



**9th**

**International  
Symposium on  
Neuropsychiatry & HIV**

**New Advanced EEG Technique  
(LORETA – Low Resolution Electromagnetic Tomography)  
to Early Detect and Monitor HIV Brain Damage**

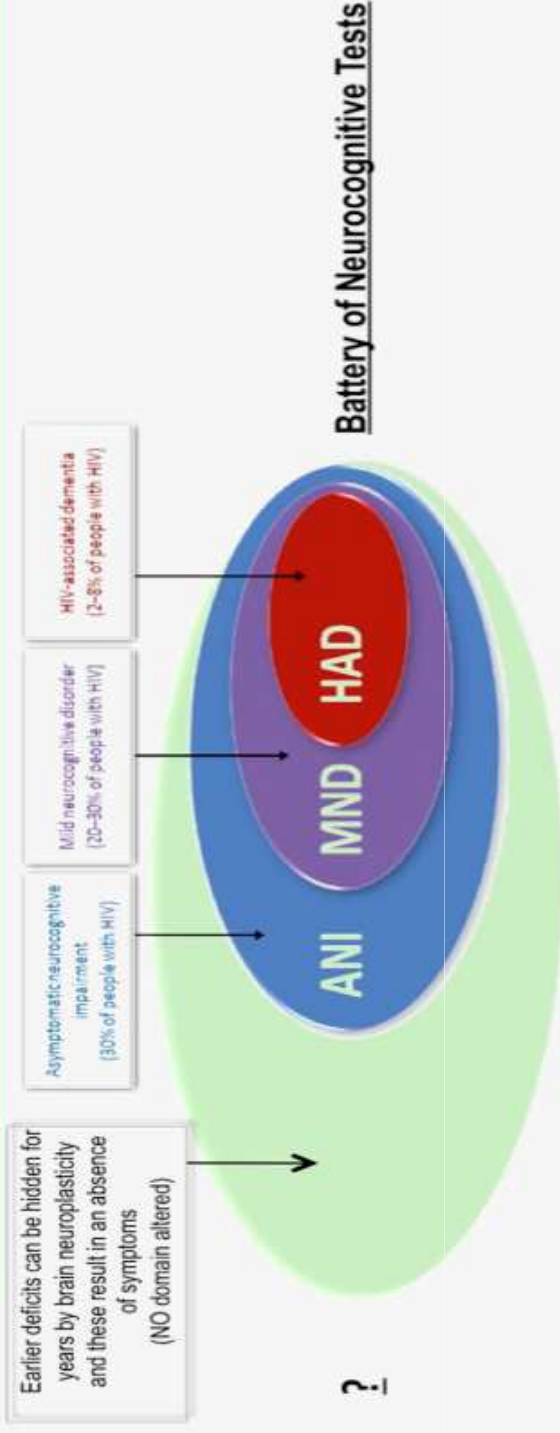
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# BACKGROUND

What about neurocognitive damage in asymptomatic naïve HIV?

