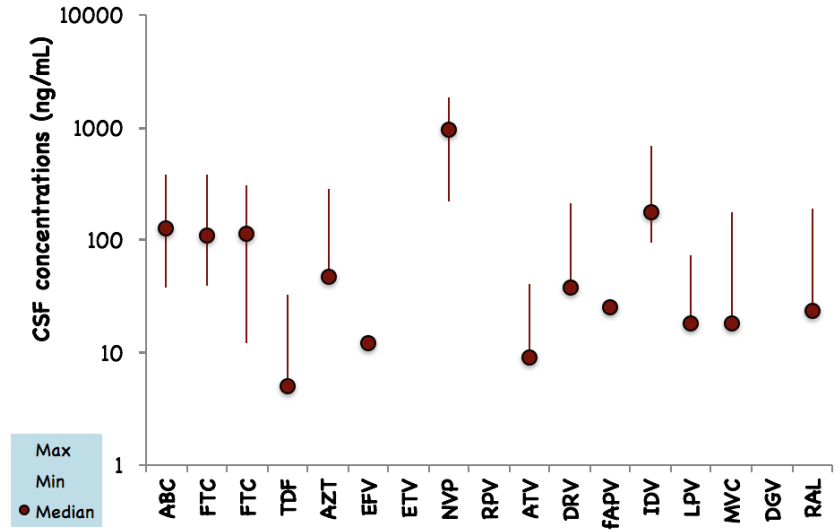
WM = White Matter; GP = Globus Pallidus (Deep Gray Matter); CGM = Cortical Gray Matter

Across all drugs, concentrations were lower in CGM than in the other two regions (p=0.01, paired signed rank test)

Bumpus et al, CROI 2015, Abstract 436


receptor mediated transcytosis
transcellular lipophilic pathway
paracellular aqueous pathway
efflux pumps
adsorptive mediated transcytosis
cell mediated transcytosis
neuron
Healthy Blood-Brain Barrier
Diseased Blood-Brain Barrier
astrocyte
pericyte
monocytes
microglia
perivascular macrophage
basal lamina
liposome
ultrasound
nanoparticle

High variability in CSF exposure

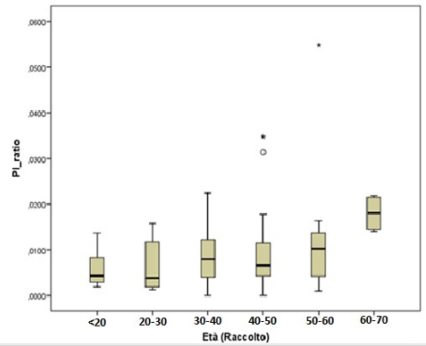


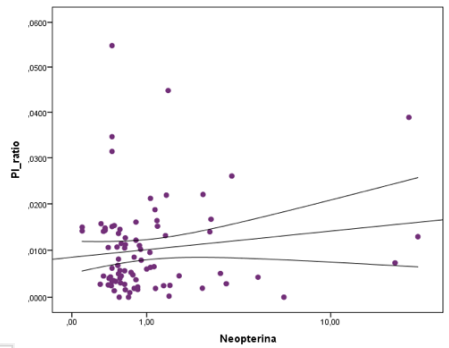
Calcagno A, et al. (

Determinants of PI CSF to plasma ratios

n=137 (79 DRV/r, 31 ATV/r e 27 LPV/r)

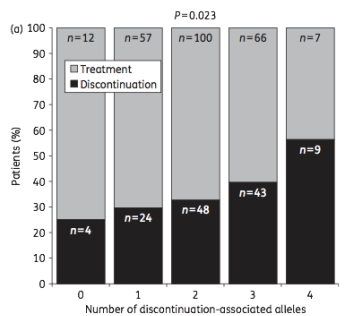
- Multivariate linear regression analysis adjusted for age, CSAR, time after dose and *ABCB1* 3435C>T
- **Age (p=0.01) and CSF neopterin (p=0.05)**



