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Cognitive Outcome in HIV-Individuals with cART Containing ABC/AZT

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Abstract

Objective: The aim of our study was to investigate whether an antiretroviral regimen including ABC and AZT can be used to improve or maintain neuropsychological and neurophysiological parameters and effectively suppress HIV Viral Load (VL) in the Cerebrospinal Fluid (CSF).

Design: An open prospective observational study

Methods: 11 HIV-infected patients of all disease stages were assessed at four visits: before combined antiretroviral treatment (cART) was started or changed as well as 6, 12 and 24 months later. At each visit subjects underwent comprehensive neuropsychological (NP) testing as well as neurological and neurophysiological exam. HIV VL was measured in paired plasma and CSF samples. NP results were compared to a historical untreated matched control group and correlated to HIV duration, viral load as well as CD4 nadir.

Results: 3 patients fulfilled the criteria of Asymptomatic Neurocognitive Impairment (ANI) at baseline. A group comparison to the untreated control group at baseline revealed significantly worse results in the study population in 4 cognitive domains: executive and visuoperceptual functions, figural memory and verbal fluency. Executive function correlated significantly with the CSF viral load. At the end of the observational time all treated study patients showed normal NP performance while the untreated controls deteriorated in motor functions.

Conclusions: HIV-individuals, who were treated with the CNS penetrating drugs ABC and AZT, have shown neurocognitive improvement compared to an untreated control group suggesting that this treatment may prevent neurocognitive impairment in HIV infection.

Keywords: HIV associated neurocognitive deficits; Abacavir; Zidovudine; Cerebrospinal fluid

Introduction

HIV is a neurovirulent virus which causes cognitive impairment in at least 50% of individuals with HIV infection [1,2]. HIV Associated Neurocognitive Disorders (HAND) include Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND) and HIV-Associated Dementia (HAD) [3]. They are classified according to patient performance in neuropsychological testing as well as activities of daily living and behavioural functioning [3,4]. Deficits are most commonly observed on measures of information processing speed, learning, retrieval, attention/working memory and executive functions [5-7].

From a neurological point of view, the key question is whether consistent treatment with antiretroviral therapy can protect cognitive functions. Since the widespread use of Combined Antiretroviral Therapy (cART), the incidence of HAD has dramatically decreased with an actual prevalence from 1 to 35% [8]. However, a significant amount of HIV-positive patients continue to suffer from mild neurocognitive impairment with an estimated prevalence of ANI/MND between 26-76% [3,4,8]. The efficacy of an antiretroviral substance is limited to a major extent by its "Central Nervous System (CNS) penetration", as substances with inadequate blood-brain transfer induce good "systemic" virus suppression but do not provide adequate CNS treatment. Inadequate HIV suppression in the CNS compartment causes immune activation with inflammation and secondary neurodegeneration, which is expressed in the form of the neuropsychological deficits described [9]. Letendre et al. developed CNS Penetration Effectiveness Scores (CPE) for better evaluation of CNS efficacy) [10,11] rating them as 1 (insignificant penetration), 2 or 3 (intermediate penetration), or 4 (high penetration). Based on pharmacokinetic data they have rated zidovudine as 4 and abacavir as 3 meaning excellent penetration efficacy. However another concern might be that cART, with its known mitochondrial toxicity, may prove to be neurotoxic over time, leading to progression of nervous system dysfunction despite adequate viral control. ANI/MND prevalence might be also increasing, due in part to the longer life expectancy for HIV infected individuals and the resistance to cART [12].

To address these concerns, we conducted a 24 months longitudinal evaluation of CNS performance in a group of subjects before and after the initiation of cART including ABC and AZT and compared them to an untreated historic control group. Preliminary data of this project were presented at the 4th conference of Neurovirology and the abstract published [13].

Methods

Subjects

The study was approved by the institutional review board. Each patient gave a written informed consent. Subjects were enrolled in the study if they were about to start cART or if, in the opinion of their infectious disease clinician, their current cART had failed and they required a different cART regimen. Exclusion criteria were defined by: 1) age under 18; 2) acute or previous opportunistic infections or neoplasm of the CNS; 3) CNS diseases independent of HIV infection; 4) acute systemic opportunistic infections or neoplasm; 5) drug addiction or polamidon substitution; 6) gravidity or nursing period.

