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Antiretroviral treatment is generally highly effective in controlling HIV replication in the central nervous system (CNS) although resistance associated mutations may be locally selected[(1)]. Drug passage into the CNS is known to be variable, being influenced by several parameters such as protein binding, molecular weight, lipophilicity, ionization as well as by the presence of membrane transporters. According to a recently defined CNS drug penetration/effectiveness score, which was found to be associated to a significantly lower risk of viral replication in the cerebrospinal fluid (CSF), tenofovir and emtricitabine are classified as drugs with poor and good penetration, respectively.[(2)] However, a high interindividual variability of drug passage was recorded in pharmacokinetic studies. In this setting the possible role of disrupted BBB deserves consideration, since altered BBB has been frequently reported in asymptomatic HIV-positive patients (2 to 22%) and in up to 100% of those with HIV-associated encephalitis.[(3-4)] In other neurological diseases[(5)]drug penetration into CSF is known to be significantly affected by disruption of BBB, but only limited evidence of this is available in case of HIV-infected patients receiving antiretroviral treatment.[(6)]

We thus performed a pilot clinical study to investigate the effect of blood-brain barrier disruption on

tenofovir and emtricitabine passage into the CSF. HIV-positive patients under treatment with Truvada®-containing regimens who underwent a lumbar puncture for clinical reasons after having signed an informed consent were enrolled. Plasma and CSF tenofovir and emtricitabine concentrations were measured through a validated HPLC-MS system with a limit of detection of 2 and 1.5 ng/ml, respectively.[7] Albumin and IgG were measured both in plasma and CSF and albumin and IgG ratios were calculated; the Reiber index was used to evaluate BBB disruption. Data are expressed in median (interquartile range); association between variables were determined by Spearman test through SPSS 18.0 (SPSS Inc, Chicago, IL, USA).

Twenty-one patients were enrolled: 11 (52.4%) were male aged 38 (34-50) years old and presenting a BMI of 21.7 (20-24.3) Kg/m^2. Drugs other than Truvada® were mostly boosted protease inhibitors (66.7%) followed by NNRTIs (28.5%). Lumbar punctures were mainly performed to investigate neurocognitive disorders (29%) and MRI abnormalities (14%) and to follow-up opportunistic diseases (29%, non-hodgkin lymphomas, neurotoxoplasmosis and tubercular menigitis). Blood-brain barrier was altered in 9 (42.8%) patients with albumin and IgG ratios respectively of 5.2 (4.7-8) and 5.4 (3.5-8).

Plasma and CSF were sampled at different time points but within 15 minutes from each other: median time after drug intake was 15 hours (13.8-19.4). Tenofovir and emtricitabine plasma concentrations were respectively 49 ng/ml (29.5-114) and 212 ng/ml (86.5-445.5). Tenofovir (TDF) CSF median concentration was 6 (<2-8) ng/ml, and a linear correlation with plasma concentrations (p=0.018) emerged. TDF CSF-to-plasma ratio was 0.05 (0-0.13). Emtricitabine (FTC) CSF median concentration was 68 (2.5-98) ng/ml, with a significant correlation to plasma concentrations (p=0.02). FTC CSF-to-plasma ratio was 0.26 (0.05-0.41). A significant correlation between tenofovir and emtricitabine CSF-to-plasma ratios emerged (rho=0.74, p=0.002) (Fig.1a). Both TDF and FTC ratios directly correlated to albumin ratios (respectively rho=0.5 and p=0.02 and rho=0.05 and p=0.05) (Fig.1b and 1c); TDF ratios were correlated to IgG ratios (rho=0.48, p=0.03).

Some limitations of our study should be pointed out: a limited sample size, heterogeneous clinical

conditions and a single sample per patient could potentially impact on our results. Nevertheless, being blood-brain barrier abnormalities common during the course of HIV infection and pharmacokinetics parameters widely variable, these observations could improve our knowledge on CNS penetration of antiretroviral drugs.

In our patients, CSF-to-plasma ratios varied from 0 to 13% (for tenofovir) and from 5 to 41% (for emtricitabine) although median values were comparable to the ones reported in the literature.[8-9] The ratios of these two drugs with similar characteristics (high molecular weight and protein binding) were significantly correlated to each other, which suggests that the CSF penetration of both drugs can be influenced by common mechanisms and by alterations in the permeability of the BBB. Since both drugs seem to penetrate better in patients with altered BBB, we wonder whether barrier integrity should be considered as a factor potentially determining central nervous system concentrations. Barrier integrity might thus contribute to the high inter-individual variability of drug penetration into the CNS. Our findings provide support to the recently suggested[10] correlation between altered albumin ratios and the prevalence of HAND in a cohort of HAART-treated individuals, although larger cohorts need to be studied before conclusive validation of this interpretation can be established.

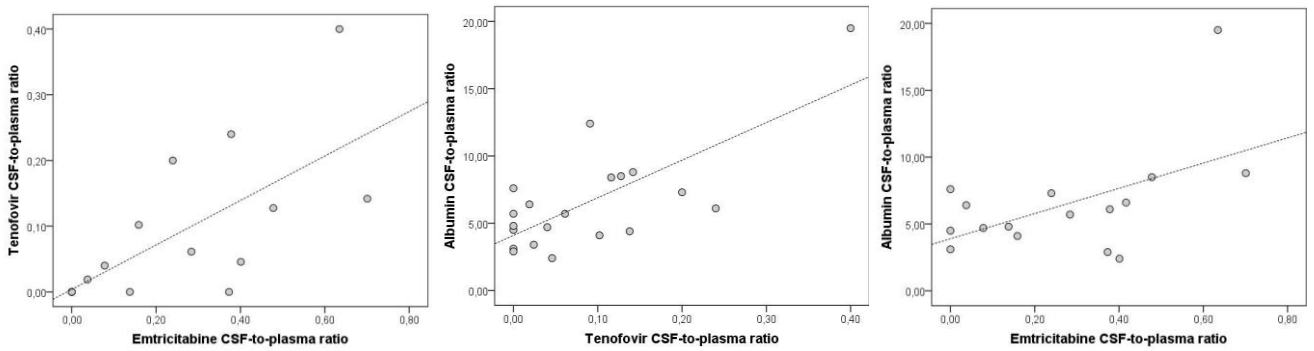

Figure 1. Scatter-dot plot of tenofovir and emtricitabine CSF-to-plasma ratios (1a), tenofovir and albumin CSF-to-plasma ratios (1b) and emtricitabine and albumin CSF-to-plasma ratios. Trendlines are represented as continuous lines.

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