Protease-Inhibitor Monotherapy: Friend or Foe?

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5th International Symposium on HIV and Psychiatry

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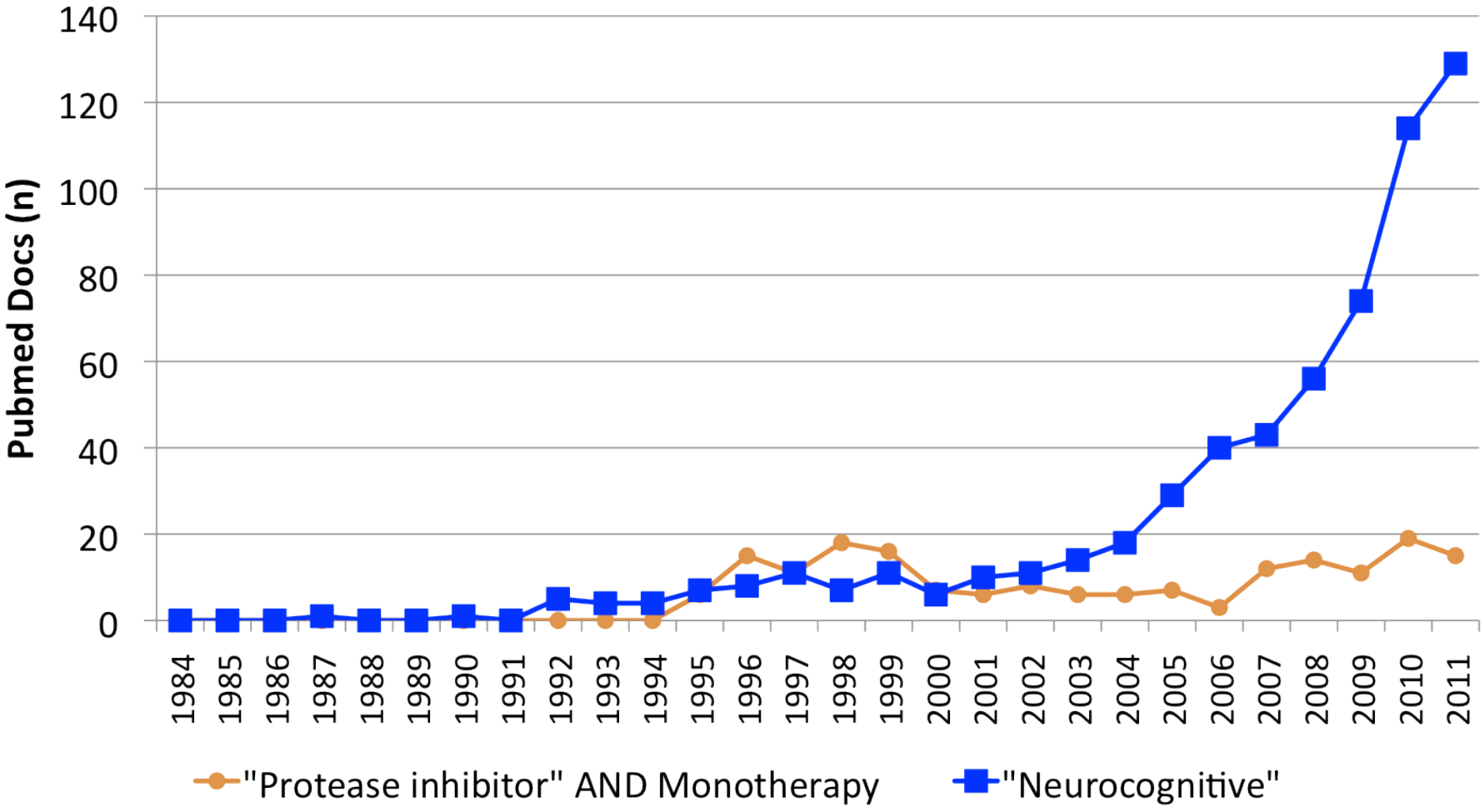
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"Protease inhibitor" AND Monotherapy
"Neurocognitive"

How HAND can be treated?
CHARTER's paradigm

Principles: HAND is associated with viral escape in the CSF and probably in the brain

Use of cART including drugs with high penetration and efficacy in CNS infected cells

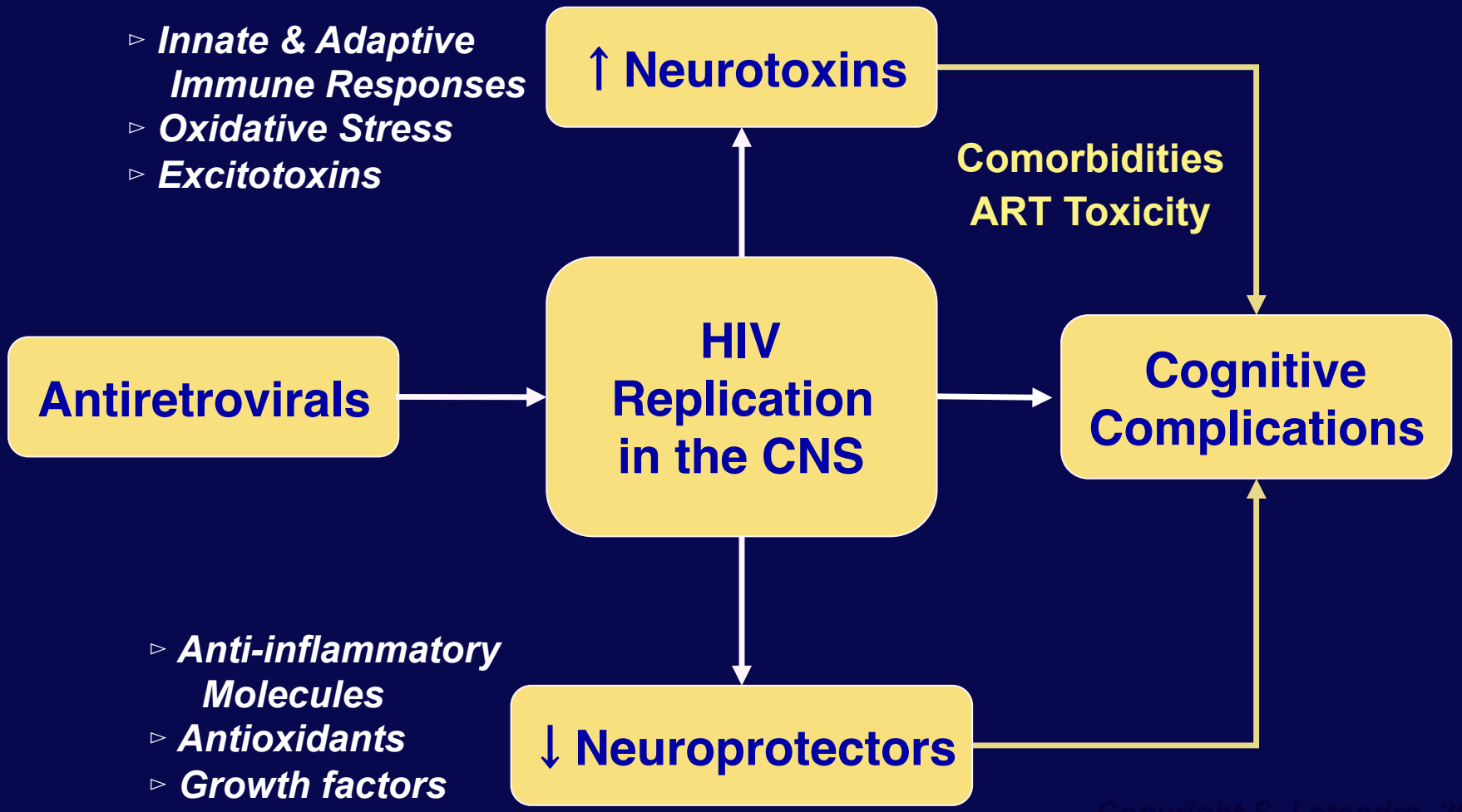
- Drug characteristics
- PK studies (CSF and brain)

