Abstract #438

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Central Nervous System (CNS) Safety of a *Kick&Kill* Strategy with Romidepsin

Sara Carrillo-Molina[1], Ignacio Martínez-Zalacaín[2], Beatriz Mothe[3], José Moltó[1], Christian Manzardo[4], Jose M. Miró[4], Pep Coll[3], Michael Meulbroek[5], Anna Prats[1], Maite Garolera[6], Tomas Hanke[7], Christian Brander[3], Carles Soriano-Mas[2], **Jose A. Muñoz-Moreno[1]**; on behalf of the ***BCN02-Neuro Study Group***

[1] Fundació Lluita contra la SIDA (FLS), Badalona, Catalonia, Spain / [2] Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Catalonia, Spain / [3] Institut de Recerca de la SIDA IrsiCaixa, Badalona, Catalonia, Spain
[4] Hospital Clínic-IDIBAPS-University of Barcelona, Barcelona, Catalonia, Spain / [5] BCN-Checkpoint, Barcelona, Catalonia, Spain / [6] Consorci Sanitari Hospital de Terrassa (CST), Terrassa, Catalonia, Spain / [7] The Jenner Institute, Oxford, UK

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BACKGROUND

- Research on compounds tested in new *kick&kill* strategies for HIV eradication should cover different clinical safety levels, including the central nervous system (CNS). That necessity becomes more important considering that reactivation of latent reservoir is aimed to be reached, and, additionally, that antiretroviral therapy cessation is a requirement of HIV eradication strategies currently.
- Romidepsin (RMD) is a potent histone deacetylase inhibitor (HDACI) that has shown efficacy on latent HIV reactivation in in vitro and in vivo studies. However, its CNS effects in HIV+ individuals are unknown to date.
- We studied the CNS safety of an HIV eradication strategy including the use of RMD in the setting of the BCN02-ROMI study, a trial that assessed the safety and effect of a *MVA.HIVconsv* vaccine in combination with RMD in early-treated HIV-infected patients.

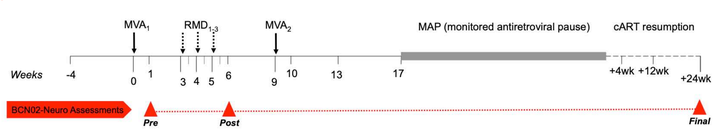
METHODS

Design and Study Population
The BCN02-Neuro substudy was an observational prospective study developed as a substudy of the BCN02-ROMI trial, which was a pilot, multicenter, single-arm study aimed at assessing the safety and effect of a combined HIV eradication strategy using an immunogenic vaccine (*MVA.HIVconsv*) in combination with RMD (3 weekly doses of 5 mg/m^2), continued by a monitored antiretroviral pause (MAP), and posterior 24-week combination antiretroviral therapy (cART) resumption (*Clinicaltrials.gov: NCT02616874*). cART resumption criterion during MAP was to present 2 consecutive plasma viral load >2,000 cop/mL. The trial was carried out in in Barcelona, Catalonia, Spain.
Participants included in the main study were early-treated HIV-infected individuals virologically suppressed for at least 3 years when recruited into the BCN02-ROMI trial. All participants (n=15) were proposed to participate in the BCN02-Neuro substudy.
Study assessments were performed before and after the use of RDM (*Pre* and *Post* assessments) and after the application of the complete eradication strategy (*Final* assessment). ***Figure 1*** shows the study design.
A group of HIV-infected early-treated individuals with clinically matched characteristics but not vaccinated was recruited additionally as control and performed the same assessments in equivalent timepoints to control expected practice effect resulting from cognitive assessments.

Dimensions and Variables
Cognitive functioning was assessed by a neuropsychological battery that covered 6 cognitive domains (1 measure per domain) and provided an standardized global composite score (NPZ-6).
Functional outcomes were assessed in terms of CNS-related adverse events (FDA-based symptom checklist), daily living functioning (assessment of daily living activities), emotional status (depression, anxiety, and stress symptoms), and quality of life (global self-reported dimension).
Neuroimaging data were collected in a 3 Tesla Magnetic Resonance Imaging (MRI) Siemens Verio scanner. A high resolution T1-weighted 3-D structural image in the axial plane was obtained for each participant in the 3 different timepoints.

