**Title:**

Cerebral function parameters in people with HIV switching integrase inhibitors: A randomised controlled trial.

**Short title:**

CNS Integrase Study

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**Abstract**

**Background:**

Different antiretroviral therapies (ART) may have differing effects on central nervous system (CNS) function. We assessed CNS pharmacodynamic effects of switching integrase inhibitor in people-with-HIV (PWH).

**Methods:**

PWH on tenofovir-DF/emtricitabine plus raltegravir 400mg twice daily with suppressed plasma HIV RNA and without overt neuropsychiatric symptoms were randomly allocated on a 1:2 basis to remain on raltegravir or switch to dolutegravir 50 mg once daily for 120 days. Pharmacodynamic parameters assessed included cognitive function (z-score composite of 7 domains), patient-reported outcome measures (PROMs; PHQ-9 and Beck’s depression questionnaires), cerebral metabolite ratios measured by proton magnetic resonance spectroscopy (H1-MRS) and plasma and cerebrospinal fluid (CSF) HIV RNA. Pharmacokinetics were also assessed in plasma and CSF. Changes in pharmacodynamics parameters and factors associated with such changes were assessed.

**Results:**

In 20 subjects (19 male, 14 of white ethnicity, median age 43 years (IQR: 11.5) and CD4+count of 717 (SD: 298) cells/µL), over 120 days there were no statistically significant changes in cognitive function [mean z-score difference (95%CI) -0.004 (-0.38/0.37); p=0.98], PROMs [PHQ-9 median score change: 0 in control arm, -0.5 switch arm (p=0.57); Beck’s depression questionnaire: -1.5 control arm, -1.0 switch arm (p=0.38)], cerebral metabolite ratios between study arms. CSF HIV RNA was <5 copies/mL at baseline and day 120 in all subjects. Geometric mean CSF dolutegravir concentration assessed pre-dose was 7.6 ng/mL (95% CI: 5.2-11.1).

**Conclusions:**

Switching integrase inhibitor in virologically suppressed PWH without overt neuropsychiatric symptoms resulted in no significant changes in an extensive panel of CNS pharmacodynamics parameters.

**Key Words:**

Cognitive function, integrase Inhibitor, raltegravir, dolutegravir, CNS, MR spectroscopy.

**Manuscript**

**Introduction**

Modern effective antiretroviral therapy (ART) suppresses plasma viremia and allows restoration of immune system function in persons with HIV (PWH). Consequently, in ART treated PWH, AIDS defining illnesses are now rare and life expectancy approaches that of the general population.1 However, when compared to the general population, the prevalence of non-infectious co-morbidities are reported to be greater and quality of life is described to be poorer in PWH.2

Central nervous system (CNS) disorders are one group of conditions which remain highly prevalent in otherwise effectively treated PWH. This includes neuropsychiatric disorders such as depression, anxiety and cognitive impairment.3, 4 Evidence suggests that different antiretroviral agents and combinations may have differing effects on cerebral function and neuropsychiatric symptomatology.5-7 The non-nucleoside-reverse-transcriptase-inhibitor efavirenz has well documented neuropsychiatric side effects8 and in more recent years, a host of CNS side effects (such as sleep disorders, dizziness, depression or anxiety) have been reportedly associated with the use of the HIV-integrase strand-transfer-inhibitors.9-13 These CNS side effects have been more frequently observed in certain populations, such as older patients, females or in PWH with underlying depression or anxiety disorders.14-15

The aim of this study was to assess the pharmacodynamics effects on the CNS of two different integrase-inhibitor containing ART regimens. To assess this, we employed an extensive battery including cognitive assessments, patient reported outcome measures (PROMs), measurement of CNS metabolites on magnetic resonance spectroscopy (MRS) imaging and measurement of several cerebrospinal fluid parameters including HIV-1 RNA, soluble biomarkers and infectivity markers. Pharmacokinetic parameters were also assessed and included integrase-inhibitor drug exposure in plasma and cerebrospinal fluid.

**Methods**

*Subject selection and study design*

This prospective, randomised, single centre study was conducted at St. Mary’s Hospital (Imperial College Healthcare NHS Trust, London, UK) from July 2015 to August 2016. PWH on ART comprising of raltegravir 400 mg twice daily plus tenofovir/emtricitabine 245/200 mg (Truvada™) with an undetectable plasma HIV-1 RNA for at least 3 months with no neurological or cognitive complaints were eligible. Exclusion criteria included previous exposure to dolutegravir, significant neurological disease, current history of major depression or psychosis, recent head injury (prior three months) and current alcohol abuse or drug dependence.

Individuals were randomised on a 2:1 basis to either switch integrase inhibitor from raltegravir to dolutegravir 50 mg once daily (S*witch Arm*) or to remain on raltegravir (C*ontrol Arm*). At baseline and after 120 days, all subjects underwent assessment of cerebral function parameters.

*Ethical considerations*

Local human ethics committee approval was granted prior to recruiting participants by the National Research Ethics Service Committee London-Central, UK (REC number 14/LO/1864). All participants were required to sign an informed consent before undergoing any screening procedures. The study was registered on the European Clinical Trials Database (EudraCT number 2014-003710-84).

