Neurocognitive function and neuroimaging markers in virologically suppressed HIV-positive patients randomised to ritonavir-boosted protease inhibitor monotherapy or standard combination ART: a cross-sectional sub-study from the PIVOT Trial

Alejandro Arenas-Pinto[1,2], Wolfgang Stöhr[1], Hans Rolf Jäger[3,] , Lewis Haddow[2], Amanda Clarke[5], Margaret Johnson[6], Fabian Chen[7], Alan Winston[8], Claudia Godi[3], Steffi Thust[3], Rita Trombin[2], Janet Cairns[1], Bhavana S Solanky[4], Xavier Golay[3], Nicholas I. Paton[1,9] for the PIVOT Neurocognitive sub-study Team*

*The members of the PIVOT Neurocognitive sub-study Team are listed in the Acknowledgements section

[1]MRC-Clinical Trials Unit at UCL, London, UK
[2]UCL Research Department of Infection and Population Health, London, UK
[3]Neuroradiology Academic Unit, UCL Department of Brain Repair & Rehabilitation, Institute of Neurology, London, UK
[4]NMR Research Unit, UCL Department of Neuroinflammation, Queen Square MS Centre, Institute of Neurology, London, UK
[5]Brighton and Sussex University Hospitals NHS Trust, Brighton, UK
[6]Royal Free Hospital, London, UK
[7]Royal Berkshire Hospital, Reading, UK
[8]Imperial College London, UK
[9]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Corresponding author:
Dr Alejandro Arenas-Pinto MBBS, MSc, PhD
MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
Aviation House
125 Kingsway
London WC2B 6NH, UK
Direct line: +44 (0)20 7670-4716

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Short summary:
In this cross-sectional sub-study of a large randomised controlled clinical trial, monotherapy with protease inhibitor showed no excess risk of cognitive impairment compared to standard cART in stable HIV+ patients. We observed no difference between arms on neuroimaging markers either.

Abstract

Objective: To determine whether treatment with ritonavir-boosted protease inhibitor (PI) monotherapy is associated with detrimental effects on neurocognitive function or brain imaging markers compared to standard antiretroviral therapy (ART).

Methods: Neuropsychological assessment and brain magnetic resonance imaging were performed at the last study visit in a subset of participants randomised to PI monotherapy (PI-mono group) or ongoing triple ART (OT group) in the PIVOT trial. We calculated a global *z*-score (NPZ-7) from the average of the individual test z-scores and the proportion of participants with symptomatic neurocognitive impairment (score >1 standard deviation (SD) below normative means in ≥2 cognitive domains and neurocognitive symptoms). In a subgroup, white matter hyperintensities, bicaudate index, global cortical (GCA) and medial temporal lobe atrophy scores and single voxel (basal ganglia) N-acetylaspartate (NAA)/Choline, NAA/Creatine and myo-inositol/Creatine ratios were measured.

Results: 146 participants (75 PI-mono) had neurocognitive testing (median time after randomisation 3.8 years), of whom 78 were imaged. We found no difference between arms in NPZ-7 score (median -0.4 (Interquartile range (IQR)=-0.7; 0.1) vs -0.3 (IQR=-0.7; 0.3) for the PI-mono and OT groups respectively, p=0.28), the proportion with symptomatic neurocognitive impairment (13% and 18% in the PI-mono and OT groups respectively; p=0.41), or any of the neuroimaging variables (p>0.05). Symptomatic neurocognitive impairment was associated with higher GCA score (OR=6.2 per additional score; 95% confidence interval (CI)=1.7-22.3 p=0.005) but no other imaging variables.

Conclusions: Based on a comprehensive neuropsychological assessment and brain imaging, PI monotherapy does not increase the risk of neurocognitive impairment in stable HIV+ patients.

Introduction

Neurocognitive impairment (NCI) is frequently reported in HIV-infected patients, with prevalence figures ranging between 40 and 60%, even after prolonged and effective viral suppression with combination anti-retroviral therapy (cART)(1-4). It has been suggested that different treatment strategies may have differential effect on viral replication in the central nervous system (CNS) and therefore, some regimens may be less effective in preventing the development or progression of NCI (5-7).