Control group

An untreated HIV positive control group was included retrospectively in order to compare neurocognitive outcome to our individuals. The controls were selected from a databank Düsseldorf and were matched in age, education and duration of HIV infection as well as CD4 Nadir.

Study procedure

The baseline evaluation was conducted before starting or changing an antiretroviral regimen. Reevaluation was performed after 6 months of stable cART as well as after 12 and 24 months. At each evaluation, participants underwent a comprehensive neuromedical evaluation to assess medication use history and antiretroviral medications, neurological examination, a comprehensive Neuropsychological Testing (NPT) battery, event related potentials, nerve conduction measurement, a spinal tap and laboratory studies including CD4 counts.

Neurologic examination

The neurological evaluation assessed level of consciousness, cranial nerves, ocular motility, facial expression, limb strength, tonus, reflexes, coordination and sensibility. Neuropathy was defined as the presence of symptoms of numbness and/or pain in the feet with absent or depressed ankle reflexes and diminished perception of pain, temperature, and vibration in the feet.

Laboratory measures

Plasma and Cerebrospinal Fluid (CSF) HIV viral loads were quantified by reverse transcriptase-polymerase chain reaction (HIV-1-Monitor, HoffmannLaRoche) using the ultrasensitive assay (nominal lower limit of quantification, 50 copies/ml). CSF examination included cell count, protein concentration, protein differentiation according to Reiber and isoelectric focussing. Virological suppression was defined as a plasma HIV RNA level of <400 cop./ml after at least 2 months of initiating or changing cART.

Resistance testing

Paired plasma samples were collected concomitantly with a CSF sample. Genotypic resistance analysis for HIV in CSF and/or plasma samples was performed in patients with detectable viral loads, (ViroSeq HIV-1 genotyping system, Fa. Abbott) and the resistance predicted using the Stanford tool (URL Stanford Resistance tool).

Neuropsychological evaluation

All participants completed a comprehensive NP testing battery composed of measures that have been shown to be sensitive to HIV-Associated Neurocognitive Disorders (HAND). The specific domains assessed were attention, executive function, verbal memory, figural memory, visuoperceptual function and verbal fluency. The test battery consisted of Rey-Osterrieth Complex figure test [14], Rey auditory verbal learning test Rey visual design learning test [15], Stroop test [16], d-2-test [17] and the Benton controlled oral word association test [18].

For each of the NP test variables above, raw scores were converted to demographically corrected T-scores using published normative data. T-scores were transformed into so called deficit scores using the formerly published following conversions: ≥ 40T=0 (no impairment); 39-35T=1 (mild impairment); 34T-30T=2 (mild to moderate impairment); 29T-25T=3 (moderate impairment); 24T-20T=4 (moderate to severe impairment); and ≤ 19T=5 (severe impairment) [19]. Using this approach has the advantage that NP performances above or within limit were given less weight, while subtle deficits can be detected [19]. To obtain a measure of global NP functioning, the deficit scores from each NP test variable were averaged to create a Global Deficit Score (GDS) for each subject. Prior research supports the validity of the GDS as an indicator of global neuropsychological functioning in persons with HIV infection [19]. A score of 0.50 or above on the GDS indicates global impairment [6,19].

Participants also completed Beck Depression Inventory (BDI) [20] at all four assessments. The BDI is a well-known 21-question self-inventory with a four-point scale for measuring the severity of depression. The score can range from ≤ 10 (no depression), 11-17 (mild depression), 18-23 (moderate depression) to above 24 points (severe depression). For this study patients with a sum score above 10 were considered to be depressive.

A historical serially tested HIV positive control group was added retrospectively in order to exclude natural stability of cognitive functioning. The group was matched with respect to age, education, disease duration and CD4 nadir. We used comparable methods of subject assessments to classify Neurocognitive Impairment (NCI). The results were categorized into cognitive domains such as attention, executive function, verbal memory, figural memory, visuoperceptual function, motor speed (not done our study population) and verbal fluency. Testing scores were transformed into modified deficit scores and compared with the study population. A depression questionnaire was also done serially in the control group.