*Cerebral function parameters*

*Cognitive testing and patient reported outcome measures*

Cognitive testing and PROMs were undertaken at baseline, day 60 and day 120. Cognitive testing comprised of a computerised battery (CogState™ Ltd, Melbourne, Australia) which has been validated for cognitive testing in several disease areas including HIV.16 The battery undertaken for our study took approximately 20 minutes to complete and comprised of 7 specific cognitive tests covering several cognitive domains (attention, psychomotor function, visual and working memory and associate learning). PROMs were Lawton’s instrumental activities of daily living scale,17 Patient Health Questionnaire-9 (PHQ-9)18 and Beck’s depression questionnaires.19

*Neuroimaging*

Cerebral proton magnetic resonance spectroscopy (1H-MRS) was performed on a Siemens MAGNETOMTM Verio 3 Tesla scanner (Siemens Healthcare GmbH, Erlangen, Germany) at baseline and day 120 with methods previously described in detail.20

Post-processing of MRS were analysed using the time-domain fitting algorithm Totally Automatic Robust Quantitation in NMR (TARQUIN™) (version 4.3.5).21 Metabolites identified included N-acetyl aspartate (NAA), Choline (Cho), myo-inositol (mI) and creatine (Cr) with all metabolites expressed as ratios to Cr.

*Cerebrospinal fluid parameters*

Cerebrospinal fluid examinations were undertaken at baseline and day 120 prior to administration of ART. Analyses included ultrasensitive HIV-1 RNA, antiretroviral drug concentration (plasma concentration also measured), tryptophan/phenylalanine metabolites, neopterin and infectivity assays.

Cerebrospinal fluid HIV-1 RNA was measured using a high sensitivity in-house assay with a detection limit of 5 RNA copies/mL.22 Concentrations of raltegravir and dolutegravir were analysed by high-performance-liquid-chromatography (HPLC) tandem mass spectrometry.23 The lower limits of quantification (LLQ) in plasma and cerebrospinal fluid were respectively 5 ng/mL and 1.950 ng/mL for raltegravir alongside 10 ng/mL and 0.750 ng/mL for dolutegravir.

Plasma and cerebrospinal fluid concentrations of tryptophan, kynurenine, phenylalanine, tyrosine and neopterin were measured using previously described methodologies.24 The kynurenine/tryptophan and phenylalanine/tyrosine ratios were calculated as indexes of indoleamine 2,3-dioxygenase (IDO-1) and phenylalanine hydroxylase (PAH) activity, respectively.

Cerebrospinal fluid infectivity assays were undertaken using cell cultures as previously described in detail.25

*Statistical analysis*

All statistical analyses were performed using SPSS (version 24.0; SPSS Inc., Chicago, IL, USA). As a proof of concept study, no specific power calculations were undertaken.

Cognitive results were analysed in accordance with CogState™ recommendations. Data are presented as global cognitive scores, calculated as a composite of all cognitive tasks. Here, the score for each participant was estimated as the z-standardised total score of all separate cognitive tasks divided by the common standard deviation at baseline.

Means and standard deviation of cerebral metabolite ratios were calculated. Absolute changes in cerebral metabolite ratios between baseline and follow-up were evaluated using a paired sample t-test.

Geometric means (GM) and 95% confidence intervals (CI) were calculated for cerebrospinal fluid and plasma concentrations of raltegravir and dolutegravir. The CI were first determined using logarithms of the individual GM values and then the calculated values were expressed as linear values. A coefficient of variation (CV, [(standard deviation/mean) × 100]) was used to express inter-patient variability in the pharmacokinetic parameters.

Comparisons between the study arms for cerebral function parameters were undertaken using appropriate statistical methods which included paired and independent t-tests, chi-squared or Fisher’s exact tests and Mann-Whitney U-test.

Paired-samples *t*-tests were undertaken to assess changes in plasma and cerebrospinal fluid concentrations for the tryptophan pathway metabolites over the study period for each arm independently. Pearson *r* correlations were used to determine associations between these biomarker concentrations and global cognitive scores for all subjects at baseline. Mixed models were constructed to investigate the relationship between changes in metabolite concentrations in plasma and cerebrospinal fluid with the global cognitive score for subjects in the dolutegravir arm (*Switch Arm*) only. The models fixed effects were global cognitive score (dependent variable) with the biomarker concentrations the independent variable. The alpha value was set at 0.05 for each analysis performed and not corrected for multiplicity.

**Results**

*Subject characteristics*

Of 28 participants screened, 22 were randomised and 20 completed study procedures (8 in the *Control Arm* and 12 in the *Switch Arm*, see *supplementary figure 1*). Baseline characteristics are shown on *Table 1*. Study drugs were generally well-tolerated with all patients reporting over 95% adherence to therapy. No safety or laboratory concerns related to study drugs were observed. One patient in the switch arm died during the study follow-up due to complications arising from a previously undiagnosed metastatic malignancy. At day 120, plasma HIV-1 RNA was < 20 copies/mL in all subjects.

