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Improved Cognitive Performance and Reduced Monocyte Activation in Virally Suppressed Chronic HIV Following Dual CCR2 and CCR5 Antagonism

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Abstract

Objective—To evaluate changes in neuropsychological (NP) performance and in plasma and cell surface markers of peripheral monocyte activation/migration following treatment with cenicriviroc (CVC), a dual C-C chemokine receptor type 2 (CCR2) and type 5 (CCR5) antagonist, in treatment-experienced, HIV-infected individuals.

Setting—Single-arm, 24-week, open-label clinical trial.

Methods—HIV-infected individuals on antiretroviral therapy (ART) ≥1 year with plasma HIV RNA ≤50 copies/ml and below-normal cognitive performance [defined as age, gender and education-adjusted NP performance (NPZ) <−0.5 in a single cognitive domain or in global performance] were enrolled. Changes over 24 weeks were assessed for global and domain-specific NPZ scores, plasma markers of monocyte/macrophage activation [neopterin, soluble (s)CD14 and sCD163] quantified by ELISA, and CCR2 and CCR5 expression on monocytes and T cells measured by flow cytometry.

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Conflicts of interest

The authors have no conflicts to declare.

Results—Seventeen of 20 enrolled participants completed the study. Improvements over 24 weeks were observed in global NPZ [median change (Δ)=0.24; p=0.008], and in cognitive domains of attention (Δ0.23; p=0.011) and working memory (Δ0.44; p=0.017). Plasma levels of sCD163, sCD14 and neopterin decreased significantly (p's<0.01). CCR2 and CCR5 monocyte expression remained unchanged; however, CCR5 levels on $CD4^+$ and $CD8^+$ T cells and CCR2 expression on $CD4^+$ T cells increased (p's<0.01).

Conclusions—CVC given over 24 weeks was associated with improved NP test performance and decreased plasma markers of monocyte immune activation in virally-suppressed, HIV-infected participants. These data potentially link changes in monocyte activation to cognitive performance. Further study of CVC for HIV cognitive impairment in a randomized controlled study is warranted.

Keywords

C-C chemokine receptor type 2 and 5 (CCR2 and CCR5); monocytes; HIV; antiretroviral therapy (ART); cognitive impairment; clinical trials

INTRODUCTION

Neurocognitive performance is compromised in approximately 30-50% of chronically HIV-infected individuals despite treatment with virally-suppressive antiretroviral therapy (ART).[1,2] Cognitive dysfunction negatively impacts daily function, quality of life, and increases morbidity and mortality.[3–5] At present, clinically approved therapies for HIV-associated cognitive impairment do not exist.[6]

The neuropathogenesis of HIV-associated cognitive impairment has not been completely defined but it is generally hypothesized that transmigration of HIV-infected monocytes into the central nervous system (CNS) provides entry of HIV into the brain and establishes a neuroinflammatory process that disrupts brain integrity and function.[7–12] Persistent immune activation, driven in part by activated monocytes, is believed to be a major component of HIV neuropathogenesis.[13] Monocyte/macrophage mediators such as soluble (s)CD163, monocyte chemoattractant protein (MCP)-1 and interleukin (IL)-6, have been linked to reduced cognitive performance among individuals on ART.[9–11,14–16] Combined, these myeloid features represent a potential target for the treatment of cognitive dysfunction among individuals on ART.

Maraviroc (MVC), a C-C chemokine receptor type 5 (CCR5) antagonist, is FDA-approved as an antiretroviral medication to be used with other antiretroviral agents in CCR5-tropic HIV-infected individuals. MVC has been associated with improved cognitive performance and reduction of plasma markers of monocyte activation.[17–19] In a previous single arm, open-label, 24-week study of MVC intensification in ART-treated, chronically infected individuals, we demonstrated improved cognitive performance, reductions in HIV DNA levels in monocytes and in sCD163 levels, a plasma marker of monocyte activation.[17] These data provide a platform for targeting chemokine receptors (CKRs) to improve cognitive performance in HIV-infected individuals.

The MCP-1/CCR2 axis has also been associated with cognitive dysfunction. In ART-naïve HIV-infected Thai individuals, lower numbers of circulating activated monocytes expressing CCR2 were linked to worse cognitive performance.[20] Reduced numbers of CCR2 expressing monocytes in the periphery suggest preferential trafficking of these cells into the brain towards MCP-1, a potent inducer of monocyte migration[21–24], contributing to neuroinflammation and reduced cognitive function.[9,21] Given the involvement of CCR2 and CCR5 in HIV-related cognitive dysfunction, pharmacotherapeutic strategies that target both CKRs may be more effective than inhibiting a single CKR.