Ritonavir (RTV)-boosted protease inhibitor (PI) monotherapy has been explored as a simplification strategy in effectively suppressed, ART-experienced patients in a number of randomised controlled trials (RCT)(8). Given that PI monotherapy includes only one active drug compared to three in standard cART regimens, the possibility of persistent viral replication within the CNS that could lead to progression of neurological complications, including NCI, has been expressed as a concern with this approach(9). Although the PIVOT trial found no evidence of accelerated neurocognitive function decline in participants on PI monotherapy compared to cART over 3-5 years of follow-up, this was based on a testing with simple battery of neuropsychological tests designed to be suitable for repeated use in large numbers of participants(10).

The aim of this sub-study was to look in more detail for evidence of neurocognitive impairment or neuroimaging abnormalities in patients taking PI monotherapy compared to patients on standard cART using a more comprehensive neuropsychological testing battery and brain magnetic resonance imaging (MRI/MRS).

Methods

PIVOT was a non-inferiority, randomised parallel-group trial (ISRCTN-04857074), conducted in 43 sites in the United Kingdom between 2008 and 2013, where 587 effectively suppressed (viral load <50 copies/mL) HIV-positive adults on cART (two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-NRTI (NNRTI) or PI) were randomly assigned 1:1 to maintain ongoing triple therapy (OT) or switched to PI-mono.

All licensed PIs were allowed, but ritonavir-boosted darunavir (DRV/r) 800mg/100mg once daily or ritonavir-boosted lopinavir (LPV/r) 400mg/100mg twice daily were recommended. The primary outcome was *loss of future drug options*, defined as new intermediate/high level resistance to drugs in contemporary use to which the patient's virus was considered to be sensitive at trial entry. Neurocognitive function was assessed in all study participants with a brief neuropsychological testing battery at baseline, week 12 and annually thereafter until the end of the study period.

This sub-study was done at 5 of the larger sites of the PIVOT trial, and offered to all participants attending the final PIVOT study visit. In addition to the standard PIVOT neurocognitive testing battery (comprising the Hopkins Verbal Learning Test-Revised (HVLT-R)(11), Color Trail tests 1 and 2 (CTT-1 and CTT-2)(12) and the Grooved Pegboard test (GPT)(13)), participants underwent additional tests: Rey Complex Figure Test (RCFT)(14), Stroop Color and Word Test (SCWT)(15), Finger Tapping Test (FTT)(16) and the WAIS-III Digit Symbol-Coding test (DST)(17) to ascertain function on the attention/psychomotor speed, executive functioning, fine motor skills and verbal and non-verbal learning and memory cognitive domains.

The presence of cognitive symptoms was assessed from responses to the relevant questions (attention, concentration, memory, problem solving or decision making within the past four weeks) on the MOS-HIV questionnaire performed at the last study visit and participants were considered symptomatic if responded "a good bit of the time" or more often to any of the questions (18). In addition participants were asked about alcohol consumption (AUDIT questionnaire(19)), recreational drug use and self-reported anxiety / depression (responses to the relevant question on EQ-5D(20)).

Neuroimaging investigations

Multimodal magnetic resonance imaging/spectroscopy (MRI/MRS) of the brain was performed using a 3 Tesla Philips Achieva System (Best, Netherlands) at the Institute of Neurology, UCL in a single scan session. Seven pre-defined measures were obtained

from the scans: 1) total volume of white matter hyperintensities, calculated from hand-drawn regions of interest (ROI) on a high-resolution 3D fluid-attenuated inversion recovery (FLAIR) sequence(21). 2) N-acetylaspartate to choline ratio (NAA/Cho), 3) N-acetylaspartate to creatine ratio (NAA/Cr) and 4) Myo-inositol to creatine ratio (mI/Cr) of the left basal ganglia, as found using the MR spectroscopy (MRS) data of a single voxel(22). Finally, 5) Global Cortical atrophy score (GCA)(23), 6) Medial Temporal Lobe atrophy score (TLA)(23) and the 7) Bicaudate Index, defined as the ratio of width of both lateral ventricles at the level of the caudate nucleus to the distance between outer tables of skull at the same level(24). Scans were analysed by individuals who were blinded to the participants' treatment allocation.