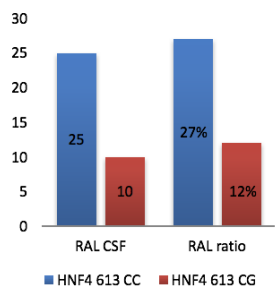


al. In preparation

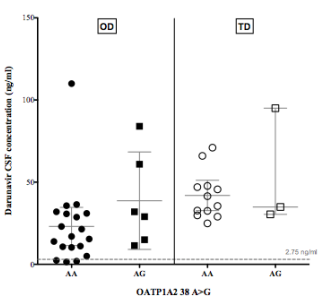
PG and CSF concentrations



EFV



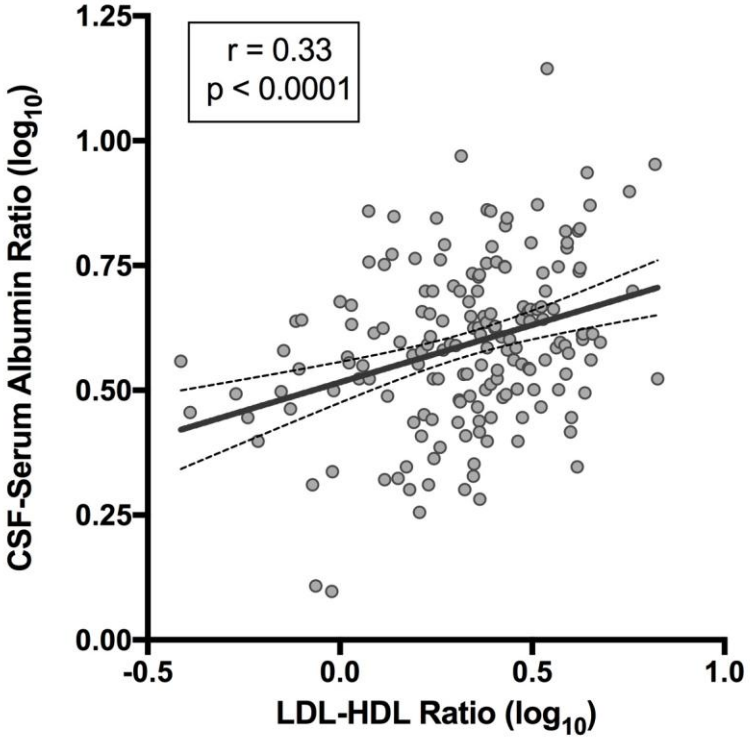
RAL

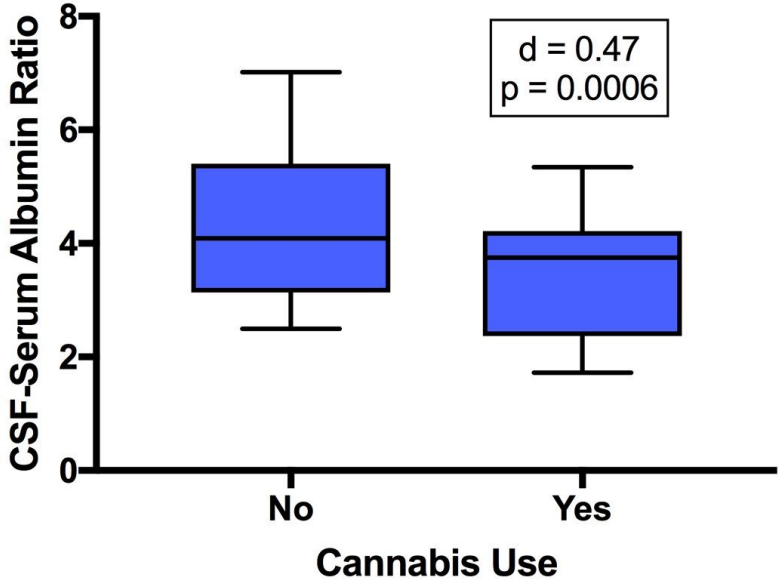


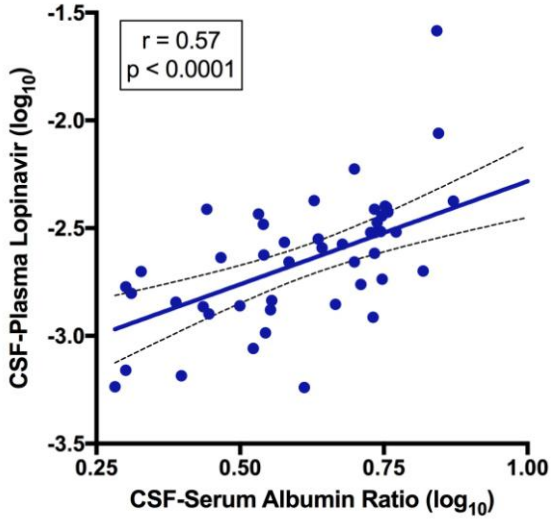
DRV/r

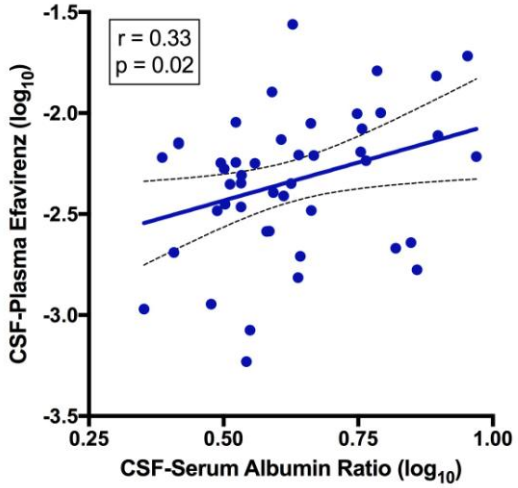
Wyen C, et al. JAC 2011, Calcagno A, et al. AIDS 2012 and JAC 2013

CSF-Serum Albumin Ratio is Associated with Lipids, Cannabis, and ART Concentrations









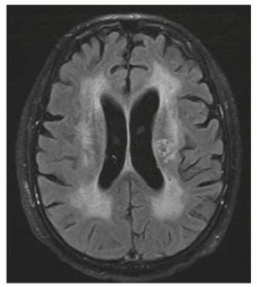
& neopterin

Symptomatic CSF escape

Two case series and few case reports

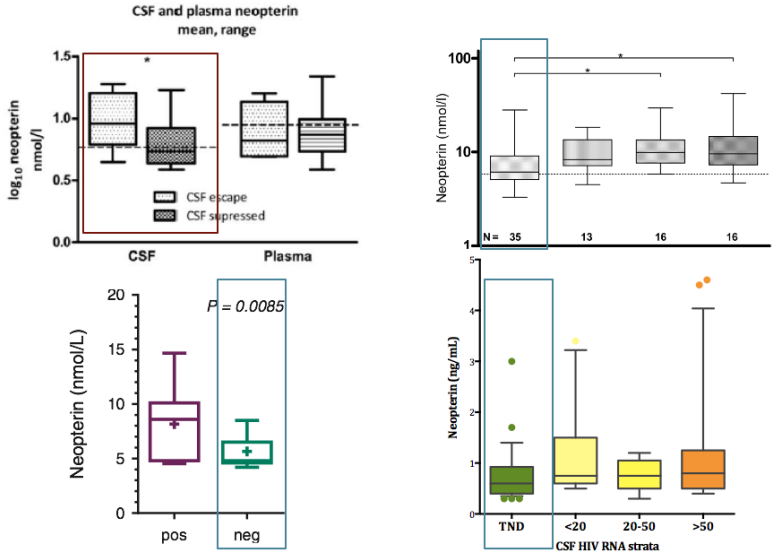
n=30

- Acute neurological symptoms
- **Resistance associated mutations**
- MRI alterations
- **Strong immune response**
- Reversibility



Canestri A, et al. CID 2010; Peluso MJ, et al. AIDS 2012; Wendel KA, et al. CID 2003; Bogoch II, et al. J Infect 2011; Binhgam MR, et al. J Int AIDS Soc 2011; Khouri MN, et al. JNV 2013; Imaz A, AIDS Res and Human Retrov 2014; Beguelin C, J Int AIDS Soc 2014, Spudich S. Curr Opin HIV/AIDS 2016.