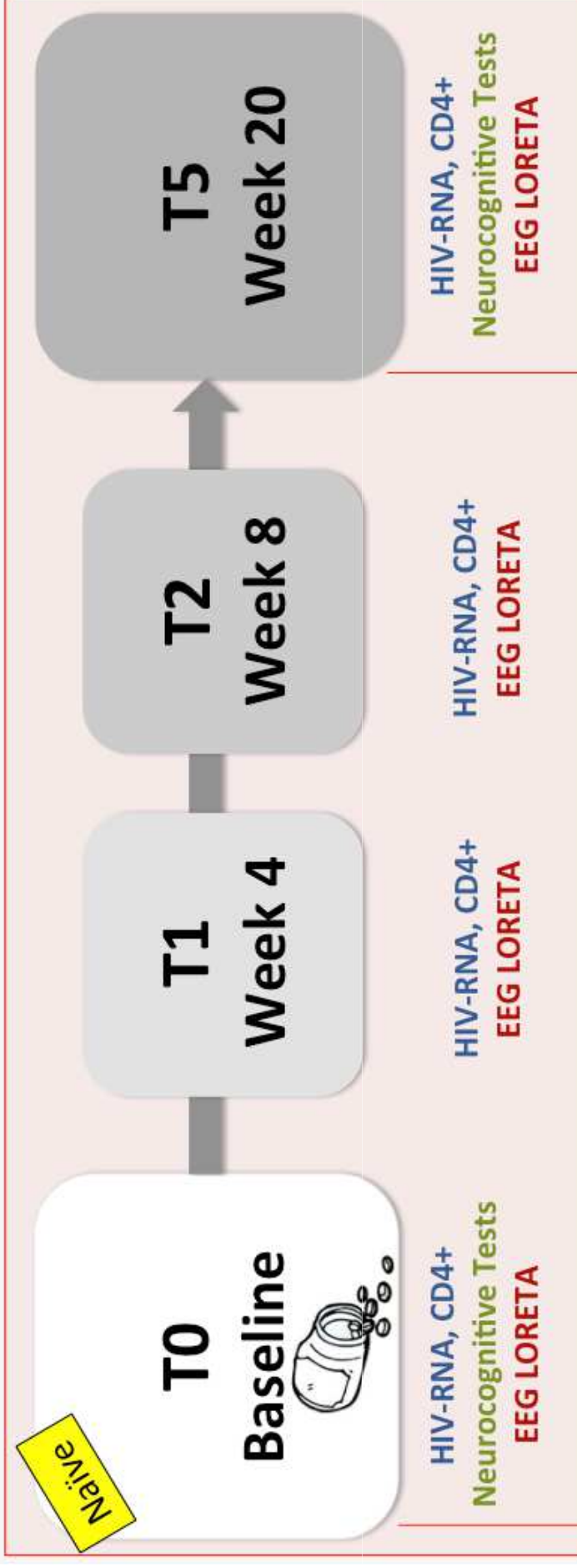


- EEG Cognitive impairment pattern:
  - pathological increase of EEG rhythms at frequencies <4 Hz (*delta*)
  - pathological decrease of dominant rhythms between 8-12 Hz (*alpha*).

- **The aim of the study is:**
  - to demonstrate that advanced EEG techniques, LORETA (Low Resolution Electromagnetic Tomography), unveil abnormalities of resting state rhythms in experienced and naïve HIV groups and their recovery after ART (compared to healthy group) .
  - to elaborate a Z-score index to identify abnormalities in single naïve HIV.

# METHODOLOGY

Study Design – Naïve HIV Subjects



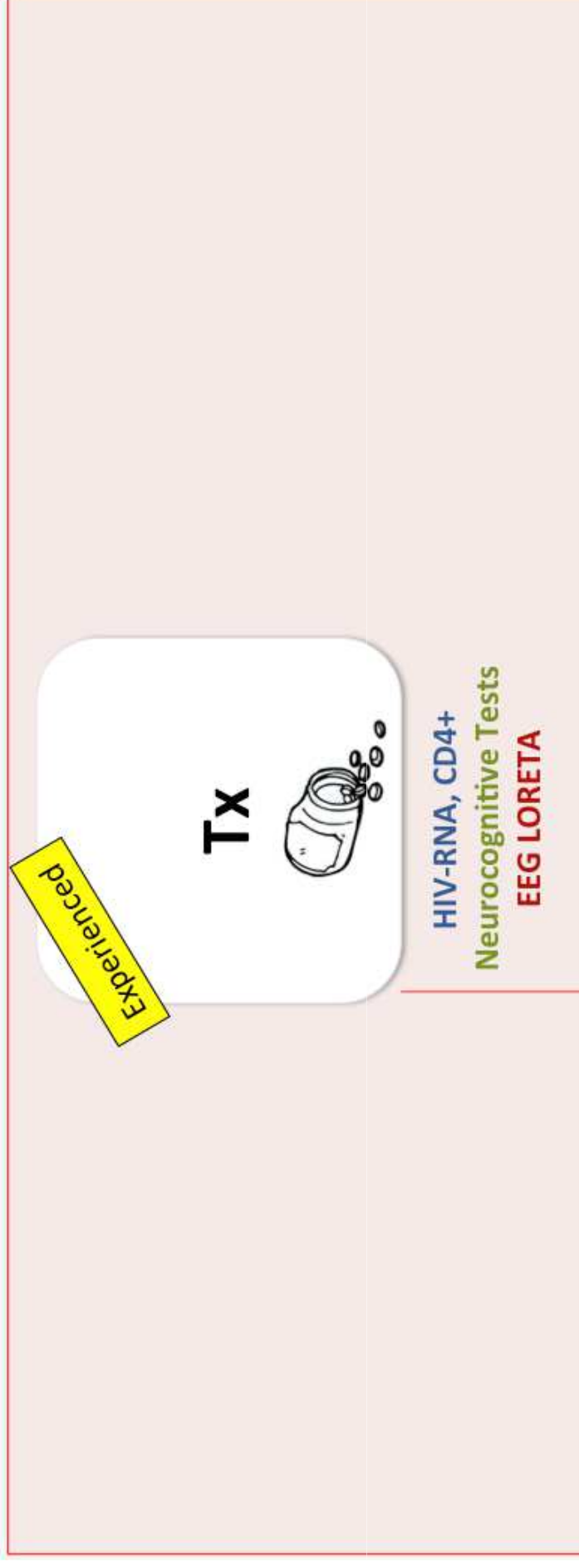
→ • **Cortical sources of resting-state EEG rhythms are abnormal in naïve HIV subjects**, Clinical Neurophysiology, 2012