Cenicriviroc (CVC) is an oral, dual CCR2 and CCR5 antagonist with nanomolar potency and a long plasma half-life[25–27] currently in Phase 3 evaluation for treatment of liver fibrosis in adults with nonalcoholic steatohepatitis (NCT03028740). In the Phase 2b CENTAUR study 652-2-203 (NCT02217475[28]), one year of CVC treatment led to twice as many participants achieving improvement in fibrosis and no worsening of steatohepatitis when compared to placebo.[29] CVC has also demonstrated anti-inflammatory and anti-fibrotic activity in animal models of liver disease, which was largely attributed to decreased monocyte/macrophage infiltration into the liver following hepatocyte injury.[30–32] In a Phase 2b clinical trial (NCT01338883) in ART-naïve, HIV-infected individuals, CVC decreased viremia and sCD14 levels (marker of monocyte/macrophage activation).[33] In an *ex vivo* study, CVC decreased HIV entry into peripheral blood mononuclear cells (PBMCs).[34] Considering the role of monocyte inflammation and migration into the CNS in the neuropathogenesis of HIV, we hypothesized that CCR2 and CCR5 blockade would improve cognitive function by decreasing monocyte activation and migration into the CNS.

METHODS

Study Design

The study was approved by the University of Hawaii Human Subjects Program, received clearance to proceed from the Food and Drug Administration (FDA) [IND 119671], and was registered at ClinicalTrials.gov (NCT02128828). Twenty chronically-infected aviremic (HIV RNA <50 copies/ml) individuals ages 18 to 70 years on uninterrupted ART for >1 year were enrolled into the single-arm, open label, 24 week pilot study. Participants were required to be on the same ART regimen for at least 6 months prior to entry. Below-normal cognitive performance was defined as performance of <−0.5 standard deviation (SD) below published normative standards in a cognitive domain or global cognitive performance (NPZ Global). Exclusion criteria included currently receiving or having used a CCR5 antagonist as part of an ART regimen within 6 months of entry, on-going need for use of medications known to have unacceptable drug-drug interactions with CVC (provided by the manufacturer of CVC), history of plasma HIV RNA >100 copies/ml within 6 months of screening, chronic hepatitis B or C or diagnosis of any other active or chronic liver disease, chronic uncontrolled seizures or significant past history of central nervous system disease or head trauma, depression (Beck Depression Inventory-II total score >29), chronic illnesses or cancers except for stable treated hypogonadism or hypothyroidism, unstable cardiovascular or cerebrovascular disease, or the following abnormal lab values: hemoglobin <8.5 g/dL, absolute neutrophil count <1000/μL, platelet count <100,000/μL, AST and ALT ≥2.5 upper

limit of normal (ULN), lipase >2.0 × ULN, estimated creatinine clearance by the Cockcroft-Gault Equation ≤30 mL/min, and bradycardia (<50 beats/min).

All study visits were conducted at a single site at the University of Hawaii (UH) Clinics at Kaka'ako. Following written informed consent and screening, CVC was administered once-daily with food in dosage adjusted for each participant's ART regimen and other medications as per the manufacturer's recommendations. Individuals with ART regimen consisting of a nucleoside reverse transcriptase inhibitor (NRTI) and unboosted/boosted atazanavir or boosted darunavir received 50 mg (1 tablet) of CVC, individuals taking dolutegravir or raltegravir-based ART received 200 mg (4 tablets) of CVC, and individuals receiving efavirenz received 400 mg (8 tablets) daily. Research bloods were drawn at entry and at weeks 4, 8, 12, and 24.

Neuropsychological Evaluation

Neuropsychological (NP) testing was conducted at entry and week 24 by trained psychometrists. Testing was conducted in a quiet room and participants were provided breaks as needed throughout the testing sessions. The test battery (Table 1) was comprised of measures known to be sensitive to HIV-related infection including: attention (A); working memory (WM); psychomotor speed (PM); visuospatial reasoning (VPR); executive function (EF); learning and memory (LM) and gross motor (GM).[35,36] Raw scores were converted into standardized z-scores according to demographically-adjusted norms.[37,38] Global cognitive function (Global NPZ) was defined by aggregating the domain specific NP Z-scores.