Neuro-penetration

- In vitro studies
- Clinical and virological studies

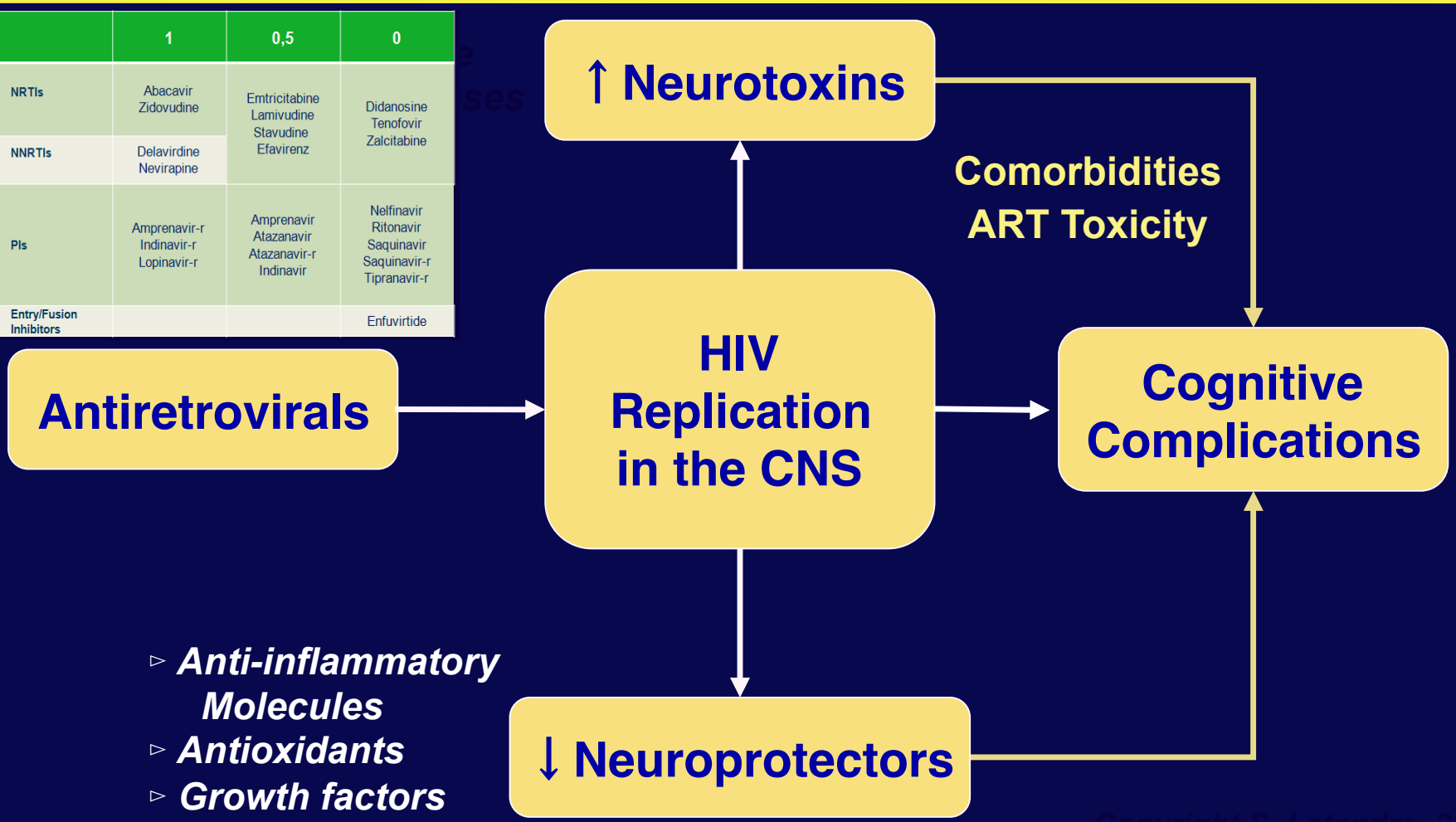
Neuro-efficacy

Treating HIV in the CNS Must Consider the Multifactorial Pathogenesis



Treating HIV in the CNS Must Consider the Multifactorial Pathogenesis

	1	0,5	0
NRTIs	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine Efavirenz	Didanosine Tenofovir Zalcitabine
NNRTIs	Delavirdine Nevirapine		
PIs	Amprenavir-r Indinavir-r Lopinavir-r	Amprenavir Atazanavir Atazanavir-r Indinavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors			Enfuvirtide



CNS Penetration Effectiveness Ranks 2010

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

Letendre SL, et al. 17th CROI 2010, Abstract 172

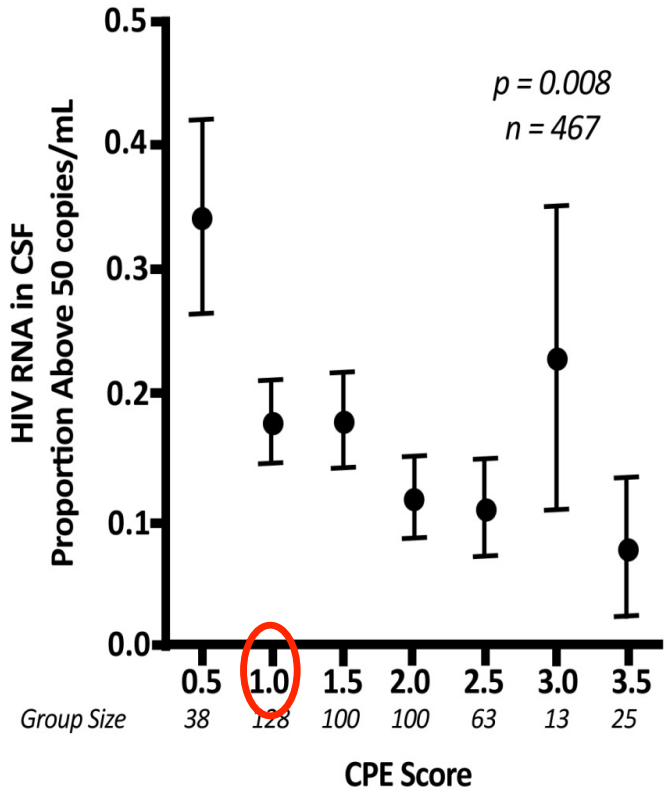
Example total CPE scores for combination treatments

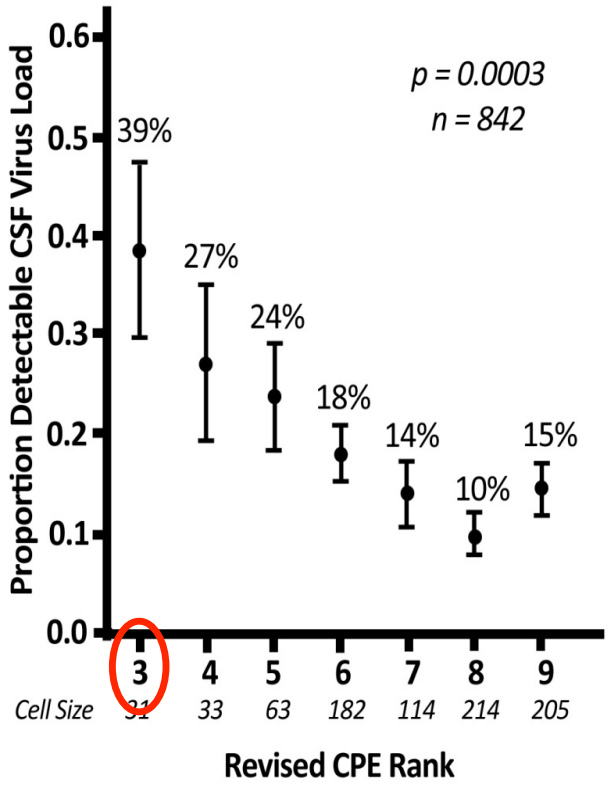
Treatment	CPE score
ZDV/3TC/NVP	10
ABC/3TC/EFV	8
TDF/FTC/EFV	7
TDF/FTC/ATV/r	6
DRV/r monotherapy	3
LPV/r monotherapy	3

NB: The score has not been validated for monotherapy

Letendre S, et al. CROI 2010. Abstract 172.

Typical CPE scores of PI monotherapy





Letendre S, et al. 17th CROI, San Francisco CA 2010, Oral #172

Questions

- Is bPI monotherapy a risk factor for CSF viral escape?
- Is bPI monotherapy a risk factor for HAND?
- Is bPI monotherapy a protective factor for HAND?

Answers

Questions

- Is bPI monotherapy a risk factor CNS Adverse Events in clinical trials?

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Protease inhibitor monotherapy and the CNS: peace of mind?

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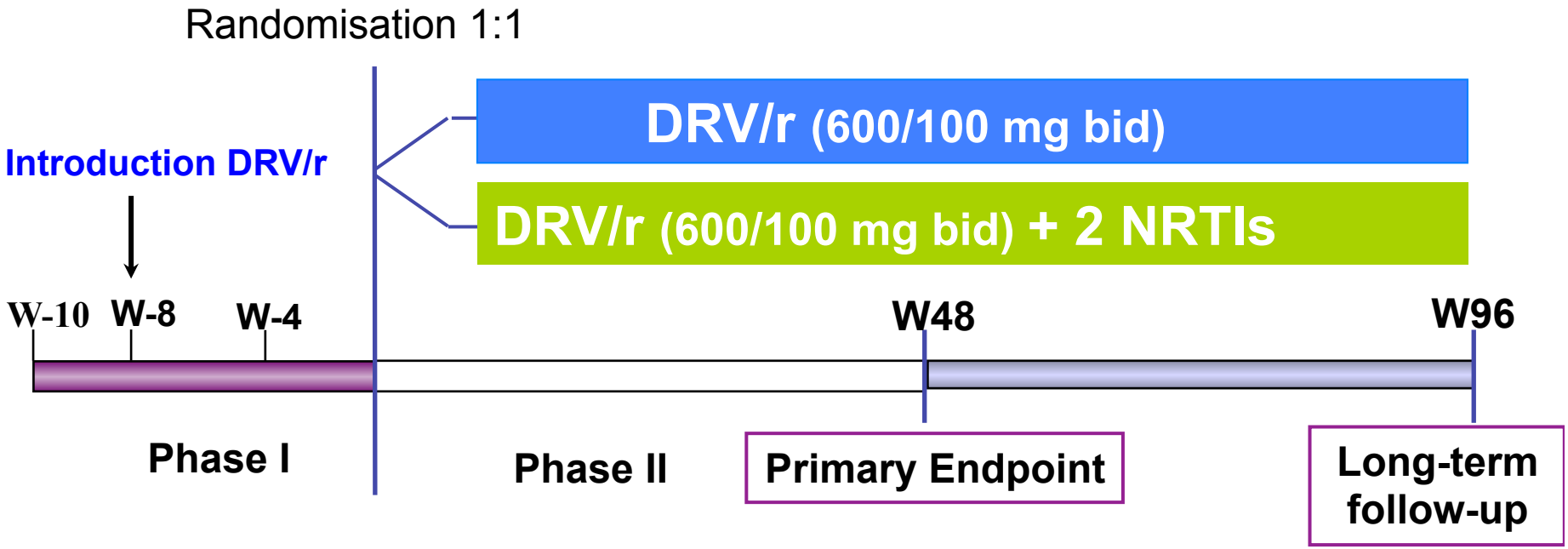
Table 2. Clinical trials of bPI monotherapy: efficacy, CPE score and neuropsychiatric outcomes

