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Rivastigmine for HIV-associated neurocognitive disorders

A randomized crossover pilot study

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Objective: To assess the efficacy and safety of rivastigmine for the treatment of HIV-associated neurocognitive disorders (HAND) in a cohort of long-lasting aviremic HIV+ patients.

Methods: Seventeen aviremic HIV+ patients with HAND were enrolled in a randomized, double-blind, placebo-controlled, crossover study to receive either oral rivastigmine (up to 12 mg/day for 20 weeks) followed by placebo (20 weeks) or placebo followed by rivastigmine. Efficacy endpoints were improvement on rivastigmine in the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog) and individual neuropsychological scores of information processing speed, attention/working memory, executive functioning, and motor skills. Measures of safety included frequency and nature of adverse events and abnormalities on laboratory tests and on plasma concentrations of antiretroviral drugs. Analyses of variance with repeated measures were computed to look for treatment effects.

Results: There was no change on the primary outcome ADAS-Cog on drug. For secondary outcomes, processing speed improved on rivastigmine (Trail Making Test A: $F_{1,13} = 5.57$, $p = 0.03$). One measure of executive functioning just failed to reach significance (CANTAB Spatial Working Memory [strategy]: $F_{1,13} = 3.94$, $p = 0.069$). No other change was observed. Adverse events were frequent, but not different from those observed in other populations treated with rivastigmine. No safety issues were recorded.

Conclusions: Rivastigmine in aviremic HIV+ patients with HAND seemed to improve psychomotor speed. A larger trial with the better tolerated transdermal form of rivastigmine is warranted.

Classification of evidence: This study provides Class III evidence that rivastigmine is ineffective for improving ADAS-Cog scores, but is effective in improving some secondary outcome measures in aviremic HIV+ patients with HAND.

GLOSSARY

AD = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale–Cognitive subscale; **CANTAB** = Cambridge Neuropsychological Test Automated Battery; **cART** = combined antiretroviral therapy; **ChEI** = cholinesterase inhibitors; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **HAD** = HIV-associated dementia; **HAD-A** = Hospital Anxiety and Depression scale–anxiety; **HAD-D** = Hospital Anxiety and Depression scale–depression; **HAND** = HIV-associated neurocognitive disorders; **HDS** = HIV Dementia Scale; **LP** = lumbar puncture; **MND** = mild neurocognitive disorders; **MOS-HIV** = Medical Outcome Study HIV Health Survey; **NNRTI** = non-nucleoside reverse transcriptase inhibitors; **PD** = Parkinson disease; **QoL** = quality of life; **SWM** = Spatial Working Memory; **TDM** = therapeutic drug monitoring; **TMT** = Trail Making Test.

HIV-associated neurocognitive disorders (HAND) remain common in the era of combined antiretroviral therapy (cART),[1–3] even in the context of long-lasting viral load suppression.[4] For this reason, the study of adjunctive cognitive enhancers to treat HIV+ patients with HAND appears of major importance. To date, the efficacy of cholinesterase inhibitors (ChEI) has never been investigated.

A putative favorable effect of ChEI in patients with HAND has been hypothesized based on similarities existing between HAND and Alzheimer disease (AD). Indeed, there is evidence for increased amyloid deposition in the brains of patients with AIDS at autopsy,[5,6] even in cART-treated patients,[7] and for reduced levels of amyloid-β 1-42 in the CSF of patients with HAND.[8,9] Additionally,

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amyloid-β precursor protein was detected in the brains of asymptomatic HIV+ patients, demonstrating an early deposit of this neurotoxic protein.[10]

The status of the cholinergic system has not been examined in patients with HAND. However, in a cellular model of HIV-associated dementia (HAD), the adjunction of galantamine, a ChEI, resulted in the inhibition of microglial activation induced by HIV-1 protein gp120.[11] Interestingly, choline acetyltransferase, a major enzyme in the synthesis of acetylcholine, is also markedly diminished in the putamen and hippocampus of simian immunodeficiency virus–infected monkeys early in the course of infection.[12] Based on the above data, we conducted a randomized, double-blind, placebo-controlled, crossover pilot study to assess the efficacy and safety of rivastigmine, a ChEI, to treat HAND in a cohort of long-lasting aviremic HIV+ patients.

