

No changes in HIV suppression and inflammatory markers in CSF in patients randomly switched to DTG + 3TC

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Summary: A major concern of HIV dual therapy is a potential lower efficacy in viral reservoirs, especially in the central nervous system (CNS). Dolutegravir+Lamivudine may maintain viral control without changes in inflammatory/injury markers within the CNS reservoir.

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Abstract

A major concern of HIV dual therapy is a potential lower efficacy in viral reservoirs, especially in the central nervous system (CNS). We evaluated HIV RNA, neuronal injury and inflammatory biomarkers and dolutegravir (DTG) exposure in cerebrospinal fluid (CSF) in patients switching to DTG+lamivudine (3TC). All participants maintained viral suppression in plasma and CSF at week 48. We observed no increase in CSF markers of inflammation or neuronal injury. Median (IQR) total and unbound DTG in CSF were 7.3(5.9-8.4) ng/mL and 1.7(1.2-1.9) ng/mL, respectively. DTG+3TC may maintain viral control without changes in inflammatory/injury markers within the CNS reservoir.

Key words: dolutegravir, lamivudine, CNS, inflammation, neuronal damage, concentrations

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Background

For many years, the standard-of-care for antiretroviral therapy (ART) has consisted of a regimen of 3 agents that includes 2 nucleoside reverse transcriptase inhibitors (NNRTIs) plus a third drug from a different class. As people with HIV infection live longer, interest in simplification strategies reducing long-term drug exposure and potential side effects has grown. ART has improved considerably with the use of less toxic drugs, lower dosing requirements, and better efficacy. Moreover, the availability of drugs with a high genetic barrier reduces the likelihood of resistance mutations. These characteristics have made it possible to construct regimens with 2 drugs that may be equally effective in suppressing HIV replication but preserve drugs for future administration, thus reducing toxicity and cost. However, a major concern of dual therapy is the potential lower efficacy in viral reservoirs, especially in the central nervous system (CNS). Several markers in cerebrospinal fluid (CSF) and plasma have been proposed to assess HIV-related intrathecal inflammation and neuronal damage. TREM2 is a receptor glycoprotein that belongs to the immunoglobulin superfamily. In the brain, TREM2 is a more specific marker for activation of microglia and macrophages than neopterin, since the secreted form of the receptor is expressed exclusively on myeloid cells such as macrophages and microglia, but not on astrocytes [1]. YKL40 is also a marker of the activation of different cell types, especially astrocytes [2]. Neurofilament light chain (NFL) is a major structural component of myelinated axons that is essential for maintaining axonal caliber and facilitating effective nerve conduction. CSF concentrations of NFL are a sensitive marker of CNS injury in a number of neurological diseases, including HIV-related neuronal injury [3].

Moreover, although dolutegravir (DTG) penetration in CSF has been assessed [4,5], no data have been reported to date on unbound DTG concentrations in CSF. The unbound or free fraction of a drug is usually the portion that exerts a pharmacologic effect and may therefore prove to be more accurate for predicting efficacy than the total concentration. The aim of this study was to evaluate HIV RNA, neuronal injury, inflammatory markers, and total and unbound DTG in CSF in a group of virologically suppressed patients who switched from a 3-drug regimen to DTG plus lamivudine (3TC) dual therapy and were followed for 48 weeks.

Methods

This is a prospective, single arm sub-study of the DOLAM study. Briefly, DOLAM is an open-label randomized controlled trial (DOLAM, EudraCT: 2015-000274-35) in which HIV-1-infected adults on triple ART with <50 copies/mL for ≥ 12 months, no viral failure or resistance mutations to the study drugs and a CD4 nadir >200 cells/mm³, and HBsAg negative were randomized 1:1 (stratified by baseline third agent class) to continue triple ART or to switch to DTG+3TC. Consecutive patients enrolled in 2 centers and randomly assigned to switch to DTG+3TC were asked to participate in the Neuro sub-study. CSF and blood samples were obtained 24 hours postdose at baseline and week 48. HIV-1 RNA was determined in plasma and CSF using a real-time PCR HIV-1 RNA (LOD 40 copies/mL, Abbot Laboratories, Des Plaines, IL, USA) in the Microbiology Department of Bellvitge University Hospital, Barcelona, Spain.