*Cognitive results and patient reported outcome measures*

Baseline cognitive performance and changes over the study period as shown in *Table* 2. No statistically significant differences between the study groups were observed in changes in global cognitive score or in individual cognitive domains (all p-values >0.1. No differences in changes in depression questionnaires between the study arms were observed at day 120 from baseline (p=0.57 for PHQ-9 and p=0.38 for Beck’s, *see Table 2*). The result of the Lawton’s instrumental activities of daily living scale questionnaire was 8 for all patients at all time-points.

*Neuroimaging*

Cerebral metabolite ratio results are shown on *Table 3*. No statistically significant changes in cerebral metabolite ratio were observed over the study period between the two study treatment groups and no significant associations were observed between the PROMs and changes in cerebral metabolite ratios (p>0.2 for all associations).

*Cerebrospinal fluid and plasma parameters*

In all individuals, cerebrospinal fluid HIV-1 RNA was undetectable (<5 copies/mL) at both baseline and day 120. Cerebrospinal fluid GM concentrations of raltegravir for the *Control Arm* at baseline (n=8), *Control Arm* at day 120 (n=8) and *Switch Arm* at baseline (n=12) were 16.2 ng/mL (95% CI: 9.4-27.9), 15.0 ng/mL (95% CI: 8.6-26.3) and 14.8 ng/mL (95% CI: 8.2-26.8), respectively. Cerebrospinal fluid GM concentrations of dolutegravir for the *Switch Arm* at day 120 (n=12) was 7.6 ng/mL (95% CI: 5.2-11.1). See *table 4* for full pharmacokinetic results.

Concentrations of tryptophan, kynurenine, phenylalanine, tyrosine and neopterin, and the tryptophan/kynurenine and phenylalanine/tyrosine ratios, are shown in *Table 5*. In the *Switch Arm*, mean plasma concentration of tryptophan increased significantly from baseline to day 120 (mean increase, 4.84 μmol/L; *p*=0.038; 95% CI, -0.32 to 9.37). No other statistically significant changes in concentrations of the other measured plasma biomarkers were observed in either arm. Statistically significant differences in plasma tryptophan (*p*=0.011) and cerebrospinal fluid neopterin concentrations (*p*=0.049) were observed between arms at day 120.

All cerebrospinal fluid samples displayed dose-response curves allowing quantification of antiretroviral activity on infectivity assays. At a 1:4 dilution, all cerebrospinal fluid samples from both study arms presented near-maximal inhibition at both time points. Infectivity model half maximal inhibitory IMIC50 expressed as CNS Anti-Retroviral scores (-Log2IMIC50) of cerebrospinal fluid samples did not show statistically significant changes between baseline and day 120 for both study groups (p=0.36 for control group and p=0.27 for switch group).

*Associations with tryptophan metabolites*

No statistically significant associations were observed between plasma kynurenine or tyrosine pathway metabolites and global cognitive scores at baseline (all p values>0.1). Cerebrospinal fluid phenylalanine concentrations positively correlated with baseline global cognitive scores (r=0.489, unadjusted *p*=0.024), as did cerebrospinal fluid phenylalanine/tyrosine ratios (r=0.567, unadjusted *p*=0.007).

In the mixed model analysis of the *Switch Arm* (dolutegravir), plasma kynurenine/tryptophan ratio concentrations correlated with changes in global cognitive scores, such that for every 1 µmol/L increase observed in kynurenine/tryptophan ratio, a 0.019-point decrease was observed in the global cognitive scores (unadjusted *p*=0.021), indicating poorer cognitive performance as the kynurenine/tryptophan ratio increases. No other statistically significant associations were observed for the other biomarkers tested in either plasma or cerebrospinal fluid.

**Discussion**

In this randomized, prospective study, comparing switching integrase inhibitor-based ART in PWH without overt neuropsychiatric symptoms, we observed no differences in cognitive function or other cerebral function parameters over a 120-day period. Strengths of our study include the randomized approach to the study design and the detailed cerebral function assessments which were included, namely cognitive function, PROMs, neuroimaging parameters and several cerebrospinal fluid parameters.

In large cohort studies neuropsychiatric adverse events have been reported to frequently observed in PWH on integrase inhibitors with the presence of neuropsychiatric adverse events to be associated with an increased risk of discontinuing ART therapies.13 We specifically recruited PWH without overt neurological symptomatology. During the follow up period no neuropsychiatric adverse events evolved in our study. It is likely the population we have recruited were less prone to develop such neuropsychiatric side effects given we recruited individuals tolerating a raltegravir containing ART regimen without adverse events who were willing to switch the integrase inhibitor component of their ART regimen.26