METHODS

Study subject recruitment. From March 2009 to April 2010, recruitment of participants was performed within the Swiss HIV Cohort Study at the HIV outpatients clinics of both Lausanne and Geneva University Hospitals, and in affiliated private practices.

Inclusion criteria were 1) undetectable HIV-1 RNA concentrations in both plasma (<20 copies/mL for >3 months before study entry) and CSF (<200 copies/mL) and 2) diagnosis of HAND (mild neurocognitive disorders [MND] or HAD) according to the Frascati criteria.[13] Patients with asymptomatic neurocognitive impairment were not considered for the study. Exclusion criteria were 1) history of major CNS opportunistic infection affecting the brain, 2) any other opportunistic infection not affecting the brain <12 months before study entry, 3) active recreational drug use, 4) major depression according to *DSM-IV* criteria or any other known psychiatric condition possibly interfering with the safe conduct of the study, 5) brain MRI showing mass effect or signs indicating an ongoing tumor or abscess, and 6) use of cholinergic or anticholinergic agents within 2 weeks prior to screening. Patients with incidental comorbid conditions (e.g., history of remote drug abuse, hepatitis C coinfection) were not excluded.

Standard protocol approvals, patient consents, and organization. The trial was held in both the Lausanne (designated as coordinating center) and the Geneva University Hospitals. It was approved by the internal review boards of both university hospitals and by the Swiss Agency for Therapeutic Products (SWISSMEDIC, no. 2008DR3368). Rivastigmine was purchased from Novartis. The CHUV pharmacy department was in charge of preparing identical placebos, packaging all capsules, and distributing study drugs to both sites. HIV+ patients who met the inclusion criteria for participation in the trial received written information about the study procedure and possible side effects of rivastigmine, and signed written informed consent.

Safety phone calls were planned once a week to ensure adherence to treatment (estimation of the number of forgotten doses) and record adverse events. Patients with mild side effects were instructed by phone on how to reduce drug doses. Those with more severe adverse events were scheduled for an intermediate medical visit at study site. Every 2 weeks, drug escalation was reminded during the phone call. At the end of each study arm, the remaining capsules were computed (adherence check). Patients were not asked to guess whether they were taking rivastigmine or placebo. They were informed that the investigators were blinded to treatment arms and that randomization would be known at the end of the study.

The study was conducted in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki.

Study design. This was a randomized, double-blind, placebo-controlled, crossover study. The primary research question assessed by Class III evidence was to evaluate whether rivastigmine was safe and could improve global cognition as measured by the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog)[14] in aviremic HIV+ patients with HAND. Secondary research questions assessed by Class III evidence concerned efficacy on specific cognitive domains and quality of life (QoL).

At the screening visit, patients underwent a complete neurobehavioral examination to assess the presence of HAND (detailed hereafter). Patients fulfilling the diagnostic criteria for MND or HAD and agreeing to participate in the study were planned for a second visit within 7 days to complete the following assessments: 1) physical and neurologic examination, 2) brain MRI to exclude acute ongoing pathologies and guarantee that lumbar puncture (LP) could be performed safely, 3) serial blood testing consisting of complete blood count, coagulation function tests, electrolytes (Na, K, glucose), renal (urea, creatinine) and liver function tests (transaminases, alkaline phosphatase, and bilirubin), 4) measurement of the plasmatic activity of acetylcholinesterase to monitor adherence to treatment, using the QuantiChrom™ Acetylcholinesterase Assay Kit (BioAssay Systems, Hayward, CA) according to manufacturer's instructions, 5) routine therapeutic drug monitoring (TDM) of measurable cART (nonnucleoside reverse transcriptase inhibitors [NNRTI], protease inhibitors, and integrase inhibitors) to subsequently verify the absence of significant interaction with rivastigmine, and 6) LP to ensure undetectable viral load in the CSF. Patients who fulfilled all the criteria were randomized and started the study immediately.