Study	Group (*n*)	CPE score 2010	Percentage HIV RNA <50 copies/mL (plasma); ITT, M and S=F[a] (week of follow-up)	Neurocognitive performance, mean ± SD (weeks of follow-up)	Percentage of patients with CNS adverse events (week of follow-up)
OREY[57]	atazanavir/r (61)	2	67% (48)	NA	8% (48)[b]
OK04[4]	lopinavir/r (100)	3	77% (96)	NA	NA
	lopinavir/r+2 NRTIs (98)	7–9	77.6% (96)	NA	NA[c]
Sprinz *et al.*[46]	lopinavir/r (27)	3	63% (96)	NA	NA[d]
MOST[40]	lopinavir/r (29+13)[e]	3	79.3% (96)[f]	NA[g]	NA[h]
	lopinavir/r+2 NRTIs (31)	7–9	100% (96)[f]	NA[g]	NA
MONET[48,49]	darunavir/r (127)	3	84.3% (48)–74.8% (96)	8.9 ± 2.8 (48)[i]	16% (48)–21% (96)
	darunavir/r+2 NRTIs (129)	7–9	85.3% (48)–80.6% (96)	9.0 ± 2.6 (48)[i]	16% (48)–19% (96)
MONOI[44]	darunavir/r (103)	3	88% (96)	NA	NA[j]
	darunavir/r+2 NRTIs (104)	7–9	84% (96)	NA	

dTransient neurocognitive impairment in a patient receiving lopinavir/ritonavir monotherapy resolved after reinduction with two NRTIs.
j: Transient acute neurological symptoms (seizures in an epileptic patient and atypical headache) in two patients in the monotherapy arm resolved after reinduction with two NRTIs.

MONOI Study Design

- Multicenter open label randomized study



Main inclusion criteria

- cART ≥ 18 months
- CD4 count ≥ 200 cells/mm^3
- Viral load <400 copies/ml in the last 18 months and <50 copies/ml at entry
- No history of PI failure and naïve to darunavir

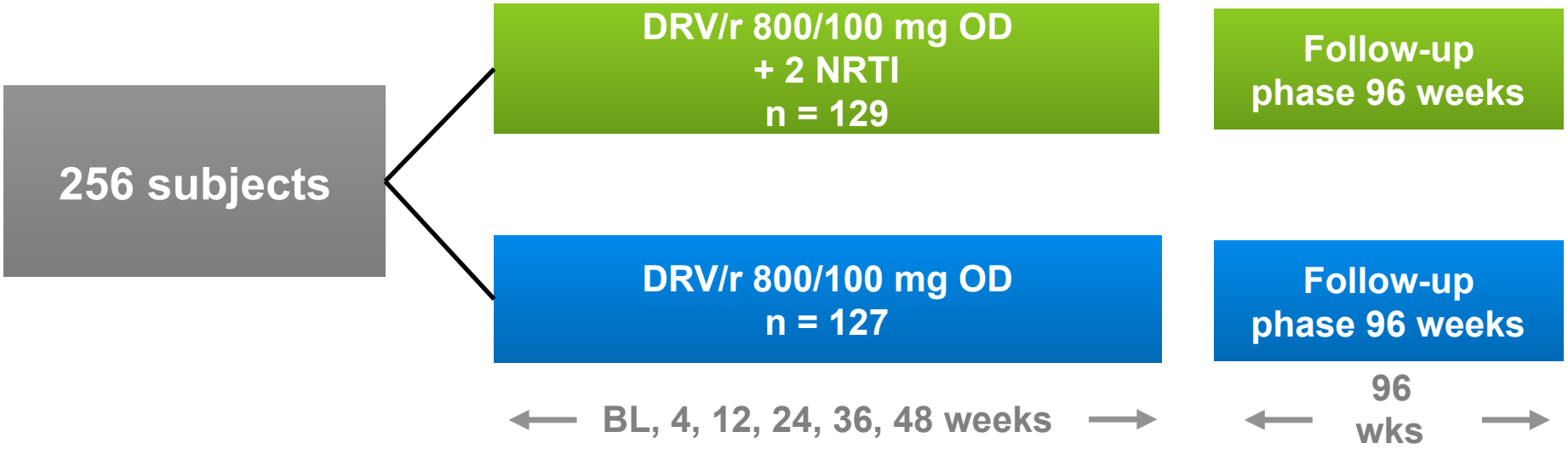
MONOI Serious Adverse events

	DRV/r + 2 NRTIs n=15	DRV/r n=14
Infections	2	2
Psychiatric Events	1	0
CNS disorders	1	3*
Cardiovascular	2	1
Cancer	0	3
Lipodystrophy	0	1
Surgery	6	3
GI disorders	1	0
Hepatic transaminases increase	1	1
CPK	1	0

*one HIV encephalitis and one neurological symptoms possibly related to HIV, both possibly related to study treatments

MONET: Trial Design

- Inclusion: Taking 2 NRTI + either NNRTI or boosted PI at screening (stratified)
- HIV RNA <50 copies/mL for at least 6 months, no prior use of darunavir (DRV)
- No history of virological failure



Primary Endpoint at Week 48: HIV RNA <50 copies/mL (TLOVR). Per Protocol, Switch = Failure

Winston A, Arribas J, Adverse Events / Lipodystrophy Workshop, Rome, Italy, June 2011 [abstract P049]

MONET trial – baseline characteristics, use of NRTIs in control arm and mean CPE score

Parameter	DRV/r + 2NRTI (n=129)	DRV/r (n=127)
Male	83%	78%
Caucasian	90%	92%
Baseline CD4 count <350 cells/uL	12%	14%
Use of PI at screening	57%	56%
Use of NNRTI at screening	43%	44%
Use of NRTIs in control arm (CPE score)		
ABC/3TC (5)	31%	
ZDV/3TC (6)	10%	
TDF/3TC (3)	7%	
TDF/FTC (4)	46%	
Other (5)	6%	
Mean CPE Score	**8**	**3**

Winston A, Arribas J, Adverse Events / Lipodystrophy Workshop, Rome, Italy, June 2011 [abstract P049]

MONET: Clinical Adverse Events up to Week 144

	DRV/r + 2NRTI N=129	DRV/r N=127
At least one SAE, n (%)	14 (11%)	14 (11%)
Deaths, n (%)	0 (0%)	0 (0%)
Grade 1-4 AE, n (%)	107 (83%)	113 (89%)
Grade 1-4 psychiatric AE, all cause, n (%)	23 (18%)	19 (15%)
Grade 1-4 nervous system AE, all cause, n (%)	26 (20%)	30 (24%)
Grade 2-4 psychiatric AE, drug related, n (%)	0 (0%)	2 (1.6%)
Grade 2-4 nervous system AE, drug related, n (%)	4 (3.1)	5 (3.9%)

Two patients discontinued from the trial with nervous system or psychiatric adverse events:

One patient discontinued from the DRV/r monotherapy arm for headache
One patient discontinued from the DRV/r + 2NRTI arm for disturbance in attention

Winston A, Arribas J, Adverse Events / Lipodystrophy Workshop, Rome, Italy, June 2011 [abstract P049]

MONET trial: Number of patients with Grade 1-4 Nervous System Adverse Events (all-cause) up to Week 144

	DRV/r + 2NRTI N=129	DRV/r N=127
Total, n (%)	26 (20.2%)	30 (23.6%)
Convulsion	2	0
Disturbance in attention	2	0
Dizziness	3	3
Headache	10	12
Hypoasthaesia	2	4
Migraine	2	0
Paraesthaesia	2	3
Sciatica	2	1
Syncope	0	2

*** Individual adverse events reported in at least two patients per treatment arm**

Winston A, Arribas J, Adverse Events / Lipodystrophy Workshop, Rome, Italy, June 2011 [abstract P049]

MONET trial: Grade 1-4 Psychiatric Adverse Events up to Week 144*

	DRV/r + 2NRTI N=129	DRV/r N=127
Total	**23 (17.8%)**	**19 (15.0%)**
Anxiety	**2**	**2**
Depression	**7**	**12**
Drug dependence	**2**	**0**
Insomnia	**5**	**1**
Psychotic disorder	**0**	**2**
Sleep disorder	**6**	**4**

*** Individual adverse events reported in at least two patients per treatment arm**

Winston A, Arribas J, Adverse Events / Lipodystrophy Workshop, Rome, Italy, June 2011 [abstract P049]

Questions

- Is bPI monotherapy a risk factor for CSF viral escape?
- Definition:
  - HIV-1 RNA above levels of detection of standard assays in CSF despite having undetectable levels in blood.
  - Viral rebound with a CSF viral load 1 log higher than their plasma.