In a retrospective cross-sectional study assessing tryptophan metabolism in individuals with acute HIV infection, increased kynurenine/tryptophan ratios have been reported to be associated with increased depressive symptoms.(Reference to 27, Grill et al) In this study, PWH with cognitive impairment higher phenylalanine/tyrosine ratios, representing an increased CNS PAH activity, were observed when compared to PWH without cognitive disorders.27 In another retrospective cross-sectional study in virologically-suppressed PWH, higher phenylalanine/tyrosine ratios were observed but these were not associated with cognitive impairment.(Reference to 24, Keegan et al) In this second study, a trend towards lower plasma kynurenine/tryptophan ratios was associated with both cognitive impairment and depression.24 In a prospective study assessing PWH switching from efavirenz-based ART to dolutegravir-based ART, an increase in plasma kynurenine concentrations and improvements in CNS toxicity scores was reported.28 In our study we did not observe differences in either ratio in plasma or cerebrospinal fluid between study arms. However, plasma kynurenine/tryptophan ratio concentrations were found to be negatively correlated with lower global cognitive scores in the switch arm. These results should be interpreted with caution since this model was not adjusted for multiplicity and changes in the kynurenine/tryptophan ratio or global cognitive score in the individual study arms were not observed separately in the individual study arms. In addition, this significant relationship was not reciprocated for the cerebrospinal fluid kynurenine/tryptophan ratio.

A difference in mean plasma tryptophan concentrations was observed between the study groups (p=0.011) at day 120. This appears to be driven by an increase in plasma tryptophan in the switch arm (mean change 4.84 µmol/L; SD: 7.12) and a decrease in the control arm (mean change -4.6 µmol/L; SD: 6.61). Corresponding changes in kynurenine concentrations or the kynurenine/tryptophan ratio were not observed indicating that the observed changes are unlikely related to changes in IDO-1 enzyme activity as both changes in tryptophan and kynurenine concentrations would be expected. Given these differences are unlikely to be related to changes in IDO-1 enzyme activity it is possible the differences are not related to ART treatment effects in our study. Other possible explanations for the changes in plasma tryptophan concentration we have observed may be related to dietary intake which is known to affect plasma tryptophan concentration.29, 30

We observed a difference in mean cerebrospinal fluid neopterin concentration between study arms at follow up (p=0.049). This difference was driven by a decrease in cerebrospinal fluid neopterin concentration in the control arm (mean change -1.93 nmol/L; SD: 2.54). This change in cerebrospinal fluid neopterin concentration was not associated with any other clinical parameters and therefore any clinical relevance of this observation is unclear. Neopterin was included as a marker of immune activation based on its correlation with IDO activity.31 Whilst cerebrospinal fluid neopterin levels have been shown to decrease after initiating ARV therapy, they do not appear to return to the normal ranges which would be expected in all subjects even following up to a decade of suppressive ART. This may indicate a persistent low level intrathecal immune activation in PWH on otherwise suppressive ART.32-33

Cerebrospinal fluid concentrations of dolutegravir [7.6 ng/mL (95% CI, 5.2-11.1] were in a similar range to those previously reported [13 ng/mL (range,4-18 ng/mL)].34 Other studies have described associations between dolutegravir cerebrospinal fluid concentration and neuropsychiatric adverse events.35 Given our study comprised of PWH without overt neuropsychiatric adverse events, we do not have the ability to link the cerebrospinal fluid exposure of dolutegravir to such events. Other limitations of our study are the small sample size, the relative young age of the participants and the small number of female participants.14

In summary, we observed no significant changes in clinical, cerebral imaging parameters or cerebrospinal fluid biomarkers in this comprehensive assessment of cerebral pharmacodynamic and pharmacokinetic parameters in virologically suppressed PWH without overt neuropsychiatric switching integrase inhibitor.