Sample size calculation

The hypothesis was that PI monotherapy is not inferior to cART on the NPZ-7 score. We assumed no difference in mean NPZ-7 between the two randomisation arms, and that a difference of ≤0.4 between arms could be regarded as non-inferior. A sample size was calculated to give 80% power to exclude a difference of greater than 0.4 between the arms (2-sided α=0.05) (assuming a standard deviation of 0.8, based on the variation of the NPZ-5 score in the main PIVOT trial at baseline(25). The sample size for MRI scans was limited due to feasibility and funding constraints.

Statistical analysis

Raw scores for each cognitive test were transformed to *z*-scores using the manufacturers' normative data adjusted for age (all tests) and years of education (CTT, SCWT). For the GPT and FTT, the z-scores for the dominant and non-dominant hands were averaged. The SCWT was scored as average of word, color, and color-word sub-tests. Cognitive domain z-scores were calculated by averaging the scores of the relevant tests when appropriate. NPZ-7 scores were then calculated by averaging all 7 cognitive domains. For all individual test z-scores and the NPZ-7, values below zero denote below-average neurocognitive function compared to the reference population. For the purposes of group comparisons, we defined neurocognitive impairment as a z-score <-1

of the normative mean in at least two cognitive domains (similar to the Frascati definition of NCI)(26). Symptomatic neurocognitive impairment was defined as neurocognitive impairment with reported symptoms (an answer of "a good bit of the time" or worse to any of the four components of question 10 (assessing problem solving and decision-making, memory, attention and concentration) of the MOS-HIV QoL questionnaire) (27). A sensitivity analysis was performed assuming verbal and non-verbal learning and verbal and non-verbal memory are expression of the same cognitive domains resulting in a sub-study NPZ-5 with two tests for each domain.

Primary analyses were according to intention to treat (ITT). Additional sensitivity analyses were performed based on actual treatment taken. Proportions were compared using chi-square or Fisher's exact tests as appropriate. Continuous test scores were compared using t-test or Mann-Whitney rank tests. Multivariable logistic, ordered logistic and linear regression models were used to examine associations with neurocognitive impairment and the following variables: gender, age, ethnicity, years of education, nadir and current CD4+ T-cell count, time known HIV+, current and past smoking and use of recreational drugs and alcohol. Correlations between individual test z-scores within each cognitive domain were explored using Pearson coefficient. Moderate correlation was defined based on coefficients ranging from 0.4 to 0.6 whereas coefficients >0.6 were considered evidence of strong correlations.

The main PIVOT protocol and this sub-study protocol were approved by the Cambridgeshire 4 Research Ethics Committee and all relevant R&D offices. All participants provided written informed consent.

Results

Study population

Of 219 PIVOT participants who attended their final trial visit (median 3.8 years from randomisation) at the 5 participating sites, 146 (67%) (75 PI-mono, 71 OT) were enrolled in the sub-study (Fig 1). Enrolled participants were older and more commonly had VL

suppression (<50 copies/ml) than those who were not enrolled at the sites (Supplementary Table 1).

Sub-study participants were mainly white men, with a median of 15 years formal education, and substantial rates of self-reported anxiety / depression (32%), smoking (24%), risky alcohol consumption (36%) and current recreational drug use (31%) (Table 1, supplementary Table 2a and 2b). Participants in the PI-mono group were older (mean 49 versus 46 years; p=0.022), and fewer were cigarette smokers (15% versus 34%; p=0.01) compared to those in the OT group (Table 1). At the time of the sub-study visit, 49 (65%) of those in the PI-mono group were taking PI-monotherapy (41 DRV/r, 6 LPV/r, 2 atazanavir (ATV/r)) and 4 in the PI-group and 12 in the OT group were taking efavirenz.

Neurocognitive function

We found no difference between the groups in the median z-score on any individual test or cognitive domain (Table 2). There was also no difference between study groups in summary NPZ-7 score (-0.4 in the PI-mono group vs -0.3 in the OT group; p=0.25; difference 0.14 (95% CI -0.10 to 0.39); non-inferiority criterion formally met). Furthermore, we found no difference between groups when average z-score on the PIVOT short battery (NPZ-5; p=0.31) or the additional four sub-study tests (p=0.20) were compared separately. There also was no relationship between randomised arm and NPZ-7 score in multivariable regression analyses; the only independent associations with the lower NPZ-7 score were older age and black ethnicity (Table 3). The results were unchanged in sensitivity analyses based on treatment taken at the time of the sub-study, or using sub-study NPZ-5 as outcome instead of NPZ-7.