During the first arm (20 weeks), the drug dosage started at 1.5 mg/day and was progressively increased every 2 weeks (3 mg, 4.5 mg, 6 mg, 9 mg, and 12 mg/day). The procedure was identical for rivastigmine and placebo. At the end of first arm, the complete set of assessments previously described was performed again. A washout period of 6 weeks was then observed to avoid any carryover effect of the drug such as it was demonstrated in a similar designed study conducted in Parkinson disease (PD) dementia.[15] The procedure during the second arm was similar and was preceded by a third neurobehavioral examination. At the end of the second arm, the complete set of assessments was performed for the last time.

Neurobehavioral examination. ***Neuropsychological testing.*** HIV+ participants underwent the ADAS-Cog,[14] originally developed to assess cognitive dysfunction in patients with AD and systematically used in clinical trials assessing ChEI, and a neuropsychological evaluation of cognitive domains known to be impaired in patients with HAND: 1) information processing speed (Reaction Time [RTI] from the Cambridge Neuropsychological Test Automated Battery [CANTAB],[16] Trail Making Test part A [TMT-A],[17] Wechsler Adult Intelligence Scale–III Symbol Digit test)[18]; 2) attention/working memory (CANTAB Rapid Visual Information Processing and Spatial Working Memory [SWM, error component],[16] digit spans backward/forward)[18]; 3) executive functioning (TMT part B [TMT-B],[17] CANTAB

SWM [strategy component], and Stockings of Cambridge)[16]; and 4) motor skills (RTI [motor component]).[16] For all the tests used, a *z* score was calculated based on available normative data. Finally, the HIV Dementia Scale (HDS)[19] and International HDS[20] were performed.

Psychiatric questionnaires. Trained psychologists (S.S., A.R.A., M.M.) conducted an interview at baseline using a French questionnaire assessing the presence of mood disorders according to the *DSM-IV* diagnostic criteria (Questionnaire de Santé du Patient) to rule out major depression. Current mood was then assessed at each visit using the Hospital Anxiety and Depression scale[21] addressing depressive (HAD-D) and anxious (HAD-A) symptoms, separately. Patients were considered to express depressed or anxious signs if the HAD-D or HAD-A subscale score was ≥10/21.

Functional assessment. The impact of cognitive difficulties on everyday functioning (e.g., housework, social life, employment) was evaluated at each visit through the subjective complaints reported by HIV+ patients.[4] In addition, we administered the Medical Outcome Study HIV Health Survey (MOS-HIV),[22] a questionnaire assessing health-related QoL.

Outcome measures. The primary endpoint for efficacy was designed as an improvement from baseline to week 20 (on drug) in the ADAS-Cog score. Other individual neuropsychological scores were secondary endpoints. Additional efficacy measures included change in self-reported QoL (MOS-HIV). Concerning safety, endpoints were the frequency and nature of adverse events, abnormalities on laboratory tests, and TDM of antiretroviral drugs.

Statistical methods. Power calculation was based on the results of previous clinical trials using rivastigmine in patients with AD and patients with PD. The study was initially designed to provide a ≥80% power to detect a ≥2.8-point difference between rivastigmine and placebo on the ADAS-Cog, and a ≥0.3–0.5 point difference on the CANTAB tests, requiring a sample size of 24 patients.