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**References:**

1. Dore GJ, McDonald A, Li Y, et al. Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. Aids 2003,17:1539-1545.
2. Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. Aids 2010,24:1243-1250.
3. Nightingale S, Winston A, Letendre S, et al. Controversies in HIV-associated neurocognitive disorders. Lancet Neurol 2014; 13(11):1139-1151
4. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007,69:1789-1799.
5. Winston A, Duncombe C, Li PC, et al. Does choice of combination antiretroviral therapy (cART) alter changes in cerebral function testing after 48 weeks in treatment-naive, HIV-1-infected individuals commencing cART? A randomized, controlled study. Clin Infect Dis 2010,50:920-929.
6. Winston A, Arenas-Pinto A, Stohr W, Fisher M, Orkin CM, Aderogba K, et al. Neurocognitive function in HIV infected patients on antiretroviral therapy. PLoS One 2013,8:e61949.
7. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol 2008,65:65-70
8. Ciccarelli N, Fabbiani M, Di Giambenedetto S, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. Neurology 2011,76:1403-1409.
9. [Menard A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Menard%20A%5BAuthor%5D&cauthor=true&cauthor_uid=28441180), [Montagnac C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Montagnac%20C%5BAuthor%5D&cauthor=true&cauthor_uid=28441180), [Solas C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Solas%20C%5BAuthor%5D&cauthor=true&cauthor_uid=28441180), et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in Europe. [AIDS.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Neuropsychiatric+adverse+effects+on+dolutegravir%3A+an+emerging+concern+in+Europe) 2017 May 15;31(8):1201-1203
10. Borghetti A, Baldin G, Capetti A, et al., Odoacre Study Group. Efficacy and tolerability of dolutegravir and two nucleos(t)ide reverse transcriptase inhibitors in HIV-1-positive, virologically suppressed patients. AIDS 2017; 31:457–459.
11. Bonfanti P, Madeddu G, Gulminetti R, et al., CISAI Study group. Discontinuation of treatment and adverse events in an Italian cohort of patients on dolutegravir. AIDS 2017; 31:455–457.
12. [Elzi L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Elzi%20L%5BAuthor%5D&cauthor=true&cauthor_uid=28692533), [Erb S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Erb%20S%5BAuthor%5D&cauthor=true&cauthor_uid=28692533), [Furrer H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Furrer%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28692533), et al; [Swiss HIV Cohort Study Group](https://www.ncbi.nlm.nih.gov/pubmed/?term=Swiss%20HIV%20Cohort%20Study%20Group%5BCorporate%20Author%5D). Adverse events of raltegravir and dolutegravir. [AIDS.](https://www.ncbi.nlm.nih.gov/pubmed/28692533) 2017 Aug 24;31(13):1853-1858
13. [Lepik KJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lepik%20KJ%5BAuthor%5D&cauthor=true&cauthor_uid=29424784), [Yip B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yip%20B%5BAuthor%5D&cauthor=true&cauthor_uid=29424784), [Ulloa AC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ulloa%20AC%5BAuthor%5D&cauthor=true&cauthor_uid=29424784), et al. Adverse drug reactions to integrase strand transfer inhibitors. [AIDS.](https://www.ncbi.nlm.nih.gov/pubmed/29424784) 2018 Apr 24;32(7):903-912
14. [Hoffmann C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hoffmann%20C%5BAuthor%5D&cauthor=true&cauthor_uid=27860104), [Welz T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Welz%20T%5BAuthor%5D&cauthor=true&cauthor_uid=27860104), [Sabranski M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sabranski%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27860104), et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. [HIV Med.](https://www.ncbi.nlm.nih.gov/pubmed/27860104) 2017 Jan;18(1):56-63
15. Llibre JM, Montoliu A, Miro JM, et al. Piscis Cohort group. Discontinuation of dolutegravir, elvitegravir/cobicistat and raltegravir because of toxicity in a prospective cohort. HIV Med. 2019 Mar;20(3):237-247.
16. Overton ET, Kauwe JS, Paul R, Tashima K, Tate DF, Patel P, et al. Performances on the CogState and standard neuropsychological batteries among HIV patients without dementia. AIDS Behav 2011; 15(8):1902-1909
17. Lawton MP and Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9: 179-186
18. Spitzer RL, Kroenke K, Williams JBW. Patient Health Questionnaire Study Group. Validity and utility of a self-report version of PRIME-MD: the PHQ Primary Care Study. JAMA. 1999;282:1737–44
19. Beck AT, Ward C H, Mendelson M, et al. An inventory for measuring depression. Archives of General Psychiatry 1961; 4: 561-571
20. Mora-Peris B, [Bouliotis G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bouliotis%20G%5BAuthor%5D&cauthor=true&cauthor_uid=29438199), [Ranjababu K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ranjababu%20K%5BAuthor%5D&cauthor=true&cauthor_uid=29438199), et al. Changes in cerebral function parameters with maraviroc-intensified antiretroviral therapy in treatment naive HIV-positive individuals. [AIDS.](https://www.ncbi.nlm.nih.gov/pubmed/29438199) 2018 May 15;32(8):1007-1015
21. Scott J, Underwood J, Garvey LJ, Mora-Peris B, Winston A. A comparison of two post-processing analysis methods to quantify cerebral metabolites measured via proton magnetic resonance spectroscopy in HIV disease. Br J Radiol 2016; 89(1060):20150979
22. Mora-Peris B, Watson V, Vera JH, Weston R, Waldman AD, Kaye S, et al. Rilpivirine exposure in plasma and sanctuary site compartments after switching from nevirapine-containing combined antiretroviral therapy. J Antimicrob Chemother 2014; 69(6):1642-1647
23. Else L, Watson V, Tjia J, Hughes A, Siccardi M, Khoo S, et al. Validation of a rapid and sensitive high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay for the simultaneous determination of existing and new antiretroviral compounds. J Chromatogr B Analyt Technol Biomed Life Sci 2010; 878(19):1455-1465
24. Keegan MR, Chittiprol S, Letendre S et al. Tryptophan metabolism and its relationship with depression and cognitive impairment among HIV-infected individuals. International Journal of Tryptophan Research 2016; 9: 79-88
25. Mora-Peris B, Winston A, Garvey L, Else LJ, Shattock RJ, Herrera C. HIV-1 CNS in vitro infectivity models based on clinical CSF samples. J Antimicrob Chemother 2016; 71(1):235-243
26. [Yombi JC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yombi%20JC%5BAuthor%5D&cauthor=true&cauthor_uid=29628511). Dolutegravir Neuropsychiatric Adverse Events: Specific Drug Effect or Class Effect. [AIDS Rev.](https://www.ncbi.nlm.nih.gov/pubmed/29628511) 2018 Jan-Mar;20(1):14-26.
27. Grill M, Gisslen M, Cinque P, et al. Kynurenine-tryptophan and phenylalanine-tyrosine levels in cerebrospinal fluid in HIV infection; 19th Conference on Retroviruses and Opportunistic Infections; March 5–8; Seattle, WA. 2012. p. 463
28. [Keegan MR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Keegan%20MR%5BAuthor%5D&cauthor=true&cauthor_uid=30478800), [Winston A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Winston%20A%5BAuthor%5D&cauthor=true&cauthor_uid=30478800), [Higgs C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Higgs%20C%5BAuthor%5D&cauthor=true&cauthor_uid=30478800), et al. Tryptophan metabolism and its relationship with central nervous system toxicity in people living with HIV switching from efavirenz to dolutegravir. [J Neurovirol.](https://www.ncbi.nlm.nih.gov/pubmed/30478800) 2018 Nov 26. doi: 10.1007/s13365-018-0688-3.
29. [Seyedsadjadi N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Seyedsadjadi%20N%5BAuthor%5D&cauthor=true&cauthor_uid=30114226), [Berg J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Berg%20J%5BAuthor%5D&cauthor=true&cauthor_uid=30114226), [Bilgin AA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bilgin%20AA%5BAuthor%5D&cauthor=true&cauthor_uid=30114226), [Braidy N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Braidy%20N%5BAuthor%5D&cauthor=true&cauthor_uid=30114226), [Salonikas C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Salonikas%20C%5BAuthor%5D&cauthor=true&cauthor_uid=30114226)and [Grant R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Grant%20R%5BAuthor%5D&cauthor=true&cauthor_uid=30114226). High protein intake is associated with low plasma NAD+ levels in a healthy human cohort. [PLoS One.](https://www.ncbi.nlm.nih.gov/pubmed/30114226) 2018 Aug 16;13(8):e0201968.
30. Strasser B, Gostner JM, Fuchs D. Mood, food and cognition: role of tryptophan and serotonin. Curr Opin Clin Nutr Metab Care. 2016;19:55–61
31. Dahl V, Peterson J, Fuchs D, Gisslen M, Palmer S, Price RW. Low levels of HIV-1 RNA detected in the cerebrospinal fluid after up to 10 years of suppressive therapy are associated with local immune activation. AIDS. 2014;28(15):2251-8
32. Hagberg L, Cinque P, Gisslen M, Brew BJ, Spudich S, Bestetti A, et al. Cerebrospinal fluid neopterin: an informative biomarker of central nervous system immune activation in HIV-1 infection. AIDS Res Ther. 2010;7:15.
33. Dahl V, Lee E, Peterson J, Spudich SS, Leppla I, Sinclair E, et al. Raltegravir treatment intensification does not alter cerebrospinal fluid HIV-1 infection or immunoactivation in subjects on suppressive therapy. J Infect Dis. 2011;204(12):1936-45.
34. [Letendre SL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Letendre%20SL%5BAuthor%5D&cauthor=true&cauthor_uid=24944232), [Mills AM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mills%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=24944232), [Tashima KT](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tashima%20KT%5BAuthor%5D&cauthor=true&cauthor_uid=24944232), et al; [extended ING116070 study team](https://www.ncbi.nlm.nih.gov/pubmed/?term=extended%20ING116070%20study%20team%5BCorporate%20Author%5D). ING116070: a study of the pharmacokinetics and antiviral activity of dolutegravir in cerebrospinal fluid in HIV-1-infected, antiretroviral therapy-naive subjects. [Clin Infect Dis.](https://www.ncbi.nlm.nih.gov/pubmed/24944232) 2014 Oct;59(7):1032-7
35. [Elliot ER](https://www.ncbi.nlm.nih.gov/pubmed/?term=Elliot%20ER%5BAuthor%5D&cauthor=true&cauthor_uid=29771285), [Wang X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wang%20X%5BAuthor%5D&cauthor=true&cauthor_uid=29771285), [Singh S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Singh%20S%5BAuthor%5D&cauthor=true&cauthor_uid=29771285), et al. Increased Dolutegravir Peak Concentrations in People Living With Human Immunodeficiency Virus Aged 60 and Over, and Analysis of Sleep Quality and Cognition. [Clin Infect Dis.](https://www.ncbi.nlm.nih.gov/pubmed/?term=cognitive+AND+Dolutegravir) 2019 Jan 1;68(1):87-95

