COMPARISON OF THE EFFECTS OF INTEGRASE INHIBITORS AND EFAVERENZ ON BRAIN BIOCHEMISTRY

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TARGET AUDIENCE: Researchers and clinicians interested in the use of magnetic resonance spectroscopy (MRS) for assessing the effects of antiretroviral therapy (ART) for human immunodeficiency virus (HIV)

BACKGROUND: Many classes of effective antiretroviral therapy are now available for the over 35 million individuals worldwide currently living with HIV[1]. While ART has dramatically improved the overall health of those infected with HIV, studies have suggested that HIV-associated neurocognitive disorders (HAND) are present in 40% of treated patients[2]. Efavirenz (EFV) is a highly effective agent and one of the first-line therapies for HIV infection. However, it is known to be one of the agents which causes central nervous system toxicity. Common side effects with EFV use include depression, anxiety, and insomnia[3] and direct neurotoxic effects have been shown[4]. Given the increased risks of these neurocognitive symptoms this agent may need to be used with caution for vulnerable populations, such as older patients[5] as the HIV population ages. Integrase inhibitors, the newest class of antiretrovirals, have been shown to be highly effective and well tolerated by patients[6]. This study aims to determine whether switching from an EFV-based regimen to an integrase inhibitor-based regimen would produce milder neurotoxic side effects using MRS to measure biological changes associated with these clinical symptoms.

MRS is well suited for measuring the neurophysiological effects of EFV. Neurochemical changes which are associated with HAND include decrease in N-acetylaspartate (NAA)[7] and higher choline (Cho) with worsening HAND[8]. Furthermore, ɣ-amino butyric acid (GABA), an inhibitory neurotransmitter, has been found to be reduced in conditions related to HAND such as insomnia[9], depression[10], and anxiety[11]. Therefore, this marker can potentially be used to monitor the effects of treatment[11].We, therefore, propose a prospective single arm study to evaluate changes in brain chemistry associated with switch of EFV to an integrase inhibitor in relatively asymptomatic HIV-infected patients.

METHODS: Seven HIV-infected patients (age: 46 ± 8.9, 5 males) who had been on EFV-based therapy for at least greater than 6 months with undetectable virus were recruited, consented and enrolled by the Partners IRB. Patients with other co-morbidities which could affect neuroimaging results, such as CNS infection or neurological disorders, were excluded from the study. Each subject was scanned at baseline during EFV-based ART and then after 8 weeks of ART switch to an integrase inhibitor with the same backbone ART combination of emtricitabine and tenofovir using the same protocol. The scanner used to monitor the participants was a Siemens 3T Skyra scanner with a 32-channel head coil. There were two MRS methods performed during this experiment: 1) 1D single voxel spectroscopy (SVS) using conventional PRESS and 2) 2D spectral MRS using single-voxel localized correlated spectroscopy (2D COSY). Voxels were acquired using 64 increments of 0.8 ms with a starting TE=30 ms and 8 averages. Voxels were positioned at the posterior (PCG) and anterior (ACG) cingulate gyrus. 1D data was post-processed using LCModel, 2D COSY using FelixNMR. The peak used to measure GABA was found at approximately 3.0PPM on the F1 axis and 1.9PPM on the F2 axis. The peak used to measure creatine was found at approximately 3.0PPM along both F1 and F2 axes. Metabolites were expressed as ratios to creatine (Cr+PCr), the reference metabolite throughout the study.

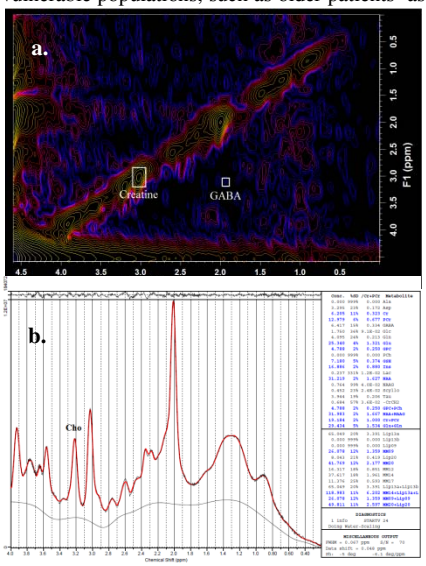

Fig. 1. a. 2D COSY spectrum of the PCG of Patient #4, GABA marked **b.** LCModel-processed 1D SVS spectrum of the PCG of Patient #4, choline marked