Table 1. Studies including data on the percentage of patients on conventional antiretroviral treatment with detectable HIV RNA levels in the CSF and HIV RNA <50 copies/mL in plasma

Study	*n*	HIV RNA cut-off used in CSF (copies/mL)	Percentage of patients above HIV RNA cut-off in CSF and <50 HIV RNA copies/mL in plasma	CPE score predictive value
Eden *et al.*[26a]	69	50	10	no
Letendre *et al.*[9]	300	2	26	NA
Letendre *et al.*[55]	842	50	4	NA
Marra *et al.*[22]	NA	50	0	NA
Yilmaz *et al.*[56]	94	50	2	NA
Antinori *et al.*[24]	107	50	15.2	yes

Pérez-Valero et al. J Antimicrob Chemother doi:10.1093/jac/dkr229

If a patient is supressed (<50 copies/mL) in blood on PI monotherapy is the risk of a CSF viral > 50 copies/mL higher than for a patient in triple therapy?

Discordance Between Cerebral Spinal Fluid and Plasma HIV Replication in Patients with Neurological Symptoms Who Are Receiving Suppressive Antiretroviral Therapy

Ana Canestri,[1,7] François-Xavier Lescure,[3] Stephane Jaureguiberry,[1] Antoine Moulignier,[3] Corinne Amiel,[4] Anne Geneviève Marcelin,[2,6,7] Gilles Peytavin,[5] Roland Tubiana,[1,7] Gilles Pialoux,[3,6] and Christine Katlama[1,6,7]

[1]Service de Maladies Infectieuses et Tropicales and [2]Laboratoire de Virologie, Hôpital Pitié-Salpêtrière, [3]Service de Maladies Infectieuses et Tropicales and [4]Laboratoire de Virologie, Hôpital Tenon, and [5]Service de Toxicologie, Hôpital Bichat-Claude Bernard, Assistance Publique–Hôpitaux de Paris, [6]Université Pierre et Marie Curie Paris, and [7]Institut National de la Santé et de la Recherche Médicale, U943, Paris, France

Objective. We report data on 11 patients with neurological symptoms and human immunodeficiency virus (HIV) cerebrospinal fluid (CSF) viremia contrasting with suppressed plasma HIV RNA during receipt of combined antiretroviral therapy.

Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir

Incorrect attribution of cerebrospinal fluid HIV-1 virological escape and lymphocytic meningitis to lopinavir/ritonavir monotherapy

Lopinavir monotherapy and CSF replication

Table 3: Plasma viral load, CD4+ and week of LP

Subject	Weeks of LPV/r	Pre-treatment plasma CD4+ cells/mm^3	Plasma CD4+ cells/mm^3 at time of LP	Plasma copies/ml (bDNA)	CSF HIV RNA copies/mL
003	48	228	449	< 75	< 50
004	48	482	546	< 75	< 50
010	48	204	646	< 75	< 50
016	48	308	471	< 75	< 50
017	48	257	515	< 75	< 50
031	32	530	599	< 75	< 50
032 (Sample 9/06)	36	171	348	< 75	251
032 (Sample 1/07)	48	- -	399	< 75	747
036	32	272	458	< 75	< 50
037	32	143	265	< 75	< 50
041	32	516	371	< 75	< 50
044	24	186	769	< 75	< 50

Yeh et al. CROI 2007

AIDS. September 2010

Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir

MOST STUDY

Table 2. Summary of all patients with treatment failure in blood or detection of elevated HIV-RNA in CSF at any time during the study.

Patient group and ID[1]	Sex	Pre-treatment	CD4 nadir (/μl)	Treatment arm[2]	Week on study/MT	log RNA blood	log RNA CSF	WBC count CSF (/μl)	Protein CSF (g/l)	CD4 cell at term[5]	Symptoms of acute HIV infection
Blood failure											
101	Male	ATV/r, TDF, 3TC	57	MT	12	4.3	5.1	124	0.6	680	Yes
108	Female	LPV/r, ZDV, 3TC	5	DS	60/12	4.2	3.1	10	0.4	361	Yes
126	Female	LPV/r, ABC, 3TC	149	MT	12	4.1	5.0	67	0.9	380	No
302	Male	EFV, ZDV, 3TC	7	MT	24	3.0	4.1	10	0.4	130	Yes
303	Male	LPV/r, TDF, 3TC	54	MT	6	5.0	nd[3]	nd	nd	250	No
713	Female	EFV, TDF, 3TC	160	MT	24	3.0	3.7	29	0.4	710	Yes
CNS +RNA MT											
107	Male	LPV/r, TDF, FTC	211	DS	96/48	<1.6	2.9	3	nd	nd	No
703	Male	ATV/r, TDF, 3TC	370	DS	66/18	2.2	3.4	56	0.7	1030	No
704	Female	LPV/r, ABC, 3TC	100	MT	63	2.3	4.3	47	0.7	380	Yes
707	Male	TDF, 3TC, ZDV, EFV	130	DS	68/20	2.1	3.4	15	0.4	780	No
702	Male	LPV/r, 3TC, ZDV	120	DS	72/24	<1.6	2.1	2	0.4	1050	No
709	Male	LPV/r, TDF, FTC	20	MT	37	<1.6	2.4	1	0.2	410	No
714	Female	ABC, ZDV, 3TC, LPV/r	220	MT	48	1.9	2.5	22	0.4	680	No
124	Female	LPV/r, ZDV, 3TC	17	MT	44	<1.6	1.9	2	0.2	474	No
CNS +RNA CT											
709	Male	LPV/r, TDF, FTC	20	BL	0	<1.6	1.6	1	0.5	360	No
309	Male	ATV/r, TDF, FTC	126	BL	0	<1.6	1.7	1	0.4	333	No
110	Male	TDF, 3TC, EFV	185	BL	0	<1.6	1.9	2	0.5	447	No
703	Male	ATV/r, TDF, 3TC	370	DS	48/0	<1.6	1.6	2	0.9	1010	No

Gutmann C et al. AIDS 2010, 24:2347–2354

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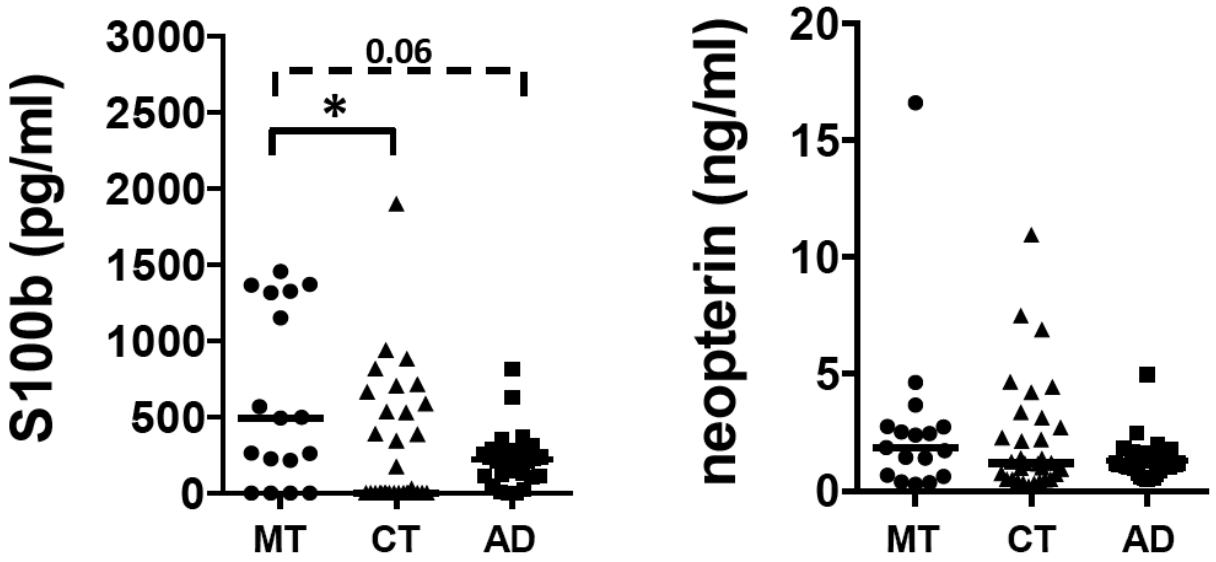
Gutmann C et al. AIDS 2010, 24:2347–2354