Markers of neuronal damage and inflammation were measured in CSF using enzyme-linked immunosorbent assay (ELISA) at the University of Gothenburg, Sweden and the University of Innsbruck, Austria.

Neuronal damage marker in CSF: The CSF NFL concentration was measured using an in house ELISA, as previously described in detail [6]. Inflammatory markers in CSF: Soluble TREM2 was measured using an in-house immunoassay, as previously described in detail [7]. The CSF YKL-40 (also known as chitinase 3-like 1) concentration was measured using the Human Chitinase 3-like 1 Quantikine ELISA Kit (R&D Systems, Inc., Minneapolis, MN, USA).

DTG concentrations: Total and unbound DTG mass concentrations in plasma and CSF were measured using validated UHPLC-MS/MS methods (assay calibration ranges were 10.0–10,000 $\mu\text{g/L}$ and 1.00–1000 $\mu\text{g/L}$ for total and unbound DTG in plasma, and 0.500–100 $\mu\text{g/L}$ for total and unbound DTG in CSF). A rapid equilibrium dialysis procedure was assessed before the determination of plasma and CSF unbound fractions. Imprecisions, absolute relative biases, normalized-matrix factors, and normalized recoveries were $\leq 13.2\%$, $\leq 9.9\%$, 95.1%–100.8%, and 97.3%–102.8%, respectively. All the performance characteristics evaluated met the FDA criteria [8].

Written informed consent for the Neuro sub-study was obtained prior to enrolment. The study was approved by the local ethics committee and the Spanish Agency of Medicines and Medical Devices.

Statistics: Descriptive results are presented as medians with the range. Wilcoxon's signed-rank test was used for comparisons between follow-up and baseline results, except in variables with left-censored data, where the paired Prentice-Wilcoxon test for censored paired data was used. The correlation of the slopes obtained from standard linear regression models was calculated in order to evaluate potential associations between cytokine markers, blood plasma viral load, and CD4 counts. All tests were 2-sided and a P value < 0.05 was regarded as significant. Analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA), R (version 3.1.0), and Minitab (version 16).

Results

We enrolled 15 patients; baseline and week 48 plasma and CSF samples were available for all 15 patients. Three patients were female. Median (IQR) age was 46 years, median (IQR) CD4 T-cell count was 746 (356) cells/ μ l, and nadir CD4 T-cell count was 302 (165) cells/ μ l. Median (min-max) time since HIV diagnosis was 14 years (4-32). Patients had no history of AIDS, CNS disease or HIV-related neurologic complications. All patients were on stable triple therapy and had no history of virological failure to regimens containing 3TC/FTC or an integrase strand transfer inhibitor (INSTI) according to the inclusion/exclusion criteria. Most switched from an NNRTI-based regimen (60%) followed by INSTI (26.7%). All patients maintained plasma viral suppression at baseline and at weeks 12, 24, 36, and 48. HIV RNA in CSF was <40 copies/mL at baseline and at week 48 in all participants. No significant changes between baseline and week 48, were observed in median (IQR) CSF cells (<0.001 $\times 10^9$ /L and <0.001 $\times 10^9$ /L) or proteins [0.3 g/L (0.1) and 0.4 g/L (0.2) p:0.2]. The median (min-max) cerebrospinal fluid (CSF)/serum quotient of albumin (QAlb) at week 48 was 5.3 (3.9-9.2). However three patients presented abnormal age corrected QAlb suggesting some degree of blood-brain barrier (BBB) dysfunction. NFL median change from baseline to week 48 was not statistically significant [median (IQR) NFL at baseline, 498.8 ng/L (378.5-621.6); median (IQR) NFL at week 48, 457(375.9-566.7); p=0.2. No significant changes were observed in median sTREM-2 values at baseline, 1415.5 (1151.5-2027.8); and week 48 [1375.4 (1058.2-2423.9); p=0.2] or in YKL40 values at baseline 99 (79.4-129.5) and week 48 [102 (85.8-123); p=0.5] (Table 1). NFL and sTREM-2 showed a modest decline over 48 weeks, however we found a small effect size (r <0.3) in both variables (0.2 and -0.2 respectively).