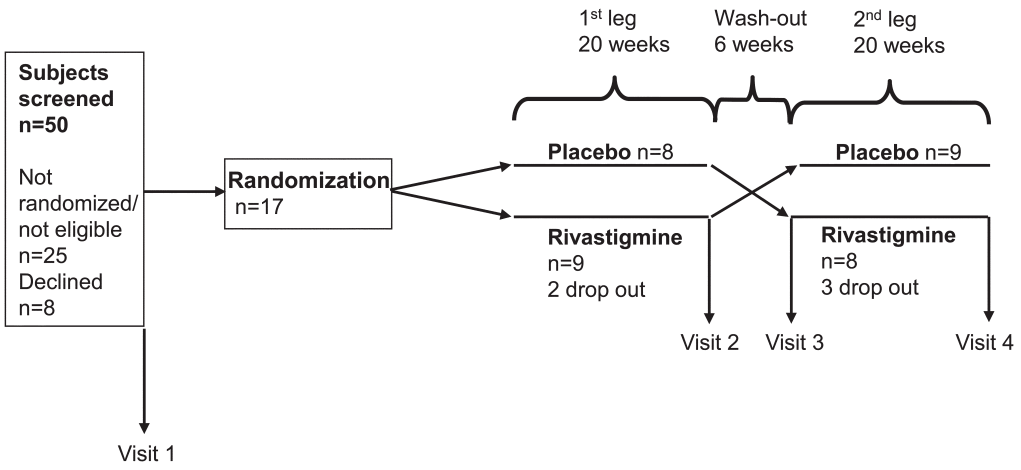
Statistical analyses were conducted using a Stata 11 software package. Differences at baseline between patients enrolled in arm 1 (rivastigmine followed by placebo) vs arm 2 (placebo followed by rivastigmine) on demographic and clinical variables, mood symptoms, behavioral, and QoL scores were examined using χ^2 tests for the comparison of categorical variables, and *t* tests or Mann-Whitney rank sum tests (depending on the distribution) for the comparison of continuous variables. Significance was set at $p < 0.05$ for all statistics. Results are expressed in mean ± SD, except for Mann-Whitney rank sum tests, expressed in median ± interquartile intervals.

To estimate the efficacy of rivastigmine, the difference between the score obtained for a single measure at the beginning and at the end of each 20-week study period was computed (visit 2 − visit 1 and visit 4 − visit 3) for each participant, and the difference between these 2 values was used as a combined outcome for each subject. On this outcome, analysis of variance with repeated measures, with treatment (rivastigmine vs placebo) as a within effect and sequence of treatment (arm 1 vs arm 2) as a between factor, were performed. Each outcome was considered as a single dependent variable and, since only one statistical analysis was performed per outcome, corrections for multiple comparisons were not applied. Patients with one or more missing values in a study period were excluded from efficacy analyses of that period.

RESULTS

Baseline characteristics. From the 50 HIV+ patients screened, 17 (12 men/5 women, age 55.1 ± 9.7 years, years of education 12.6 ± 2.8) fulfilled inclusion criteria and agreed to participate in this clinical trial (figure 1). Their mean disease duration since diagnosis and mean time with undetectable HIV viremia were 14.2 ± 7.1 and 5.1 ± 3.5 years, respectively. The mean CD4 count was 668.9 ± 222.2 cells/mm^3 and the mean CD4 nadir was 176.6 ± 100.7 cells/mm^3. All participants were on stable antiretroviral regimen for a mean time of 2.1 ± 1.6 years. Four patients changed their cART during the course of the study because of tolerability issues (interactions with use of proton pump inhibitors in one, dyslipidemia in the second, nightmares in the third, altered renal function consecutive to nephrectomia in the fourth patient). Changes were not related to rivastigmine, as reflected by the fact that 3 patients were on placebo at the time of treatment change. They increased the CNS penetrating-effectiveness score by 1 point in 2 patients (1 on placebo and 1 on drug). At enrollment, all patients were found to have mild to moderate cognitive impairment with decreased everyday functioning, thus

Figure 1 Study design and flow diagram of trial participation



fulfilling diagnostic criteria for MND. No patient was diagnosed with HAD.

