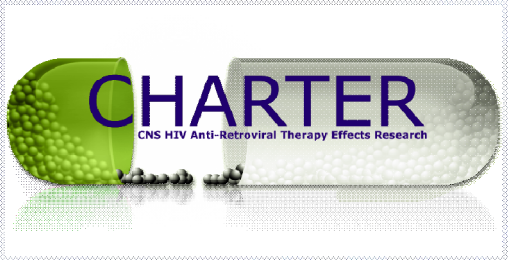

Incidence, Risk Factors and Neurocognitive Impact of CSF Viral Escape: Longitudinal Analysis in CHARTER & HNRP Cohorts.

Pérez-Valero I, Letendre S, Deutsch R, Heaton R, Ellis R, Franklin D, Clifford DB, McCutchan J, McArthur J, Morgello S, Gelman B, Collier A, Grant I and the CHARTER & HNRP groups.

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Background

- CSF viral escape (CVE), HIV-RNA >50 cop/mL in CSF while HIV-RNA <50 cop/mL in plasma, is an infrequent event observed despite ART.
- It is unclear if CVE is single entity or is the reflection of different pathogenic conditions with different outcomes[1,2].
- A potential deleterious effect of CVE on neurocognitive performance has been hypothesized but has not been proved.
- The incidence of CVE is unknown; Risk factors for CVE have not been identified and the effect of CVE on neurocognitive evolution is unexplored.

1. Peluso MJ et al. AIDS 2012;26:1765-74 & Canestri A et al. Clin Infect Dis 2010;50:773-8.
1. Eden A et al. J Infect Dis 2010;202:1819-25/

Objective

- Determine the incidence, the risk factors and the effect of CVE on neurocognitive evolution in two large US HIV cohorts:
  - » The CHARTER Cohort
  - » The HNRP Cohort at UC San Diego

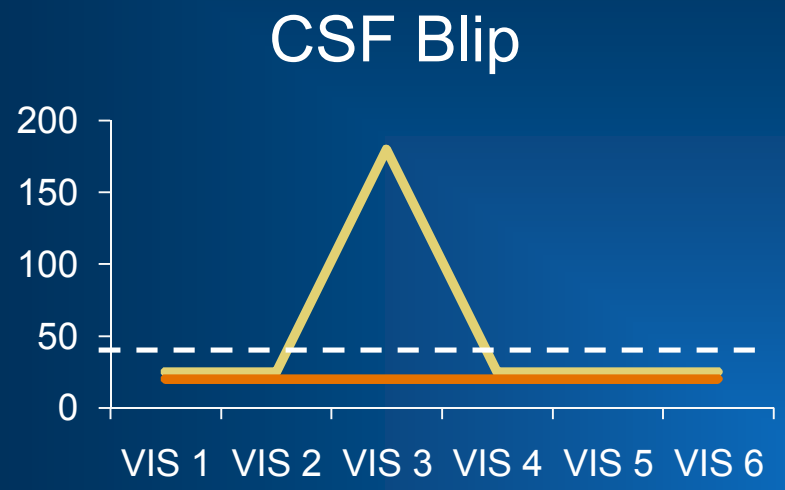
Study design (I)