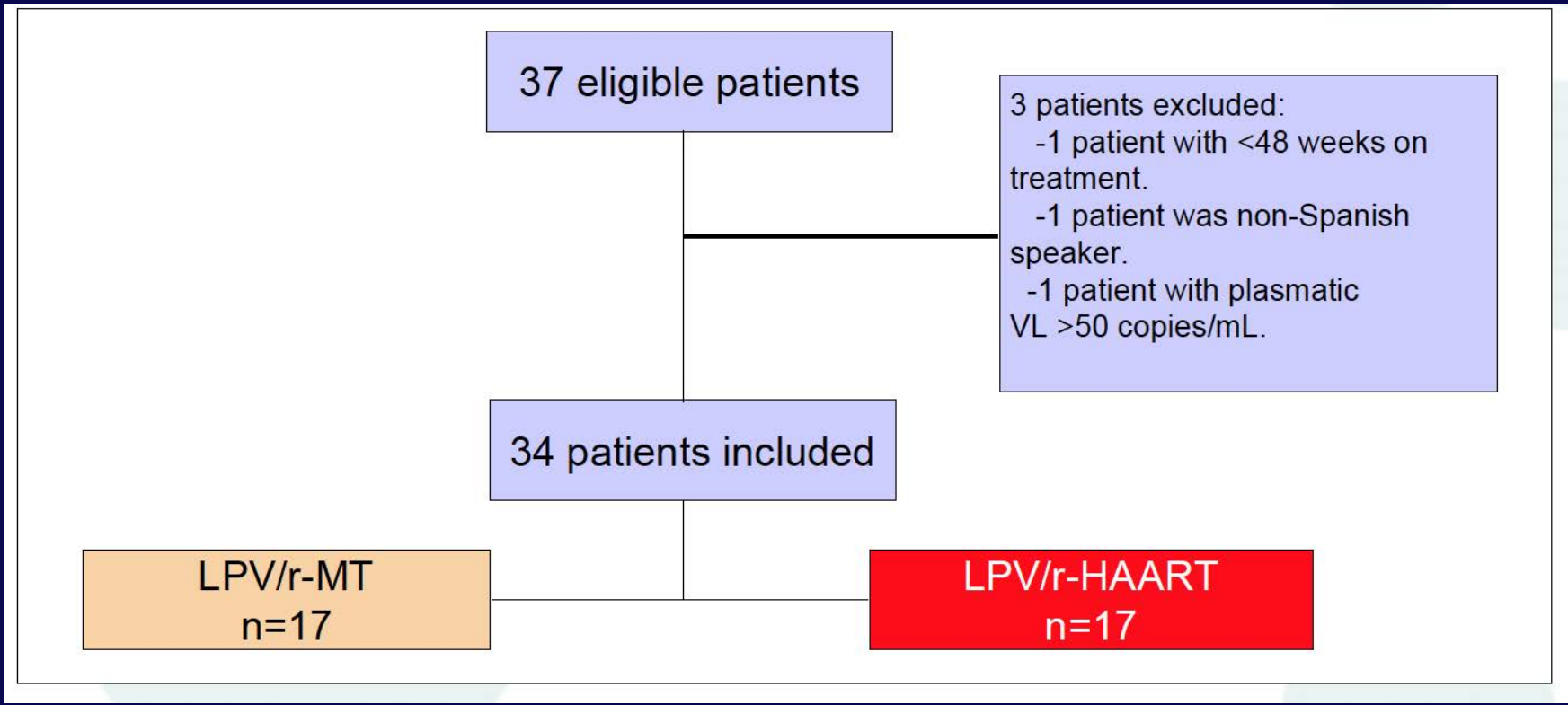
Biomarkers in the CSF: MT vs CT

- - Microglia: **Neopterin: No diferences MT vs CT.**
- - Astrocytes: **S100-β: Increased in MT.**
- - Neurons: **Amyloid-β 1-42: No changes**
- - Neurons: **Total Tau: No changes**
- - Neurons: **Phospho: No changes**



Du-Pasquier R et al. 19th CROI 2012

Long-Term Monotherapy With Lopinavir/ritonavir (>2 years) is not Associated with Greater HIV-Associated Neurocognitive Impairment



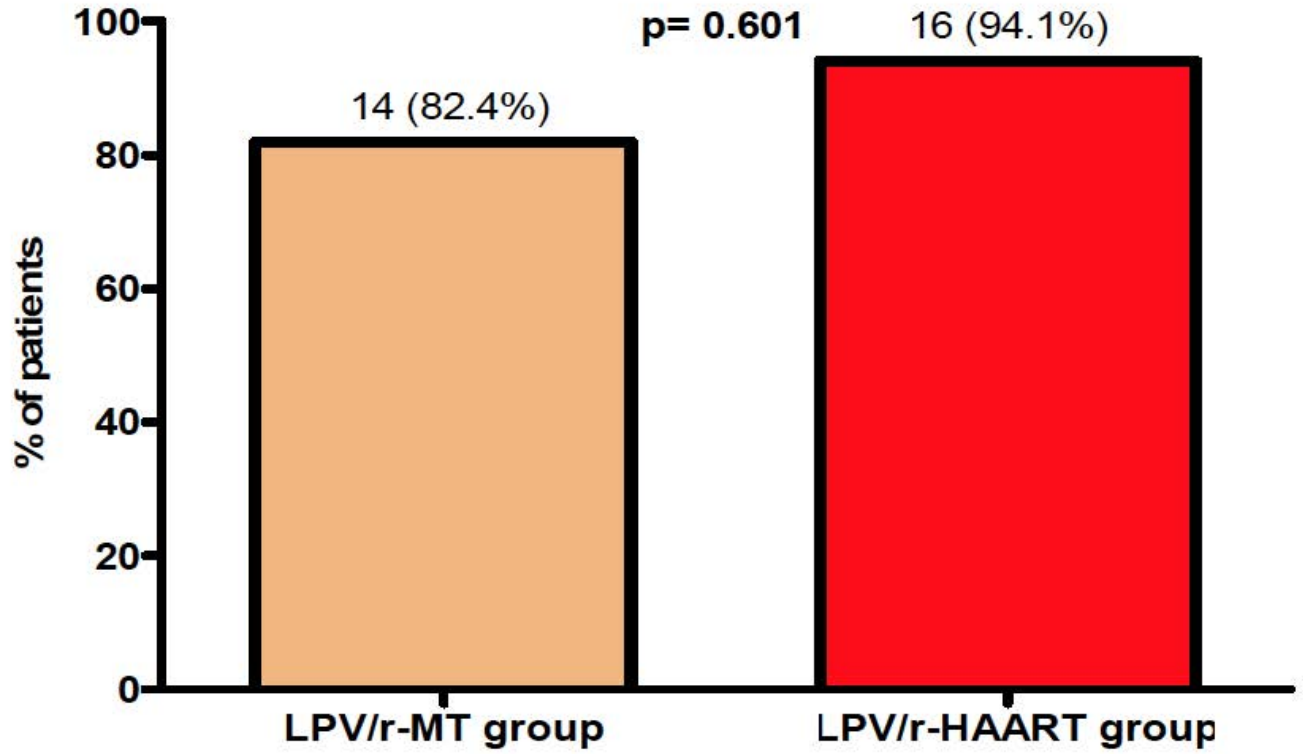
All more than 2 years on MT

Santos J et al. CROI 2012. Abstract #E-117

	LPV/r-MT	LPV/r-HAART	*P* value
Age	45.2 (38.9-48.7)	47.3 (42.9-50.1)	0.547
Male	15 (88.2)	14 (82.4)	0.628
MSM	10 (58.8)	7 (41.2)	0.294
Median years of education[a]	12 (9-17)	9 (8-12)	0.06
CDC stage C	2 (11.8)	3 (17.6)	0.064
Median CD4+ nadir (cells/mm^3)[a]	186 (118-294)	169 (61-293)	0.744
Median prior ARV regimens[a]	6 (2-10)	2 (1-4)	**0.018**
Median prior NNRTIs[a]	1 (0-2)	0 (0-1)	0.085
Median prior PIs[a]	2 (1-3)	1 (1-2.5)	0.401
Median prior NRTIs[a]	5 (3-6)	3 (2-5)	0.164
Median time since HIV diagnosis (years)[a]	17.1 (8.3-20.4)	8.7 (5.0-18.1)	0.076
Median time on treatment (years)[a]	10.6 (6.1-17.9)	7.3 (3.2-14.8)	0.088
Median time on virological suppression (years)[a]	6.9 (5.5-8.9)	3.4 (2.3-5.1)	**<0.001**
Median time on LPV/r based treatment (years)[a]	3.8 (2.7-4.8)	3.7 (2.4-4.7)	0.524
Current NRTI backbone			
TDF + FTC	-	14 (82)	-
ABC + 3TC	-	2 (12)	-
AZT + ddI	-	1 (6)	-
VL zenith (log)[a]	4.8 (3.8-5.5)	4.9 (4.5-5.4)	0.564
Median CD4+ T cell count (cells/mm^3)[a]	736 (579-856)	570 (419-818)	0.085

Santos J et al. CROI 2012. Abstract #E-117

Figure 2. Patients with complete CSF-virological suppression (RNA HIV <1 copy/mL).



Santos J et al. CROI 2012. Abstract #E-117

Questions

- Is bPI monotherapy a risk factor for HAND?

MOST STUDY

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Patient group and ID[1]	Sex	Pre-treatment	CD4 nadir (/µl)	Treatment arm[2]	Week on study/MT	log RNA blood	log RNA CSF	WBC count CSF (/µl)	Protein CSF (g/l)	CD4 cell at term[5]	Symptoms of acute HIV infection
Blood failure											
101	Male	ATV/r, TDF, 3TC	57	MT	12	4.3	5.1	124	0.6	680	Yes
108											Yes
126											No
302											Yes
303											No
713											Yes
CNS											
107											No
703											No
704											Yes
707											No
702											No
709											No
714	Female	ABC, ZDV, 3TC, LPV/r	220	MT	48	1.9	2.5	22	0.4	680	No
124	Female	LPV/r, ZDV, 3TC	17	MT	44	<1.6	1.9	2	0.2	474	No
CNS +RNA CT											
709	Male	LPV/r, TDF, FTC	20	BL	0	<1.6	1.6	1	0.5	360	No
309	Male	ATV/r, TDF, FTC	126	BL	0	<1.6	1.7	1	0.4	333	No
110	Male	TDF, 3TC, EFV	185	BL	0	<1.6	1.9	2	0.5	447	No
703	Male	ATV/r, TDF, 3TC	370	DS	48/0	<1.6	1.6	2	0.9	1010	No

Changes in NP test results did not differ between patients who had detectable HIV-RNA in CSF vs. those with Suppressed RNA in CSF

Gutmann C et al. AIDS 2010, 24:2347–2354

No correlation between risk of neuropsychiatric adverse events and CSF Penetration Effectiveness (CPE) score in the MONET trial of darunavir/ritonavir (DRV/r), with or without nucleoside analogues (NRTIs).