Nine patients were randomized to arm 1 and 8 to arm 2. Treatment arms were comparable with respect to demographics and clinical characteristics except for duration of aviremia and duration of cART (table 1). Baseline cognitive scores were equal in both treatment arms (table 2). One patient enrolled in arm 2 had to be excluded during the study because of reported active drug use. Final analysis was performed on 12 patients remaining on treatment until study termination and 3 patients withdrawing because of side effects when already taking high doses of treatment (9–12 mg/day) and thus close to study end. Adherence measured during phone calls and by capsules counts was satisfactory (≤2 missed tablets per week). Acetylcholinesterase activity measured in the plasma decreased in 9 patients (reduction rate 41.7 ± 19.5%), thus indicating good compliance, whereas levels did not change in 6 patients.

Efficacy analyses. Changes on rivastigmine and placebo for each efficacy measure are reported in table 3. There was no improvement on drug on the primary outcome ADAS-Cog (figure 2A). Concerning secondary outcomes, one measure of processing speed improved due to treatment effect (TMT A) (figure 2B). There was no other improvement on drug but one measure of executive functioning just failed to reach significance (CANTAB SMW [strategy component]).

Safety analyses. Rivastigmine induced mild to moderate adverse events in 9 patients (nausea/vomiting, unsteadiness). In these cases, the attitude was to reduce the dosage to the previous level (causing no side effects). Five patients could not sustain the maximal dose of 12 mg/day of rivastigmine and performed the study at an inferior dosage (9 mg/day). Four patients withdrew because of persistent nausea (n = 1), nightmares/anxiety (n = 1), and cutaneous rashes (n = 2). Among the patients who did not drop out, the mean dose of rivastigmine at study end was 10.3 ± 2.7 mg/day.

Blood analyses did not reveal severe abnormalities on rivastigmine. However, slightly increased levels of glucose (n = 7; mean level after rivastigmine: 7.2 ± 1.3 mmol/L [normal range 3.7–5.6 mmol/L]) and transaminases (ALAT) (n = 3; mean level after rivastigmine: 64.5 ± 4.5 U/L [normal range 9–36 U/L]), and decreased levels of hemoglobin (n = 3; mean level after rivastigmine: 120.7 ± 5.1 g/L [normal range 133–177 g/L]), were observed in some patients after 20 weeks of rivastigmine.

TDM did not show any significant negative impact of rivastigmine on plasma concentrations of antiretroviral agents. A downward trend of antiretroviral levels in 4 patients taking NNRTI (2 patients on efavirenz, 1 on nevirapine, and 1 on etravirine) and 1 patient receiving a raltegravir-based regimen was observed. HIV RNA levels did not change during exposure to rivastigmine (<20 copies in all patients throughout the study).

DISCUSSION This pilot study suggests that a treatment of rivastigmine for 20 weeks improves psychomotor speed and, marginally, executive functioning

Table 1 Baseline demographics and clinical characteristics

	Treatment arm 1 (rivastigmine–placebo) (n = 9)	Treatment arm 2 (placebo–rivastigmine) (n = 8)	*p* Value[a]
Age, y, mean (SD)	54.71 (9.52)	54.58 (10.33)	0.979
Education, y, mean (SD)	12.22 (3.31)	12.63 (2.33)	0.778
Male, n (%)	5 (44)	7 (88)	0.294
HIV diagnosis, y, mean (SD)	15.73 (6.83)	11.82 (7.11)	0.267
Duration of aviremia, y, mean (SD)	7.02 (3.25)	2.97 (2.10)	0.009[b]
CD4 count, mean (SD)	660.89 (265.94)	659.0 (167.33)	0.987
Nadir CD4 count, mean (SD)	141.22 (90.21)	209.38 (100.21)	0.161
Duration of cART treatment, y, median (IQR)	14.7 (2.24)	12.02 (8.41)	0.027[b,c]
CPE score, mean (SD)	8.11 (2.52)	7.0 (0.76)	0.251
HDS score, mean (SD)	8.94 (4.34)	9.94 (3.28)	0.606
International HDS score, mean (SD)	8.83 (2.54)	8.56 (1.40)	0.792
HAD-A score, mean (SD)	9.11 (5.01)	10.50 (3.51)	0.523
HAD-D score, mean (SD)	6.56 (5.41)	7.0 (4.31)	0.855