Event related potentials (ERPs)

Neuropsychological testing was combined with recording ERP´s, a more objective method for the intraindividual decline in cognitive functions. ERPs were recorded with a standardized classical auditory odd-ball paradigm on a Dantec Counterpoint Mk2 (version. 2.20). The auditory stimulus was delivered binaurally through headphones at an intensity of 70 dB and a frequency of 1 kHz for the frequent "non-target" tone (80%) or 2 kHz for the "target" tone (20%). The frequent-rare sequence was randomly presented with an interstimulus interval of 1-2 ms and tone duration of 50 ms. Subjects were instructed to close their eyes and to count the target stimuli mentally.

For recording we used Ag/AgCl disk scalp electrodes, placed on derivations corresponding to Fz, Cz and Pz positions of the

international 10-20 system and referenced to bilateral mastoid electrodes. To detect and filter eye movements an electrooculogram was monitored. The target and non-target stimuli responses were separately averaged online. Approximately 25-50 target stimuli were delivered in one session and repeated.

Nerve conduction measurements

We used routine nerve conduction measurements for the sural, peroneal and median nerve. Parameters included: Distal Motor Latency (DML), Nerve Conduction Velocity (NCV), Compound Nerve Action Potential (CNAP) and minimal F-wave latency.

Statistics

Because sample sizes were relatively small, and the distribution of the clinical variables in most cases deviated significantly from normal, a series of nonparametric Wilcoxon signed-rank tests were used in a repeated measures design to assess the direction and magnitude of changes between time counts. When a significant change in one of these variables occurred, Spearman's rho correlations were performed to determine if the change was related to variability among subjects in length of time between changes in antiretroviral status. Given the exploratory nature of the study, small sample size, and multiple comparisons, to avoid type 1 error, p values ≤ 0.01 were considered significant. The comparison with the control group was done by *t*-tests and the correlation analysis by using a Pearson correlation with a significance level of 0.05.

Results

Baseline

11 subjects were evaluated at baseline before cART or after the previous treatment regimen failed and before initiating a different cART regimen. Previous antiretroviral treatment had been received by 2 patients (AZT/3TC; AZT/3TC/NFV). The remaining 9 subjects were antiretroviral naive. Baseline demographic and selected clinical characteristics are shown in Table 1.

The neurological exam revealed signs of distal symmetric neuropathy in two subjects while the remaining 9 had an unremarkable neurological examination. All but one participant had a significant plasma VL (>200 cop./ml) and nine out of 11 a detectable CSF viral load at baseline.

9 patients received a genotypic and phenotypic drug resistance in plasma and CSF before cART was changed or initiated. There was only one patient (number 10) pre-treated with AZT, 3TC and NVF and a phenotype resistance against 3TC.

Follow up

All subjects were followed up at least 12 months and 7 subjects 24 months. Participants received in median 3 antiretrovirals (range 3-5) during the follow up period: ABC (300 mg/d) and AZT (300 mg/d) as a mandatory part in this study; 63.6% an additional NRTI (3TC) and 36.4% received also PI´s (IDV, LPVr, RTV). Antiretroviral treatment in patient 10 with a phenotype resistance against 3TC was changed to ABC, AZT, IDV, RTV. The CPE score of the antiretroviral regimen was at least 9 in all patients (Table 4) (**Letendre, 2010**).

Baseline characteristics	
Age in years	37 (24-52)
Male	100%
Caucasian	100%
Education in years	12 (10-12)
Beck depression score	7.5 (1-31)
CD4 (cells/µl)	260 (42-802)
HIV viral load plasma (cop./ml)	57400 (176-5400000)
CDC classification 1 2 3	n 1 6 4
CSF characteristics	
HIV viral load CSF (cop./ml)	2410 (not detectable - 2900000)
Protein in mg/dl	45.4 (32.5-99.6)
Cells/µl	6.3 (1.3-141.3)
Oligoclonal bands	in 4 patients positive
IgG synthesis in %; Range	0-43

Table 1: Baseline demographic and selected clinical characteristics; Values are median (range) unless otherwise specified; Cop./ml=copies per ml.

The laboratories, neuropsychological and neurophysiological follow up results are summarized in Tables 2 and 3. The CD4 cell count significantly increased during the follow up period ($p<0.01$). Plasma and CSF viral load decreased significantly from baseline to the first follow up after 6 months ($p<0.01$). VL in plasma was undetectable in 91% (10/11) after 6 months, in 82% (9/11) after 12 months and in all participants after 24 months (7/7). CSF VL was suppressed in 91% (10/11) after 6 months and in all patients after 12 and 24 months, respectively.