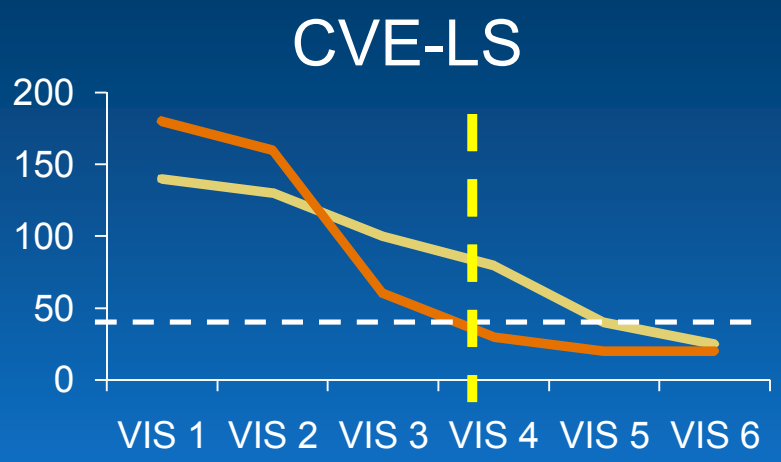
- Longitudinal analysis including individuals enrolled in CHARTER & HNRP cohorts (2003-2011).
- Selection criteria at inclusion:
  - » To be an HIV-infected patient on stable ART (≥ 6 months).
  - » To have an undetectable level of HIV RNA in plasma (<50 cop/mL).
  - » To have a paired CSF/plasma HIV RNA quantification.
  - » To have completed all visit procedures including a complete neurocognitive assessment.
- We recorded and analyzed data from following visits of selected patients.

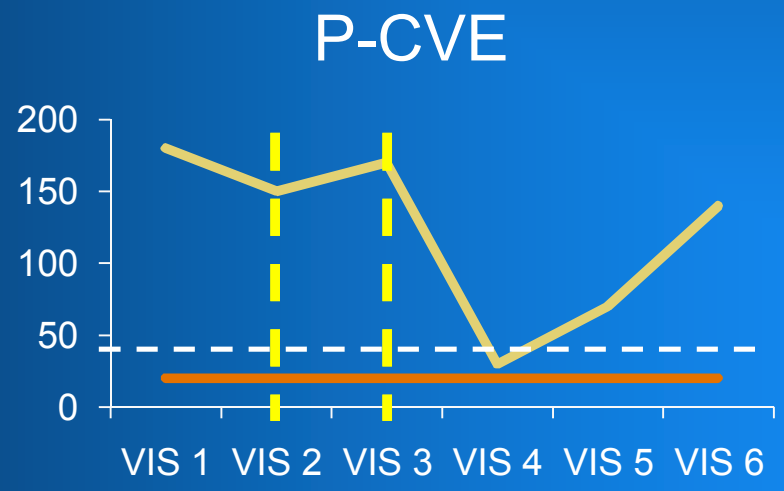
Study design (II)

- Visit type classification:
  - » CSF viral escape (defined as in the background).
    - CSF Blips: Single occurrence of CVE while suppressed in plasma.
    - Persistent CSF: ≥2 consecutive CVE while suppressed in plasma.
    - CVE-LS: CVE next to a period of loss of HIV-suppression in plasma.
  - » Control (HIV RNA <50 cop/mL in plasma and CSF)
  - » LVS (HIV RNA >50 cop/mL in plasma) – Censored for analysis.

Subtypes of CVE





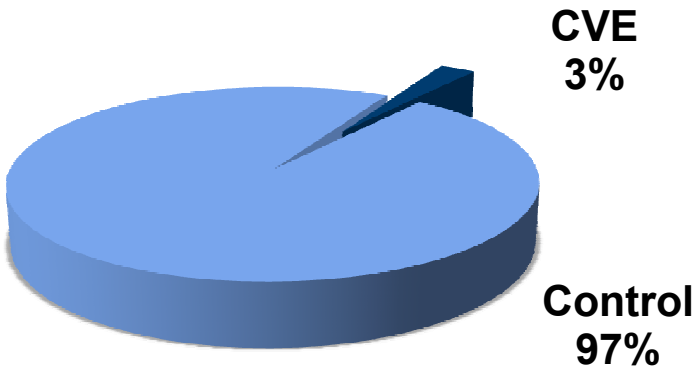


Statistical methods

- Incidence of CVE (global and by subtypes) was calculated and reported as incidence rates.
- Mixed model logistic regression (10% significance level) was used to estimated risk factors of CVE: An univariable model was run for each factor. Detected factors were analyzed in a multivariable models using backwards elimination based on corrected AIC. Factors were reported using the odds ratio.
- Neurocognitive performance, analyzed using a multiple linear regression model including demographics & GDS change, was compared in subjects with and without CVE that were always undetectable in plasma and have never performed a previous neurocognitive assessment.