Alan Winston[1], Jose Arribas[2], Andrew Hill[3], Yvon van Delft[4], Christiane Moecklinghoff[5]

1.St Mary's Hospital, London, UK

2.2. Hospital la Paz, Madrid, Spain

3. Pharmacology Research Laboratories, University of Liverpool, UK

4. Janssen-Cilag EMEA, Tilburg, Netherlands

5. Janssen-Cilag EMEA, Neuss, Germany

12th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV
London, United Kingdom, November 2010 [poster]

Methods – FAHI questionnaire

Study subjects also self-scored an assessment of clarity of thinking, concentration and memory, using part of the Functional Assessment of HIV Infection (FAHI) Quality of Life questionnaire (Cella 1996).

Patients were asked about three measures of cognitive functioning: “my thinking is clear”, “I have trouble concentrating” and “I have trouble remembering things”.

•For each question, patients gave a score of either 0 (not at all), 1 (a little bit), 2 (somewhat), 3 (quite a bit) and 4 (very much).

•The mean scores were compared between treatment arms at each timepoint using t-tests. The total score from the three questions was also compared between the treatment arms.

References
- Cella, D et al (1996). Development and validation of the Functional Assessment of Human Immunodeficiency Virus Infection (FAHI) quality of life instrument. Quality of Life Research 1996, 5, 450-463.

Results – FAHI questionnaire – cognitive function

FAHI questionnaire results

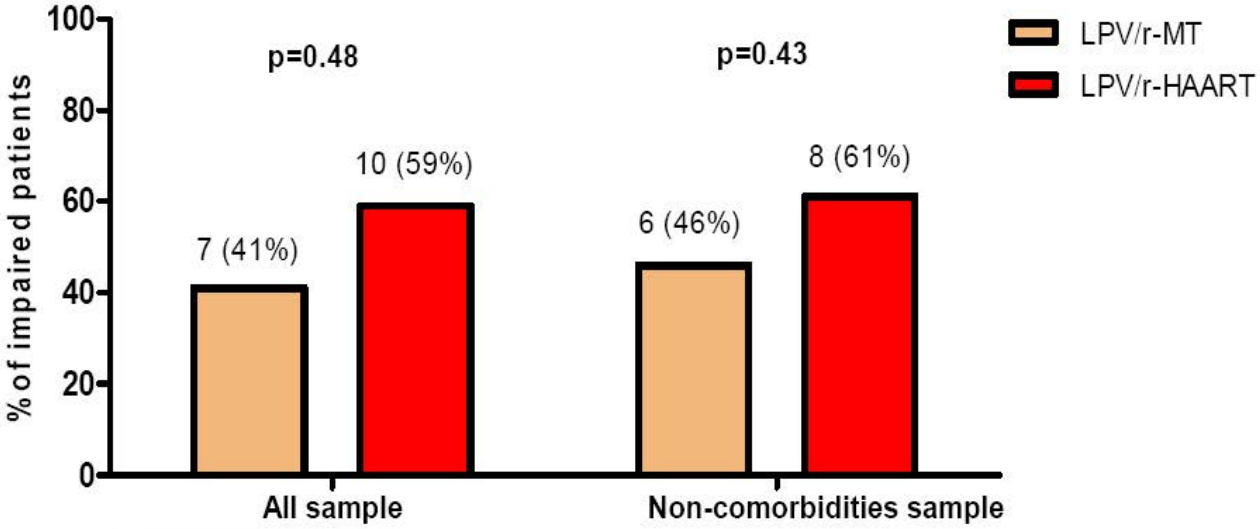
- There were no significant differences between the treatment arms for any of the FAHI scores on cognitive function during 96 weeks of follow up.

	DRV/r+2NRTIs	DRV/r
Cognitive Function (mean, 95% confidence intervals)	**(N=129)**	**(N=127)**
Baseline	**8.8 (8.3 – 9.2)**	**8.9 (8.5 – 9.4)**
Week 24	9.0 (8.5 – 9.6)	9.0 (8.5 – 9.5)
Week 48	8.9 (8.4 – 9.5)	9.0 (8.5 – 9.5)
Week 72	9.0 (8.5 – 9.6)	8.7 (8.2 – 9.2)
Week 96	**8.8 (8.3 – 9.3)**	**8.9 (8.4 – 9.5)**

Neurocognitive funcion after >2 ys of LPV/r Monotherapy

- 34 patients with VL<50 cop/mL and >2 ys of therapy:
  17 LPV/r monotherapy; 17 LPV/r+2 NRTIs.
- Neurocognitive evaluation: NPZ-7

Figure 3. Percentages of subjects with neurocognitive impairment.



Confounding comorbidities included: depression or anxiety disorders, drug use, presence of a psychiatric diagnosis, psychopharmacologic treatment, or current or past opportunistic infection involving CNS.

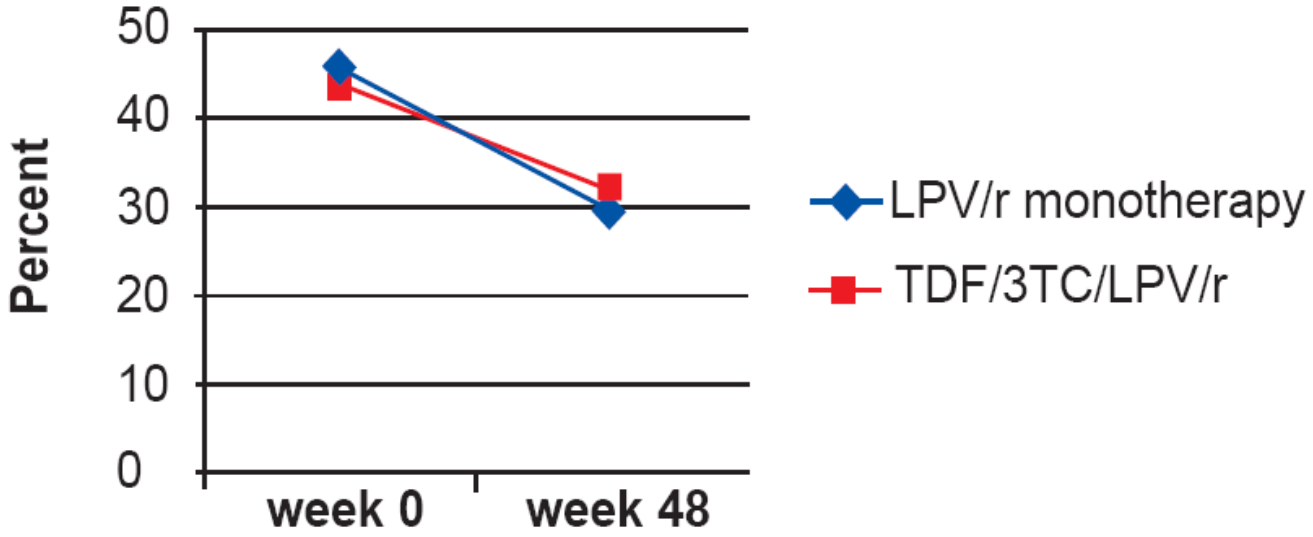
Considering neurocognitive functioning, values were mildly better in MT group. In total sample, GDS was 0.23 in MT group and 0.46 in HAART group (p=0.025), and in non-comorbities sample 0.25 and 0.5 (p=0.04), respectively.

Santos JR et al. 19th CROI 2012

Neurocognitive evolution in patients changed to 2nd line therapy with LPV/r

- Thai patients failing 1st antiretroviral regimen (VL >1000): 43 LPV/r monotherapy; 50 TDF/3TC/LPV/r.
- Neurocognitive evaluation: NPZ-5

Figure 2. Prevalence of Neurocognitive impairment at weeks 0 and 48*



* No statistical difference between arms; p>0.05 both at weeks 0 and 48

Bunupuradah T et al. 19th CROI 2012

Questions

- Is bPI monotherapy a protective factor for HAND?

Treating HIV in the CNS Must Consider the Multifactorial Pathogenesis

	1	0,5	0
NRTIs	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine Efavirenz	Didanosine Tenofovir Zalcitabine
NNRTIs	Delavirdine Nevirapine		
PIs	Amprenavir-r Indinavir-r Lopinavir-r	Amprenavir Atazanavir Atazanavir-r Indinavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors			Enfuvirtide