**Table 1.** Patient demographics and clinical characteristics

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter**  Mean (SD) unless otherwise stated | **Overall** | **Study arms** | |
| Control Arm | Switch Arm |
| N | 21 | 8 | 13 |
| Age, years (IQR) | 43 (11.5) | 39.5 (15.5) | 43 (13) |
| Male, n (%)  Ethnicity (%)  White  Black  Other | 20 (95.2)  14 (66.7)  2 (9.5)  5 (23.8) | 7 (87.5)  5 (62.5)  1 (12.5)  2 (25) | 13 (100)  9 (69.2)  1 (7.7)  3 (23) |
| BMI | 26.1 (3.2) | 27.4 (3.4) | 25.4 (2.9) |
| Baseline absolute CD4+ count (cells/µL) | 717 (298) | 688 (395) | 736 (237) |
| Baseline CD4+ percentage, median (IQR) | 34 (14.5) | 35.5 (24.2) | 34 (13) |
| Day 120 parameters | | | |
| Number completing all study procedures | 20 | 8 | 12 |
| HIV RNA <20 copies/mL, n (%) | 20 (100) | 8 (100) | 12 (100) |
| Absolute CD4+ count (cells/uL) | 768 (389) | 807 (535) | 742 (277) |

Table 1 legend: SD = standard deviation, IQR = interquartile range, BMI=body mass index.