→ • **Abnormal cortical sources of resting state electroencephalographic rhythms in single treatment-naïve HIV individuals: a statistical Z-score**, Clinical Neurophysiology, 2016

→ • **Antiretroviral therapy effects on sources of cortical rhythms in HIV subjects – Responders vs Mild Responders**, Clinical Neurophysiology, 2014

# METHODOLOGY

Study Design – Experienced HIV Subjects



- *Cortical sources of resting-state EEG rhythms in “experienced” HIV subjects under antiretroviral therapy, Clinical Neurophysiology, 2014*



# METHODOLOGY



- INCLUSION CRITERIA**
- HIV infection
  - MMSE >25
  - good knowledge of written and spoken Italian language
  - informed consent

**EXCLUSION CRITERIA**

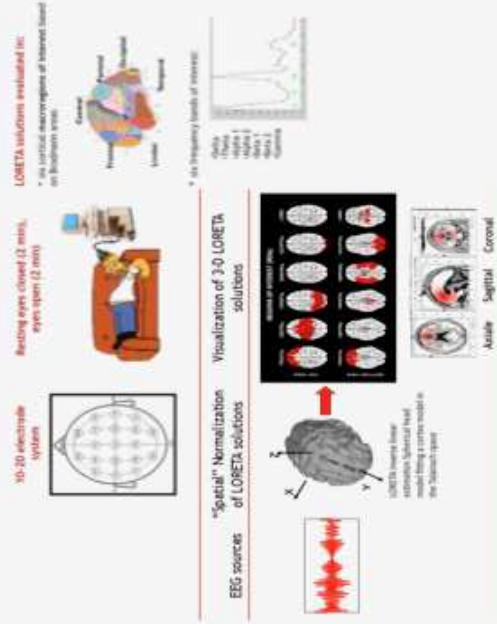
- pregnancy
- seizures
- mental retardation
- neurosurgery
- history of head injury with loss of consciousness for greater than 10 min
- acute illness
- intelligent quotient (IQ) score lower than 70
- major neurological and psychiatric disorders (schizophrenia or bipolar disorder as defined by Diagnostic and Statistical Manual of Mental Disorders fourth edition, DSM-IV)
- medical disorders such as hypertension, chronic obstructive pulmonary disease, Type 1 diabetes, cirrhosis, hepatic encephalopathy, ocular disorders, etc.
- positive urine toxicology or breathalyzer tests or recent (past year) dependence upon alcohol, cocaine or opiates
- HBV/HCV coinfection
- NeuroAIDS
- Brain cancer

- Routine laboratory exams
- Treponema screening (RPR/VDRL, TPHA)
- EBV, CMV, TOXO serology
- HBC/HCV screening
- Urine toxicology screening
- HIV-RNA (copies/ml)
- CD4+ count (cells/uL)



**LORETA**

**Low Resolution Electromagnetic Tomography**



EEG sources of LORETA solutions

"Spatial" Normalization

Visualization of 3-D LORETA solutions

LORETA inverse filter

Resting eyes closed (2 min), eyes open (2 min)

10-20 electrode system

LORETA solutions evaluated in:
 

- as cortical neuroimages of interest based on frequency band
- as frequency bands of interest

