FOURTH INTERNATIONAL MEETING

on HIV Infection and the Central Nervous System

Treating the Brain in the HAART Era

Monte Porzio Catone, Rome, Italy

July, 15-16 2011

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AYLIN YILMAZ (Göteborg, Sweden)
CHRISTINE ZINK (Baltimore, USA)

Presentation

HIV-associated dementia has been one of the most threatening complications of HIV infection. Although its incidence has dramatically decreased among people receiving a combination antiretroviral treatments, milder forms of neurocognitive impairment are becoming highly prevalent even in successfully treated HIV-positive persons.

Despite significant progress in understanding the pathogenesis of brain infection by HIV, the mechanisms involved in the currently observed forms of cognitive impairment are only initially being characterized. As a consequence, optimal management tools are still lacking. This meeting has the objectives of reviewing concepts on HIV brain infection in the current era, addressing unsolved issues and discussing control strategies for the future

Friday, July 15

08.00-08.30 Registration of Participants
08.30-09.00 Welcome Remarks

Neurological and Cognitive Impairment Before and After Treatment in the Current Era

Chairmen: R.W. Price (San Francisco, USA) and M. Andreoni (Rome, Italy)

09.00-09.20 SIV Model of CNS Disease and Response to Treatment • C. Zink (*Baltimore, USA*)
09.20-09.40 Neurological and Cognitive Impairment in Resource Poor Areas • A.C. Meyer (*San Francisco, USA*)
09.40-10.00 CNS Involvement in Acute Infection • S. Spudich (*New Haven, USA*)
10.00-10.20 Prevalence of Severe Neurological Impairment • N. Obel (*Copenhagen, Denmark*)
10.20-10.40 Prevalence of Milder Neurocognitive Impairment • R. De Pasquier (*Lausanne, Switzerland*)

10.40-11.00 COFFEE BREAK

Causes and Contributors of Cognitive Impairment in the Current Era

Chairmen: K. Robertson (Chapel Hill, USA)

11.00-11.20 Potential Role of Metabolic Problems in CNS Dysfunction • E. Martinez (*Barcelona, Spain*)
11.20-11.40 The Impact of Aging on CNS Function in HIV Infection • S. Swindells (*Omaha, USA*)

OPEN SESSION I

Chairmen: J. Arribas (Madrid, Spain) and A. Cingolani (Rome, Italy)

11.40-11.55 Neurocognitive Profile of HIV Associated Neurocognitive Disorders (HAND), 1996 to 2010: Results from an Observational Cohort • V. Tozzi *(Rome, Italy)*
11.55-12.10 Neuropsychological Outcomes in Adults Commencing Anti-retroviral Treatment in South Africa • J. Joska *(Cape Town, South Africa)*
12.10-12.25 Application of the Framingham Stroke Risk Calculator to a Stroke-free Sample of HIV+ Adults • R. Ellis *(San Diego, CA, USA)*
12.25-12.40 New Evidence of Vascular-related Metabolic Injury in the Brain of HIV+ Individuals • L. Cysique *(Sydney, Australia)*

12.40-14.10 LUNCH AND POSTER VIEWING

Friday, July 15

The CNS, Macrophages and Immune Activation in Relation to Viral Eradication

Chairmen: P. Portegies (Amsterdam, The Netherlands) and B.J. Brew (Sydney, Australia)

14.10-14.30 The experience from clinical trials • A. Winston (*London, UK*)
14.30-14.50 Viral compartmentalization and tropism in CNS • R. Swanstrom (*Chapel Hill, USA*)
14.50-15.10 Macrophages and other cellular sites of CNS infection by SIV and HIV • K. Williams (*Boston, USA*)
15.10-15.30 Neuropathology in treated patients • J. Bell (*Edinburgh, UK*)

Evaluating Neurological Disease in Treated Patients

Chairmen: R. Ellis (San Diego, USA) and V. Tozzi (Rome, Italy)

15.30-15.50 Neuropsychological Testing • K. Robertson (*Chapel Hill, USA*)
15.50-16.10 Non Conventional MR Imaging • B. Ances (*St. Louis, USA*)
16.10-16.30 Measuring HIV Replication in the CSF • P. Cinque (*Milan, Italy*)
16.30-16.50 Markers of Immune Activation and Tissue Damage in the CSF • M. Gisslen (*Göteborg, Sweden*)

16.50-17.10 COFFEE BREAK

OPEN SESSION II

Chairmen: G. Arendt (Duesseldorf, Germany) and F. Starace (Modena, Italy)