Abbreviations: cART = combined antiretroviral therapy; CPE = CNS penetrating-effectiveness; HAD-A = Hospital Anxiety and Depression scale–anxiety; HAD-D = Hospital Anxiety and Depression scale–depression; HDS = HIV Dementia Scale; IQR = interquartile range.
[a] Statistics are *t* tests, except where noted.
[b] Significant.
[c] Mann-Whitney rank sum test.

Table 2 Baseline neuropsychological results (standardized *z* scores)[a]

	Treatment arm 1 (rivastigmine–placebo) (n = 9)	Treatment arm 2 (placebo–rivastigmine) (n = 8)	*p* Value
ADAS-Cog	−0.50 (1.30)	−1.53 (1.19)	0.113
RTI reaction time	−0.63 (1.16)	−3.31 (4.77)	0.122
RTI movement time	0.16 (1.39)	−0.34 (1.51)	0.488
RVIP	−1.34 (1.16)	−1.97 (0.79)	0.216
SWM errors	−1.22 (0.88)	−0.73 (0.72)	0.237
SWM strategy	−1.15 (0.59)	−0.51 (1.28)	0.201
Trail Making Test A	−2.02 (2.26)	−2.49 (2.44)	0.682
Trail Making Test B	−3.16 (4.10)	−2.21 (1.91)	0.561
SOC correct problems	−1.07 (0.77)	−0.41 (1.15)	0.202
Symbol Digit test	−1.00 (1.23)	−1.08 (0.71)	0.868
Digit span backward	−1.22 (1.34)	−1.95 (1.65)	0.334
Digit span forward	−0.44 (1.25)	−1.24 (0.96)	0.165

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive subscale; RTI = reaction time; RVIP = rapid visual information processing; SOC = Stockings of Cambridge; SWM = Spatial Working Memory.
[a] Values are mean *z* scores (SD). Statistics are *t* tests.

Table 3 Analysis of variance with repeated measures computed for each efficacy variable on a combined outcome ([rivastigmine visit 2 − visit 1] − [placebo visit 2 − visit 1]), using treatment (rivastigmine vs placebo) as a within effect and sequence of treatment (arm 1 vs arm 2) as a between factor[a]

	Mean combined outcome (SD)	*F*[b]	*p* Value
ADAS-Cog	−0.09 (1.14)	$F_{1,13} = 0.31$	0.589
RTI reaction time	−0.53 (2.94)	$F_{1,13} = 1.87$	0.195
RTI movement time	0.68 (2.62)	$F_{1,13} = 0.45$	0.512
RVIP	−0.12 (1.26)	$F_{1,13} = 0.03$	0.858
SWM errors	0.19 (1.24)	$F_{1,13} = 0.08$	0.786
SWM strategy	0.44 (0.88)	$F_{1,13} = 3.94$	0.068
Trail Making Test A	1.20 (1.89)	$F_{1,13} = 5.57$	0.034[c]
Trail Making Test B	0.22 (3.28)	$F_{1,13} = 0.06$	0.816
SOC correct problems	0.26 (0.95)	$F_{1,12} = 1.17$	0.301
Symbol Digit test	0.11 (0.66)	$F_{1,13} = 0.27$	0.613
Digit span backward	0.08 (2.17)	$F_{1,13} = 0.00$	0.946
Digit span forward	−0.03 (2.21)	$F_{1,13} = 0.03$	0.867
MOS-HIV perceived health[d]	0.20 (21.18)	$F_{1,13} = 0.06$	0.804
MOS-HIV social function[d]	−9.53 (56.09)	$F_{1,13} = 0.70$	0.418
MOS-HIV cognitive function[d]	16.87 (34.76)	$F_{1,13} = 2.71$	0.124
MOS-HIV mental health[d]	4.67 (31.24)	$F_{1,13} = 0.12$	0.730
MOS-HIV global quality of life[d]	14.73 (43.58)	$F_{1,13} = 1.45$	0.249