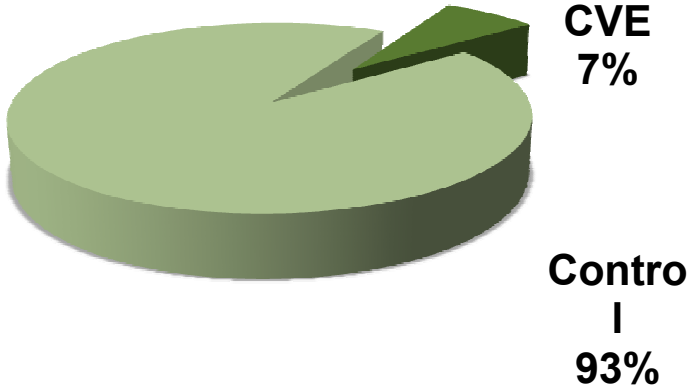
Subjects and Visits distribution

INDIVIDUALS



N = 849

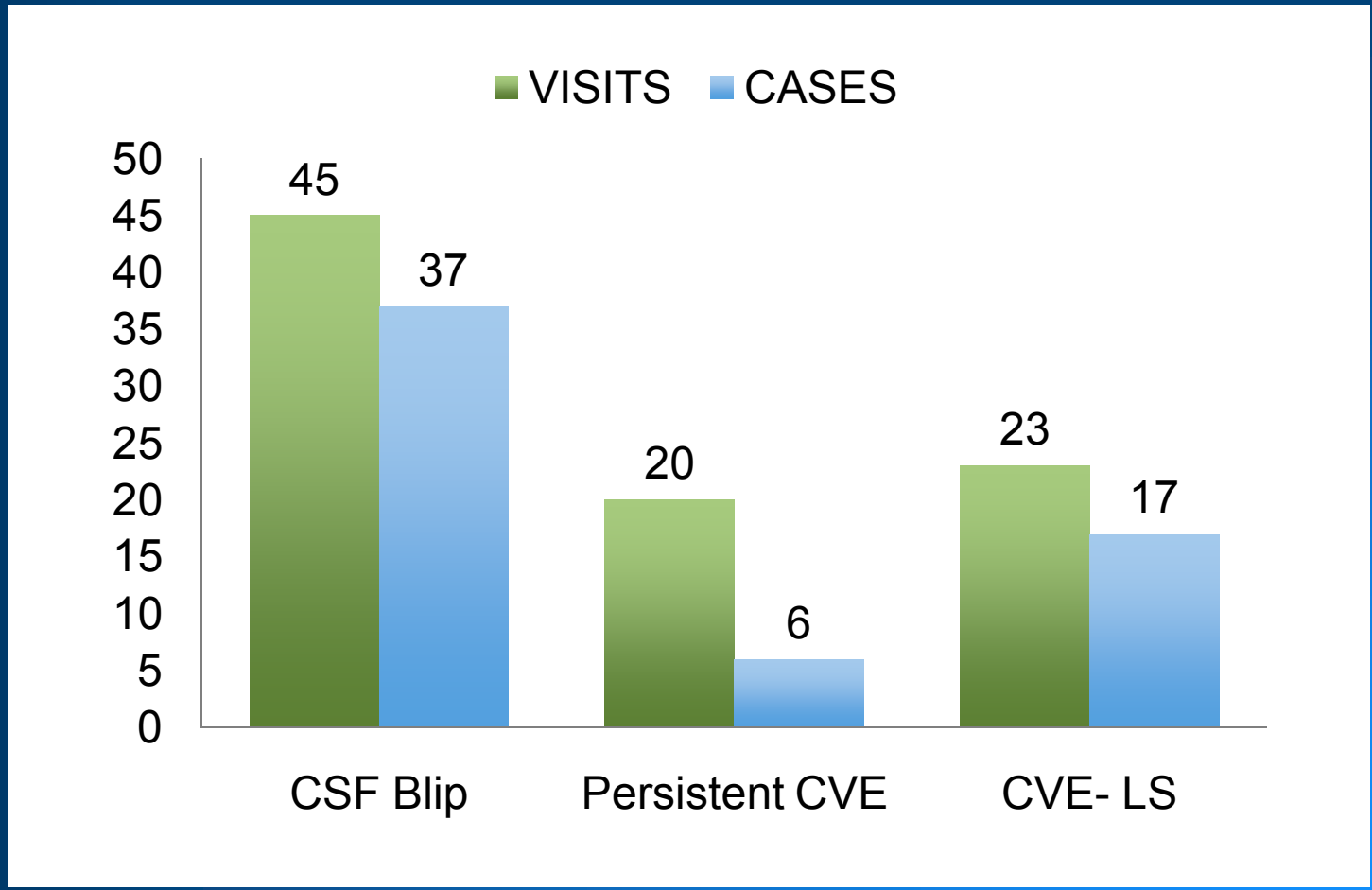
VISITS



N = 3392

Median time of follow up: 2.5 years (IQR 1-4.8)

CVE cases distribution by subtypes



Demographics & NP at baseline

Variable	CVE n=60	No CVE* N=789
Age (years), *X (SD)*	43.1 (7.6)	44.9 (9.2)
Gender (male), *%*	85%	80.6%
Ethnicity (Caucasian), *%*	48.3%	50%
Years of education, *X (SD)*	13 (2.5)	12.8 (2.7)
HCV Ab+, *%*	**18.8%**	**24.6%**
Neurocognitive performance		
GDS, *median (IQR)*	0.4 (0.15-0.75)	0.32 (0.11-0.72)
Neucognitively impaired, *N (%)*	**37.7%**	**37.2%**

* CSF HIV-RNA<50

HIV factors at baseline

Variable	CVE n=60	No CVE N=789
AIDS (CDC), %	**90%**	**69%**
CD4 nadir, *median (IQR)*	61 (9-183)	129 (25-237)
Years since first HIV+, *median (IQR)*	13 (8.9-16.6)	11.4 (5.5-16.5)
Years on ART ever, *median (IQR)*	6.5 (3.3-10.4)	6.1 (2.9-9.8)
Current ART regimen type		
NNRTI + N(t)RTIs, %	**16.7%**	**36.9%**
PI/r + N(t)RTIs, %	**60%**	**48.9%**
Other ART regimens, %	23.3%	14.2%
CPE Score, *median (IQR)*	7 (6-9)	7 (6-9)

Incidence rate of CVE (global and by subtypes)

CSF VIRAL ESCAPE (Global)	INCIDENCE RATE
CSF Viral Escape (all types)	37.4 cases per 1000 person-years

SUBTYPES OF CVE	INCIDENCE RATE
CSF Blips	19.1 cases per 1000 person-years
Persistent CSF Viral Escape	8.5 cases per 1000 person-years
CVE - LS	9.8 cases per 1000 person-years

Risk factors for CVE

Univariable mixed models

Variable	Risk direction	p Value
Plasma HIV RNA (0-50 cop/mL)	---	NC*
Years of follow up	Shorter	0.08
Protease inhibitor based ART	PI Use	< 0.01
CSF protein level	Higher	< 0.01
CSF Pleocytosis (>5 WBC)	Present	< 0.01
CSF Red Blood Cell count	Higher	0.03