Assessments of Plasma Derived Soluble Biomarkers

Plasma sCD163, sCD14 and neopterin were quantified at entry and weeks 8, 12 and 24 by single analyte ELISA array (Trillium Diagnostics; Bangor, ME; R&D Systems, Minneapolis, MN and Thermo Scientific, Waltham, MA, respectively).

Quantification of Monocyte and T Cell Subset Frequencies and CKR Expression

Monocyte and T cell subpopulations were measured at entry and week 24 after CVC by flow cytometry. Briefly cryopreserved PBMCs were placed in 96 well polypropylene round bottom plates and stained with Live/Dead® Fixable Red Dead Cell Stain (Invitrogen, Carlsbad, CA) for 15 min at room temperature followed by two, 10 min sequential incubations with conjugated monoclonal antibodies (mAbs) against CCR2 (AlexaFluor647, Catalog Number [Cat] 558406) and CCR5 (Phycoerythrin (PE), Cat 555993) at 37 ºC.[39] Cells were then stained at room temperature for 30 min with mAbs against CD3 (Brilliant Violet (BV) 711, Cat 317328), CD4 (peridinin chlorophyll protein) PerCP-Cyanine (Cy)5.5, Cat 300530), CD8 (PE-Cy5, Cat 555368), CD14 (AlexaFluor700, Cat 557923), CD16 (BV421; Cat 343113), CD7 (PE-Cy7, Cat 343113), CD19 (PE-Cy7, Cat 557835), CD20 (PE-Cy7, Cat 560735), CD11b (AlexaFluor488, Cat 557701) and human leukocyte antigen-D related (HLA-DR) (Allophycocyanin (APC)-H7, Cat 561358). Cells were fixed with 1% PFA and data were acquired on a custom 4-laser BD LSRFortessa (BD Bioscience, San Jose, CA). Compensation and gating analyses were performed using FlowJo (FlowJo LCC, Ashland, OR). All mAbs were purchased from BD Bioscience (San Jose, CA) except for

Live/Dead Stain (Invitrogen, Carlsbad, CA), and CD3-BV711, CD4-PerCP-Cy5.5 and CD16-BV421 (BioLegend, San Diego, CA). The gating strategy for identification of $CD4^+$ and $CD8^+$ T cells, and monocyte subsets, along with CKR expression is shown in Supplemental Figure 1. Median viability for the frozen PBMC samples was 93.8% (interquartile range 25^{th}–75^{th} [IQR]: 89.7-96.1%). Samples were excluded if the viability was below 80%.

Monocyte subset counts were calculated by multiplying monocyte number (Mono/μl) from the white blood cell count obtained from the clinical laboratory values and the percent frequency generated by flow cytometry. $CD4^+$ and $CD8^+$ T cell counts were obtained from the white blood cell count.

Statistical Analyses

Descriptive statistics for all continuous and categorical variables are reported as median (IQR) and n (percent), respectively. Wilcoxon Signed Rank test was used to assess changes from entry to week 24 and Spearman correlation was used to assess the relationship between continuous variables. The magnitude of change from entry to week 24 in NP testing was examined in relation to the standard error of measurement (SEM) estimates where applicable based on prior studies.[40] All statistical analyses were performed using SAS version 9.4 (Cary, NC: SAS Institute Inc. 2002-2012). A two-sided p-value <0.05 was regarded as statistically significant for all tests, while p-values between 0.05 and 0.1 were reported as trends.

RESULTS

Study Participant Clinical and Demographic Characteristics

Seventeen of the 20 enrolled participants completed the study. One participant withdrew from the study due to grade 1 nausea, and 2 participants left the study for non-medical personal issues. Baseline participant characteristics of the 17 participants who completed the study are found in Table 2. The participants were generally older, male except for one participant, with a long history of living with HIV and being on ART. Of the 17 participants, 6 were on dual NRTIs (all on tenofovir/emtricitabine) and protease inhibitor (PI) regimens utilizing boosted atazanavir or boosted darunavir; 7 were on dual NRTIs (either tenofovir/emtricitabine or abacavir/lamivudine) and Integrase Inhibitor (INSTI) therapy with either dolutegravir or raltegravir; and one was on a dual NRTI (tenofovir/emtricitabine) and a non-nucleoside reverse transcriptase inhibitor (NNRTI, efavirenz). The other 3 patients were on less common regimens consisting of a triple NRTI regimen (zidovudine, lamivudine and abacavir); triple NRTI (tenofovir, emtricitabine, abacavir) plus an NNRTI (efavirenz); and dual NRTI (tenofovir, emtricitabine) plus a PI (darunavir) and an INSTI (raltegravir).

