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## Cerebrospinal Fluid Abacavir Concentrations in HIV-positive Patients Following Once-daily Administration

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1 **Cerebrospinal Fluid Abacavir Concentrations in HIV-positive Patients Following Once-daily**  
2 **Administration**

3  
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34

35

36 **Abstract**

37 **Abacavir is a widely used nucleotide reverse transcriptase inhibitor whose cerebrospinal fluid**  
38 **(CSF) exposure has been previously assessed in twice-daily recipients. We studied abacavir**  
39 **CSF concentrations in 61 and 9 HIV-positive once-daily and twice-daily abacavir intakers.**  
40 **Patients on once-daily abacavir had higher plasma and CSF concentrations (96 vs. 22 ng/mL,**  
41 **p=0.038 and 123 vs. 49 ng/mL, p=0.038) but similar CSF-to-plasma ratios (0.8 vs. 0.5,**  
42 **p=0.500). CSF abacavir concentrations were adequate in once-daily receiving patients.**

43

44 **Introduction**

45 [Abacavir](#) (ABC) is a largely used once-daily HIV nucleoside reverse transcriptase inhibitor  
46 included in first-line regimens by international guidelines.(1) Even though the clinical relevance is  
47 debated, higher penetration of antiretrovirals into the cerebrospinal fluid (CSF) has been associated  
48 with a lower concentrations of CSF HIV RNA and, in some studies, with better cognitive  
49 function.(2)(3) The concentration penetration/effectiveness score (CPE) ranks ABC as 3 (out of 4)  
50 and therefore the compound has been included within the medium-high score stratus. However  
51 most of the data were generated with the 300 mg twice-daily dose: its CSF to plasma ratio (CPRs)  
52 was reported to be 36% (28-46) although with significant variability.(4) The aim of this study was  
53 to compare CSF concentrations (and CPRs) in patients administered once versus twice-daily ABC.

54

55 **Methods**

56 ABC-administered patients undergoing lumbar punctures for clinical reasons or included in  
57 longitudinal studies were included in Turin (Ospedale Amedeo di Savoia, ASL "Città di Torino")  
58 and Rome (Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani"); signed informed  
59 consent was given by all subjects and ethics approval was obtained by each Institution (Comitato  
60 Etico Interaziendale di Orbassano, n. 103/2015). Plasma and CSF samples were concomitantly  
61 obtained (less than 30 minutes apart). ABC concentrations were measured at steady state in the  
62 same externally validated laboratory (University of Torino) through a validated HPLC/MS-MS  
63 method (with a limit of detection of 4.88 ng/mL).(5) Trough concentrations were those withdrawn

64 21-27 (once-daily) and 10-14 (twice-daily) hours after drug intake.  
65 CSF to serum albumin ratio (CSAR, calculated as CSF albumin (mg/L)/serum albumin (g/L)), was  
66 used to evaluate BBB function. BBB damage definition was derived from age-adjusted  
67 Reibergrams (normal if below 6.5 in patients aged <40 years and below 8 in patients >40 years).(6)  
68 Data are expressed as medians (interquartile range) and compared through non-parametric tests  
69 (Spearman's test for linear correlation and Mann-Whitney or Kruskal-Wallis for when a categoric  
70 variable was compared with a linear one). All concentrations were used for identifying predictors of  
71 CSF penetration while only trough values were used for comparing once and twice-daily  
72 administration. Coefficients of variation (CV) are calculated as the ratio between the standard  
73 deviation and the mean.

74 Key ligands in this article are hyperlinked to corresponding entries in PubChem, the Open  
75 Chemistry Database, available at <https://pubchem.ncbi.nlm.nih.gov>.

76

## 77 Results

78 70 patients (85.7% male, 95% Caucasians) were included; age (years) and BMI (kg/m<sup>2</sup>) were 50.2  
79 (46.2-58.7) and 23.4 (20.9-25.6), respectively In 60 patients chronic hepatitis status was known: 21  
80 (35%) per HCV+, 3 (5%) were HBV+ and 6 (10%) had a previous diagnosis of liver cirrhosis.  
81 Fourty four subjects (62.8%) were asymptomatic and received LPs for non Hodgkin's lymphoma  
82 staging (33, 47.1%, ) or in the context of longitudinal studies (11, 15.7%); among the remaining 26  
83 patients HIV-encephalopathy (8, 11.4%), HIV-associated neurocognitive impairment (6, 8.6%),  
84 CNS opportunistic infections (6, 8.6%) and various neurological presentations (6 including two  
85 cases of seizures of new onset). Baseline features are listed in Table 1.