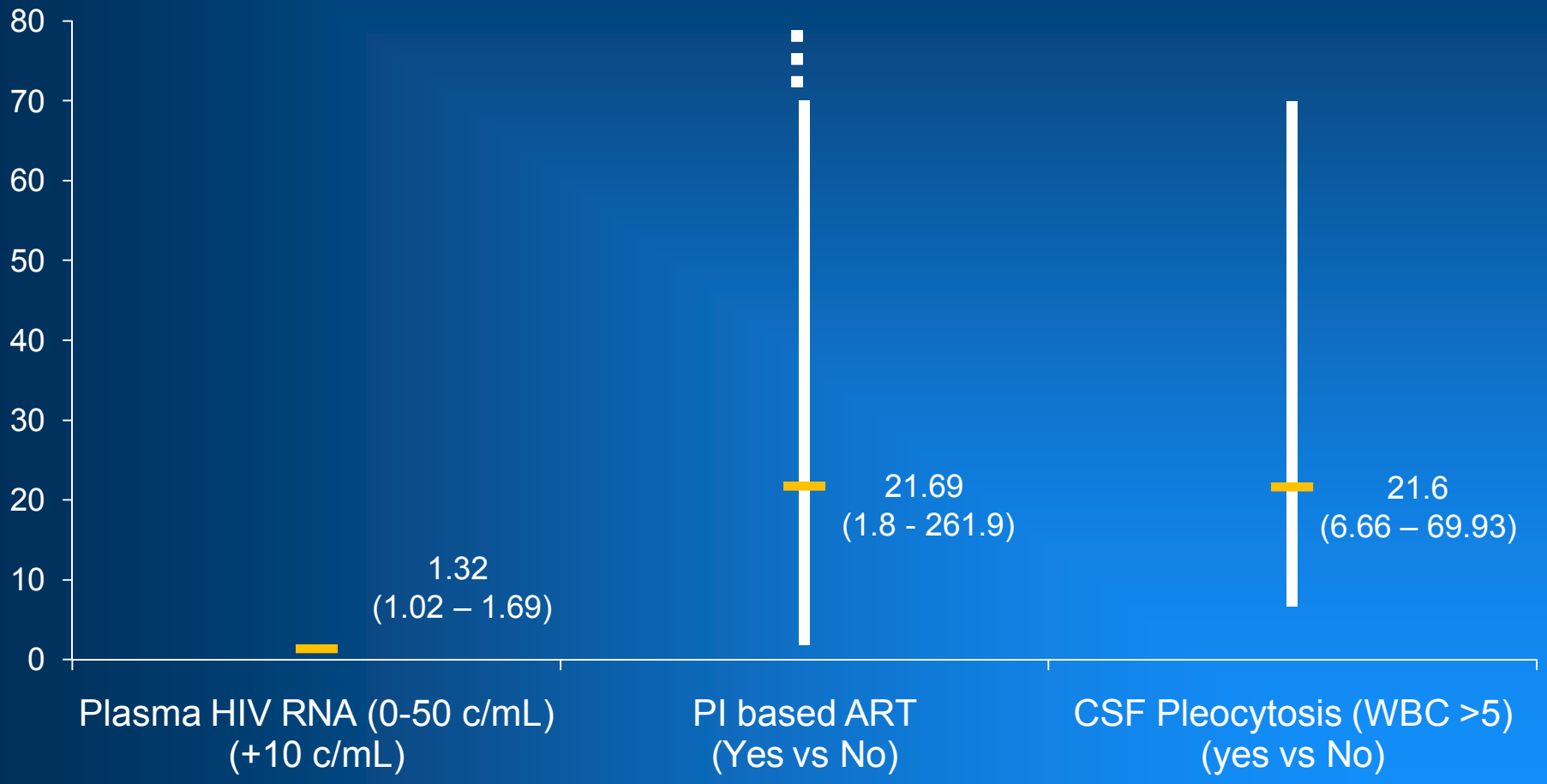
* No convergence (to a stable p-Value).