Moderate correlation was observed between tests measuring the same cognitive domain, except in the case of tests measuring fine motor skills. Similarly, there was strong correlation between tests measuring verbal learning and memory and non-verbal learning and memory (Supplementary table 3).

Considering the whole sub-study population, there were no differences between the groups in the proportion of participants with overall neurocognitive impairment (45% in the PI-mono vs 49% in the OT group; p=0.63) or in the proportion of participants with symptomatic neurocognitive impairment (13% in the PI-mono vs 18% in the OT group; p=0.41; Table 2). There also was no association between study arm and overall neurocognitive impairment or symptomatic neurocognitive impairment using logistic regression adjusting for age, ethnicity, education and nadir CD4 count . The only significant association with overall neurocognitive impairment was with black ethnicity (OR=5.5; 95%CI 1.8-16.2; p=0.002); there were no significant associations found with symptomatic neurocognitive impairment.

Neuroimaging markers

Brain MRI/MRS was performed in 78 of the 146 sub-study participants (53%, 39 on each study arm). There were no differences between participants with and without neuroimaging in any of the measured variables (Supplementary table 4). We found no differences between arms in any of the neuroimaging measures (Table 4). No associations were found between any of the neuroimaging measures and test-specific, domain or global (NPZ-7) z-scores (data not shown) or the presence of overall neurocognitive impairment (Table 5).

We also did not find any association between neuroimaging measures and the presence of symptomatic neurocognitive impairment, apart from GCA where we found a higher risk with increasing scores (OR 6.2; 95% CI 1.7-22.3; p=0.005) (Table 5). However, further analyses suggested that this was driven by the significant association of GCA scores with neurocognitive symptoms irrespective of neurocognitive test performance.

Discussion

Our findings support the results of the main PIVOT trial that found no difference in neurocognitive function between PI monotherapy and triple therapy arms over 3-5 years of follow-up (also consistent with 48 week changes in another PI monotherapy trial)(10,

28). The findings of this sub-study strengthen the earlier conclusions by extending the neurocognitive assessment to include a more comprehensive neuropsychological testing battery than the brief one used for longitudinal assessment in these trials, which would be expected to be more sensitive in detecting between-group differences if they existed. In particular, the sub-study battery included two different tests to measure some of the cognitive domains explored (i.e. attention-concentration, executive functioning and fine motor skills) which is recommended (26). In addition, we added tests to explore non-verbal learning and memory, which are domains less likely to be affected by unmeasured cultural factors(25). We also collected additional information on comorbid conditions such as alcohol or recreational drugs use and mood disorders to allow analyses to be adjusted for these important factors.

The consistent results in this sub-study between the expanded battery and the short battery (used in the main trial) also lend confidence to the validity of neurocognitive testing results reported for the main trial. Extensive and detailed longitudinal investigation of neurocognitive function in large, multi-centre, strategy, randomised controlled trials would have been very difficult to implement and extremely onerous. Therefore, more pragmatic approaches, as the one we implemented in PIVOT, are probably more appropriate.

The proportion of sub-study participants that met the definition of impairment used for this study was high (45%). However, the proportion of participants meeting the criteria for symptomatic neurocognitive impairment, a more relevant clinical endpoint (29, 30), was much lower (15.8%). The absence of between-group differences on the neurocognitive tests, whether based on a composite z-score or on a threshold classification, as well as the absence of differences on neuroimaging investigations lends support to the conclusion from the main PIVOT trial (and other studies) that there is no added risk from PI monotherapy (28, 31).

Different neuroimaging techniques have been used to identify markers of HIV-associated neurocognitive impairment, including magnetic resonance spectroscopy (MRS), and the effect of different treatment options on these markers has been explored in treatment

naïve patients starting cART(32). However, information on effectively suppressed patients is lacking, and in particular there are very limited data comparing neuroimaging markers between patients on PI monotherapy and cART(33).

Consistent with our results, associations between imaging markers of cerebral atrophy and neurocognitive impairment have been previously reported in both naïve and ART-experienced patients (34-36). However, in our study, the association between an atrophy measurement, higher GCA score, and cognitive function was limited to those with symptomatic impairment. Conversely, cortical atrophy has also been described in patients with long-term HIV disease with normal cognitive function (37) whereas symptomatic neurocognitive impairment has been associated with longer duration of both HIV disease and exposure to cART (38). Our participants were very ART-experienced patients and free from virological failure (at baseline) but cognitive symptoms were not infrequent (23%). However, we found no association between any HIV or ART-related variables and neurocognitive function, symptoms or neuroimaging measurements.