Assemble Sagittal Coronal

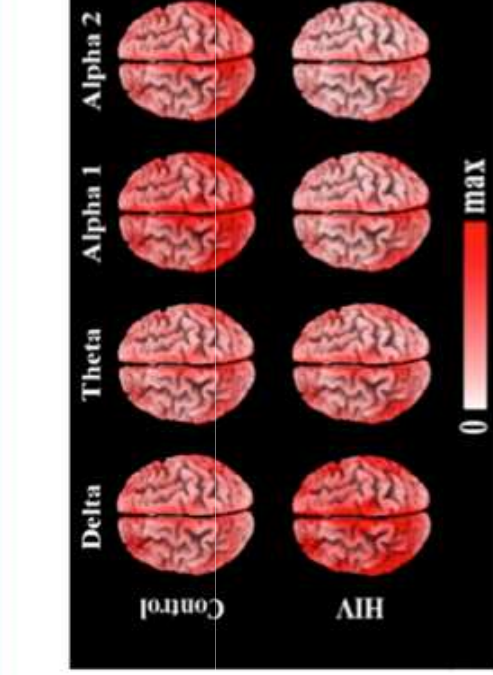
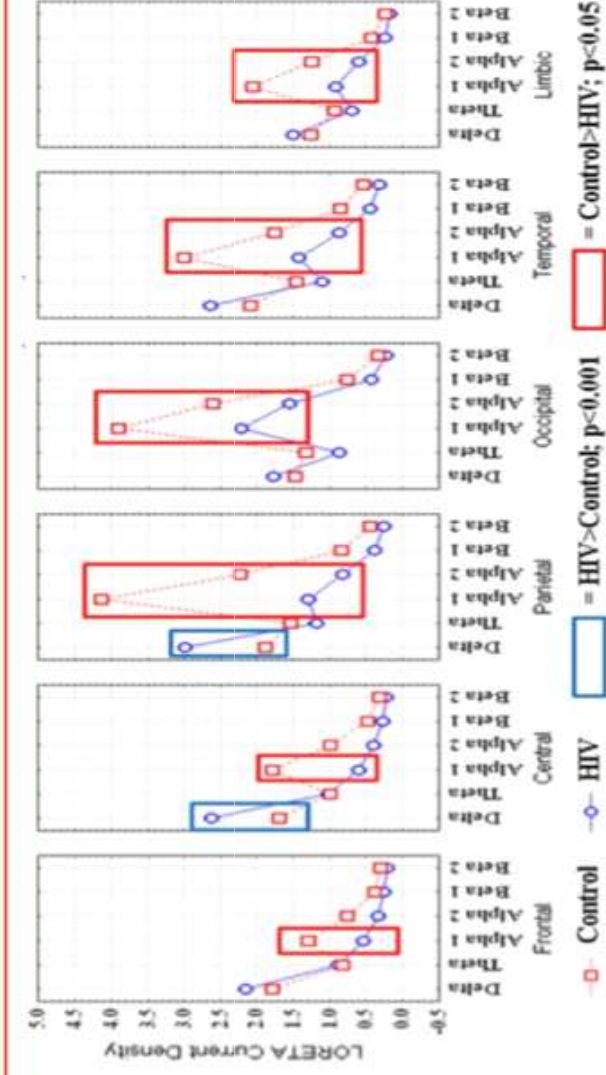
**Battery of neurocognitive Test**

- Memory
- Language
- Attention
- Executive Function
- Visual-Spatial
- MMSE

# RESULTS (1)

LORETA abnormalities: Naïve HIV > Healthy Control Group

Central and parietal delta sources showed a higher amplitude in the HIV group at baseline than in the control healthy group, the opposite was true for alpha.