86 Most frequent co-administered drugs were PIs (67.1 %) followed by NNRTIs (28.6%), NRTIs-only  
87 (5.7%) and INSTIs (5.7%). CD4+ T lymphocyte cell count was 302/uL (137-462). After excluding  
88 patients with plasma HIV RNA >1000 copies/mL (n=3), 62 subjects had available plasma and CSF  
89 HIV RNA: they were below 50 copies/mL in 47 (74.6%) and 43 (68.3%) subjects. CSF escape  
90 (defined as detectable HIV RNA in CSF while undetectable in plasma or CSF HIV RNA  $\geq 1$  Log<sub>10</sub>

91 higher than plasma level) was observed in 13 individuals (20.6%); no association was observed  
92 between ABC levels, detectability or schedule of administration and the prevalence of CSF escape.  
93 Samples were withdrawn over the range interval but after a median of 12 hours (12-20) after drug  
94 intake; 18 were trough samples. Median ABC plasma and CSF concentrations were 58 ng/mL (<1-  
95 815, CV=140%) and 106 ng/mL (21-304, CV=149%). ABC CPRs ranged from 0 to 4.92 [median  
96 0.80, IQR (0.17-1.87), CV=99%]. Among those with undetectable plasma concentrations (17, 25%),  
97 9 were non-detectable in the CSF while 8 showed low but detectable CSF concentrations [35 ng/mL  
98 (11-67)]. A direct correlation was observed between ABC plasma concentrations and time from  
99 drug intake ( $\rho=0.406$ ,  $p=0.005$ ); this was not observed for CSF concentrations ( $\rho=0.212$ ,  
100  $p=0.148$ ) and CPRs ( $\rho=-0.092$ ,  $p=0.582$ ).

101 The drug was administered once-daily in 61 (87.1%) patients; CSF ABC concentrations over time  
102 are shown in figure 1 (stratified by frequency of intake). The two groups' baseline characteristics  
103 were comparable with the exception of non-significantly higher CD4 cell count (332 vs. 155/uL,  
104  $p=0.062$ ) in the once-daily group. Patients on once-daily ABC had higher plasma and CSF  
105 concentrations (96 vs. 22 ng/mL,  $p=0.038$  and 123 vs. 49 ng/mL,  $p=0.038$ ) but CPRs were similar  
106 (0.8 vs. 0.5,  $p=0.500$ ). Trough values showed the same trend: higher plasma concentrations (1377  
107 vs. <4.88 ng/mL,  $p=0.02$ ) but similar CSF values (152 vs. 24 ng/mL,  $p=0.08$ ) and CPRs (0.2 vs. 0,  
108  $p=0.08$ ). In once-daily recipients CSF ABC concentrations were associated with ABC plasma levels  
109 ( $\rho=0.865$ ,  $p<0.001$ ) and, weakly, with age ( $\rho=0.275$ ,  $p=0.046$ ): patients receiving PIs had higher  
110 CSF [220 (64-529) vs. 70 (17-134) ng/mL,  $p=0.013$ ] and plasma [500 (35-1531) vs. 42 (<4.88-100)  
111 ng/mL,  $p=0.002$ ] concentrations. HCV+ once-daily recipients showed higher CPR as compared to  
112 HCV- subjects [1.57 (0.80-2.35) vs. 0.36 (0.12-1.28),  $p=0.007$ ].

113 CSAR were available in 28 patients: median value was 5.35 (4.12-6.87) with 4 individuals (14.3%)  
114 presenting an altered blood brain barrier permeability. No linear correlation was observed between  
115 CSAR and ABC CSF concentrations or CSF to plasma ratios (as well as no effect of an impaired  
116 BBB was noted).

117 No difference was observed in ABC CSF to plasma ratios according to neurological confounding  
118 conditions and or CSF HIV-1 escape (Kruskal-Wallis and Mann-Whitney tests  $p$  values > 0.05).

119

120 Discussion

121 In this small study we observed that patients on once-daily abacavir had CSF ABC concentrations  
122 and CSF to plasma ratios higher than previously reported (in median 80%). Our control group of  
123 twice-daily recipients was small (n=9) but showed higher CPRs than what reported by Capparelli  
124 (36%) and Antinori (4%).(7) This may be explained by the significant interpatient variability, by the  
125 concomitant use of PIs (not reported in the previous studies) and potentially by the older age of our  
126 patients. Protease inhibitors may influence drug penetration by inhibiting drug efflux transporters  
127 such as p-glycoprotein and breast cancer resistant protein as shown in vitro by Marzolini et al.(8)  
128 Age may be a contributing factor in increasing drug concentration in the CSF: increased blood brain  
129 barrier permeability, lower CSF production and reduced transporters' function have been suggested  
130 in older adults.(9)(10) The only available, but yet unpublished, study reported a steep increase in  
131 CSF tenofovir and efavirenz concentration with increasing age.(11) Additionally a high prevalence  
132 of CSF escape was observed and this may have influenced our results (in terms of confounding  
133 conditions or pharmacokinetic features following ongoing inflammation). Nevertheless when  
134 abacavir (coadministered with lamivudine and dolutegravir) was administered to naïve patients an  
135 excellent efficacy in the CSF (both 2 and 16 weeks after treatment initiation) confirming the drug  
136 compartmental efficacy when used in combination with other active compounds.(12)

