Ignacio Perez-Valero | Pº Castellana 261 | Madrid 28034, Spain | +34917277099 | ignacio.perez@salud.madrid.org

NEUROCOGNITIVE AND VOLUMETRIC CHANGES AFTER 24 WEEKS OF DTG/3TC/ABC DISCONTINUATION

1901

I. Perez Valero[1], A. Cabello[2], P. Ryan[3], S. de la Fuente Moral[4], I. Santos[5], M.J. Vivancos[6], M. Gorgolas[2], G. Cuevas[3], A. Díaz De Santiago[4], L. García-Fraile[5], J.I. Bernardino[1], E. Valencia[1], M. Montes[1], G. Rua[1], M. Yllescas[7], A. González[1]

1. Hospital Universitario La Paz, 2. Hospital Fundación Jimenez Diaz, 3. Hospital Infanta Leonor, 4. Hospital Puerta de Hierro, 5. Hospital de la Princesa, 6. Hospital Universitario Ramón y Cajal, 7. Fundación SEIMC/GESIDA. All from Madrid, Spain

BACKGROUND

To determine in a clinical trial designed to assess if neuropsychiatric adverse events (AEs) observed in some patients after starting dolutegravir (DTG) are due to DTG or to another concomitant conditions.

METHODS

Randomized (1:1), open-label, multisite clinical trial designed to assess reversibility of neuropsychiatric adverse events and patient-reported symptoms after switching DTG/lamivudine/abacavir (DTG/3TC/ABC) to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (ELV/COBI/FTC/TAF).

Study design: Reported in the figure.

Procedures: Headache, insomnia, abnormal dreams, dizziness, fatigue, lack of concentration, nervousness, anxiety, depression and Suicidality, the most common neuropsychiatric AEs reported in DTG/3TC/ABC label and in local clinical experience were documented at each visit and graded in a manner based on the AIDS Clinical Trials Group (ACTG) Division of AIDS scale (2014). To assess the effect of switching DTG/3TC/ABC to ELV/COBI/FTC/TAF on these EAs, a score (DREAM) resulting of adding the grade of these AEs was calculated. In addition to that score, each participant also completed the Hospital Anxiety & Depression Scale (HADs) and the Pittsburgh Sleep Quality Index (PSQI) questionnaires.

Statistics: Raw results on DREAM, HADs and PSQI scores were normalized (0-100) and then changes from baseline were compared at each visit using t-test, McNemar test or generalized estimating equations (for longitudinal linear models). We analyzed differences at week 4 between study arms (primary objective) and changes in the DREAM, HADs and PSQI scores after switching to ELV/COBI/FTC/TAF at weeks 4, 12 and 24 week (secondary objectives).

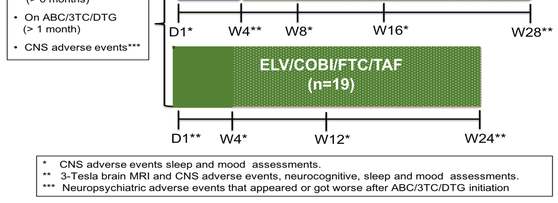
BASELINE CHARACTERISTICS

	DTG/3TC/ABC N (19)	ELV/COBI/FTC/TAF N (19)
Age, mean (SD)	40.2 (10.1)	45.6 (8.9)
Gender: Male, n (%)	19 (100)	18 (94.7)
Ethnicity: Caucasian, n (%)	16 (84.2)	18 (94.7)
Illicit drug use, mean (SD)	6 (31.6)	5 (26.3)
Neuropsychiatric comorbidities, n (%)	4 (21.1)	5 (26.3)
Years since HIV diagnosis, mean (SD)	9.4 (9.2)	9 (7.9)
Years of HIV-undetectability, mean (SD)	4.5 (4.2)	5.6 (4.9)
Months on DTG/3TC/ABC, mean (SD)	15.5 (8.8)	19.3 (8.1)
CD4 Nadir, mean (SD)	416 (218)	413 (225.5)
Previous AIDS diagnosis, mean (SD)	1 (5.2)	4 (21.1)
Current CD4 cell count, mean (SD)	772 (402.6)	748.3 (317.6)
Cognitive function: GDS, mean (SD)	0.2 (0.3)	0.4 (0.5)
Neurocognitive impairment, n (%)	5 (26.3)	5 (26.3)
Positive anxiety screen: HADs, n (%)	12 (63.2)	13 (68.4)
Positive Depression screen: HADs, n (%)	6 (31.6)	8 (42.1)
Positive Insomnia screen: PSIQ, n (%)	17 (89.5)	17 (89.5)