CVC Tolerance by Study Participants

A total of 58 clinical adverse events were observed in 14 participants (n=49, grade 1 and n=9, grade 2). Grade 2 clinical adverse events included: loose stools (n=2; 10%), nausea (n=1; 5%), abdominal cramps (n=1; 5%), and fatigue (n=1; 5%). Additionally, 17 laboratory adverse events were reported in 6 participants while on study drug (n=13 grade 1; n=2 grade

2 and n=2 grade 3). The grade 2 adverse events included elevated lipase and creatinine. The grade 3 adverse events included asymptomatic elevated lipase at weeks 24 and 28, both of unclear relationship to CVC. Average/overall compliance was 95%. The lowest compliance recorded in a patient was 65% between weeks 4 and 8. At all other time points recorded, compliance was at least 80%.

Changes in Neuropsychological Performance after CVC Treatment

After 24 weeks, significant improvements were noted in Global NPZ, attention and working memory (Table 3; Figure 1). Trends towards improved psychomotor speed and visuospatial performance were also observed (Table 3; Figure 1). No significant changes were seen in executive function, learning and memory, or gross motor (Table 3; Figure 1).

In the attention domain, trends towards improvements in performance were observed on the CalCap Choice test (median increase=0.57 [−0.45, 1.18], p=0.071) and Digit Span Total (median increase=0.33 [0, 0.66], p=0.094; Supplemental Table 1). Within the working memory domain, the greatest change was evident on the Letter Number Sequencing test (median increase=0.33 [0, 1.00]; p = 0.030), with a less robust effect seen on Digit Span (median increase=0.33 [0, 1.33]; p = 0.065)) and no significant change on CVLT-II trial B were noted (Supplemental Table 1). Comparisons of change in performance relative to the SEM of each neuropsychological measure revealed that initiation of CVC was associated with improvements in performance that exceeded the SEM on the Letter Number Sequencing test.[40]

Changes in Monocyte/Macrophage Activation

After 24 weeks of CVC, significant declines in plasma sCD163, sCD14, and neopterin were observed (Table 3). The trajectories of individual and overall trends are shown in Figure 2.

Changes in Leukocyte Counts

After 24 weeks, significant declines in total monocyte and classical monocyte counts along with significant increases in $CD4^+$ T cell and $CD8^+$ T cell counts were observed (Table 3). No significant changes were noted with $CD4^+/CD8^+$ ratios or the intermediate and non-classical monocyte subset counts (Table 3).

Changes in CCR2 and CCR5 Expression on Monocyte and T Cell Populations

Monocytes are composed of three distinct phenotypic subsets based on CD14 and CD16 expression into classical, intermediate and non-classical monocytes.[41] Functionally these are defined by having scavenging/phagocytic, inflammatory and patrolling properties, respectively.[42,43] After 24 weeks, we observed a trend towards increased CCR2 expression on classical monocytes (Table 3). No significant changes were observed in CCR2 expression on intermediate and non-classical monocytes or in CCR5 expression on any of the monocyte subsets (Table 3). A significant increase in CCR2 levels on $CD4^+$ T cells and significant increases in CCR5 expression on $CD4^+$ and $CD8^+$ T cells were noted (Table 3).

Correlations at Entry Between Leukocyte Measurements, Soluble Markers of Monocyte/Macrophage Activation and Neuropsychological Testing

At entry, higher CCR2 levels on non-classical monocytes correlated with better performance on tests of attention (rho=0.637; p=0.026). Higher CCR5 expression on classical monocytes correlated with greater classical monocyte counts (rho=0.587; p=0.045). Additionally, sCD14 positively correlated with non-classical monocyte counts (rho=0.755; p=0.005). Trends noted at entry included a positive correlation between CCR5 levels on non-classical monocytes and non-classical monocyte counts (rho=0.559; p=0.059) and negative correlations between CCR5 on $CD4^+$ T cells and visuospatial performance (rho= −0.574; p=0.065), and between sCD14 and psychomotor speed (rho= −0.458; p=0.064). No correlations were noted between sCD163 and neopterin, and monocyte counts, CKR expression or performances on neuropsychological measures.