Study Endpoints
Primary study endpoint was change in global cognitive functioning (NPZ-6) from *Pre* to *Final* assessment. Secondary endpoints were change in functional and neuroimaging outcomes in the same timeframe.
Data analyses involved Chi square, *t*, and ANOVA tests. A repeated-measure ANOVA was applied to evaluate between-group differences. Neuroimaging data were pre-processed and analyzed using MATLAB 7.14 and SPM12.

Figure 1. *Study design.*



Abbreviations: cART, Combination Antiretroviral Therapy, MVA, MVA.HIVconsv vaccine; RMD, Romidepsin.

RESULTS (I)

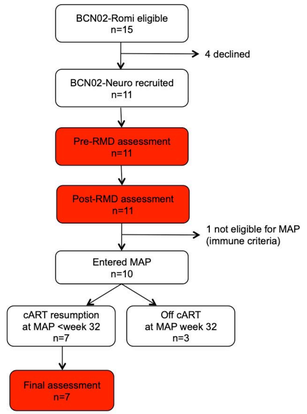
Sample Characteristics
A total of 11 individuals from the main study accepted to participate. Ten patients were recruited as controls. Study participants were mostly men (95%), getting infected having sex with other men (95%), with a mean (SD) age of 40 (9) years. All demographic and clinical variables were balanced between groups. ***Table 1*** shows the characteristics of the study sample.
In the Intervention group, all participants underwent *Pre* and *Post* assessments. After *Post* assessment, 1 patient did not fulfill immune criteria to interrupt therapy and 10 entered the MAP stage. Out of them, 3 maintained virological control without requirement of cART resumption and 7 reinitiated therapy. MAP mean (min-max) time was 3.9 (2.3-5.3) weeks. ***Figure 2*** shows the study flowchart in the Intervention group.

Table 1. *Characteristics of the study sample.*

	Intervention (n=11)	Control (n=10)	*p* Value
Age, years	42 (6)	38 (11)	0.322
Male, n (%)	10 (91)	10 (100)	0.247
Years of education	13 (3)	14 (2)	0.642
Route of transmission, n (%)			
MSM	10 (91)	10 (100)	0.247
Heterosexual	1 (9)	0 (0)	
On ARV therapy	11 (100)	10 (100)	-
Weeks on current ARV regimen	155 (8)	164 (13)	0.060
CD4 cell count	922 (364)	781 (392)	0.404
CD8 cell count	692 (338)	647 (183)	0.738
CD4/CD8 ratio	1.39 (0.31)	1.35 (0.64)	0.853
Undetectable plasma viral load, n (%)	11 (100)	10 (100)	-
Confounding comorbidities, n (%) [a]	0 (0)	1 (10%)	0.214
Cognitive complaints, n (%) [b]	5 (45)	1 (10)	0.062
NPZ-6	0.28 (0.64)	0.28 (0.63)	0.982

Values are mean (SD), except when specified. [a] According to Frascati criteria (2007). [b] According to EACS proposal (2018).

Figure 2. *Flowchart in the Intervention group.*



Cognitive and Functional Outcomes
Baseline cognitive functioning was comparable between groups, as well as functional outcomes. Cognitive change from *Pre* to *Post* assessment was equivalent between groups (mean NPZ-6, SD): 0.14 (0.31) vs 0.03 (0.32); p=0.45. Intra-group changes also did not show differences. Change in functional outcomes was not significant for any dimension, again considering both between-group and intra-group comparisons. ***Figures 3a, 3b, 3c,*** and ***3d*** show some of the main cognitive and functional results from *Pre* to *Post* assessment.