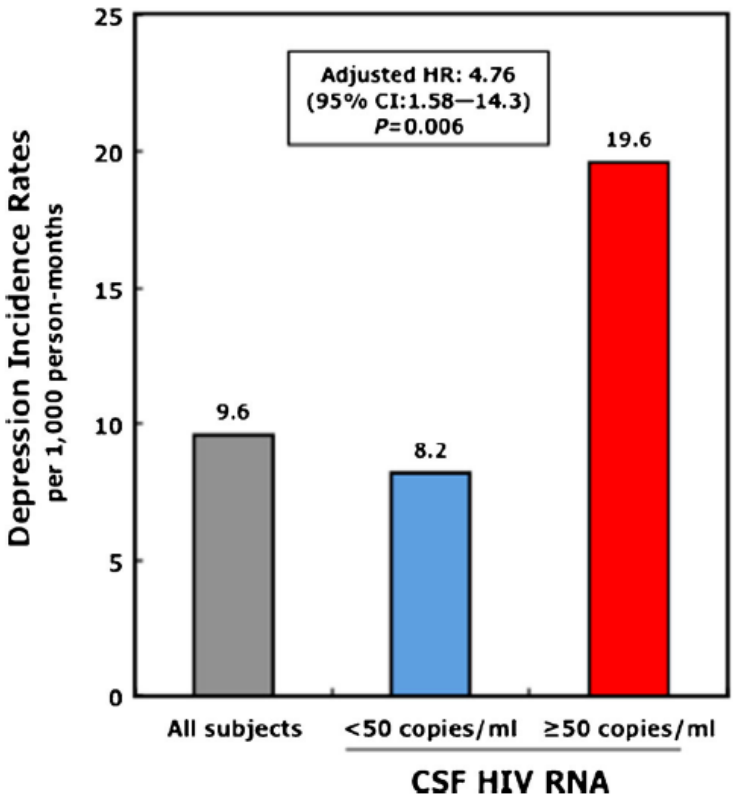
CSF low level replication & neopterin

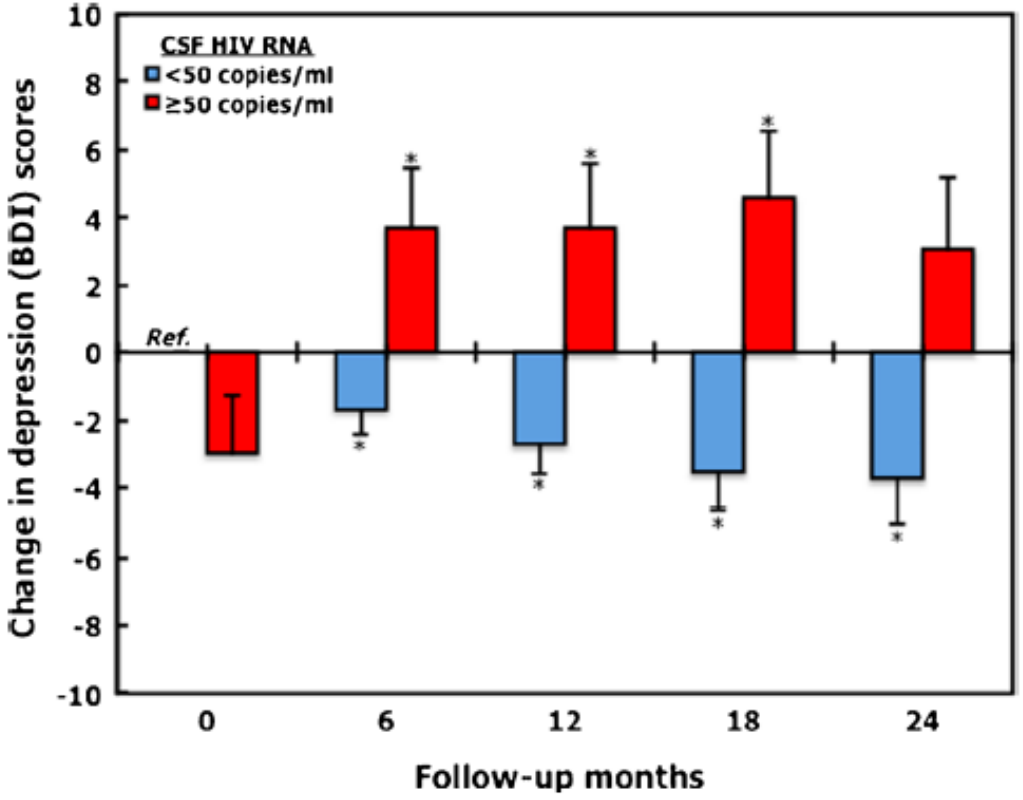


Eden A, et al. JID 2010; Yilmaz A, et al. JAIDS 2008; Dahl V, et al. AIDS 2014; Motta I, et al. *Under review*

	Drug	CPE score	95% Inhibitory Quotients	Macrophage efficacy score	in vitro neurotox
NRTIs	Abacavir	3	NA	3	+
	Emtricitabine	3	NA	12.5	0
	Lamivudine	2	NA	50	+
	Tenofovir disoproxil fumarate	1	NA	50	0
	Zidovudine	4	NA	50	+
NNRTIs	Nevirapine	4	NA	20	+
	Efavirenz	3	6.4	100	++
	Etravirine	2	5.1	NA	+
	Rilpivirine	3?	NA	NA	+
PIs	Atazanavir	2	0.4	NA	+
	Atazanavir/r	2	2.8	NA	+
	Darunavir/r	3	8.2-18.5	NA	0
	Lopinavir/r	3	1.5	NA	NA
INIs	Raltegravir	3	0.7	NA	+
	Elvitegravir/r	3?	NA	NA	+
	Dolutegravir	4?	NA	NA	+?
EIs	Maraviroc	3	NA	NA	0
	Enfuvirtide	1	NA	50	NA

CSF Viral Escape May Be Associated with Depression





Hammond et al, J Neurovirol 2016, PMID: 26727907

Questions for Consideration

- Do CNS drug characteristics and pharmacokinetics matter in the management of antiretroviral therapy?
- How does CSF pharmacology vary over time?
- Are CSF drug concentrations an adequate surrogate for brain tissue concentrations?
- Is CSF viral escape a clinically important entity?
  - Does it influence risk for other neuropsychiatric disorders?
- Are the factors that influence CSF pharmacology to complex to integrate into patient care?

NEUROTICISM AND ITS INFLUENCE ON ANTIRETROVIRAL THERAPY

10th Symposium on Neuropsychiatry and HIV

Dr. Daniel Hernández Huerta
Psychiatry Department
Ramon y Cajal University Hospital
Madrid, Spain

Carlos Velo (H. Doce de Octubre), Isabel Cuéllar-Flores (H. Clínico San Carlos), Talía Sainz (H. La Paz), Cristina García-Navarro (H. Doce de Octubre), Carolina Fernández-McPhee (H. Gregorio Marañón), José Tomás Ramos (H. Clínico San Carlos), María Luisa Navarro (H. Gregorio Marañón), Sara Guillén (H. de Getafe) y María Isabel González-Tomé (H. Doce de Octubre).