Cognitive test results

3 patients showed relevant cognitive deficits at baseline (GDS ≥ 0.5; abnormal in at least 2 domains with 1SD) which were not relevant during daily activities (ANI) (Table 4). While 2 of them had a CD4 cell count below 200/µl, one patient had CD4 cells of 802/µl at baseline. All of them improved cognitively over time; however the difference did not reach significant levels (repeated measurement analysis, multilevel model analysis, Wilcoxon test). Table 4 summarizes the GDS for each individual at serial time points. In patient 3 neuropsychological improvement correlated to a constant suppression of HIV in the CSF and a remission of inflammatory changes in the CSF compartment. However neuropsychological impairment was also seen in patient 11, who had no detectable CSF HIV VL at any time.

	baseline	**Follow up**		
	n=11	6 months n=11	12 months n=11	24 months n=7
Normal neurological exam; n (%)	9 (81.8)	10 (90.1)	9* (81.8)	5* (71.4)
Distal symmetric neuropathy, n (%)	2 (18.2)	1 (9.1)	1 (9.1)	1 (14.3)
Global deficit Score	0.01 (0-0.93)	0.33 (0-0.67)	0.33 (0-0.67)	0.33 (0-0.37)
ERP P300 in ms	350 (313-363)	338 (307-369)	344 (303-381)	338 (295-356)
Beck depression - no depression n=(%)	9 (2-31) 7 (63.6%)	7 (2-33) 9 (81.8%)	4 (2-42) 7 (63.6%)	5.5 (0-19) 5 (71.4%)
plasma HIV VL (cop./ml)	57400 (176-5400000)	57a (2-98600)	74 a (2-7880)	n.d. (n.d.-85)
CSF HIV VL (cop./ml)	2410 (n.d.-2900000)	n.d.b (n.d.-6475)	n.d.b (n.d.-83)	n.d.
CD4 cell count (cells/µl)	260 (42-802)	457 c (92-1020)	511 c (124-1050)	717 (270-1120)
Virological suppressed**, n. (%)	1 (9)	9 (81.8)	9 (81.8)	7 (100)

Table 2: Clinical and laboratory characteristics at serial time points; Values are median (range) unless otherwise specified; * One subject represented with a meralgia paraesthetica; **in plasma and CSF; HIV RNA<200cop./ml; [a] significantly different from baseline VL (p<0.01); [b] significantly different from baseline VL (p<0.01); [c] significantly different from baseline (p<0.01); Abbreviations: VL viral load; n.d. not detectable.

Global deficit score (GDS) did not change significantly during observational time (Table 2) for the whole study group. Those results were reflected in the results of the ERP´s. During the study period no significant change in P300 latencies were observed (Table 2).

However correlation analysis revealed a significant correlation of executive function and CSF viral load, while other cognitive domains (attention, verbal memory, figural memory, visuoperceptual function, verbal fluency as well as depression) did not. There was also no correlation of functional outcome in the different cognitive domains in terms of age, HIV duration, CD4 nadir as well as HIV viral load in plasma.

3 subjects were considered to be mildly depressed at baseline visit (patients 5, 7 and 8); while 1 was severely depressed (patient 2). All 4 patients were cART naïve at baseline. Those subjects however have not shown global cognitive impairment. Overall the profile of the Beck depression inventory total scores did not change significantly over time.

	cerebrospinal fluid analysis				**HIV VL CSF (cop./ml)**				**HIV VL plasma (cop./ml)**				**CD4/µl**
	1	2	3	4	1	2	3	4	1	2	3	4	1
1	OCB	OCB	OCB	/	1570	n.d.	n.d.	/	260000	98600	7880	/	140
2	OCB	2% M	OCB	/	5900	n.d.	n.d.	/	66200	57	74	/	334
3	24 WBC, 43% G, 48% A, 70% M	13 WBC, 15% G, 4% A, 22% M	6% G, 11% M	normal	2.9 Mill.	6475	83	n.d.	5.4 Mill.	139	1510	n.d.	42
4	14 WBC, 33% G, OCB	38% G, OCB	29% G, OCB	28% G, OCB	57400	137	54	n.d.	35100	120	n.d.	n.d.	280
5	6 WBC	normal	normal	normal	1545	n.d.	n.d.	n.d.	22370	n.d.	n.d.	n.d.	196
6	OCB	normal	normal	normal	2410	n.d.	n.d.	n.d.	118000	117	165	n.d.	439