* No significant differences were observed between study groups

Our trial confirms that most of the neuropsychiatric symptoms detected in patient on DTG/3TC/ABC are true drug-related adverse events that improve, together with neurocognitive performance, after switching to ELV/COBI/FTC/TAF.

STUDY DESIGN



* CNS adverse events sleep and mood assessments.
** 3-Tesla brain MRI and CNS adverse events, neurocognitive, sleep and mood assessments.
*** Neuropsychiatric adverse events that appeared or got worse after ABC/3TC/DTG initiation

TREATMENT EFFICACY (WEEK 24)

	WEEK 24
HIV RNA <50 cop/mL, n (%)	36 (94.8)
HIV RNA >50 cop/mL, n (%)	0 (0)
HIV RNA missing value, n (%)	1 (2.6)
Treatment discontinuation due to AEs*, n (%)	1 (2.6)

* Drug abuse

CHANGES IN CNS ADVERSE EVENTS

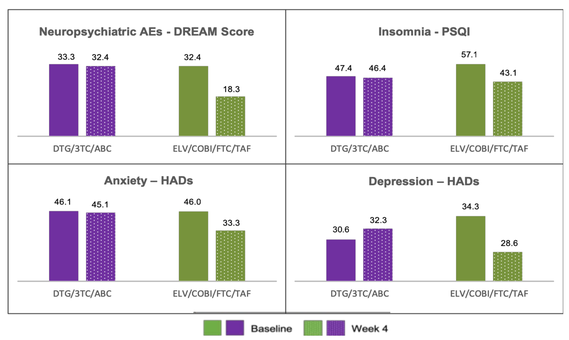
The proportion of participants reporting grade II-III neuropsychiatric adverse events decreased after switching DTG/3TC/ABC to ELV/COBI/FTC/TAF.

	BASELINE (n=38)	WK 4 (n=38)	WK 12 (n=38)	WK 24 (n=37)
Insomnia, (%)	73.7	34.2*	18.4*	8.1*
Abnormal dreams, (%)	31.6	13.2*	5.3*	8.1*
Impaired concentration, (%)	57.9	21.1*	13.2*	16.1*
Nervousness or irritability, (%)	47.4	15.8*	10.5*	10.8*
Asthenia or fatigue, (%)	55.3	26.3*	21.1*	24.3*
Symptoms of anxiety, (%)	42.1	18.4*	7.9*	10.8*
Symptoms of depression, (%)	34.2	18.4*	5.3*	13.5*
Suicidality, (%)	8	0	0	0

* Significant differences from baseline.

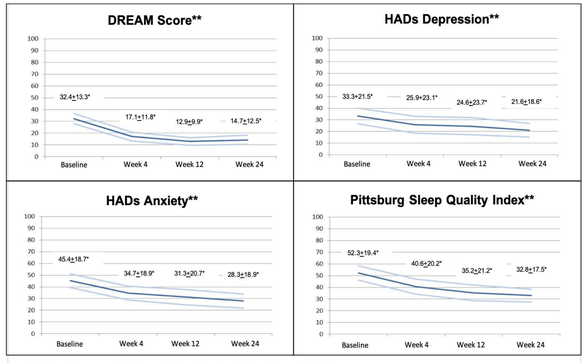
DIFFERENCES IN THE CHANGE OF CNS SCORES BETWEEN STUDY ARMS

We observed significant differences in changes of all neuropsychiatric scores, at week 4, among patients switched to ELV/COBI/FTC/TAF and those remaining on DTG/3TC/ABC



CHANGES IN CNS SCORES

We observed significative changes in all neuropsychiatric scores 24 weeks after switching to ELV/COBI/FTC/TAF.