17.10-17.25 Distinct Detection of HIV-Associated Neurocognitive Dysfunction According to Clinician and Patient Perception: Findings from the NEU Study • J.M. Moreno *(Barcelona, Spain)*
17.25-17.40 Progressive Brain Injury among Neurologically Asymptomatic Subjects in the Setting of Chronic HIV Infection and cART: The HIV Neuroimaging Consortium Cohort Study • B. Navia *(Boston, USA)*
17.20-17.55 Low Nadir CD4+ Counts and Disrupted MRS Brain Metabolite Levels are Associated with Reduced Brain Volume in HIV/AIDS • J. Harezlak *(Indianapolis, USA)*
17.55-18.10 Antiretroviral Regimen Efficacy in Monocyte/Macrophages Associated with Cognitive Function • C. Shikuma *(Honolulu, USA)*

Saturday, July 16

Targeting CNS Infection

Chairmen: A. McCutchan (San Diego, USA) and C.F. Perno (Rome, Italy)

08.30-08.50 Treating Immune Activation • P. Hunt *(San Francisco, USA)*
08.50-09.10 Antiretroviral Treatment of Macrophage Infection • S. Aquaro (*Rome, Italy*)
09.10-09.30 Pharmacogenomics and CNS Treatment • D. Haas (*Nashville, USA*)
09.30-09.50 Pharmacological Considerations of CNS Treatment • A. Calcagno (*Turin, Italy*)
09.50-10.10 CNS Antiretroviral Drug Penetration • A. Yilmaz *(Göteborg, Sweden)*
10.10-10.30 The CPE Score • S. Letendre (*San Diego, USA*)

10.30-11.00 COFFEE BREAK

Roundtable Discussion of CNS Evaluation and Treatment Recommendations (part I)

Chairmen: A. Antinori (Rome, Italy) and J. Eron (Chapel Hill, USA)

11.00-11.20 Weighting CNS Infection in Systemic cART • A. Antinori *(Rome, Italy)*
11.20-12.30 Presentation of Guidelines for Treatment of HIV Infection of the CNS in Different Countries

12.30-13.30 LUNCH AND POSTER VIEWING

Roundtable Discussion of CNS Evaluation and Treatment Recommendations (part II)

13.30-15.30 Evaluation (Screening and Diagnosis)
Chairmen: K. Robertson (Chapel Hill, USA) and P. Cinque (Milan, Italy)

15.30-15.50 COFFEE BREAK

15.50-17.50 Treatment
Chairmen: R.W. Price (San Francisco, USA) and M. Gisslen (Göteborg, Sweden)

Conclusions - End of the Meeting
M.C.E. (Medical Continuous Education) - Questionnaire

General Information

CONGRESS VENUE
VILLA MONDRAGONE
Via Frascati 51 - 00040 Monte Porzio Catone - Roma

CME
The request for CME credits has been forwarded to the Italian Ministry of Health for Italian participants.
Nr. 265-7507 - Nr. 15 CME credits
The Congress is intended for medical practitioners, psychologist and psychiatrist.
Main Areas of Interest: Infectious Diseases - Microbiology and Virology

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REGISTRATION FEE
Participant € 300,00 + VAT 20% = € 360,00

THE REGISTRATION FEE INCLUDES:
- Participation in the scientific work
- Congress kit
- Certificate of attendance
- CME certificate
- Coffee breaks and working breakfasts for the whole period
- Dinner of July 15th.

CERTIFICATE OF ATTENDANCE
The Certificate of Attendance will be delivered at the end of the Meeting to all the partecipants registered at the desk of the Organizing Secretariat.

ORAL COMMUNICATIONS AND POSTERS
The scientific programme of the conference will include Sessions of Oral Communications and Discussions of Posters.
Ten minutes will be allocated for the presentation of each communication, after which there will be a 5-minute discussion.
Material to hang the Posters will be available near the display area. The presence of one of the authors is requested for the discussion of the Posters.

SLIDES AND INTERNET POINTS
A computerized projection will be provided by technicians.
Please provide the file of your presentation in electronic format. Slide and Internet Point is located in the Executive Room.

OFFICIAL LANGUAGE
English

How to Reach Us

Villa Mondragone is a part of the Tuscolanum complex of villas together with twelve monumental Renaissance buildings lying on the tops of the Latium Volcano to the south-east of Rome.
It is set on top of a hill 416 meters above the sea level, between Frascati and Monte Porzio Catone (to which it belongs).
To get some information about how to reach us please use Google Maps or follow the indications below.