7	141 WBC, ACBB	ACBB	9 WBC, ACBB, OCB	6 WBC, ACBB	6420	n.d.	n.d.	n.d.	36200	n.d.	n.d.	n.d.	158
8	33 WBC, 14% G, OCB, 49% M, ACBB	54% G, OCB, 76% M	39% G, OCB, 76% M	/	361	n.d.	n.d.	/	57400	n.d.	n.d.	/	601
9	28 WBC, OCB, ACBB	OCB, ACBB	ACBB	/	5530	n.d.	n.d.	/	224800	92	n.d.	/	226
10	normal	normal	normal	normal	n.d.	n.d.	n.d.	n.d.	7930	n.d.	109	85	260
11	normal	normal	OCB	OCB	n.d.	n.d.	n.d.	n.d.	176	n.d.	140	n.d.	802

Table 3: Pathological parameters in repeated cerebrospinal fluid analysis and HIV viral load in the CSF/plasma and CD4 cell count at baseline; OCB- oligoclonal IgG bands; WBC- white blood cell counts/µl; G; M, A-quantitative intrathecal production of IgG, IgM, IgA; ACBB - altered CSF-blood-barrier (albumin CSF/serum quotient); Abbreviations: VL viral load; n.d. not detectable.

Control group

None of the controls did show cognitive abnormalities that would reach the definition of ANI in the beginning of the evaluation. They remained mainly stable over a comparable observational time. The only difference was a significant worsening of motor functions over time, which was not included in the testing repertoire of our study population. Only one patient fulfilled the criteria of ANI at the end of the observation period.

There was no correlation of the functional outcome in the different domains in terms of age, HIV duration and CD4 nadir. The CSF viral load however was not available for the control patients.

	GDS				cART	CPE (Letendre et al, 2008)	CPE (Letendre, 2010)
	1	2	3	4			
1	0.52	0.67	0.42	/	AZT/3TC, ABC	2.5	9
2	0	0.03	0.03	/	AZT/3TC, ABC	2.5	9
3	0.92	0.37	0.67	0.33	AZT/3TC, ABC, IDV, RTV	3.5	13
4	0	0.57	0.33	0	AZT/3TC, ABC	2.5	9
5	0	0.33	0.17	0.33	AZT/3TC, ABC	2.5	9
6	0	0.17	0.17	0.33	AZT/3TC, ABC	2.5	9
7	0	0	0	0.17	AZT/3TC/ABC, LPV/r	3.5	12
8	0.01	0.17	0.17	/	AZT/3TC, ABC	2.5	9
9	0.17	0.5	0.33	/	AZT/3TC, ABC	2.5	9
10	0.5	0.33	0.5	0.33	ABC, AZT, IDV, RTV	3	11
11	0.93	0.47	0.53	0.37	AZT/3TC, ABC	2.5	9

Table 4: Individual global deficit scores (GDS) in repeated testing at baseline (1) as well as 6 (2), 12 (3) and 24 (4) months after starting or changing cART. The table also includes the specific cART as well as the CPE scores according to (Letendre, 2010; Letendre et al, 2008)

However a group comparison to the study group at baseline revealed significant differences with disadvantage to the study group for executive function, figural memory, visuoperceptual function and verbal fluency. The difference paled of and was not detectable at the end of the study.

Discussion

We have shown that HIV-infected patients undergoing antiretroviral treatment with a CPE score of at least 9 including AZT and ABC have shown preserved or improved cognitive functions during observational time of up to 24 months.

Subjects were carefully characterized at baseline, as well as re-evaluated after 6, 12 and 24 months to quantify neuropsychological improvement in 6 cognitive domains. 27% of our patients fulfilled the criteria of ANI at baseline, but had normal test results at the end of observation period, while the others remained normal in NP performance. A comparison to a historical and fairly matched untreated control group showed that our study population started with significantly worse results in executive function, figural memory, visuoperceptual function and verbal fluency, which were no longer detectable after 1 and/or 2 years of treatment. Therefore one cannot consider just a natural course of disease.