Fig 3a. *Pre-Post NPZ-6.*

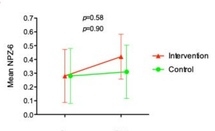


Fig 3b. *Pre-Post CNS symptoms.*

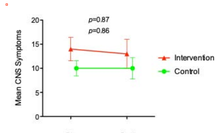


Fig 3c. *Pre-Post impaired daily areas.*

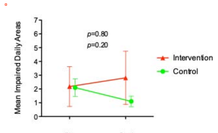


Fig 3d. *Pre-Post quality of life.*

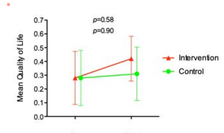


Fig 4a. *Pre-Final NPZ-6.*

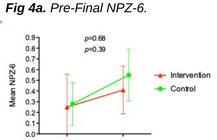


Fig 4b. *Pre-Final CNS symptoms.*

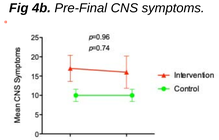


Fig 4c. *Pre-Final impaired daily areas.*

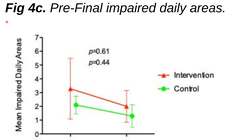
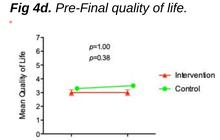


Fig 4d. *Pre-Final quality of life.*



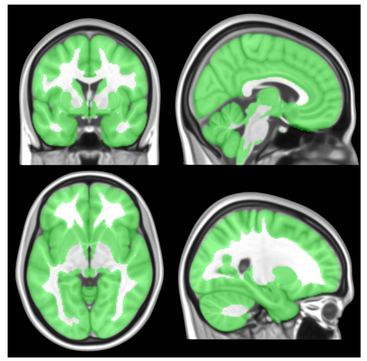
CNS symptoms assessed by a FDA-based checklist of CNS symptoms. Daily living areas assessed by an adapted version of the IADL scale. Quality of life assessed by an adapted version of the MOS-HIV questionnaire. P values result from intra-group repeated-measure ANOVA: upper values indicate Intervention Group intra-group comparison, values below indicate Control Group intra-group comparison.

RESULTS (II)

Regarding *Final* assessment, cognitive differences were not found between groups or intra groups at the end of the study. With respect to functional outcomes, all scores were also similar. ***Figures 4a, 4b, 4c,*** and ***4d*** show some of the main cognitive and functional results from *Pre* to *Final* assessment. Study variables in the 3 participants who remained off cART were collected and analyzed at a comparable timepoint. No differences were observed in cognitive or functional outcomes intra group or compared with the Intervention and Control groups.

Neuroimaging Outcomes
No differences were found when neuroimaging analyses applied whole-brain voxel-wise comparisons, either at *Post* or *Final* assessments. All brain regions studied, including subcortical areas involving cortico-striate circuits (i.e., caudate nucleus, ventral striatum/nucleus accumbens, putamen, pallidum, and thalamus) and frontal cortex areas (i.e., dorsomedial, dorsolateral, cingulate, ventromedial, medial orbitofrontal, and lateral orbitofrontal cortex), showed no longitudinally volumetric or structural discrepancies between the Intervention and Control groups at any of the study timepoints. ***Figure 5*** represents a graphical summary of the cerebral areas included in the neuroimaging analyses.

Figure 5. *Brain areas covered in the neuroimaging analyses.*



CONCLUSIONS

- ✓ No detrimental effects on cognitive status, functional outcomes, and neuroimaging parameters were observed after the use of 3 weekly infusions of RMD (5 mg/m^2) in the setting of a *kick&kill* eradication strategy for HIV cure.
- ✓ After a short MAP with plasma viral load threshold criteria of >2,000 cop/mL and 24 weeks follow-up of cART resumption, no negative contributing effects were observed in cognitive, functional, or neuroimaging outcomes.
- ✓ The HIV cure approach investigated in this small trial, including the use of a *MVA.HIVconsv* vaccine, administration of RMD, cART interruption, and posterior 24-week therapy reinitiation, appears to be safe for the CNS.

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