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive subscale; MOS-HIV = Medical Outcome Study HIV Health Survey; RTI = reaction time; RVIP = rapid visual information processing; SOC = Stockings of Cambridge; SWM = Spatial Working Memory.
[a] Values are *z* scores, except where noted.
[b] Treatment main effect.
[c] Significant.
[d] Raw scores.

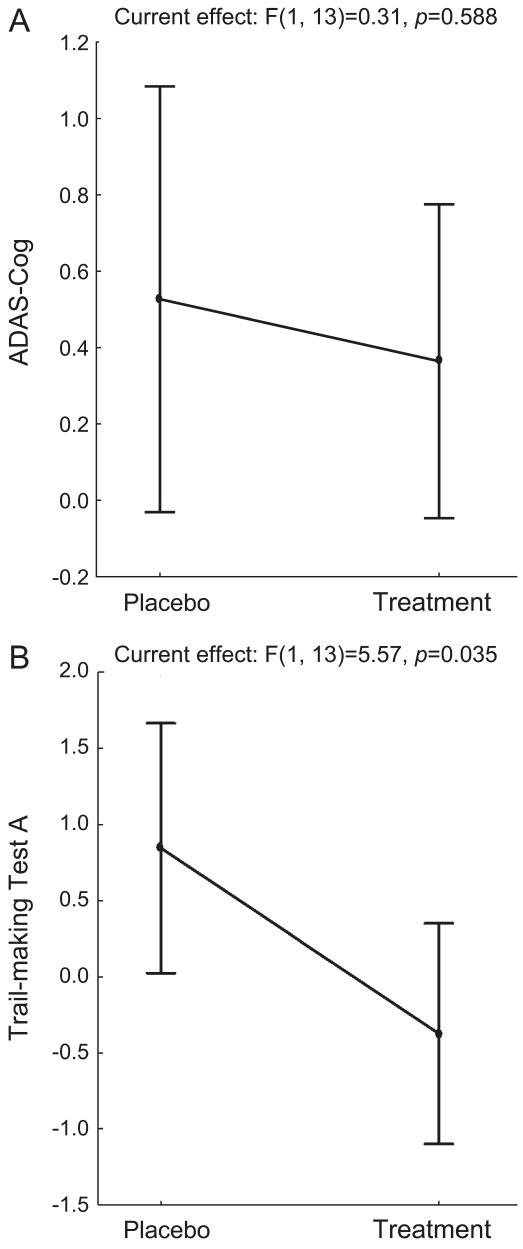
in HIV+ patients with HAND and undetectable HIV viral load in both plasma and CSF. No significant change was detected in the primary and other secondary endpoints. Our cohort was small and the above results need to be confirmed in a larger trial, but these findings appear encouraging.

Indeed, several cognitive enhancers and neuroprotective agents with different modes of action (antioxidants,[23–25] antiapoptotic drugs,[26,27] calcium channel blockers,[28] CCR5 antagonists,[29] platelets activating factors antagonists,[30] tumor necrosis factor antagonists,[31] *N*-methyl-D-aspartate antagonist,[32,33] and minocycline[34]) have already been studied in patients with HAND without convincing results. As a matter of fact, none of these compounds is currently recommended in practice. Rivastigmine may represent a treatment alternative in aviremic patients with HAND.

Rivastigmine was preferred to the other ChEI drugs currently in use, donepezil and galantamine, because of a lower risk of interactions with cART. Indeed, rivastigmine is not metabolized by cytochrome P450 (CYP450) and, most importantly, does not affect it. TDM ensured that rivastigmine had globally no significant negative influence on plasma concentrations of cART. The possible downward trend observed on NNRTI levels would need further analyses on a larger cohort to be confirmed. In fact, the small cohort, the variety of cART used, and the fact that some patients changed their regimen during the study precluded precise statistics.