↑ Neurotoxins

Comorbidities
ART Toxicity

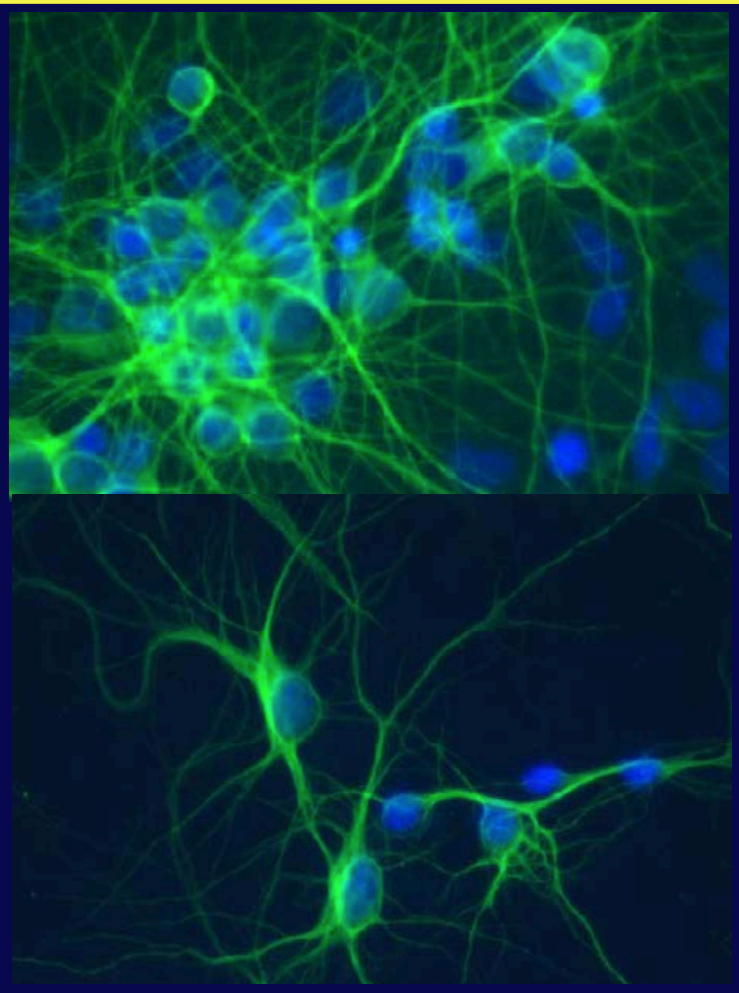
	1	0,5	0
NRTIs	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine Efavirenz	Didanosine Tenofovir Zalcitabine
NNRTIs	Delavirdine Nevirapine		
PIs	Amprenavir-r Indinavir-r Lopinavir-r	Amprenavir Atazanavir Atazanavir-r Indinavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors			Enfuvirtide

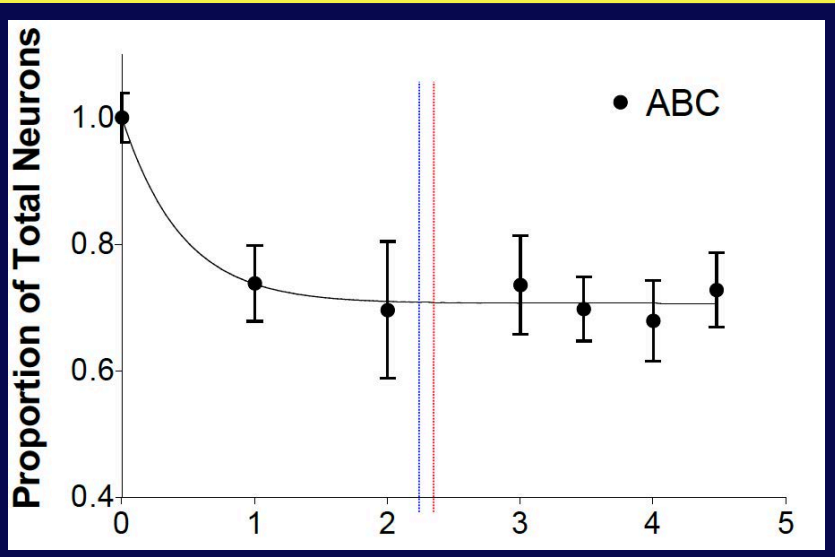
Antiretrovirals → HIV Replication in the CNS → Cognitive Complications

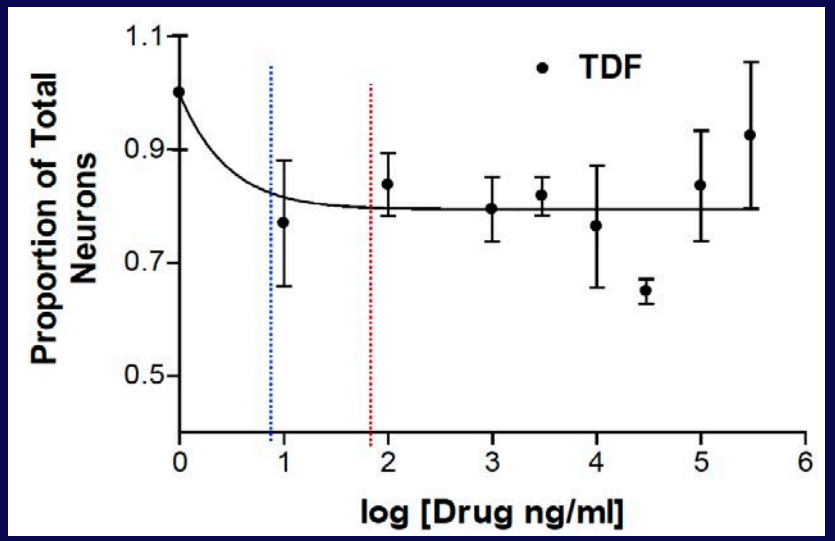
- *Anti-inflammatory Molecules*
- *Antioxidants*
- *Growth factors*

↓ Neuroprotectors

In Vitro Evidence of Antiretroviral Neurotoxicity







Liner et al, 17th CROI 2010, **Abstract 435**

Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance

Christina M. Marra[a], Yu Zhao[b], David B. Clifford[c], Scott Letendre[d], Scott Evans[b], Katherine Henry[e], Ronald J. Ellis[f], Benigno Rodriguez[g], Robert W. Coombs[h], Giovanni Schifitto[i], Justin C. McArthur[j] and Kevin Robertson[k] for the AIDS Clinical Trials Group 736 Study Team

Conclusion: Antiretroviral regimens with good CNS penetration, as assessed by CPE rank, are more effective in controlling CSF (and presumably CNS) viral replication than regimens with poorer penetration. In this study, antiretrovirals with good CNS

AIDS. 2009 Jul 17;23(11):1359-66.

Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance

Conclusion: Antiretroviral regimens with good CNS penetration, as assessed by CPE rank, are more effective in controlling CSF (and presumably CNS) viral replication than regimens with poorer penetration. In this study, antiretrovirals with good CNS penetration were associated with poorer neurocognitive performance. A larger controlled trial is required before any conclusions regarding the influence of specific antiretrovirals on neurocognitive performance should be made.

AIDS 2009, **23**:000–000

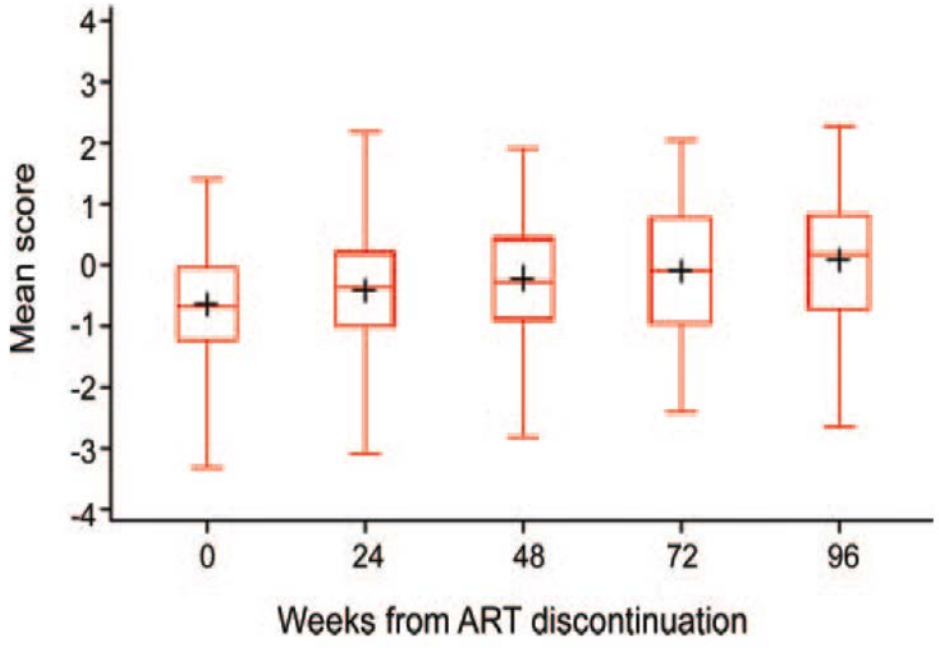
AIDS. 2009 Jul 17;23(11):1359-66.

Neurocognitive effects of TREATMENT INTERRUPTION in stable HIV-positive patients in an observational cohort

Table 2 Disease and treatment characteristics at baseline

Characteristics	Values
Preentry CD4 cell count, cells/mm^3	
Median (Q1-Q3)	833 (668-989)
≤500	12 (7%)
>500	155 (93%)
Preentry HIV-1 viral load level, copies/mL	
Median (Q1-Q3)	<50 (<50-146)
≤50	106 (64%)
≤400	137 (82%)
51-200	24 (14%)
201-400	7 (4%)
401-5,000	23 (14%)
5,001-55,000	5 (3%)
>55,000	2 (1%)

Figure 1 Plot of mean neuropsychological summary score following treatment interruption



Robertson KR et al. Neurology 2010;74(16):1260

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LETTER TO THE EDITOR

Changes in Cerebral Function Parameters in HIV Type 1-Infected Subjects Switching to Darunavir/Ritonavir Either as Monotherapy or with Nucleoside Analogues

Lucy Garvey,[1] Chris Higgs,[2] Perry Mohammed,[3] Andrew Hill,[4] Joanna M. Allsop,[5] Simon D. Taylor-Robinson,[1] Mark Nelson,[2] and Alan Winston[1]

Table 1. Cerebral Function Parameters and Antiretroviral Regimens at Baseline and Week 48