DTG plasma and CSF concentrations were determined at week 48. Median (IQR) total and unbound DTG concentrations in plasma were 2484.1 (1450.6) ng/mL and 13.1 (9.6) ng/mL, respectively. Median (IQR) total and unbound DTG in CSF were 7.3 (2.5) ng/mL and 1.7 (0.7) ng/mL, respectively. Thus, the unbound fraction of DTG was 0.5% of the total drug, while in CSF this proportion was 23% (Table 1). The total DTG CSF to plasma ratio was 0.003, whereas the unbound DTG CSF to plasma ratio was 0.12. Individual data are represented in Figure 1.

Discussion

There is strong evidence of the virologic efficacy of DTG+3TC in ART-naïve and treatment-experienced adults with HIV-1 infection [9-10]; however, data regarding potential viral reactivation in anatomical reservoirs following treatment simplification are scarce. In a small pilot study published elsewhere, Giannella et al. [11] did not detect concerning signals with respect to the efficacy of DTG+3TC in controlling genital HIV RNA shedding (semen and cervicovaginal fluid).

We report the results of a sub-study of a randomized clinical trial. Subjects switched their treatment from stable triple therapy to dual therapy with DTG+3TC. All participants underwent lumbar puncture to assess viral suppression, inflammatory markers, and neuronal damage at baseline and week 48. Plasma and CSF DTG exposure was also evaluated. We found no evidence of viral escape, neuronal damage, or changes in inflammatory markers within the CNS reservoir after 48 weeks of dual therapy.

HIV enters the CNS early after transmission and persists throughout the course of infection. After crossing the blood-brain barrier, HIV productively infects perivascular macrophages and microglia. Activation of these cells leads to an inflammatory response [12]. Earlier studies have shown that, despite achieving an undetectable plasma HIV RNA through sustained ART, people living with HIV often have elevated levels of immune activation markers in CSF [13]. It remains unclear whether the residual immune activation is the result of ongoing persistent viral replication within the CNS or whether it is generated by other processes. Replication-induced intrathecal inflammation is associated with dendritic injury, neuronal dysfunction, and cell death. In our study, we found no evidence that deintensification of treatment increases viral replication or intrathecal inflammation.

DTG and 3TC reach effective concentrations in the CSF. However we found that unbound DTG concentrations in CSF were only 23% of total CSF concentrations, although unbound DTG CSF

exceeded the EC_{50} (0.2 ng/mL) by 8-fold. Letendre et al. [4] reported that total DTG concentrations in CSF might be comparable to plasma unbound concentrations, suggesting penetration of the CNS by passive diffusion of the free plasma fraction. Gelé et al. [5] also assumed that diffusion of DTG would predict protein-free drug concentrations in CSF.

Conventionally, drugs in CSF are assumed to be largely unbound due to the relative lack of proteins in the absence of marked inflammation or any breach of the blood-brain barrier. Small changes in BBB permeability may also promote important changes in the proportion of CSF unbound drug. Given that the concentrations of albumin and α -1 acid glycoprotein (the proteins mainly involved in drug binding in plasma) in CSF are far lower than in plasma, drug may be binding onto other unspecified molecules.