Our study has some limitations. The sub-study recruited a subset of randomised participants (67% of those at the participating sites). Although there is the possibility of selection bias, the overall similarity of those recruited to the overall trial population at the sites (minor differences in age and proportion with VL suppression below 50 copies/ml) suggests this is unlikely to have had an important effect. Furthermore, the fact that neurocognitive results in this sub-study are consistent with the results of the main trial (no differences between treatment arms) also strengthens confidence in their validity. Participants in clinical trials generally tend to be highly selected and this may impact generalisability. This may be the case in this trial and sub-study, since in PIVOT all participants were free of previous episodes of virological failure suggesting high level of adherence to their ART and the prevalence of comorbid conditions likely to affect cognition, such hepatitis C co-infection or CNS opportunistic infections was very low. However, the study population was very homogeneous and therefore ideal to assess cognitive function in effectively suppressed patients with no major comorbidities. The criteria used to define neurocognitive symptoms and the definition of neurocognitive

impairment we used were somewhat arbitrary, but that we considered appropriate for the population studied based on the available data collected in the main trial. In addition, a similar threshold approach is commonly used. (39-41). Alternative thresholds might give different overall proportions of patients classified as neurocognitively impaired, but this is of less relevance for this study which focuses on the comparison of treatment groups. The conclusions were the same, whether the analyses were based on this threshold approach or on composite z scores. The cross-sectional study design is also a limitation for the neuroimaging component since we have no baseline imaging and could not assess any difference between arms in change over time.

In summary, using a comprehensive neuropsychological testing battery, this analysis confirms previous observations made using brief testing batteries showing no excess risk of cognitive impairment in patients on PI-mono compared to standard cART(10, 28). The absence of differences between arms on detailed MRI/MRS analysis also supports the earlier conclusion that PI-monotherapy does not carry a substantive risk of CNS damage and should give confidence to patients and physicians who wish to use this therapeutic option for long-term management of HIV infection.

Table 1. Characteristics of sub-study participants by randomisation arm

	PI-mono (N=75)	**OT (N=71)**	**p**	**Overall (N=146)**
Age, Mean (SD)	49 (9)	46 (8)	0.02	48 (9)
Sex, N (%)				
Male	63 (84.0)	63 (88.7)	0.41	126 (86.3)
Ethnicity, N (%)			0.41	
White	58 (77.3)	61 (85.9)		119 (81.5)
Black	14 (18.7)	8 (11.3)		22 (15.1)
Other	3 (4.0)	2 (2.8)		5 (3.4)
Years of formal education, Median (IQR)	15 (12 - 18)	15 (13 - 18)	0.53	15 (12 - 18)
CD4 cell count nadir, Median (IQR)	170 (90 - 250)	191 (100 - 269)	0.41	180 (90 - 260)
CD4 cell count at entry, Median (IQR)	621 (467 - 760)	650 (540 - 830)	0.27	640 (483 - 785)
HIV-RNA <50 copies/ml, N (%)	72 (96.0)	67 (95.7)	1.00	139 (95.9)
Risky alcohol consumption, N (%)[1]	22 (29.3)	30 (42.9)	0.09	52 (35.9)
Recreational drugs use, N (%)			0.54	
In the past	26 (35.1)	30 (44.1)		56 (39.4)
Currently	25 (33.8)	19 (27.9)		44 (31.0)
Smokers at sub-study visit, N (%)	11 (14.7)	24 (33.8)	0.01	35 (24.0)
Depression/anxiety[2]			0.63	
Moderate	24 (34.8)	20 (29.4)		44 (32.1)
Severe	2 (2.9)	4 (5.9)		6 (4.4)
Neurocognitive symptoms [3]	17 (23.0)	16 (22.5)	0.95	17 (23.0)
ART exposure at sub-study visit			<0.001	
2NRTI + 1NNRTI	9 (12.0)	22 (31.0)		31 (21.2)
2NRTI + 1PI	15 (20.0)	40 (56.3)		55 (37.7)
PI monotherapy	49 (65.3)	5 (7.0)		54 (37.0)
Other ART combination	2 (2.7)	3 (4.2)		5 (3.4)
Off ART	0 (0.0)	1 (1.4)		1 (0.7)