HIV awareness in young population: Differences between HIV positive young adults infected due to vertical transmission and their HIV-negative peers. NeurocoRISpe and FARO projects

Mutua Madrileña 2012/0077, Gilead Fellowship2013/0071, FIS PI15/00694. M. Isabel González-Tome (Principal Investigator-PI); RED RD16/0025/0019,RD16/0025/0024ISCIII/FEDER. Marisa Navarro, Mª Isabel González-Tomé (PI); FIPSE 3608229/09. José Tomás Ramos Amador

Relationship between methadone therapeutic use and adherence to antiretroviral therapy in Spain

Carlos Parro Torres
Hospital General Universitario Gregorio Marañón
Madrid, Spain

Management of a HIV-infected patient with a psychiatric disorder

Maria Ferrara, Modena, Italia
Guida Da Ponte, Lisboa, Portugal
Jordi Blanch, Barcelona

CLÍNIC Corporació Sanitària

CLÍNIC BARCELONA Hospital Universitari

Practical training on diagnosis and management of clinical CNS problems in HIV-infected patients

Prevention of neurocognitive impairment in HIV-infected patients

Paola Cinque
Department of Infectious Diseases
San Raffaele Scientific Institute, Milano, Italy

HIV and the Central Nervous System – Diagnosing HAND

- Gabriele Arendt
- Dept. of Neurology, University of Duesseldorf, Medical Faculty
- 10th International Symposium on Neuropsychiatry & HIV, Barcelona, May 26-27th, 2017

Workshop. Practical Training on diagnosis and management of clinical CNS problems in HIV-positive individuals

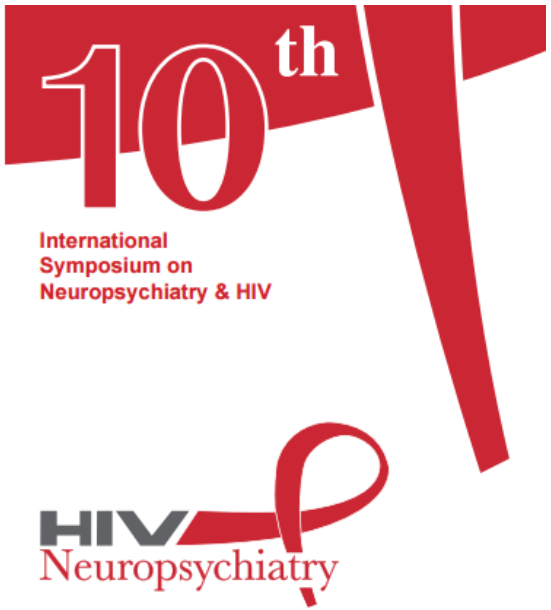
Treatment

Alan Winston Andrea Calcagno

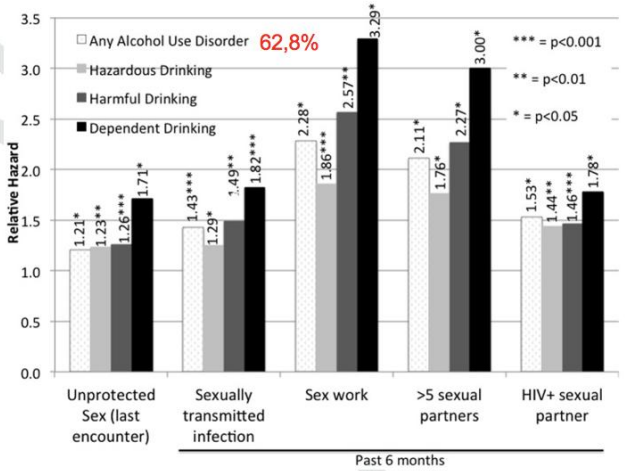
Neuropsychiatric consequences of substance use

Jordi Blanch

Hospital Clínic de Barcelona
Parc Sanitari Sant Joan de Déu
Universitat de Barcelona
CIBERSAM



Alcohol and HIV



Ludford et al. PLoS One. 2013

Methamphetamine

National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

- CNS stimulant: euphoric, stimulating, aphrodisiac
- obtained: drugs marketed or clandestine laboratories
- white, crystalline, odorless and bitter powder
- smoking, inhaling, injecting or taking oral
- Inhibits ejaculation
- Greater use in MSM
- "Crystal", "crystal met", "meth"

MSM using MA

- Increased risk of
  - Unprotected anal intercourse
  - Group sex
  - Having multiple sexual partners
  - Contact sexual partners online
  - Sexual relations with UDVP
  - Be intoxicated while keeping rrssbe
- Unrelated to the HIV- infection

AIDS PATIENT CARE and STDs
Volume 26, Number 1, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/apc.2011.0153

BEHAVIORAL AND PSYCHOSOCIAL RESEARCH

A Systematic Review of Behavioral and Treatment Outcome Studies Among HIV-Infected Men Who Have Sex with Men Who Abuse Crystal Methamphetamine

Radha Rajasingham, M.D.,[1] Matthew J. Mimiaga, Sc.D., M.P.H.,[2,3,5] Jaclyn M. White, M.P.H.,[3] Megan M. Pinkston, M.A., Ph.D.,[4] Rachel P. Baden, M.D.,[1] and Jennifer A. Mitty, M.D., M.P.H.[1]

Methamphetamine and VIH

- more consumption (20-30%) in MSM that are HIV + compared to HIV- (Buchacz et al., 2005, Forrest et al., 2010, Mansergh et al., 2006; Schwarcz et al., 2007).
- higher VL (Ellis et al., 2003, Fairbairn et al., 2011, King et al., 2009, Feldman 2015)
- lower CD4 count (Shoptaw et al., 2012)
- accelerates the progression of the disease (Carrico, 2011).
- increased risk of transmission (Cohen 2011)
- neurotoxic (Silverstein 2011)
- changes the BBB (Northrop 2015)

Spain's crystal-meth problem may be about to get worse (Business Insider 17 Nov 2016)

Spanish police broke up a drug ring smuggling methamphetamine using packages of chocolates, December 2014.