**Table 2.** Changes in cognitive function and patient reported outcome measures by study arm at day 120

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline** | |  | **Changes at day 120 from baseline** | | | |
| **Control arm** | **Switch arm** |  | **Control arm** | **Switch arm** | **Difference Control vs. Switch arm** | |
| N=8 | N=12 |  | N=8 | N=12 | Mean score difference (95%CI) | *P-value* |
| **Cognitive testing**, Z- score\* (SD) | | | | | | | |
| Global cognitive score | 0.25 (0.54) | -0.15 (0.70) |  | 0.14 (0.37) | 0.14 (0.40) | -0.004 (-0.38/0.37) | 0.98 |
| **Patient reported outcome measures**, median (range) | | | | | | | |
| Patient Health Questionnaire-9 | 2 (0/6) | 2 (0/9) |  | 0 (-5/1) | -0.5 (-5/3) | - | 0.57\*\* |
| Beck’s depression questionnaire | 3 (1/12) | 1 (0/20) |  | -1.5(-10/2) | -1.0 (-15/9) | - | 0.38\*\* |

Table 2 legend: SD = standard deviation; CI = confidence interval;

\* lower result represents worse performance; higher results represent better performance. \*\*Independent samples Mann-Whitney U-test

**Table 3.** Changes in cerebral metabolites over 120 days and correlations with PROMs (depression questionnaires)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cerebral metabolite ratios** | **Baseline values, mean (SD)** | | **Change between study groups over 120 days, mean (SD)** | | | **Correlation with change**  Correlation coefficient (P-value) | |
|  | Control arm | Switch arm | Control arm | Switch arm | Control vs. Switch arm |  |  |
|  | n=8 | n=12 | n=7 | n=12 | *P-value* | PHQ-9\* | *Beck’s\** |
| Frontal Grey Matter |  |  |  |  |  |  |  |
| NAA/Cr | 1.04 (0.11) | 1.00 (0.09) | -0.06 (0.16) | 0.08 (0.14) | 0.07 | -0.38 (0.10) | -0.22 (0.36) |
| Cho/Cr | 0.22 (0.02) | 0.24 (0.03) | 0.01 (0.02) | -0.01 (0.04) | 0.21 | 0.43 (0.06) | 0.36 (0.13) |
| mI/Cr | 0.57 (0.06) | 0.58 (0.11) | 0.04 (0.03) | 0.07 (0.41) | 0.85 | 0.13 (0.60) | -0.27 (0.25) |
| Frontal White Matter |  |  |  |  |  |  |  |
| NAA/Cr | 1.28 (0.41) | 1.16 (0.15) | -0.13 (0.34) | 0.01 (0.13) | 0.20 | -0.18 (0.44) | 0.08 (0.73) |
| Cho/Cr | 0.32 (0.04) | 0.31 (0.04) | 0.004 (0.05) | 0.01 (0.05) | 0.75 | -0.26 (0.28) | -0.07 (0.78) |
| mI/Cr | 0.71 (0.19) | 0.63 (0.12) | 0.02 (0.05) | 0.005 (0.11) | 0.82 | 0.09 (0.72) | -0.01 (0.95) |
| Right Basal Ganglia |  |  |  |  |  |  |  |
| NAA/Cr | 0.97 (0.18) | 0.92 (0.20) | -0.13 (0.24) | .0066 (0.33) | 0.35 | -0.06 (0.80) | 0.006 (0.98) |
| Cho/Cr | 0.25 (0.02) | 0.23 (0.02) | -0.03 (0.03) | -0.004 (0.05) | 0.21 | -0.03 (0.89) | 0.14 (0.56) |
| mI/Cr | 0.48 (0.10) | 0.38 (0.10) | -0.04 (0.10) | 0.07 (0.19) | 0.16 | 0.10 (0.65) | 0.23 (0.33) |

Table 3 legend: SD= standard deviation; PHQ-9= Patient Health Questionnaire-9; NAA= N-acetyl aspartate; Cr= creatinine; Cho= choline; mI= myoinositol.

\* Correlation between change in cerebral metabolite ratios over 120 days and change in questionnaires over 120 days.