FROM LEONARDO DA VINCI AIRPORT (FIUMICINO)

LEONARDO EXPRESS TRAIN (direct train) • High train to the Train Station Roma Termini, leaving every 30 minutes (from 6:37 a.m. to 11:37 p.m.); journey duration: 31 minutes. Then, go on from Termini (see indications below)

METROPOLITAN TRAIN (FM1 line) + TUBE • Take the Leonardo Express Train of the FM1 Line to Roma Tiburtina. From Monday to Saturday it leaves every 15 minutes (from 6:27 a.m. to 9:27 p.m.) Sunday and high days every 30 minutes (from 5:57 a.m. to 11:27 p.m.). Go down at Tuscolana station and take the tube metro (line A, Ponte Lungo stop) to the last stop Anagnina. Then, go on from Anagnina (see the indications below). - *The last journeys from Anagnina and Battistini stop are at 10:00 p.m. because of some works in progress. Two high-frequency bus lines, MA1 and MA2 , will cover the range between 10:00 p.m. to 11:30 p.m. from Monday to Friday and on high days, and on Saturday till 00:30 a.m.*

BUS • Blue Co.Tra.L. bus to Roma Termini. Then, go on from Termini (see indications below). - *For further information visit the web site of Aeroporti Di Roma.*

TAXI • The journey by taxi should cost between 70,00 € and 80,00 €: follow the indications about the best way to reach us. - *The taxi should leave you at the internal gate of Villa Mondragone instead of the main entry in Via Frascati 51; there is a not enlighten and one-kilometre climb before getting to the Villa.*

FROM THE GIOVAN BATTISTA PASTINE AIRPORT (CIAMPINO)

BUS • Blue Co.Tra.L. bus (one line only) to the tube, direction Anagnina. Then, go on from Anagnina (see indications below).

TAXI • The journey by taxi should cost between 45,00 € and 55,00 €: follow the indications about the best way to reach us. *The taxi should leave you at the internal gate of Villa Mondragone instead of the main entry in Via Frascati 51; there is a not enlighten and one-kilometre climb before getting to the Villa.*

FROM THE TERMINI TRAIN STATION

TRAIN • Take the train destination FRASCATI. For the timetable of the train please consult the website www.trenitalia.it. Once You arrive at Frascati station, go the stairs up and go to the main square, called Piazza Marconi, and take a taxi to the Villa.

TUBE • Take the line A of the tube Metro until the last stop Anagnina. Then, go on from Anagnina (see indications below). *The last journeys from Anagnina and Battistini stop are at 10:00 p.m. because of some works in progress. Two high-frequency bus lines, MA1 and MA2 , will cover the range between 10:00 p.m. to 11:30 p.m. from Monday to Friday and on high days, and on Saturday till 00:30 a.m.*

TAXI • The journey by taxi should cost between 60,00 € and 70,00 €: follow the indications about the best way to reach us. *The taxi should leave you at the internal gate of Villa Mondragone instead of the main entry in Via Frascati 51; there is a not enlighten and one-kilometre climb before getting to the Villa.*

FROM THE LAST STOP OF A LINE TUBE ANAGNINA

BUS • Take the blue Co.Tra.L. bus direction Rocca Priora (platform 6) which goes across Monte Porzio Catone and go down at Hotel Villa Vecchia stop (it should be the fifth stop but it is by request so please ask the driver before getting off the bus). There are some other buses from Anagnina to Rocca Priora passing through Grottaferrata but they are not suitable.

BY CAR OR TAXI

From the A1 Milano-Napoli highway or from A24 Roma-L'Aquila/Pescara highway • Follow the direction ROMA SUD, Monte Porzio Catone exit. From this exit, turn right. Go along Via Fontana Candida and Via Pilozzo until a crossroads. Turn right via Frascati (the second big road on the right). As you get to the number 51 get into the gate on the left, just after the villa Vecchia Hotel (or Vignola Restaurant) and follow the tree-lined road until a "T" crossroads. Go on taking the left until the entry of the Villa. - *From the highway exit there are some traffic signals indicating Villa Mondragone and Villa Vecchia.*

FROM THE CITY-CENTRE • Take the ring (G.R.A.) towards the A1 Roma-Napoli highway, then the Monte Porzio Catone exit. From the highway exit, turn right. Go along Via Fontana Candida and Via Pilozzo until a crossroads. Turn right via Frascati (the second big road on the right). As you get to the number 51 get into the gate on the left, just after the villa Vecchia Hotel (or Vignola Restaurant) and follow the tree-lined road until a "T" crossroads. Go on taking the left until the entry of the Villa. - *From the highway exit there are some traffic signals indicating Villa Mondragone and Villa Vecchia.*

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ABSTRACTS BOOK

Oral Communications

Neurocognitive Profile of HIV Associated Neurococognitive Disorders (HAND), 1996 to 2010: Results from an Observational Cohort

OC1

V. Tozzi, P. Balestra, P. Lorenzini, R. Libertone, G. Picchi, M. Zaccarelli, G. Liuzzi, A. Sampaolesi, G. Cataldo, S. Menichetti, M. Giulianelli, P. Narciso, A. Antinori

INMI L. Spallanzani, Clinical Department, Rome, Italy

Background: HIV associated neurococognitive disorders (HAND) remain a prevalent condition despite HAART. We performed a 15-year survey to assess the magnitude and nature of cognitive impairment across the HAART era.