Lab equipment allegedly used to produce synthetic drugs recovered by Spanish police, September 2016

10th International Symposium on Neuropsychiatry & HIV

Barcelona May 26-27, 2017
www.neuropsychiatry-hiv.com

HIV Neuropsychiatry

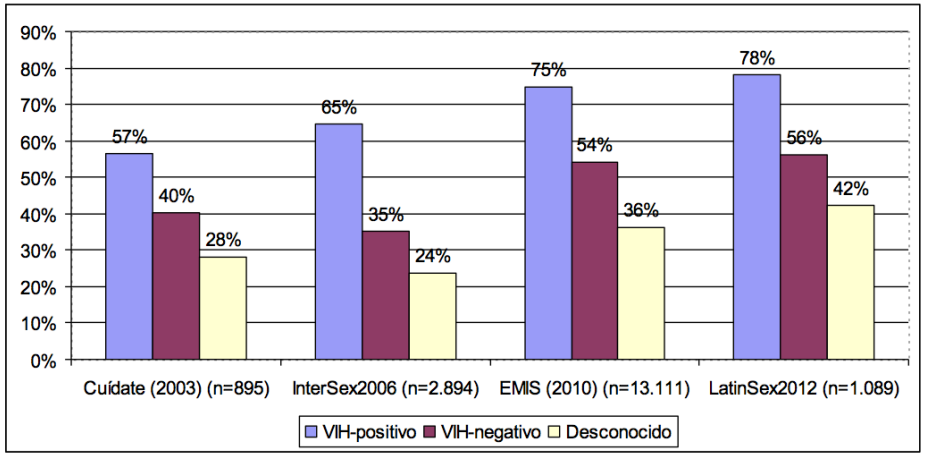
"Sex on drugs" (ChemSex): Psychosocial impact on the life of a group of gay, bisexual and other MSM from Barcelona City

Percy Fernández-Dávila, Ph.D

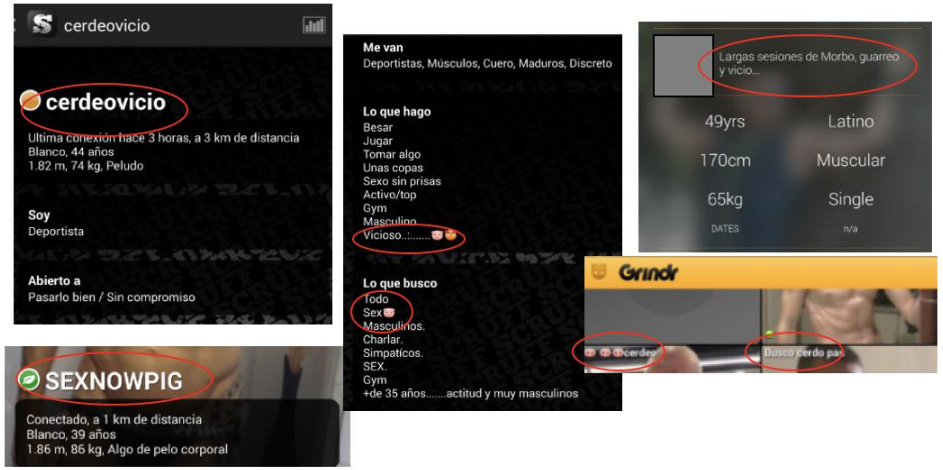
CEEIS Cat
Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya

Generalitat de Catalunya
Agència de Salut Pública de Catalunya
Subdirecció General de Drogodependències

Drug use by HIV serostatus



Search for sex partners by apps



Mental health impact

Cuando yo cogía el metro, una paranoia de que toda la gente me está mirando, empezaba a sudar, y después no tenía ganas de salir de mi casa. Cuando empezaba a tomar más y más, no tenía ganas de salir de la casa, antes tenía esta paranoia, de que va a salir alguien del agujero de la puerta, que alguien hay del otro lado… Ahí pasas a no disfrutar más… ENT15, 44 años, latinoamericano.

Mental health harms: depression

Quedé con otro chico el sábado porque yo iba colocado el viernes, y como la tina te coloca mucho, le dije: "voy a follar contigo" y fue otra vez. Y luego estuve con una depresión durante la semana.

P: ¿Y cuánto te tomó recuperarte?

No me he recuperado todavía.

P: ¿De qué?

De la depresión, del ansia que provocó y todo, no estoy diciendo que ha sido la droga, pero ha sido el desencadenante de todo que a lo mejor tenía dentro. ENT17, 40 años, europeo.

Risk behavior, effect on HIV-infection and neuropsychiatric consequences of substance use

Maria Martínez-Rebollar

Hospital Clínic-Fundació Clínic
Barcelona

ChemSex use in Barcelona

Poster P1.06

BCN checkpoint
HOMBRES SEXUALIDAD SALUD

Chemsex en la cohorte Barcelona Checkpoint: un fenómeno con tendencia al alza asociado a un aumento del riesgo de infección por VIH

Los datos sobre chemsex de la cohorte Barcelona Checkpoint muestran que se trata de un fenómeno minoritario (6,4%) pero con tendencia al alza, observándose un incremento en el consumo de sustancias asociadas al chemsex en los últimos años.

XVIII Congreso Nacional sobre el sida e ITS
Sevilla, 22-24 de marzo de 2017
"VIH y VHC: dos epidemias convergentes"

SLAMMING: ACTITUDES, USOS, CUIDADOS Y RIESGOS EN UN GRUPO DE HOMBRES GAIS Y BISEXUALES QUE HACEN CHEMSEX EN LA CIUDAD DE BARCELONA

Percy Fernández Dávila[1,2], Cinta Folch[1], Víctor Galán[3], Ana I. Ibar[2], Xavier Roca i Tutusaus[2], Xavier Majó i Roca[2], Luis Villegas[2], Jordi Casabona[1]

[1] Centre d'Estudis Epidemiològics sobre les ITS i la Sida de Catalunya; [2] Stop Sida; [3] Subdirecció General de Drogodependències, Agència de Salut Pública de Catalunya

El slamming es una práctica todavía minoritaria entre quienes hacen ChemSex; aunque se la percibe en ascenso.

CHEMSEX Y SU RELACIÓN CON LA INFECCIÓN POR EL VIH EN UN GRUPO DE HOMBRES GAIS Y BISEXUALES DE LA CIUDAD DE BARCELONA

Percy Fernández Dávila[1,2], Cinta Folch[1], Víctor Galán[3], Ana I. Ibar[2], Xavier Roca i Tutusaus[2], Xavier Majó i Roca[2], Luis Villegas[2], Jordi Casabona[1]

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XVIII Congreso Nacional sobre el sida e ITS
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"VIH y VHC: dos epidemias convergentes"

A pesar que no se puede afirmar una relación directa entre ChemSex y el VIH, los datos del estudio parecen mostrar que existe una asociación. El potencial impacto del ChemSex sobre el TAR y la salud es algo que se conoce pero que no se tiene muy presente. Se

Increasing evidence of HIV, AHC, STIs and other complications associated with Chemsex use