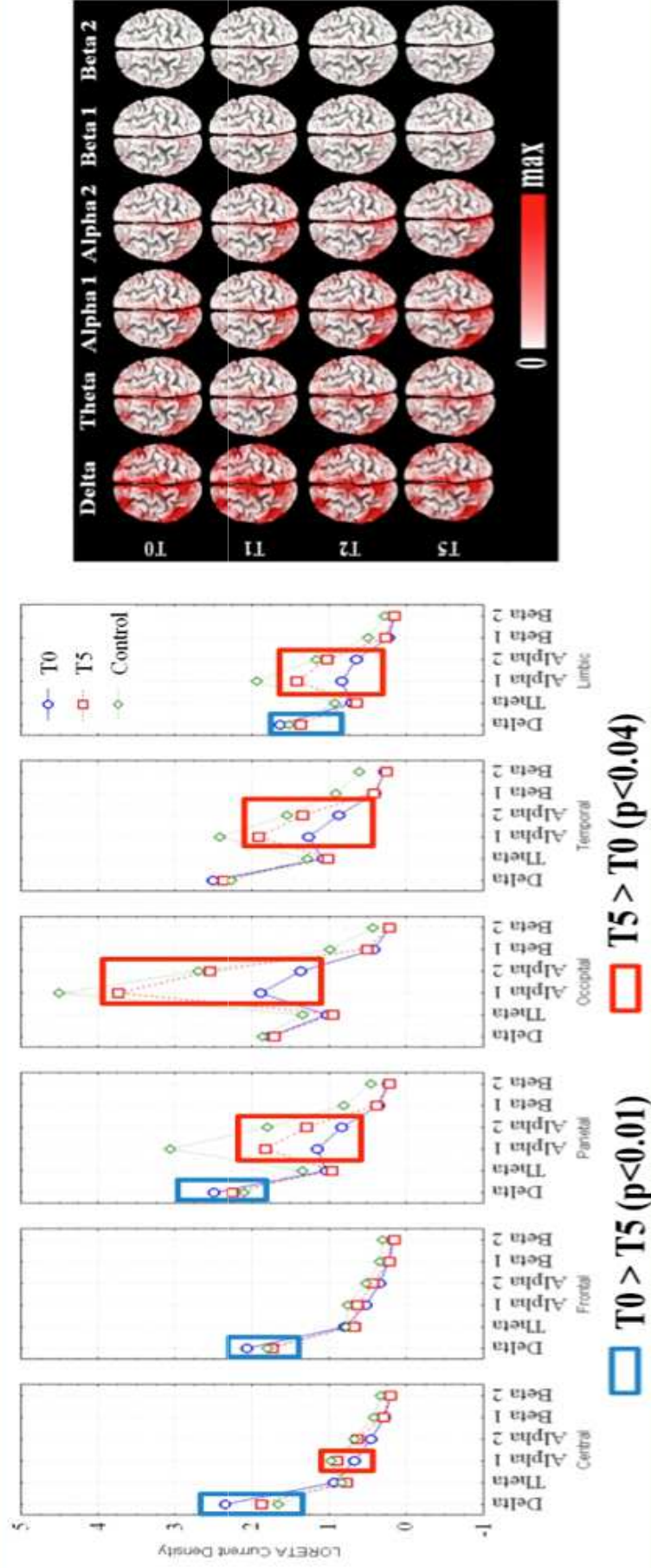


refers to the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns Control > HIV ( $p < 0.05$ ).  
 refers to the cortical regions and frequency bands in which LORETA solutions presented statistically significant LORETA patterns HIV > Control ( $p < 0.001$ ).

# RESULTS (2)

## LORETA abnormalities: Improvement during ART (T0-T5)

Compared to the baseline, the treated subjects were characterized by a recovery of the EEG rhythms in lower central and parietal delta sources and higher parietal, occipital and temporal alpha1 sources.

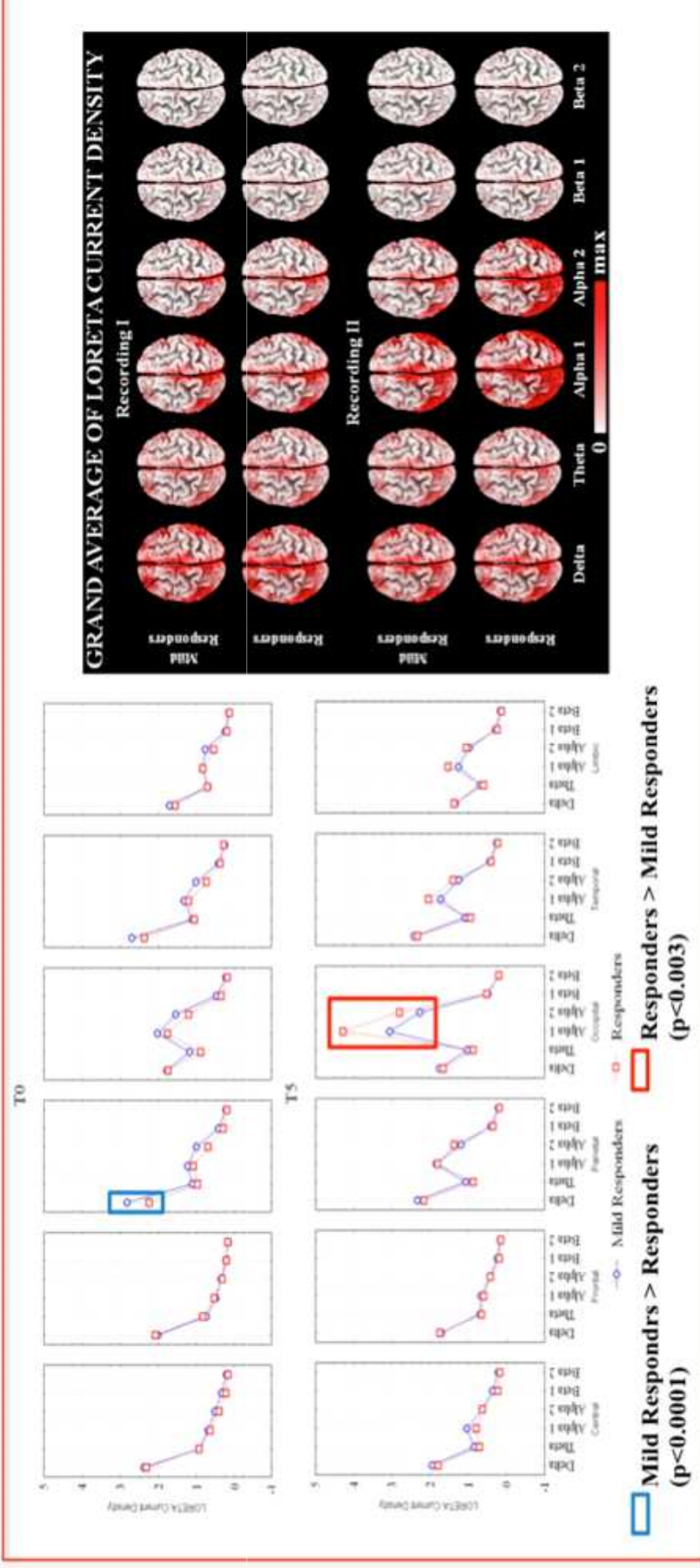


# RESULTS (3)

## LORETA abnormalities improvement at T5 depending on CD4+ count

The HIV subjects were divided in two sub-groups on the basis of the effect of ART on CD4 count at T5:

- **Mild Responders:** those showing a CD4 count difference between T5 and T0 <100 cells/uL
- **Responders:** those showing a CD4 count difference between T5 and T0 >100 cells/uL



Parietal DELTA T0: Mild Responders>Responders  
Occipital APLHA T5: Responders>Mild Responders

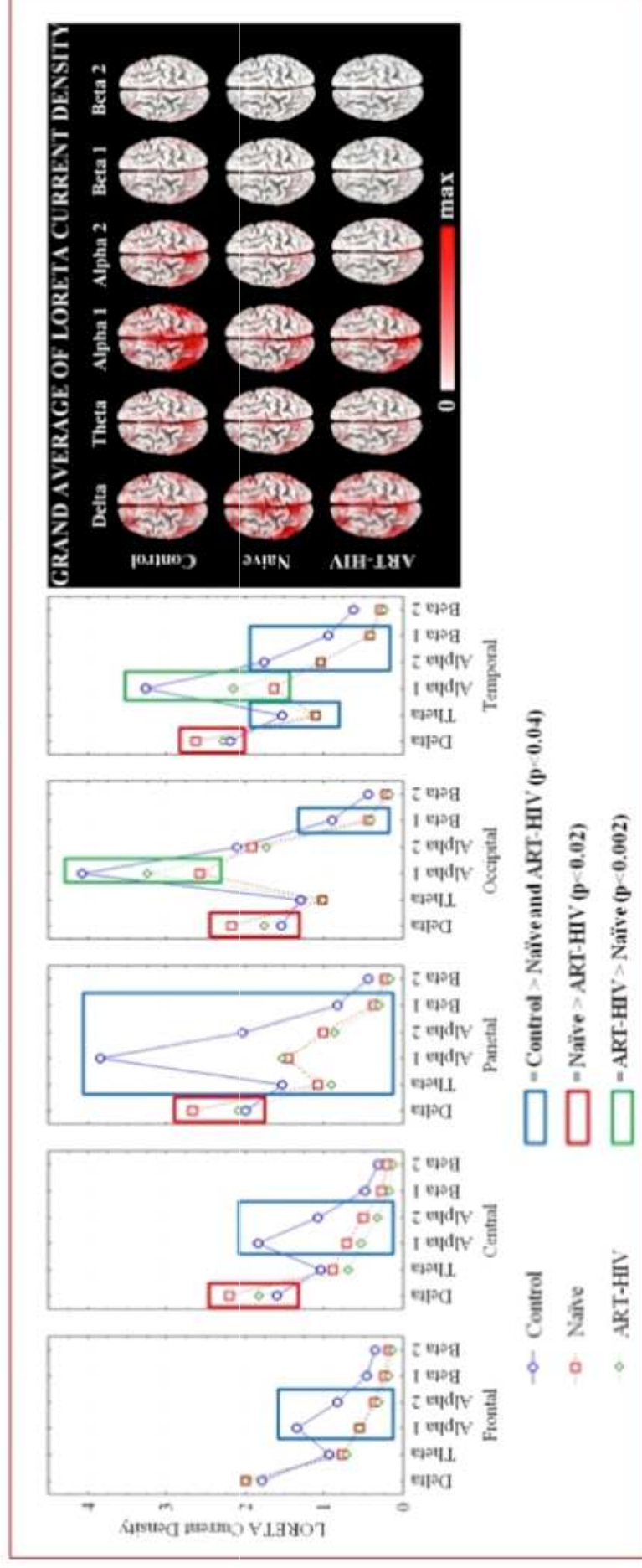


# RESULTS (4)

EEG sources are abnormal in Experienced HIV, but not so pronounced compared to naïve

Experienced abnormalities are less pronounced compared to naïve patients, but they never fully reach the performance of the control group.

## ::: ART-HIV vs naïve vs Control :::



Alpha 1 (central, occipital and temporal)  
 Alpha 2 widespread  
 Beta 1 (parietal, occipital, temporal)  
 Beta 2 (temporal)  
 → Lower amplitude in the Experienced compared to Control Healthy Group  
**(Control > Experienced)**

Alpha 1 (occipital and temporal) → higher amplitude in Experienced compared to naïve HIV (**Experienced > Naïve**)  
 Delta widespread → lower amplitude in the Experienced compared to naïve **Naïve > Experienced**