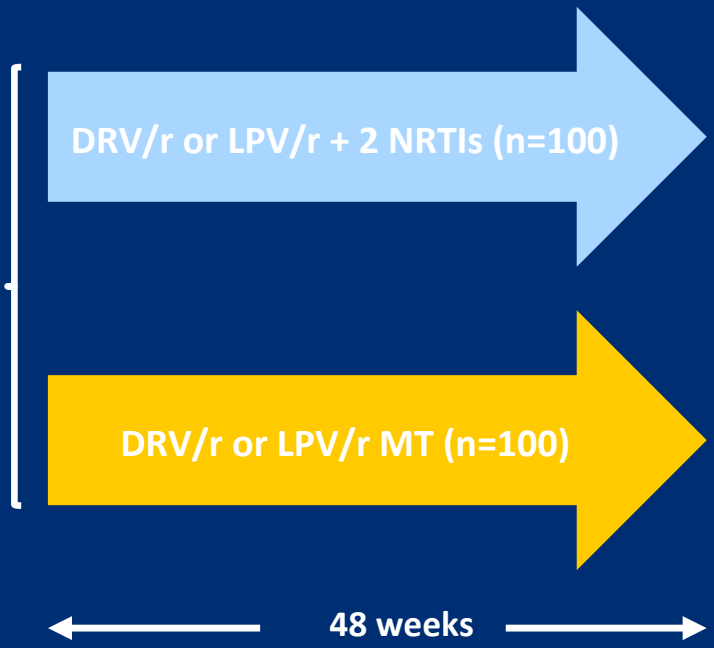
Cerebral function parameter/antiretroviral regimen	*Mean (SD) result/regimen*		*Mean (SD) absolute change*
	Baseline	*Week 48*	
Subject			
1	TDF, DDI, ATV/r	TDF, FTC, DRV/r	
2	TDF, FTC, LPV/r	DRV/r	
3	ABC, 3TC, ATV/r	DRV/r	
4	TDF, FTC, LPV/r	TDF, FTC, DRV/r	
5	ABC, 3TC, SQV/r	DRV/r	
Frontal gray matter metabolite ratios			
NAA/Cr	1.45 (0.29)	1.39 (0.21)	−0.06 (−0.21)
Cho/Cr	0.66 (0.11)	0.55 (0.06)	**−0.11 (−0.17)**
mI/Cr	0.82 (0.23)	0.60 (0.12)	**−0.22 (−0.3)**
Frontal white matter metabolite ratios			
NAA/Cr	1.66 (0.50)	1.52 (0.11)	−0.13 (−0.47)
Cho/Cr	1.06 (0.14)	0.98 (0.15)	**−0.09 (−0.17)**
mI/Cr	0.89 (0.29)	0.88 (0.35)	**−0.01 (−0.2)**
Right basal ganglia metabolite ratios			
NAA/Cr	1.62 (0.10)	1.67 (0.2)	**0.05 (−0.2)**
Cho/Cr	0.89 (0.13)	0.84 (0.02)	**−0.05 (−0.13)**
mI/Cr	0.83 (0.22)	0.67 (0.14)	**−0.16 (−0.18)**

Answers

Picasso study

Inclusion criteria:

- Stable HAART (1yr)
  - 2 NRTIs + PI*
  - PI* MT
- HIV RNA < 50 (1yr)
- Pts. w. cofounders excl**.



End points (MT vs. TT):

- Prevalence of HAND
- Evolution of NP
- % Viral escape
- Risk factors for HAND (MT)
- Neurological markers
- Neuro-image (MRI)

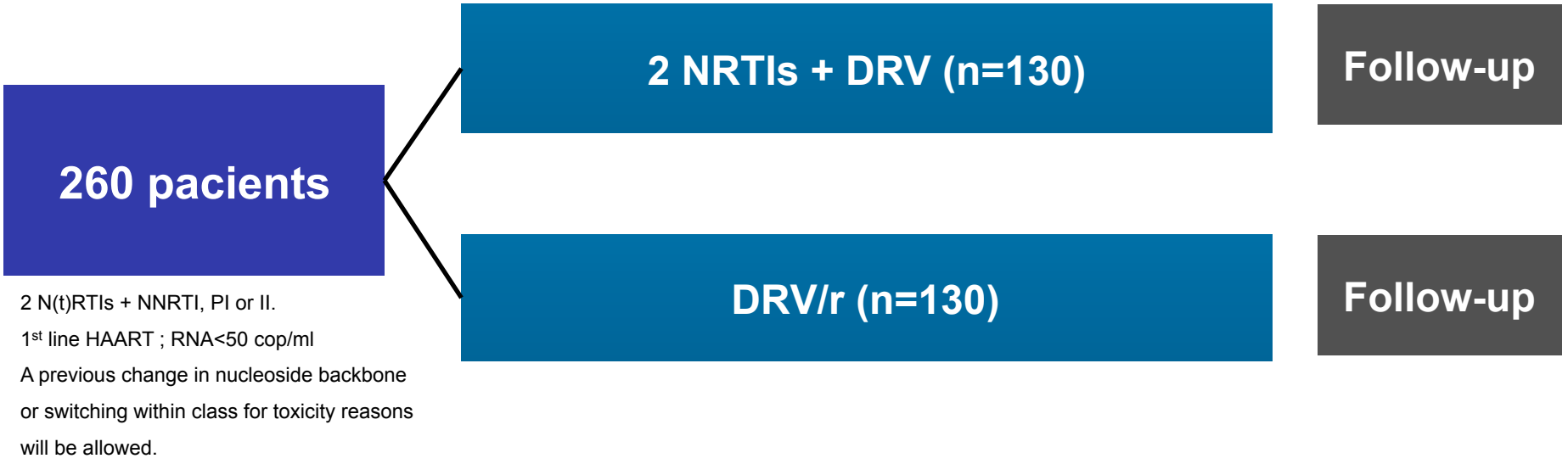
Basal and follow up visit procedures:

- Clinical evaluation, neurocognitive testing (NPZ-7), blood
- LP & MRI (only patients with neurocognitive impairment)
- NP evaluators are blind for HAART regimen

* DRV/r or LPV/r

** (neurological or psychiatric illness, drug or alcohol abuse, unable to be tested)

PROTEA



Primary endpoint: The primary objective is to demonstrate non-inferiority in terms of the percentage of subjects RNA<50 copies/mL after 48 weeks of follow-up after switching to DRV/r monotherapy vs triple therapy containing DRV/r (FDA Snapshot method).

Secondary endpoints: To evaluate the correlation of plasma HIV-1 RNA, cerebrospinal fluid (CSF) HIV-1 RNA, and neurocognitive function of DRV/r monotherapy vs triple therapy containing DRV/r at Week 48. To evaluate and compare change in neurocognitive function of DRV/r monotherapy vs triple therapy containing DRV/r over 48 and 96 weeks.

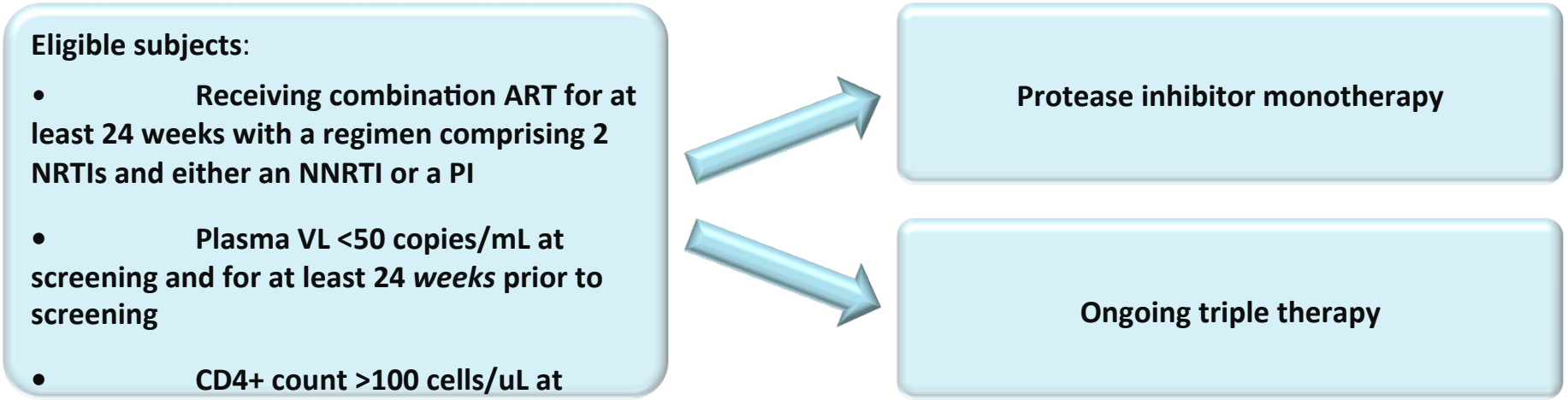
PROTEA secondary objectives

- Change in ***neurocognitive function*** over 48 and 96 weeks
- Rate of VL after 48 and 96 weeks, using the time to loss of virologic response (TLOVR) method
- Correlation of plasma HIV-1 RNA and ***neurocognitive function*** at Weeks 48 and 96
- ***Correlation of plasma VL, CSF VL, and neurocognitive function*** at Week 48
- Loss of treatment options at Weeks 48 and 96, as defined by treatment-emergent phenotypic drug resistance
- Evolution of the viral genotype over 48 and 96 weeks
- Safety and tolerability over 48 and 96 weeks

Methods

Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in the long term management of HIV infection

- multicentre study across UK
- over 40 sites
- open label, randomised study



Study ongoing; fully recruited as of Autumn 2010

Total number recruited 587

Protease-Inhibitor Monotherapy: Friend or Foe?

- Still unknown.
- More studies needed.
- Apparently no increased risk in short term studies.