- Associations with sexual-risk behaviour (Colfax & Guzman, 2006; De Ryck, Van Laeken, Noestlinger, Platteau, & Colebunders, 2013; Drumright et al., 2007; Heiligenberg et al., 2012; McCarty-Caplan, Jantz, & Swartz, 2014; Pappas & Halkitis, 2011; Prestage et al., 2009; Santos et al., 2013; Sewell J , 2017)
- Association with facilitacion HIV: (Buchacz et al., 2005; Macdonald et al., 2007; Plankey et al., 2007; Prestage et al., 2009; Ostrow et al., 2009;)
- Association with facilitacion STI and AHC (Hirshfield, Remien, Walavalkar, & Chiasson, 2004; Ottaway Z, 2017; Hegazi A, 2017)
- Potencial risk of serious overdose and death (Hockenhull J, 2017; Caldicott, Chow, Burns, Felgate, & Byard, 2004; Liechti & Kupferschmidt, 2004).
- Drug-drug interactions (Pichini S, 2016; Bracchi M, 2015)

Incidence of HepC among HIV + MSM, 2000–2015

Incident HCV infection by baseline demographics

	N of event	Person Years	Incidence/100PY	CI.lower	CI.upper	IRR	p value
Overall	149	12573	1.185	1.002	1.391	-	-
Age							
≤30	37	2796	1.323	0.932	1.824	1	-
31-40	57	4755	1.199	0.908	1.553	0.906 (0.589-1.409)	p=0.642
41-50	46	3826	1.202	0.88	1.604	0.909 (0.577-1.441)	p=0.666
>50	9	1196	0.753	0.344	1.429	0.569 (0.241-1.2)	p=0.126
Race							
White	105	8202	1.28	1.047	1.55	1	-
Black	15	1254	1.197	0.67	1.974	0.934 (0.505-1.613)	p=0.807
Other	28	2918	0.96	0.638	1.387	0.75 (0.475-1.146)	p=0.176
Hispanic							
No	110	8978	1.225	1.007	1.477	1	-
Yes	39	3595	1.085	0.771	1.483	0.885 (0.598-1.287)	p=0.516
Meth/IDU use (ever)							
None	21	4424	0.475	0.294	0.726	1	-
Meth only	86	5991	1.436	1.148	1.773	**3.024 (1.860-5.132)**	**p<0.001**
IDU only	2	32	6.296	0.762	22.743	**13.167 (1.497-53.965)**	**p<0.001**
Meth+IDU	17	739	2.301	1.341	3.684	**4.896 (2.401-9.644)**	**p<0.001**

[10] Chaillon A, et al. In preparation

UC San Diego SCHOOL OF MEDICINE

Antoine Chaillon1, Christy M Anderson1, Thomas C Martin1, Edward R. Cachay1, David L. Wyles1, Davey M. Smith1, Susan J. Little1, Richard S. Garfein1, Natasha Martin1. Abstract 134 CROI February 13–16, 2017 | Seattle, Washington

Questions for Consideration

- **How extensively does substance use contribute to new infections? Prevent patients from seeking medical care? Affect retention in care?**
- **Is the problem growing?**
- **How can it be best managed in the individual and in the community?**

Cerebrospinal Fluid EBV Replication is Associated with Compartmental Inflammation and Pleocytosis in HIV-positive naïve and Treated Individuals

Lupia T, Milia MG, Atzori C, Audagnotto S, Imperiale D, Romito A, Scabini S, Gregori G, Lipani F, Bonora S, Di Perri G, Calcagno A.

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University of Torino
Clinic of Infectious Diseases
Ospedale Amedeo di Savoia

CLÍNIC BARCELONA Hospital Universitari

Drug abuse in HIV infected patients. *Chem-sex* role

Perelló R.

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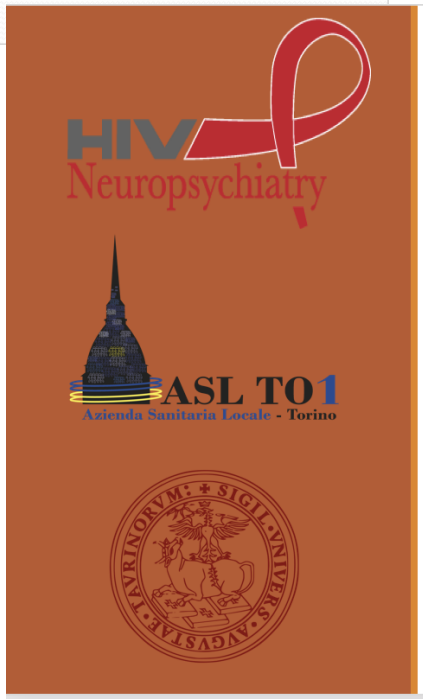


Cerebrospinal Fluid HIV-RNA and Neurocognitive Deficits:

Are Lumbar Punctures Needed in Impaired Subjects with Undetectable Plasma Viral Load?

Trunfio M, Allice T, Vai D, Atzori C, Romito A, Pirriatore V, Montrucchio C, Tettoni MC, Imperiale D, Bonora S, Ghisetti V, Di Perri G, Calcagno A

Unit of Infectious Diseases,
Department of Medical Sciences,
University of Torino, Torino

Hot topics on CNS and HIV
(most relevant presentations in conferences or articles published recently)

Paola Cinque

Department of Infectious Diseases

San Raffaele Hospital, Milan, Italy

Table 1. Summary of CSF escape cohorts or cases presented at the Global HIV-1 CSF Escape Consortium meeting

Speakers	Study site	Total number of cases	Number of cases of HIV-1 CSF escape	Neurosymptomatic	Asymptomatic	Criteria for determining CSF escape	Estimated prevalence[1]
Price, Gisslen, Cinque, Spudich, Joseph S	Multiple[2] (San Francisco, New Haven, Chapel Hill, USA; Sweden; Italy)	N/A	81	42	39	Symptomatic: PVL<50 & CVL>100 or PVL 50–100 & CVL 2 × PVL; or Asymptomatic: PVL<50 & CVL>50	N/A
Joseph S	THINC Study Sites (Chapel Hill, San Francisco, New Haven, USA)	97	6	N/A	6	PVL<40 & CVL>40 or CVL>PVL	6%
Winston (UK)	UK	142	30	3	27	PVL<50 & CVL>200 or $\log_{10}$ CVL>1.5 × $\log_{10}$ PVL	21%
Winston (Europe)	EU	134	1	1	N/A	CVL>PVL	0.7%
Ene	Romania/Adult	91	4	2	2	CVL>0.5 log of PVL	4.4%
Perez	Spain	125	4	4	N/A	PVL: not detectable; CVL: detectable	3.2%
Sacktor	Uganda	91	9	4	5	PVL: not detectable; CVL: detectable	10%
Wright	Australia	167	6	3	3	PVL: 6 months not detectable; CVL: detectable	3.5%
Dravid	India	62	17	17	0	CVL: detectable with PVL: not detectable; CVL>1 log of PVL	27.4%
Letendre	CHARTER/HNRC sites	849	60	23	37	CVL>PVL with PVL: not detectable; CVL>1 log of PVL	7%
Nath	Washington DC	56	11	7	4	PVL<40; CVL>20	20%
Gabuzda	Boston, MA/NNTC (four sites)	200/426 (626)	11/29 (40)	11/17	0/12	PVL<50, CVL>50; CVL>0.5 log of PVL	6.4%
Wojna	Puerto Rico**	380	10	3/9	6/9	CVL>PVL	2.6%