DISCUSSION

Our study demonstrated improved neuropsychological testing performance and reduced monocyte activation following 24 weeks of CVC in 17 virally suppressed HIV-infected individuals on stable ART. These data potentially link changes in monocyte/macrophage activation induced by CVC to improved cognitive performance in HIV-infected participants on virally suppressive ART.

Although the effects of CVC on cognitive performance were relatively subtle, the improvements approximated 0.5 SD, which is commonly referenced as a clinically meaningful degree of change.[44] Working memory, one of the subdomains which improved with CVC, is a specific component of executive function that is sensitive to HIV.[45] The working memory cognitive domain encompasses short-term storage and manipulation of a limited amount of information in real time[46,47] and is essential for effective implementation of daily activities such as driving, problem solving, and complex decision-making.[48]

As a single-arm study design, the potential influence of practice effects on the cognitive outcomes merits consideration. Practice effects are common and are typically pronounced between the first and second exposures.[49] The cohort recruited in the present study had undergone cognitive testing through prior longitudinal studies and therefore the impact of practice from baseline to 24 weeks in the present study is less clear. The magnitude of change in the working memory domain, particularly on the Letter Number Sequencing test, exceeded the SEM, suggesting that the magnitude of change in performance observed in the present study is unlikely to be due to practice effects.[49] However, larger studies with a demographically matched control group are needed to address the important issue of practice effects more completely.

Potential therapeutic interventions for HIV-associated cognitive difficulties are limited. Our study suggests that modulation of monocyte/macrophage activation should be considered as a potential therapeutic intervention option to improve cognitive performance. Both sCD163 and sCD14, which are shed after monocyte/macrophage activation[50–52], have been previously shown to be biomarkers of cognitive performance in HIV. In ART-treated individuals, plasma sCD163 levels are elevated among individuals with more severe

cognitive deficits.[14] Plasma sCD14 levels have also been shown to be higher in HIV-infected individuals with worse performance in attention and learning.[53] Similarly, in the Women's Interagency HIV Study (WIHS), higher plasma sCD163 levels associated with worse global cognitive performance and lower scores on tests of verbal learning, verbal memory, executive function, psychomotor speed.[15] Higher sCD14 levels were associated with worse verbal learning, verbal memory, executive function, and psychomotor speed.[15] Neopterin, which is produced by monocytes after stimulation with pro-inflammatory cytokines such as interferon-γ (IFN-γ)[54], remains elevated in treated HIV.[55–58] Although we did not observe significant correlations between sCD163, sCD14 or neopterin with cognition at baseline, the concomitant decrease in soluble markers of monocyte/macrophage activation with improved cognitive performance is suggestive of a direct link. Further studies are needed to explore the causal pathways that cannot be established in this preliminary study.

Decreases in monocyte counts in the periphery may be a result of diminished rates of egress of classical monocytes out of the bone marrow, as murine studies have demonstrated that CCR2 is required for monocyte trafficking out of the bone marrow into the circulation.[42,59] Increases in CKRs observed in our study are in concert with a double-blind, placebo controlled randomized trial of MVC where $CCR5^+$ $CD4^+$ and $CD8^+$ T cell frequencies were significantly increased in the MVC group compared to placebo.[60] Although chemokine receptor levels on the monocyte subsets from the periphery were not significantly altered by CVC, we did note a limited number of correlations between CKR expression and cognitive performances, suggesting modulation of chemokine receptors have beneficial effects. In fact, murine models have shown that decreased function of CCR5 lead to enhanced hippocampal-dependent learning and memory, while neuronal CCR5 overexpression caused memory deficits.[61] Moreover, treatment of mice with HIV peptide decreases long-term potentiation deficits that can be prevented by CCR5 knockout or knockdown.[61]

Four out of the 17 participants had worse global cognition after 24 weeks of CVC. There were no evident factors that contributed to the decline in cognitive performance in 3 out of the 4 participants. One participant tested positive for methamphetamines, marijuana and amphetamines at week 24 but not at entry, which could have affected cognitive performance at the follow-up visit. Removal of this case did not affect the pattern of results. When comparing the participants who exhibited worse cognition after 24 weeks of CVC to the remainder of the sample revealed no significant differences in clinical or laboratory parameters, including monocyte activation, leukocyte counts, age, or years infected (data not shown).