The clinical value of estimating ART drug concentrations in the CNS has been a matter of debate. A recently published paper suggests that drug concentrations of some antiretroviral agents in human brain tissue obtained in autopsy may be much higher than those in CSF [14]. However, CSF concentrations continue to represent a surrogate marker in the absence of more specific and harmless techniques and it is being used in almost all studies conducted by our and other groups. Some recent studies have observed marked differences in CSF unbound fraction with different ARV. Nguyen et al found the nonnucleoside reverse-transcriptase inhibitor etravirine to be highly protein bound in CSF [15]. Others published different results when assessing darunavir or indinavir (almost all unbound) as well as efavirenz (approximately 25% unbound) CSF concentrations. Finally, whether drug accumulation in the brain may explain lower-than-expected drug concentrations in CSF is still unknown. In our study, median unbound DTG CSF concentrations were approximately 13 times lower than the unbound fraction in blood plasma, thus reinforcing the need to measure the free fraction of drug in CSF. Similar data were published by our group with bictegravir [16].

This study has some limitations. The number of patients included is small as usual in these type of studies as an obvious consequence of the need to collect lumbar puncture samples during follow-up. We also recognize the short study period as a limitation. Longer follow up is needed to confirm the absence of changes in CSF biochemical inflammatory and neuronal damage markers. Moreover almost all participants were male, with an acceptable immune situation, no history of AIDS or CNS

complications. Hence we should extrapolate these results with caution to other HIV populations such as severely immune suppressed patients or with CNS comorbidities.

In conclusion, while waiting larger and longer studies to confirm these results our data suggest that switching to dual therapy with DTG+3TC in patients with no drug resistance or history of treatment failure may maintain viral control within the CNS reservoir and does probably not promote intrathecal inflammation or neuronal damage after 1 year of follow-up.

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KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

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ID	Gender	ART at BL	BL sTREM-2 (pg/mL)	W48 sTREM-2 (pg/mL)	BL YKL-40 (ng/mL)	W48 YKL-40 (ng/mL)	BL NFL CSF (ng/L)	W48 NFL CSF (ng/L)	BL RNA HIV CSF (copies/mL)	W48 RNA HIV CSF (copies/mL)	Total DTG plasma (ng/mL)	Unbound DTG plasma (ng/mL)	Total DTG CSF (ng/mL)	Unbound DTG CSF (ng/mL)
1	M	ABC/3TC/DTG	1416	1378	76	84	300	295	<40	<40	2213.8	12.32	6.1	1.3
2	M	ABC/3TC/NVP	805	702	90	88	268	321	<40	<40	4400	24.41	7.3	1.7
3	F	TDF/FTC/RPV	1218	1375	99	102	426	410	<40	<40	1860.3	9.59	8.2	1.8
4	M	ABC/3TC/RPV	1336	1521	118	108	567	530	<40	<40	599.6	3.62	2.9	0.8
5	M	EVG/FTC/TAF/COBI	2513	3857	203	184	520	467	<40	<40	2754.4	17.4	7.5	1.7
6	M	TDF/FTC/RPV	2083	2366	159	184	624	603	<40	<40	1659.2	8.73	6.1	1.1
7	M	TAF/FTC/DRV/COBI	557	892	55	60	279	226	<40	<40	2120.1	11.84	5.8	1.3
8	M	ABC/3TC/DTG	634	521	78	72	368	420	<40	<40	3867.5	24.07	12.1	2.8
9	F	ABC/3TC/DTG	1394	1232	94	88	452	457	<40	<40	1210.6	6.9	4.1	0.9
Patients 9, 14, and 15 had no available plasma samples for DTG concentrations. DTG concentrations are adapted to a logarithmic (Log ₁₀) scale.														
10	M	EVG/FTC/TAF/COBI	1435	1158	105	103	499	520	<40	<40	4594.7	29.82	7.7	1.8
11	M	EVG/FTC/TAF/COBI	1610	1164	124	118	619	436	<40	<40	3037.3	14.05	6.8	1.6
12	F	EVG/FTC/TAF/COBI	1085	959	75	65	708	629	<40	<40	3058.4	17.23	10.6	2.1
13	M	ABC/3TC+ATV/r	2300	2615	81	94	389	342	<40	<40	-	-	10.2	2.4
14	M	TDF/FTC+ETV	1972	2482	143	128	734	886	<40	<40	-	-	8.7	2.1
15	M	TDF/FTC/RPV	2535	2981	135	138	734	629	<40	<40	-	-	4.7	1
Median (1st – 3rd quartile)			1415.5 (1151.5 - 2027.8)	1375.4 (1058.2 - 2423.9)	99 (79.4 - 129.5)	102 (85.8 - 123)	498.8 (378.5 - 621.6)	457 (375.9 - 566.7)			2484.1 (1810.03 - 3260.6)	13.1 (9.38 - 19.07)	7.3 (5.9 - 8.4)	1.7 (1.2 - 1.9)