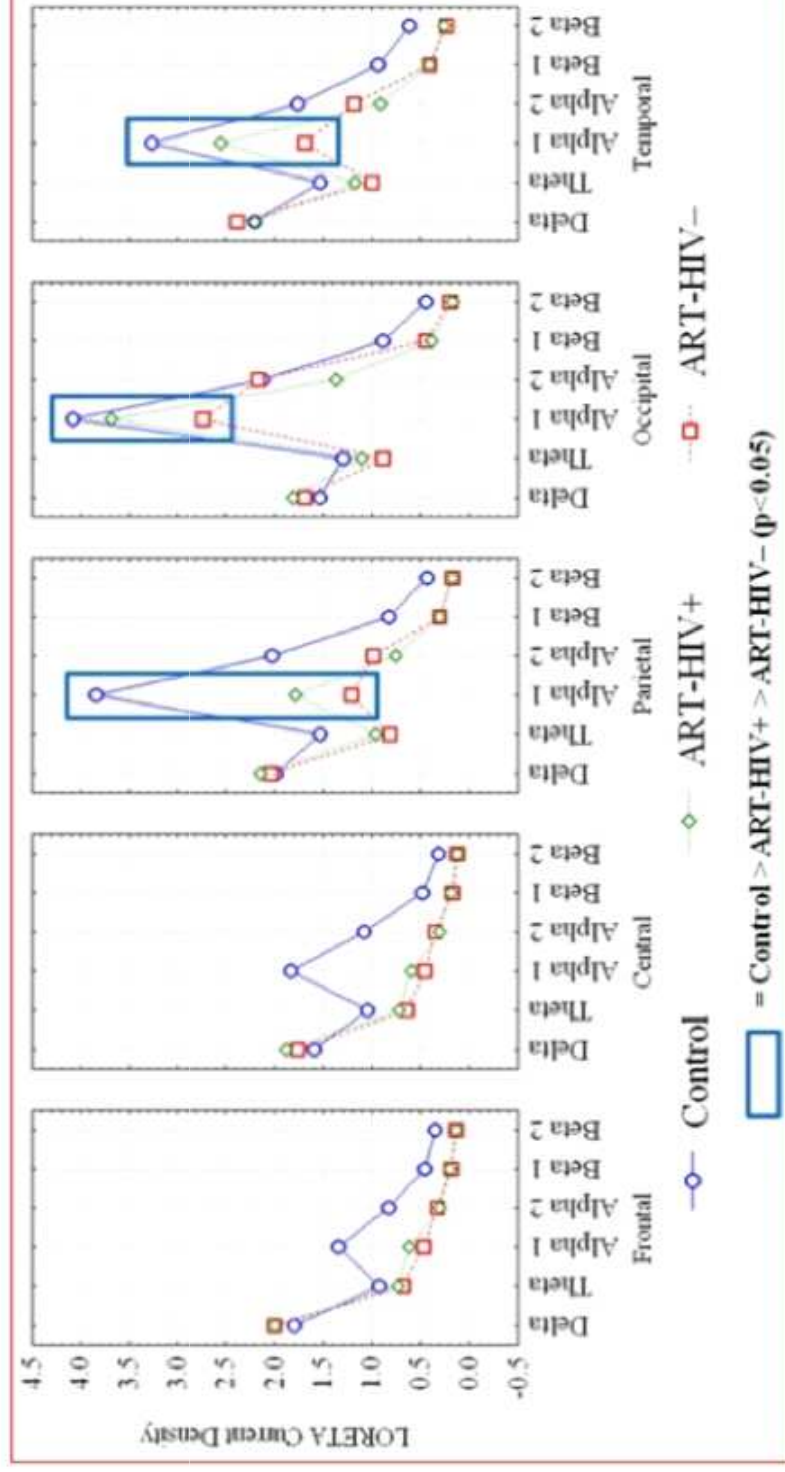
# RESULTS (5)

Experienced HIV: abnormalities more pronounced in HIV patients with CD4<500

ART-HIV- → CD4 <500 cells/uL

ART-HIV+ → CD4 >500 cells/uL

## ∴ ART-HIV+ vs ART-HIV- vs Control ∴∴



# RESULTS (6)

Z-score computation

$$z = \frac{x - \mu}{\sigma}$$

# RESULTS (6)

Z-score computation

EEG variable of interest in a given  
single treatment naïve HIV  
subject

$$z = \frac{x - \mu}{\sigma}$$

# RESULTS (6)

Z-score computation

EEG variable of interest in a given  
single treatment naïve HIV  
subject

Mean of the EEG variable  
of interest in a reference  
group of healthy subjects

$$z = \frac{x - \mu}{\sigma}$$
The diagram shows the z-score formula  $z = \frac{x - \mu}{\sigma}$ . A red circle highlights the variable  $x$ , with a red arrow pointing from it to the text 'EEG variable of interest in a given single treatment naïve HIV subject'. A green circle highlights the mean  $\mu$ , with a green arrow pointing from it to the text 'Mean of the EEG variable of interest in a reference group of healthy subjects'. The standard deviation  $\sigma$  is in the denominator.