This study was planned as a small exploratory study. The conclusions of this study are limited by the small sample size of only 17 evaluable participants. In addition, the design was that of a single arm study without a placebo control arm which limits our ability to conclusively define a causal link between CVC and changes in cognition and monocyte/macrophage immune activation. Finally it should be noted that participants enrolled in the present study were chronically-infected with a long history of ART and we cannot make any conclusions on the potential effect of CVC on individuals who are ART-naïve, or were treated early or in acute HIV infection. It is possible that CVC therapy may not have as great a response in early HIV when monocyte/macrophage inflammation is likely less than in

those with delayed therapy, but it is equally possible that early intervention with CVC soon after diagnosis in conjunction with potent ART may prevent or diminish the occurrence of even mild forms of cognitive impairment.

The results of this small single-arm study are however intriguing. Given the lack of pharmacological interventions to improve cognition in HIV-infected individuals, further study of CVC in a randomized controlled study with a placebo arm and a longer follow-up period would be important to both confirm our findings and also to determine the magnitude and relevance of outcomes to patient care. Additional points of interest include characterizing monocyte/macrophages from tissues. The observed increases in $CD4^+$ counts may indicate a restoration of the immune system and further study of the effect of CVC on T cells should be pursued. Lastly, the unexpected increase in $CD8^+$ counts also merits further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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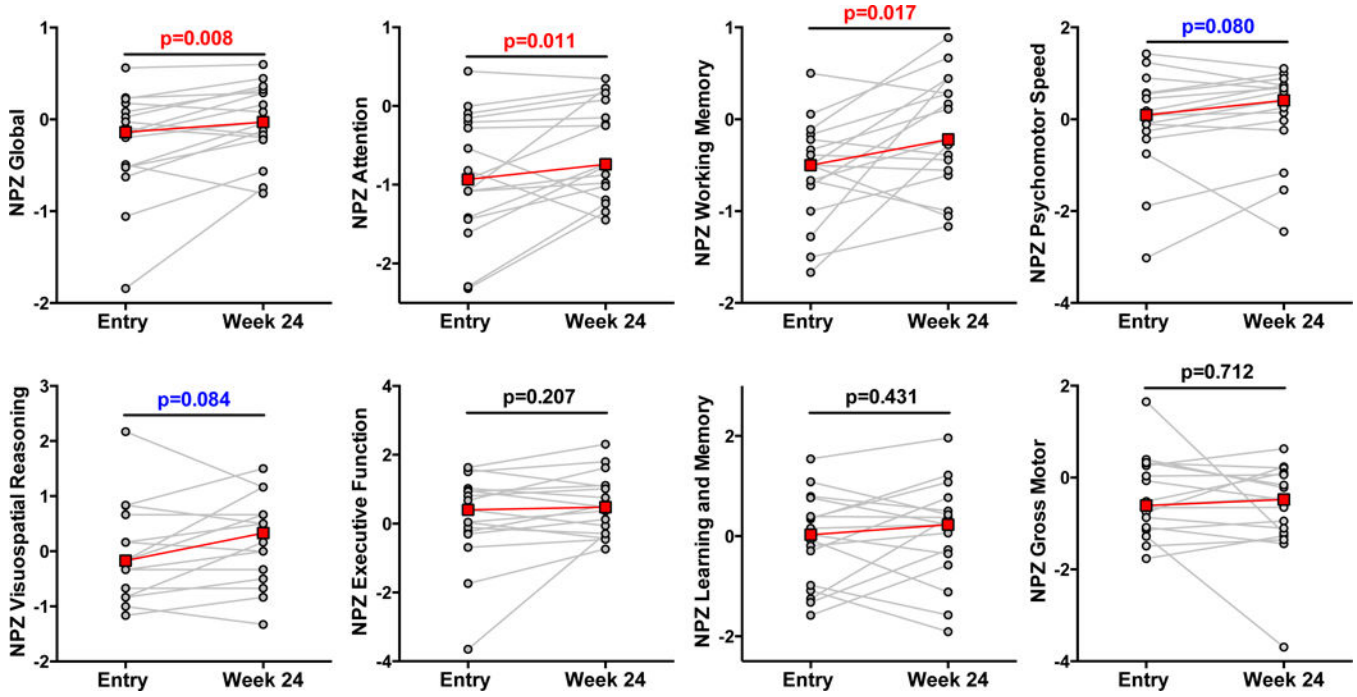

Figure 1. Neuropsychological testing

Global NPZ and subdomain NPZs of attention; working memory; psychomotor speed; visuospatial reasoning; executive function; learning and memory and gross motor were measured at entry and after 24 weeks of cenicriviroc.