Risk factors for CVE

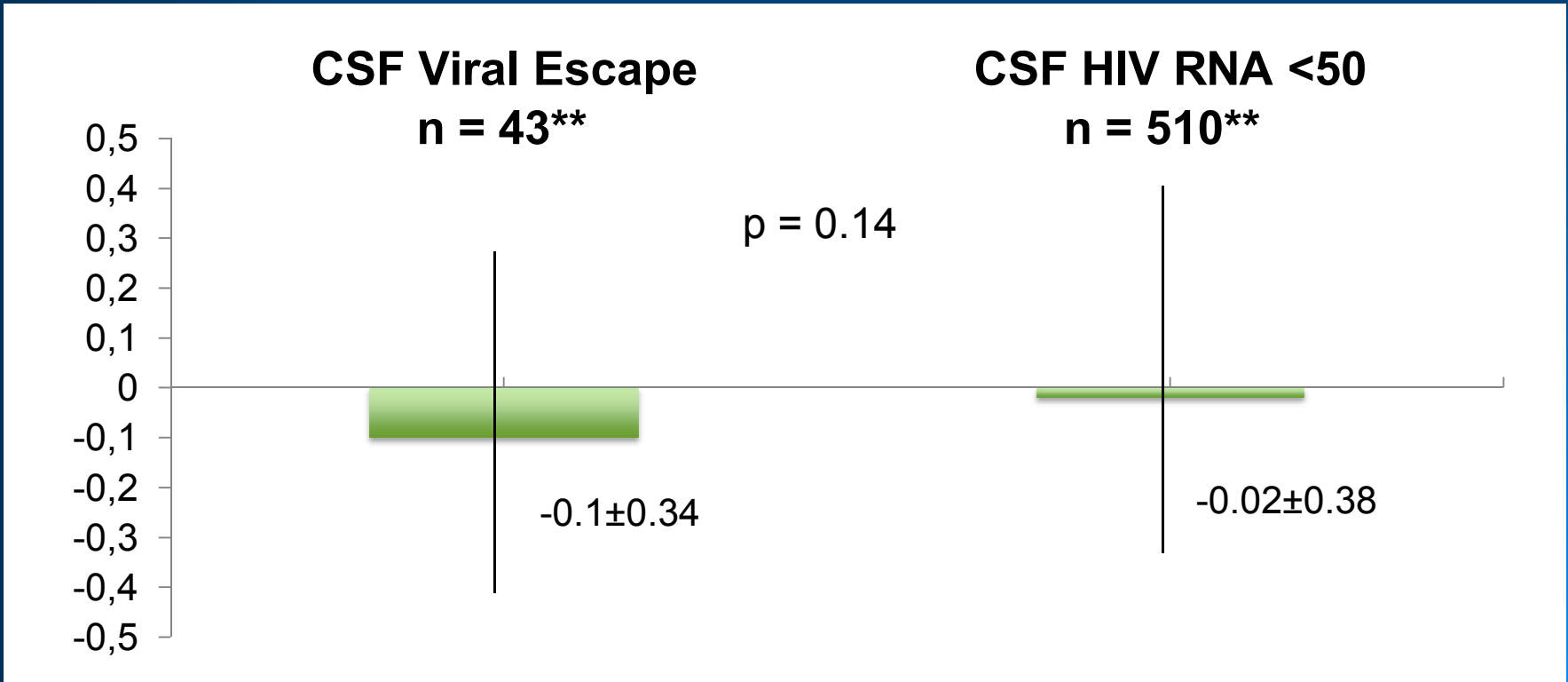
Multivariable mixed models

Variable	Risk direction	p Value
Plasma HIV RNA (0-50 cop/mL)	Higher	0.03
Protease inhibitor based ART	Present	0.02
CSF Pleocytosis (>5 WBC)	Higher	< 0.01

Odds ratios (95% CI) for factors associated with CVE



Neurocognitive evolution (by GDS change)*



** Individuals with previous neurocognitive assessments were excluded.

* *Carey CL et al.* J Clin Exp Neuropsychol. 2004;26(3):307-19.

Conclusions

- Incidence of CSF viral escape is low and the condition generally transient.
- Patients using protease inhibitor based ART and with low level viremia in plasma may be at risk for CVE.
- CSF viral escape was associated with CSF pleocytosis. Causality cannot be established based on our results.
- We were not able to demonstrate that CSF viral escape is associated with a worse neurocognitive performance.

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