[1] Based on AUDIT questionnaire score

[2] Based on EQ-5D Health Status questionnaire

[3] Based on MOS-HIV QoL questionnaire

Table 2. Neurocognitive function and impairment by study arm

	PI-mono	OT	p¶	Overall
Attention/concentration				
Color Trails Test- Part 1*	0.3 (-0.3, 0.9)	0.5 (-0.2, 0.9)	0.86	0.4 (0.2, 0.9)
Symbol-digit test	-0.7 (-1.0, 0.3)	0.0 (-0.7, 0.7)	0.10	-0.3 (-1.0, 0.3)
Executive functioning				
Color Trails Test- Part 2*	0.8 (0.2, 1.3)	0.9 (0.5, 1.3)	0.84	0.9 (0.3, 1.3)
Stroop colour-word test	-0.7 (-1.6, 0.2)	-0.3 (-1.0, 0.4)	0.16	-0.5 (-1.2, 0.3)
Fine motor skills				
Grooved Pegboard Test: both hands*	-0.1 (-0.8, 0.6)	0.1 (-0.9, 0.6)	0.25	0.0 (-0.9, 0.6)
Finger tapping: both hands	-1.8 (-2.5, -0.8)	-1.6 (-2.2, -0.8)	0.86	-1.8 (-2.5, -0.8)
Verbal learning				
Hopkins Verbal Learning test (Revised)*	-0.4 (-1.2, 0.1)	-0.1 (-1.0, 0.7)	0.45	-0.3 (-1.2, 0.4)
Verbal memory				
Hopkins Verbal Learning test (Revised)*	0.0 (-1.1, 0.8)	-0.1 (-1.0, 0.9)	0.33	-0.1 (-1.0, 0.9)
Non-verbal learning				
Rey Complex Figure test	-0.4 (-0.8, 0.3)	-0.2 (-1.4, 0.7)	0.69	-0.4 (-1.2, 0.6)
Non-verbal memory				
Rey Complex Figure test	-0.4 (-1.1, 0.2)	-0.5 (-1.5, 0.7)	0.98	-0.4 (-1.3, 0.5)
Summary z-scores				
PIVOT summary Z-score (NPZ-5)*	0.1 (-0.5, 0.6)	0.2 (-0.3, 0.6)	0.31	0.1 (-0.4, 0.6)
Sub-study summary Z-score (NPZ-7)	-0.4 (-0.7, 0.1)	-0.3 (-0.7, 0.3)	0.25	-0.3 (-0.7, 0.2)
Sub-study summary Z-score (sNPZ-5)‡	-0.3 (-0.8, 0.0)	-0.3 (-0.7, 0.3)	0.23	-0.3 (-0.7, 0.2)
Neurocognitive impairment¥, N (%)				
Symptomatic	10 (13.3)	13 (18.3)	0.41	23 (15.8)
Overall	34 (45.3)	35 (49.3)	0.63	69 (47.3)

Results presented as z-scores median (IQR) unless otherwise stated.

¶ P-values from t-test or chi^2-test.

*PIVOT neuropsychological testing battery

‡ Sub-study testing battery: Considering verbal and non-verbal learning and verbal and non-verbal memory measures of the same comains.

¥Neurocognitive impairment: defined as z-score <-1 in ≥2 cognitive domains

Table 3. Factors associated with global neurocognitive score (NPZ-7), defined as the average z-score across seven cognitive domains: Linear regression models

	Coef.	**95% CI**	**p**
PI-mono	-0.00	-0.24, 0.23	0.989
Age (per 10 additional years)	**-0.16**	**-0.31, -0.02**	**0.024**
Female gender	-0.19	-0.65, 0.28	0.421
Ethnicity (black)	**-0.71**	**-1.17, -0.25**	**0.003**
Education (per additional year)	0.02	-0.02, 0.06	0.409
Risky alcohol consumption[¥]	0.20	-0.04, 0.45	0.102
Recreational drugs use			
In the past	-0.14	-0.45, 0.17	0.372
Current use	0.08	-0.25, 0.41	0.649
Smoking			
In the past	0.04	-0.23, 0.32	0.751
Current use	-0.05	-0.37, 0.27	0.758