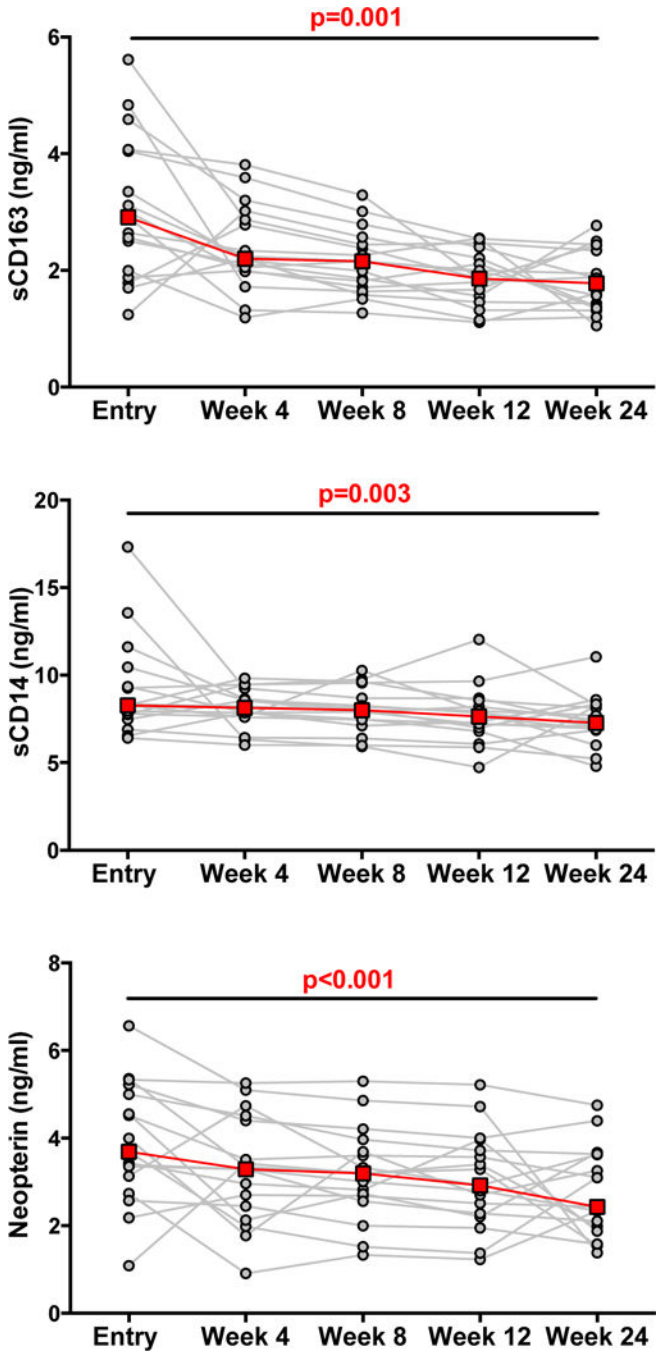

Figure 2. Plasma soluble biomarkers

Plasma sCD163, sCD14 and neopterin were measured at entry and after 4; 8; 12 and 24 weeks of cenicriviroc.

Table 1

Tests comprising each cognitive subdomain

Attention	CalCap Choice
	CalCap Sequential
	Digit Span Total
Working Memory	Digit Span Backward
	CVLT B
	Letter Number Sequencing
Psychomotor Speed	Digit Symbol
	Trail A
	Grooved Pegboard (GP) Dominant Hand (Dom)
	GP NonDom
Visuospatial Reasoning	Rey Copy
	Block Design
Executive Function	Verbal Fluency Test (FAS)
	Stroop
	Trail B
	Action
Learning and Memory	California Verbal Learning Test (CVLT) Total
	CVLT Long-Delay Free Recal
	Brief Visuospatial Memory Test (BVMT) Total
	BVMT Delay
Gross Motor	Timed Gait
	Finger Tapping – Dom
	Finger Tapping – NonDom