RESULTS: In the 2D COSY data of the PCG (example in Fig. 1a), the GABA/Cr ratios were found to be significantly increased ($p < 0.05$) after switching treatments (Fig. 2). Mean GABA/Cr ratios were 0.0117 ± 0.00314 BEFORE and 0.0173 ± 0.00654 AFTER. In 6 out of 7 cases, GABA levels were found to be increased after treatment. In the 1D SVS data of the PCG (example in Fig. 1b), a small but statistically significant increase in the GPC+PCh (choline)/Cr+PCr ratio was detected (Fig. 3). Mean Cho/Cr ratios were 0.213 ± 0.0222 BEFORE and 0.222 ± 0.0244 AFTER. In 6 out of 7 cases, Cho/Cr levels were found to be increased after treatment. For most metabolites, the data did not indicate any differences between the BEFORE and AFTER concentrations, most notable of which include NAA, myoinositol, and glutamate. No significant differences in metabolite concentrations were found in both 1D and 2D MRS data of the ACG.

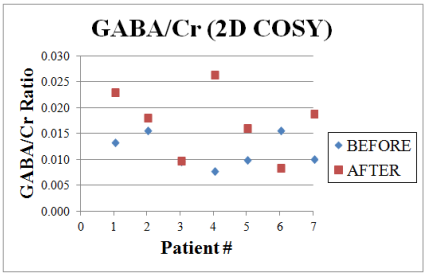

Fig. 2. Scatterplot of BEFORE and AFTER Cho/Cr ratios of 1D PCG data

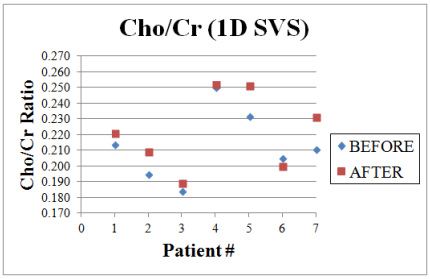

Fig. 3. Scatterplot of BEFORE and AFTER GABA/Cr ratios of 2D PCG data

DISCUSSION/CONCLUSION: HAND was found to be associated with significantly lower parietal glutamate levels among individuals with HIV[11]. In many mood disorders, including both depression and anxiety, GABA has found to be decreased[10]. Therefore, with increasingly milder neurotoxic effects, increased presences of glutamate and GABA are expected. While no change in glutamate was demonstrated in this study, the GABA/Cr ratio did indeed show significant increase. This result is in line with the hypothesis that HIV patients switching to an integrase inhibitor-based regimen may experience decreased side effects to the CNS. The increase in Cho/Cr was unexpected. Previous studies have shown the increase in Cho/Cr in HAND is thought to be due to microglial activation.

This pilot study gives evidence that neurometabolic differences between HIV-infected patients exist with different ART and could be an effective non-invasive method to measure neurotoxicity of ART. Future studies should be performed to further enhance our understanding of these clinically relevant differences and their potential in understanding the underlying mechanism of HAND, specifically the contribution of ART neurotoxicity.

REFERENCES: [1]UNAIDS. *GAP Report*; 2013. [2] Sacktor, N. J Neurovirol. (2002), [3] Clifford, D.B., et al. Ann Intern Med. (2005) [4] Marzolini, C., et al. Aids. (2001) [5] Gandhi, N.S., et al. HIV Ther. (2010) [6] Nguyen, A., et al. Aids. (2011) [7] Holt, J.L., et al. J Neurovirol. (2012) [8] Chang, L., et al. Neuroimage. (2004) [9] Winkelman, J.W., et al. Sleep. (2008) [10] Levy, L.M. and A.J. Degnan.. AJNR (2012) [11] Ernst, T., et al. J Magn Reson Imaging. (2010)