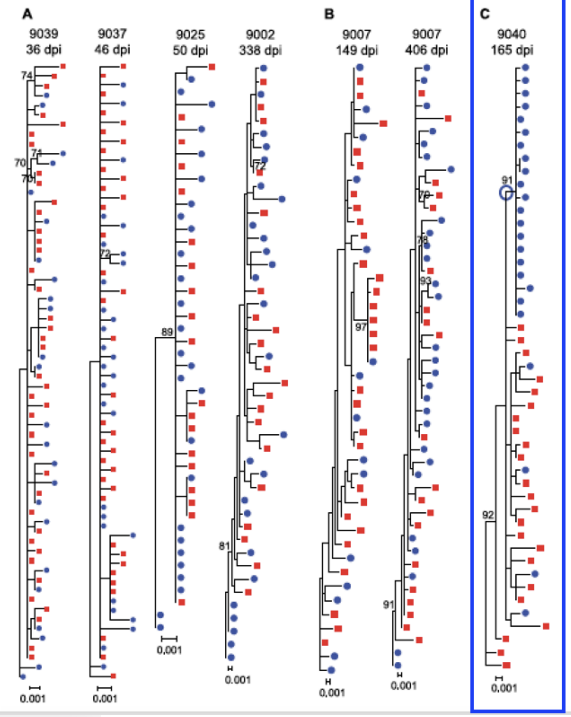
Compartmentalization and Clonal Amplification of HIV-1 Variants in CSF during Primary Infection

Shnell G. et al, J Virol 2010

Discordance = compartmentalization

CSF

plasma



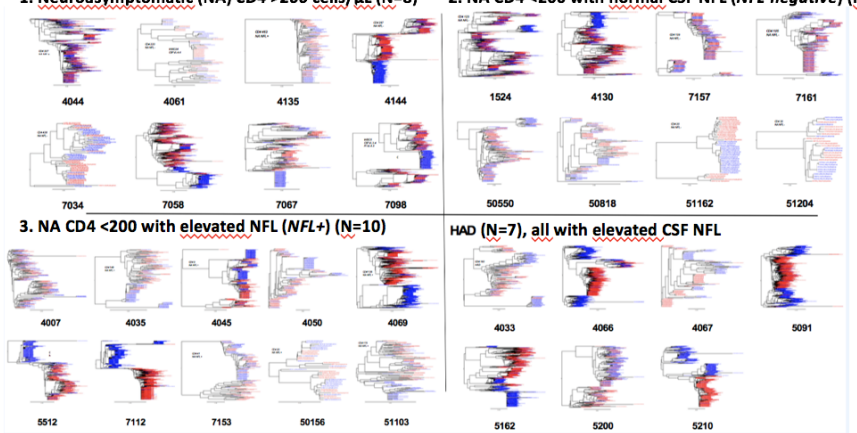
Poster # 364

CSF HIV-1 compartmentalization by *env* deep sequencing: relation to neuronal injury

Richard W. Price[1], Magnus Gisslen[2], Laura P. Kincer[3], Ean Spielvogel[3], Amy Lin[2], Jasur Eusuff[2], Serena Spudich[4], Ronald Swanstrom[3], Sarah Beth Joseph[3], and the THINC Study Group[3]

[1]University of California, San Francisco, California; [2]University of Gothenburg, Sweden; [3]University of North Carolina Chapel Hill, Yale University, New Haven, Connecticut

Contact: Richard W. Price, M.D. SFGH/UCSF HIV Neurology Research Program 1001 Potrero Avenue, Box 0870 San Francisco, CA 94110 richard.price@ucsf.edu Tel: 415-206-4487



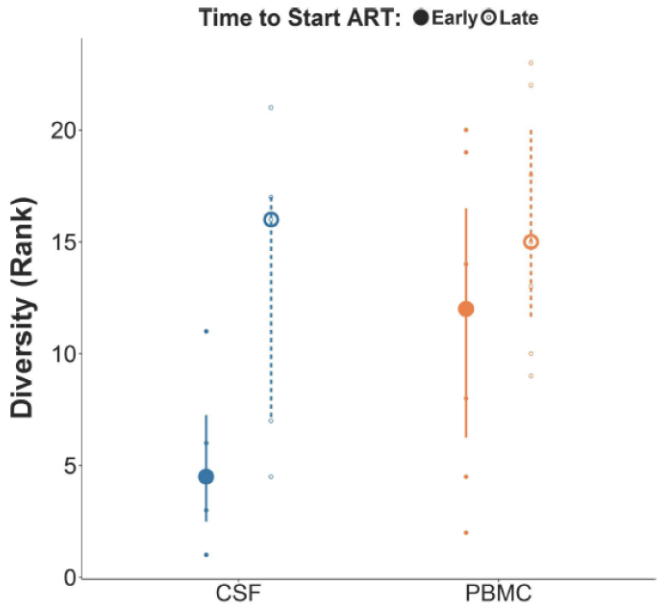
- Major (>30%) CSF *env* sequence compartmentalization in all of the 7 HAD subjects
- CSF *env* sequence compartmentalization also present in the other groups, including the two without evidence of ongoing CNS injury (normal CSF NFL)

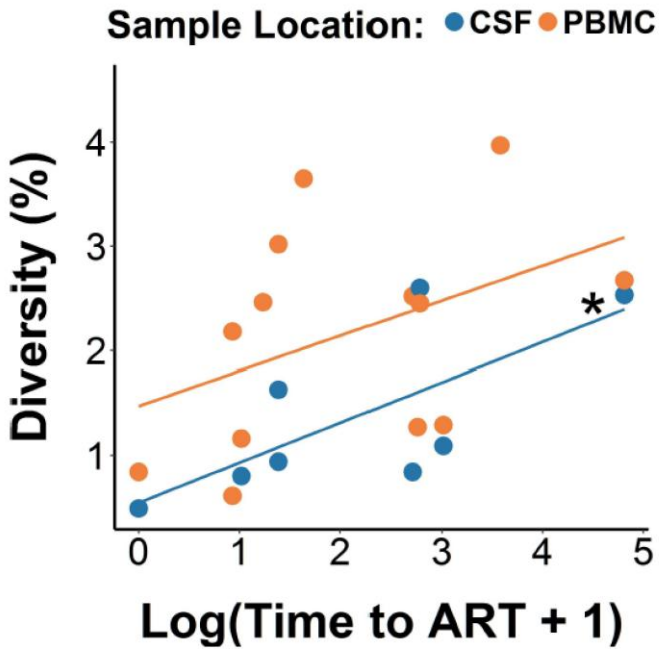
→ CSF HIV-1 compartmentalization does not provide a simple biomarker of neuropathic infection