Table 2

Participant characteristics at entry

Baseline Characteristics (n=17)	
Gender, male	16 (94%)
Caucasian	7 (41%)
Asian/Pacific Islander	6 (35%)
Other Ethnicity	4 (24%)
Age, years	55 (47, 58)
Education, years	15 (14, 16)
CD4 Nadir*, cells/mm^3	200 (90, 280)
CD4 Count, cells/mm^3	545 (404, 731)
CD4/CD8 Ratio	0.85 (0.55, 0.97)
Time on ART*[I]	15.5 (6.7, 19.5)
Years Infected*	21 (14, 25)
NRTI Use	17 (100%)
NNRTI Use	2 (12%)
PI Use	7 (41%)
INSTI Use	8 (47%)

Median (IQR) presented for continuous variables, N (%) presented for categorical variables.

[*] Self-Reported.

[I] N = 13.

Table 3

Clinical and experimental data before and after cenicriviroc

	Entry	Week 24	p Value
Cognitive Domain (NPZ Score)			
Global	−0.14 [−0.52, 0.08]	−0.03 [−0.19, 0.29]	0.008
Attention	−0.93 [−1.42, −0.21]	−0.74 [−1.02, 0.08]	0.011
Working Memory	−0.50 [−0.72, −0.22]	−0.22 [−0.56, 0.28]	0.017
Psychomotor Speed	0.09 [−0.26, 0.55]	0.41 [−0.03, 0.73]	0.080
Visuospatial Reasoning	−0.17 [−0.75, 0.41]	0.33 [−0.41, 0.66]	0.084
Executive Function	0.40 [−0.23, 0.96]	0.48 [−0.29, 1.07]	0.207
Learning and Memory	0.03 [−0.98, 0.40]	0.23 [−0.35, 0.50]	0.431
Gross Motor	−0.61 [−1.08, 0.26]	−0.48 [−1.21, 0.06]	0.712
Soluble Monocyte Activation Markers (ng/ml)			
sCD163	2.91 [2.00, 4.04]	1.78 [1.38, 2.34]	0.001
sCD14	8.28 [7.76, 9.34]	7.28 [6.90, 8.24]	0.003
Neopterin	3.69 [3.13, 5.00]	2.43 [1.98, 3.62]	<0.001
Leukocyte Counts (Cells/ul)			
Total Monocyte Count	42 [34, 61]	36 [27, 46]	0.001
Classical Monocyte Count	36 [29, 51]	34 [25, 44]	0.016
Intermediate Monocyte Count	0.36 [0.14, 1.0]	0.47 [0.26, 0.65]	>0.999
Non-Classical Monocyte Count	1.0 [0.55, 2.1]	1.2 [0.90, 1.5]	0.470
$CD4^+$ T Cell Count	545 [404, 731]	732 [397, 900]	0.030
$CD8^+$ T Cell Count	856 [476, 1192]	1028 [739, 1229]	0.035
$CD4^+/CD8^+$ T Cell Ratio	0.85 [0.55, 0.97]	0.74 [0.48, 0.95]	0.110
Chemokine Receptor Expression (Geometric Mean Fluorescence)			
CCR2 Levels on Classical Monocytes	157 [139, 188]	197 [152, 230]	0.096
CCR2 Levels on Intermediate Monocytes	46 [38, 68]	48 [21, 82]	0.970
CCR2 Levels on Non-Classical Monocytes	30 [9, 41]	27 [15, 39]	0.791
CCR5 Levels on Classical Monocytes	796 [627, 1093]	1032 [902, 1406]	0.204
CCR5 Levels on Intermediate Monocytes	781 [451, 1220]	1148 [801, 1580]	0.206
CCR5 Levels on Non-Classical Monocytes	296 [216, 345]	367 [293, 441]	0.233
CCR2 Levels on $CD4^+$ T Cells	11.9 [9.3, 15.2]	14.9 [13.4, 15.9]	0.007
CCR2 Levels on $CD8^+$ T Cells	ND	ND	ND
CCR5 Levels on $CD4^+$ T Cells	30.9 [8.0, 50.9]	67.25 [38.8, 91.4]	0.002
CCR5 Levels on $CD8^+$ T Cells	209 [106, 290]	712 [453, 816]	<0.001

ND = Not detected by flow cytometry method