[¥] AUDIT questionnaire score: Hazardous or harmful consumption and likely dependency

Table 4. Neuroimaging markers by study arm

	PI-mono (n=39)	**OT (n=39)**	**p**
WMH			
WMH present, N (%)	22 (56.4)	25 (64.1)	0.64
Volume (mm^3), median (IQR)	76 (0 – 667)	101 (0 – 347)	0.91
Atrophy measures			
GCA score, median (IQR)	1 (0 – 2)	1 (1 – 1)	0.60
TLA score, median (IQR)	1 (1 – 2)	1 (1 – 1)	0.77
Bicaudate index, median (IQR)	0.11 (0.10 – 0.13)	0.10 (0.09 – 0.12)	0.07
Single Voxel MRS			
NAA/Ch, median (IQR)	4.2 (3.9 – 4.8)	4.4 (4.0 – 4.7)	0.37
NAA/Cr, median (IQR)	1.0 (0.9 -1.0)	1.0 (0.9 – 1.0)	0.53
mI/Cr, median (IQR)	0.6 (0.5 – 0.7)	0.5 (0.5 – 0.6)	0.56

WMH: White matter hyperintensities; GCA: Global cortical atrophy score; TLA: Medial temporal lobe atrophy score; NAA/Ch: N-acetyl aspartate to choline ratio; NAA/Cr: N-acetyl aspartate to creatine ratio; mI/Cr: Myo-inositol to creatine ratio.

Table 5. Association between imaging measurements and neurocognitive impairment, defined as a z-score <-1 in at least two out of seven cognitive domains: Logistic regression models*

	Overall Neurocognitive Impairment			**Symptomatic Neurocognitive Impairment**		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
White Matter Hyperintensities						
Lesion Volume (log10) ¥	1.0	0.9, 1.1	0.857	1.1	1.0, 1.2	0.266
Atrophy scores						
GCA	1.2	0.6, 2.7	0.580	**6.2**	**1.7, 22.3**	**0.005**
TLA	1.3	0.6, 2.7	0.515	1.8	0.8, 4.4	0.173
Bicaudate index	1.1	0.6; 2.2	0.737	2.0	0.9, 4.4	0.100
Single Voxel MRS						
NAA/Ch¥	1.2	0.6, 2.6	0.590	1.9	0.8, 4.5	0.140
NAA/Cr¥	1.7	0.8, 3.4	0.164	1.9	0.9, 4.3	0.116
mI/Cr¥	1.0	0.5, 1.8	0.953	0.8	0.4, 1.5	0.454

*Adjusted for study arm allocation, age (per additional year), ethnicity (black vs other), education (per additional year on formal education) and nadir CD4 count (per 100c more)

GCA: Global cortical atrophy score; TLA: Medial temporal lobe atrophy score; NAA/Ch: N-acetyl aspartate to choline ratio; NAA/Cr: N-acetyl aspartate to creatine ratio; mI/Cr: Myo-inositol to creatine ratio.

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The PIVOT Neurocognitive sub-study Team are:

Participating Sites: Elton John Centre, Brighton: Martin Fisher, Amanda Clarke, Wendy Hadley, David Stacey. Royal Free Hospital, London: Margaret Johnson, Pat Byrne. Mortimer Market Centre, London: Lewis Haddow, Ian Williams, Nahum De Esteban, Pierre Pellegrino, Alejandro Arenas-Pinto, Rita Trombin. Royal Berkshire Hospital, Reading: Fabian Chen, Ruth Wilson, Elizabeth Green, John Masterson. St Mary's Hospital, London: Alan Winston, Scott Mullaney.

MRC Clinical Trials Unit at UCL: Alejandro Arenas-Pinto, Nicholas Paton, Wolfgang Stöhr, Karen Scott, David Dunn, Karen Sanders, Janet Cairns.

UCL Institute of Neurology: Rolf Jager, Claudia Godi, Steffi Thust, Bhavana Solanky, Marios Yiannakas, Xavier Golay.

PIVOT Trial Steering Committee: Andrew Freedman (Chair), Ben Cromarty, Danielle Mercey, Sarah Fidler, Estee Torok, Abdel Babiker, Brian Gazzard, Chloe Orkin, Nicholas Paton.

PIVOT Data Monitoring Committee: Tim Peto (Chair), David Lalloo, Andrew Phillips and Robert James.

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