**Table 4.** Pharmacokinetic parameters of integrase inhibitors in plasma and CSF over study period.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Antiretroviral concentration(ng/mL)** | **Overall**  **N=20** | | | **Control arm**  **N=8** | | **Switch arm**  **N=12** | |
|  | GM (95%CI) | | CV% | GM (95%CI) | CV% | GM (95%CI) | CV% |
| **Raltegravir at baseline** | | | | | | | |
| Plasma | 116 (66-204) | 93.8 | | 102 (34-310) | 109.9 | 126 (59-266) | 87.6 |
| CSF\* | 15.4 (10.5-22.4) | 66.3 | | 16.2 (9.4-27.9) | 60.6 | 14.8 (8.2-26.8) | 72.0 |
| CSF:Plasma % | 13.0 (8.6-19.4) | 122.9 | | 15.8 (6.4-39.3) | 125.7 | 11.2 (7.4-17.0) | 51.7 |
| **Raltegravir at follow-up** | | | | | | | |
| Plasma | - | | - | 107 (39-293) | 113.6 | - | - |
| CSF | - | | - | 15.0 (8.6-26.3) | 73.5 | - | - |
| CSF:Plasma % | - | | - | 14.0 (7.3-26.9) | 74.7 | - | - |
| **Dolutegravir at follow-up** | | | | | | | |
| Plasma | - | | - | - | - | 1052 (742-1492) | 58.3 |
| CSF | - | | - | - | - | 7.6 (5.2-11.1) | 54.7 |
| CSF:Plasma % | - | | - | - | - | 0.7 (0.6-0.8) | 28.4 |

Table 4 legend: CSF= cerebrospinal fluid; GM=geometric mean; CV= coefficient of variation.

\*One patient with [RAL]CSF<LLQ (1.950 ng/ml) in switch group

**Table 5.** Tryptophan metabolism parameters in plasma and CSF over study period

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | | Baseline result | | Changes at 120 days | | |
|  |  | Control arm (RAL)  n=8 | Switch arm (DTG)  n=12 | Control arm (RAL)  n=8 | Switch arm  (DTG)  n=12 | Control vs. Switch arm  *P-value\** |
| **Plasma** | | | | | | |
|  | TRP; µmol/L, mean (SD) | 51.15  (10.56) | 50.15  (8.03) | -4.06  (6.61) | 4.84  (7.12) | 0.011 |
| KYN; µmol/L, mean (SD) | 1.98  (0.78) | 2.07  (0.69) | -0.06  (0.40) | 0.10  (0.64) | 0.541 |
| KYN/TRP ratio; µmol/mmol, mean (SD) | 38.82  (12.90) | 41.15  (9.49) | 3.24  (11.63) | -0.55  (12.60) | 0.506 |
| PHE; µmol/L, mean (SD) | 61.65  (7.55) | 58.38  (9.05) | -3.83  (11.36) | 3.82  (8.90) | 0.109 |
| TYR; µmol/L, mean (SD) | 65.34  (8.49) | 65.44  (15.00) | -1.38  (14.82) | 3.78  (10.76) | 0.378 |
| PHE/TYR ratio; µmol/mmol, mean (SD) | 0.96  (0.15) | 0.92  (0.18) | -0.03  (0.17) | 0.01  (0.14) | 0.589 |
| NEO; nmol/L, mean (SD) | 11.83  (8.50) | 12.30  (5.89) | 3.61  (11.55) | 5.23  (15.42) | 0.803 |
| **Cerebrospinal fluid** | | | | | | |
|  | TRP; µmol/L, mean (SD) | 1.58  (0.68) | 1.67  (0.26) | 0.02  (0.33) | 0.17  (0.43) | 0.406 |
|  | KYN; µmol/L, mean (SD) | 0.07  (0.03) | 0.06  (0.03) | -0.01 a  (0.01) | 0.01 b  (0.01) | 0.130 |
|  | KYN/TRP ratio; µmol/mmol, mean (SD) | 43.39  (29.17) | 38.77  (15.78) | -5.27 a  (10.95) | -0.48 b  (10.79) | 0.513 |
|  | PHE; µmol/L, mean (SD) | 12.31  (2.43) | 11.73  (2.02) | -0.33  (1.60) | 0.22  (2.17) | 0.553 |
|  | TYR; µmol/L, mean (SD) | 12.38  (3.28) | 11.83  (2.61) | -0.14  (2.81) | 0.82  (1.94) | 0.379 |
|  | PHE/TYR ratio; µmol/mmol, mean (SD) | 1.01  (0.10) | 1.01  (0.16) | 0.00  (0.18) | -0.04  (0.14) | 0.565 |
|  | NEO; nmol/L, mean (SD) | 9.19  (8.20) | 7.70  (4.26) | -1.93  (2.54) | 0.23  (2.03) | 0.049 |

Table 5 legend: RAL, raltegravir; DTG, dolutegravir; SD= standard deviation; CI=Confidence interval; KYN=kynurenine; TRP=tryptophan; PHE=phenylalanine; TYR=tyrosine; NEO=neopterin.

\* Unadjusted P-value; a n=4; b n=6.

**Supplementary Figure 1:**

Consort diagram of participant flow



Supplementary Figure 1 legend: FTC=emtricitabine; TDF=tenofovir disoproxil fumarate, RAL= raltegravir; DTG=Dolutegravir; MRI=magnetic resonance resonance imaging; LP=lumbar puncture; ARV=antiretroviral.