* Significant changes at this timepoint from baseline (all p values <0.0015)
** Significant changes in the longitudinal model (all p values <0.001)

CHANGES IN COGNITIVE PERFORMANCE

After switching to ELV/COBI/FTC/TAF we observed significant improvements in the global NC function (mean±SD GDS change: 0.12±0.32; p=0.029) and in the speed of processing (-0.26±0.86; p<0.001), delayed recall (-0.33±0.8; p=0.019) and motor (-0.51±0.85; p=0.001) domains.

COGNITIVE SCORES	day 1 *mean±SD*	week 24 *mean±SD*	P value
Attention, mean (SD)	0.03 (0.81)	0.19 (0.78)	0.119
Executive functioning, mean (SD)	0.23 (0.74)	0.47 (0.63)	0.068
Speed of processing, mean (SD)	0.49 (0.66)	0.79 (0.68)	<0.001
Learning, mean (SD)	-0.13 (1.18)	0.11 (0.95)	0.100
Delayed Recall, mean (SD)	-0.06 (1.04)	0.25 (1.1)	0.019
Verbal Fluency, mean (SD)	0.21 (0.92)	0.32 (1.03)	0.184
Motor, mean (SD)	-0.55 (1.3)	-0.02 (1.22)	<0.001
GDS, mean (SD)	0.33 (0.4)	0.2 (0.26)	0.029

CHANGES IN BRAIN VOLUMES

After FDR adjustment, only the changes in the right frontal pole, a cerebral region involved in information processing, emotion and motivated behaviors, remained significant (p<0.03).

LEFT BRAIN REGIONS	Volume at day 1 *mean±SD*	Volume at week 24 *mean±SD*	P value	RIGHT BRAIN REGIONS	Volume at day 1 *mean±SD*	Volume at week 24 *mean±SD*	P value
Cuneus	3.81±0.48	3.9±0.5	p=0.004	**Cuneus**	4.3±0.52	4.37±0.55	p=0.02
Calcarine	3.38±0.54	3.52±0.66	p=0.01	**Calcarine**	3.5±0.51	3.64±0.59	p=0.004
Inferior occipital gyrus	5.66±0.59	5.74±0.59	P=0.02	**Inferior occipital gyrus**	5.95±0.68	6.02±0.64	p=0.02
Cerebellar vermal lobules I-V	1.72±0.19	1.8±0.19	p=0.004	**Cerebellar vermal lobules I-V**	1.53±0.16	1.6±0.17	p=0.003
Basal cerebrum and forebrain	0.7±0.09	0.72±0.08	p=0.03	**Inferior frontal angular gyrus**	3±0.43	2.96±0.42	p=0.004
Lingual gyrus	7.4±0.89	7.54±0.83	P=0.03	**Frontal pole**	3.17±0.42	3.09±0.4	P<0.001
Accumbens	0.43±0.07	0.44±0.06	p=0.006	**Caudate**	2.94±0.46	2.96±0.46	p=0.008
Central operculum	4.01±0.61	4.04±0.56	P=0.04	**CSF**	0.15±0.04	0.13±0.04	p=0.006

CONCLUSIONS

Our study shows that most neuropsychiatric symptoms detect in patients on DTG/3TC/ABC improved after switching to ELV/COBI/FTC/TAF.

This switch was also related with improvement of neurocognitive functioning and changes in brain volumes that could be useful to delve into the pathological mechanisms of DTG/3TC/ABC-related neurotoxicity.

Study sponsored by:

FUNDACIÓN SEIMC-GESIDA

Study supported with an ISR Grant from:

GILEAD