All of our patients were treated with an antiretroviral combination with a CPE score of at least 2.5 or 9 according to the modified score [10,11]. It has been shown that patients on combined antiretroviral therapy achieving a CPE ≥ 2.5 [11] have significantly lower HIV-VL in cerebrospinal fluid and display better neuropsychological performance [21,22], which is in accordance with our results. We found, that most of our HIV-individuals have shown significantly suppressed HIV CSF VL over 12 and 24 months respectively and a stable cognitive outcome over the time course of 2 years.

The neuropsychological results are underlined by a normal performance in ERP´s. Although ERP are not a direct measure of HIV associated cognitive deficits, many authors assume that they reflect certain cognitive functions that are involved in pathophysiology of HAD [23,24]. P300 represents the most important component of ERP. It is defined as an endogenous potential deriving from multifocal cortical and subcortical sources [25].

In contrast, numerous studies exist which show no improvement but in fact stagnation or deterioration of neuropsychological performance despite the use of cART regimens believed to have good

CNS effectiveness (CPE ≥ 2.5) including another abacavir trial [26,27,28]. However, the majority of patients in our study had moderately advanced HIV disease (CD>200/µl) with no or minimal neuropsychological abnormalities prior to starting antiretroviral treatment or changing into a regimen containing AZT and ABC. The study was designed to include participants with an antiretroviral failure or who were antiretroviral naïve, but there was no provision to restrict entry to those who had any neurocognitive deficit. Retrospectively this might be the greatest single shortcoming. We therefore included a historical untreated control group with similar disease activity, which could be evaluated for 7 different cognitive domains including motor functioning additional to our group. While none of them fulfilled the criteria of ANI in the beginning one did at the end. But there was a significant difference in motor functions only over time as the only domain.

One could still ask the question if the small difference we have seen reflects the natural course of the patients with respect to their performance in cognitive tasks. This would be in accordance with results of a large observational study which compared neurocognitive functions in asymptomatic HIV infected patients who were either immunologically intact or virologically controlled and HIV-seronegative people for 5 years [29]. They did not detect a greater deterioration in the asymptomatic HIV infected population even in patients with incomplete viral control.

HAND seems to differ in manifestation among individuals with HIV infection [21,30]. It was suggested to distinguish between "inactive", active"/stable and ""burned out" encephalopathy [31]. Observations suggest that patients with very rapid improvement show major neurocognitive deficits and signs of cerebral inflammation but good viral suppression. Participants who are not significantly impaired represented the majority in our study group. Those patients may represent a group with an immunologically inactive disease [31]. On the other hand our study measured cognitive changes with the GDS, a measure that ignores changes within normal range. It might be more appropriate to use scaled scores which encompass the full range of performance, capturing not only deficits, but also return to best levels of functioning.

Around one third of our patients have shown at least a mild depression at baseline with one patient fulfilling the criteria of severe depression. None of them was on antiretroviral therapy at baseline. Previous studies describe a prevalence of up to 50% with 2-22% with major depression [32-34]. One reason for the lower prevalence in our population might be that it consisted exclusively of men and depression rates are higher in women [35,36]. Those patients who were depressed have not shown global cognitive impairment. These results are in accordance with a previous study that found no correlation between severity of depressive symptoms and neuropsychological impairment [37]. Combined antiretroviral therapy did not have a significant positive or negative effect on depressive symptoms in our small population.

There are some more limitations of the study. Apart from the very small sample size, we can't exclude a certain practise effect on repeated testing. We have addressed this concern by using event related potentials as a more objective marker of cognition. Several studies also indicate that practise effects most substantially apply to the second assessment and are greatly diminished with subsequent tests (**Collie et al. 2003**) [38]. Secondly, the battery tests ideally would have been larger including also tests to detect motor dysfunction, which is assumed to be mandatory according to Antinori et al. [3] and which was the only domain that showed abnormalities in our historical control group. Another confound is the lack of a standard antiretroviral regimen in this population other than the AZT and ABC.

Nevertheless there are therapeutic implications of our study. HAND can probably be minimized by a drug regimen with a good CNS penetration (CPE at least 9) including AZT and ABC. Studies of larger more diverse groups will be needed to address the neurocognitive efficacy of an antiretroviral regimen containing ABC and AZT.

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Conflicts of Interest

None.

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