137 Limitations of current analysis include the small sample size, the inclusion of single time points and  
138 non-trough concentrations. ABC CSF concentrations and CPRs were however more stable over the  
139 time interval as compared to plasma levels and as previously reported by Cusini et al.(13)

140 In conclusion in once-daily abacavir treated HIV-positive patients, high CSF ABC and CSF to  
141 plasma ratios were observed suggesting the current CPE ranking may be appropriate even with the  
142 commonly used once a day schedule.

143

#### 144 **What is already known about this subject**

145 Abacavir is an efficacious HIV reverse transcriptase inhibitor; it is considered to be active in the  
146 central nervous system although most of the knowledge on the drug compartmental

147 pharmacokinetics was obtained in patients administered twice daily.

148

149 **What this study adds.**

150 Once daily administered abacavir is associated with cerebrospinal fluid concentrations and CSF to  
151 plasma ratios similar to what was observed in participants receiving the drug twice a day. Given the  
152 large use of this compound in single tablet regimens, this data support its  
153 neuropenetration/neuroefficacy profile.

154

155 **Acknowledgements**

156 This study was presented at the 9<sup>th</sup> Italian conference on AIDS and Antiviral Research, Siena, 2017.

157

158

159 **Tables**

	<b>Once Daily</b>	<b>Twice Daily</b>
	n or median (% or IQR)	
<b>n:</b>	61	9
<b>Age:</b> years	51 (46.4-58.1)	49.3 (43.7-60.1)
<b>Male gender:</b> n (%)	51 (83.6%)	9 (100%)
<b>BMI:</b> Kg/m <sup>2</sup>	23.4 (20.9-25.6)	25.2 (21.4-25.6)
<b>CD4:</b> Cells/uL	332 (137-524)	155 (130-275)
<b>CD4 nadir:</b> Cells/uL	132 (60-288)	94 (16-543)
<b>plasma HIV RNA:</b> Log <sub>10</sub> copies/mL	1.59 (<1.27-1.75)	1.65 (<1.27-2.17)
<b>CSF HIV RNA:</b> Log <sub>10</sub> copies/mL	1.59 (1.59-2)	1.59 (<1.27-2.03)
<b>CSF cells:</b> n/mm <sup>3</sup>	1 (0-3)	2 (1-6)
<b>CSF proteins:</b> mg/dL	42 (33-56)	39 (25-96)
<b>CSAR</b>	5.1 (4.0-6.0)	7 (6.8-7.6)
<b>Time after abacavir intake:</b> hours	13 (11.5-24)	12 (11.5-12.5)
<b>ARV classes:</b> NNRTI	20 (32.7%)	0
NRTIs only	2 (3.3%)	2 (22.2%)
PI	35 (57.4%)	7 (77.8%)
INSTI	4 (11.4%)	0
<b>Indication for LP:</b> Asymptomatic	7 (11.5%)	4 (44.4%)
HAND	6 (9.8%)	0
Neurological symptoms	4 (6.6%)	2 (22.2%)
HIV encephalopathy	7 (11.5%)	1 (11.1%)
CNS-opportunistic infections	6 (9.8%)	0
NHL	31 (50.8%)	2 (22.2%)

160

161 **Table 1. Baseline characteristics of the included patients stratified according to once-daily or**

162 **twice-daily abacavir intake.** “IQR”, interquartile range; “BMI”, body mass index; “CSF”,  
163 cerebrospinal fluid; “CSAR”, CSF to serum albumin ratio; “ARV”, antiretroviral; “NNRTI”, non  
164 nucleoside reverse transcriptase inhibitors; “NRTI”, nucleos(t)ide reverse transcriptase inhibitors;  
165 “PI”; protease inhibitor; “INSTI”, integrase strand transfer inhibitor; “LP”, lumbar puncture;  
166 HAND”, HIV-associated neurocognitive disorders; “CNS”, central nervous system; “NHL”, non  
167 Hodgkin’s lymphomas (screening for meningeal involvement).

168

169

## 170 **Figure Legends**

171

172 **Figure 1. Abacavir cerebrospinal fluid to plasma ratios according to time after dose and**  
173 **stratified for once or twice-daily schedule.**

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