Table 1. Individual patient data.

ART: antiretroviral treatment; BL: baseline; W48: week 48; M: Male; F: Female; ABC: abacavir, 3TC: lamivudine; DTG: dolutegravir; NVP: nevirapine; TDF: tenofovir; FTC: emtricitabine; RPV: rilpivirine; EVG: elvitegravir; TAF: tenofovir alafenamide; COBI: cobicistat; DRV: darunavir; ATZ/r: ritonavir-boosted atazanavir; ETV: etravirine.

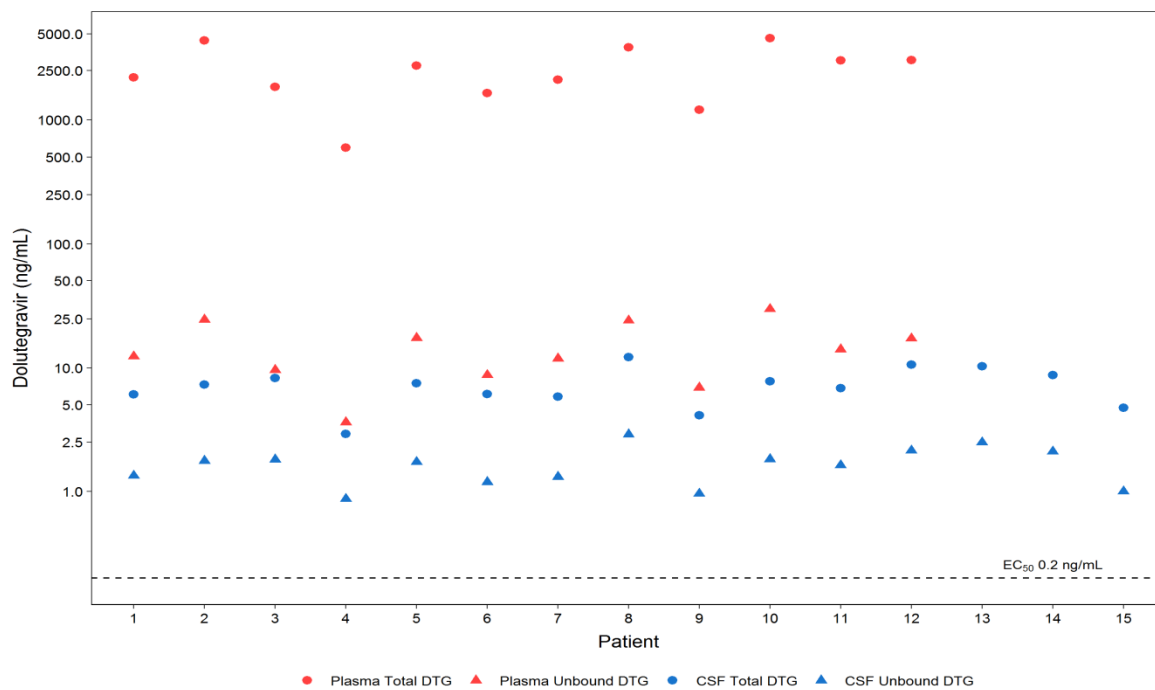


Figure 1.

Patients 13, 14 and 15 had no available plasma samples for DTG concentrations.

DTG concentration values are adapted to a logarithmic (Log₁₀) scale.

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