Early ART is Associated with lower HIV DNA Molecular Diversity and lower Inflammation in CSF but Does Not Prevent the Establishment of Compartmentalized HIV DNA Populations (Oliveira MF, PLOS Pathogens 2017)

Sequential paired blood and CSF from 16 ART-treated suppressed pts (after a median of 2.6 years from ART start):

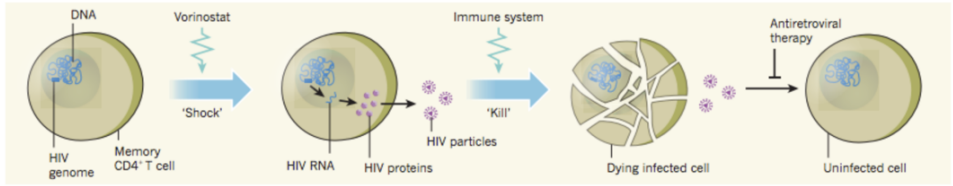
- 9 early ART (<4 months of infection)
- 7 late ART (>14 months after infection)





Early ART was associated with lower molecular diversity of HIV DNA in CSF in comparison to late ART

Latency reversing agents (LRA)

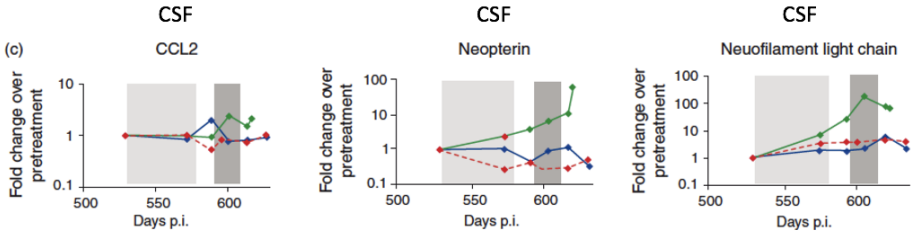


HIV: Shock and kill, SG Deeks, Nature 487, 439–440 (26 July 2012)

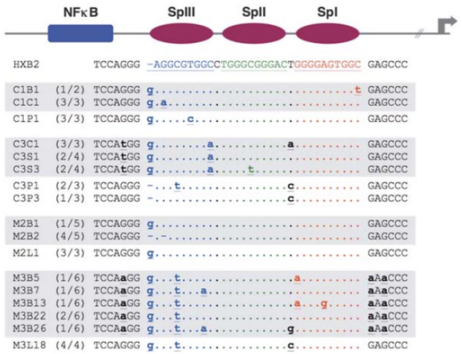
- Histone deacetylase inhibitors (HDACi, e.g., varinostat)
- Bromodomain inhibitors
- Protein kinase C agonists
- Cytokines, such as IL-2 and IL-15
- Others…

Reactivation of SIV reservoirs in the brain of virally suppressed macaques following administration of latency reversing agents (Gama L et al., AIDS 2017)

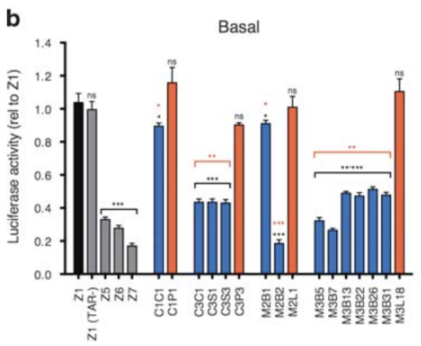
- 3 SIV-infected pigtailed macaques ART-treated since 12 days p.i.
- Macaque Mn0 (red): control
- Macaques Mn1 (blue) and Mn2 (green) treated with ingenol-B starting at 530 days p.i. with ingenol-B and ingenol-B plus vorinostat



CNS-specific regulatory elements in brain-derived HIV-1 strains affect responses to latency-reversing agents with implications for cure strategies (LR Grey, Molecular Psychiatry, 2016)



CNS-derived HIV-1 strains (grey) have LTR polymorphisms within and surrounding the Sp transcription factor motifs



LTR polymorphisms result in decreased binding to Sp1 and reduced transcriptional activity of CNS-derived HIV (orange) compared with lymphoid-derived LTRs (blue)

Questions for Consideration

- What standardized methods should be used to ensure comparability between trials?
  - Neuropsychological testing, NSS, imaging, biomarkers
  - How often should participants be assessed?
  - For how long should participants be followed?
- The Frascati guidelines are a decade old. Should they be updated considering 10 years of progress?
- What are the most promising interventions now?
  - Changing "habits": Exercise, diet
  - Treating comorbid disease: depression, substance use, sleep disorders, metabolic and vascular disease
  - Adjunctive therapies: rivastigmine, paroxetine

Questions for Consideration

- Do current ART regimens have sufficient potency outside and inside the CNS to minimize the effects of HIV replication?
  - Will we continue to see CSF viral escape?
- How will the clinical environment shift over the next 5 years (long-acting ART, new classes of drugs)
- How will we control inflammation from low-level replication and production of neurotoxic HIV proteins?
- How do we implement neurotoxicity data into the clinic?
- Will we need different treatment strategies for patients with different characteristics (e.g., aged)?

Questions for Consideration

- Do neuropsychiatric adverse events occur with both dolutegravir and elvitegravir?
  - Will bictegravir also have neuropsychiatric side effects?
  - Is raltegravir an attractive alternative for initial therapy for patients with risk factors or for switching when AEs occur?
- What is the contribution of other risk factors (e.g., abacavir, age, sex)?
- If symptoms subside but drug is continued, will cumulative injury occur with resulting long-term cognitive or mood disorders?
  - If they do, will they be reversible?

Questions for Consideration

- How extensively does substance use contribute to new infections? Prevent patients from seeking medical care? Affect retention in care?
- Is the problem growing?
- How can it be best managed in the individual and in the community?

Happy Birthday!

10th

International
Symposium on
Neuropsychiatry & HIV

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