Blood analyses did not reveal severe safety issues during the study. Side effects (mostly nausea) were frequent (76%) but did not differ in nature from

Figure 2 Efficacy analyses



Effect of rivastigmine on (A) the primary outcome Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog) and (B) the secondary outcome Trail Making Test A (figure illustrates that time necessary to complete the task is reduced on drug). Thirty-two measures were used for the analysis (placebo: n = 17; rivastigmine: n = 15). Vertical bars denote 0.95 confidence intervals.

those known to occur in patients with AD taking ChEI.[35] The dropout rate (23%) also remained comparable to those reported in clinical trials with patients with AD.[36] Tolerability issues might be solved in future studies by the use of a transdermal form of rivastigmine, currently available for the treatment of patients with AD. Rivastigmine patches provide the advantage of a continuous delivery of drug over 24 hours and were demonstrated to offer a greater tolerability than oral rivastigmine.[36] In addition, the patch provides a higher dosage (20 cm^2 patch, delivering 17.4 mg/24 hours), which offers better cognitive benefits with similar tolerability.[36]

There are several methodologic limitations to the interpretation of our results. The first one is the small size of our cohort and the attrition rate that certainly reduced the power of the study. Another issue is that some patients did not reach the target dosage of 12 mg/day of rivastigmine. Even lower doses of ChEI were reported to be effective in studies conducted with patients with AD[35] but in a small pilot study, this might have reduced the observable effects. Adherence was certainly good in at least 60% of study subjects, as indicated by a marked reduction of the plasmatic acetylcholinesterase activity. The plasmatic enzymatic activity was unchanged in the remaining 40%. Although other measures of adherence (phone calls, capsules counts) suggested that the observance was satisfactory, we cannot rule out that, in these 6 subjects (40%), the adherence was suboptimal, possibly in relation with adverse events, such as nausea. For the same reason, it is likely that blinding of the study was not perfect and that some patients guessed when they were on rivastigmine. Finally, the duration of the study was short, while clinical trials with patients with AD are generally conducted over a longer period than 24 weeks.[35]

Despite the above-mentioned issues, this pilot study is to our knowledge the first one assessing the efficacy and safety of a ChEI to treat HAND. It was conducted in a population of cART-treated patients with long-lasting undetectable plasma HIV viral load, undetectable CSF viral load, and no major psychiatric or other comorbidity interfering with cognition, thus patients who were already optimally treated, and yet had HAND.

This pilot study emphasizes that rivastigmine in aviremic HIV+ patients with HAND could be effective to improve cognitive functions typically affected by HIV, such as information processing speed. There are several safety issues, in particular nausea, which may preclude usefulness of oral rivastigmine. However, a transdermal form of rivastigmine is now available. A larger trial with this better tolerated form is warranted to confirm our findings.

AUTHOR CONTRIBUTIONS

S. Simioni: study design, collection, analysis, and interpretation of data, writing of the manuscript. M. Cavassini: study design, collection, analysis, and interpretation of data, writing and critical revision of the manuscript. J.-M. Annoni: study design, critical revision of the manuscript. M. Métral: collection of data, critical revision of the manuscript. K. Iglesias: analysis and interpretation of data, writing and critical revision of the manuscript. A. Rimbault Abraham: collection of data, critical revision of the manuscript. S. Jilek: analysis and interpretation of data, critical revision of the manuscript. A. Calmy: writing and critical revision of the manuscript. H. Muller: collection of data, critical revision of the manuscript. A. Fayet-Mello: analysis and

interpretation of data, critical revision of the manuscript. E. Giacobini: study design, critical revision of the manuscript. B. Hirschel: study design, critical revision of the manuscript. R.A. Du Pasquier: study design and supervision, collection, analysis, and interpretation of data, writing and critical revision of the manuscript.

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DISCLOSURE

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