# RESULTS (6)

Z-score computation

EEG variable of interest in a given  
single treatment naïve HIV  
subject

Mean of the EEG variable  
of interest in a reference  
group of healthy subjects

$$z = \frac{x - \mu}{\sigma}$$

Standard deviation of the EEG  
variable of interest in that  
group

# RESULTS (6)

Z-score computation

EEG variable of interest in a given  
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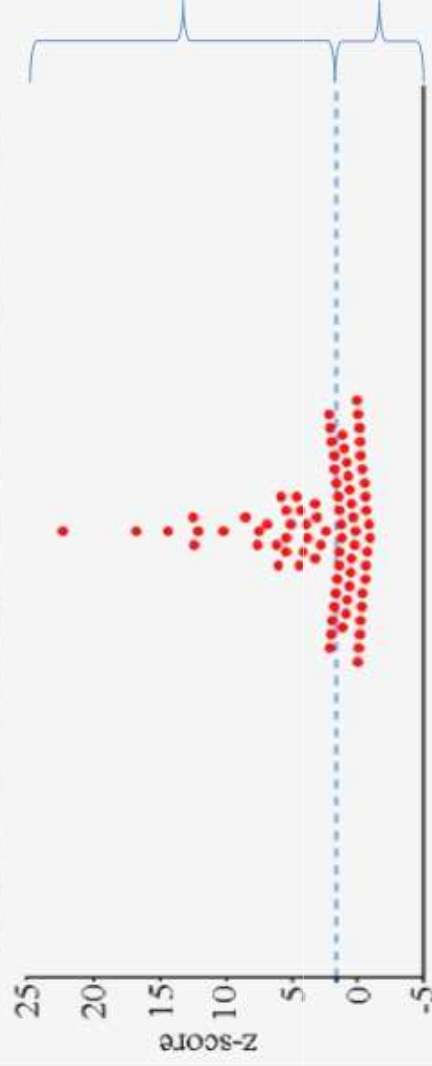
Variable of interest: parietal DELTA/ALPHA3

# RESULTS (7)

Z-score computation

82 Naive

## Z-SCORE OF PARIETAL DELTA/ALPHA3 NORMALIZED LORETA CURRENT DENSITY



**EEG+ :** naive subjects subgroup with a statistically **abnormal** EEG marker

**EEG- :** naive subjects subgroup with a statistically **normal** EEG marker

----- Significant level of z-score ( $p < 0.05$ , one tailed)

Means ( $\pm$ SE) of the personal and clinical features of two sub-groups of EEG- and EEG+ naive subjects. The two subgroups were formed to be matched for age and education from the whole HIV cohort.

	EEG-	EEG+	P values
N	40	36	
Age (years)	38.6 ( $\pm 1.7$ SE)	40.9 ( $\pm 1.5$ SE)	n.s.
Education (years)	14.4 ( $\pm 0.5$ SE)	13.5 ( $\pm 0.5$ SE)	n.s.
MMSE score	29.1 ( $\pm 0.3$ SE)	27.4 ( $\pm 0.5$ SE)	$p = 0.001$
IAF (Hz)	10.3 ( $\pm 0.1$ SE)	10.1 ( $\pm 0.1$ SE)	n.s.
CD4 count (cells/ $\mu$ l)	498.6 ( $\pm 42.6$ SE)	366.3 ( $\pm 42.4$ SE)	$p = 0.02$
VL (copies/ml)	83132.8 ( $\pm 18431.0$ SE)	240777.5 ( $\pm 88044.6$ SE)	$p = 0.03$



# CONCLUSIONS (1)

- Resting-state EEG rhythms show peculiar frequency/spatial features in naive HIV subjects with no apparent symptom of neurocognitive impairment according to the classifications of HAND compared to the control group:
  - **pathological increase of central and parietal delta sources**
  - **pathological decrease of widespread alpha sources**
- The above LORETA abnormalities tend to **improve once you start antiretroviral therapy**.
- **Also experienced subjects show EEG abnormalities** compared to healthy subjects, **but less marked than those of naïve**, suggesting a **recovery of the brain activity even if partial as a result of long term HAART**.
  - These abnormalities are more pronounced in those ones with CD4<500 cells/uL compared to those ones with CD4>500 cells/uL.
- There was a **correlation between these rhythms and immune activity**, as revealed by CD4 count in HIV subjects supporting the theory of immune-mediated mechanism of HIV neurocognitive damage.
- **Z-score** of EEG marker (Delta/Alpha3) is a useful statistical indicator which **detects abnormal EEG variables of interest in about 50% of naïve HIV subjects** compared to the healthy control subjects. Are these subjects at risk of long-term cognitive impairment?

## CONCLUSIONS (2)

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- Compared to the EEG- subjects , EEG+ subjects presented **Abnormal EEG marker, lower cognitive status, lower CD4+ count, higher Viral Load.**
- These abnormalities may provide a statistical index of “neurophysiological frailty” (less functional brain reserve) useful to enrich the instrumental assessment of the effect of HIV on brain in subjects at risk of cognitive deficits

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