Methods: Observational study of patients followed at a large HIV referral Hospital. Patients with confounding conditions were excluded. A neuropsychological (NP) battery of 12 tests on 5 domains was administered by one of us (BP) to all patients. Z scores were calculated, so that negative data indicate performances below the normative mean.

Results: A total of 591 NP examinations were included. Patients characteristics were: male gender 78%, median age 43 years, stage C CDC 46%, previous intravenous drug use 34%, mean CD4 count: 299/uL. Mean z-score values of NP test results by calendar year are reported in table 1. We failed to observe any significant change in mean NPZ-8 global deficit scores and in mean z-scores of NP tests exploring concentration and speed of mental processing, mental flexibility, memory, fine motor functioning, and visuospatial and constructional abilities.

Table 1. Mean z scores, by calendar year

	1996-98	1999-01	2002-04	2005-07	2008-10
NPZ-8 global	-1.49	-1.54	-1.63	-1.65	-1.55
Processing speed	-1.18	-1.35	-1.28	-1.39	-1.76
Mental Flexibility	-3.19	-3.59	-3.40	-3.33	-3.91
Memory	-2.00	-2.02	-2.33	-2.16	-2.30
Fine Motor	-1.76	-1.41	-1.68	-1.47	-1.65
Visuospatial	-0.80	-0.64	-0.88	-0.81	-0.05

Conclusions: We observed no significant changes in magnitude and nature of cognitive impairment across the 15 year study period. The absence of quantitative and qualitative modifications of the neuropsychological profile of HAND is consistent with the hypothesis that the underlying neuropathological mechanisms did not change significantly across the HAART era.

Neuropsychological Outcomes in Adults Commencing Anti-retroviral Treatment in South Africa

OC2

J.A. Joska*, J. Westgarth-Taylor, J. Hoare, K.G.F. Thomas, R. Paul, L. Myer and D.J. Stein

* *Department of Psychiatry and Mental Health, University of Cape Town, South Africa*

Objective: The effectiveness of highly active anti-retroviral treatment (HAART) on neuropsychological function on individuals initiating therapy in South Africa where clade C HIV is predominant is unknown. In this study we sought to describe changes in neuropsychological function in a cohort of participants over a one year period, and to describe factors associated with improvement.

Methods: Participants were recruited from primary care clinics in Cape Town, South Africa. Baseline and one-year neuropsychological function was assessed in participants using a detailed neuropsychological battery. Global deficit scores (GDS) were then generated from t-scores based on a normative dataset of HIV negative controls. Participants were stratified into three groups of neuropsychological impairment based on summary GDS at baseline. Between-group comparisons, as well as unadjusted and adjusted linear associations were evaluated.

Results: Assessments prior to HAART and a median of 11 months (IQR: 11-12) after commencement of HAART were performed on 82 participants. The group compromised 76.7% women and 91.5% isiXhosa speakers. The median age and level of education was 29 years (IQR: 27-32) and 10 years (9-12) respectively. The baseline median CD4 count was 166 (IQR: 118.5-211.5). The mean change in summary GDS score for all participants was 0.13. Participants differed significantly across summary GDS severity groups for education and change in GDS. In unadjusted models there was an association between male gender, lower education, lower baseline CD4 count and worse baseline GDS with a greater degree of GDS change. When these variables were included in a final adjusted model, only severity of baseline GDS remained significant, while the summary model was highly significant (p= 0.00). CD4 cell count at baseline and follow-up were not associated with greater improvement in GDS.

Conclusions: In this descriptive cohort study, individuals with predominantly clade C HIV commencing HAART, who had greater baseline neuropsychological impairment, improved the most over one year. Participants with less education also tended to improve more over one year. These effects may be explained in part by the effect of HAART, although test and participant characteristics such as practice effects could not be ruled out. Studies utilizing larger sample sizes and control conditions are needed to establish whether these effects are clinically meaningful.

Application of the Framingham Stroke Risk Calculator to a Stroke-Free Sample of HIV+ Adults

OC3

R. Ellis, D. Croteau, P. Riggs, S. Letendre, L. Delano-Wood, R. Deutsch, S. Woods

Background: In previous population-based studies of healthy older adults, increasing Framingham stroke risk scores, a potential marker of subclinical cerebrovascular disease, correlate with poorer cognitive performance, regardless of whether a clinical stroke has actually occurred. Cognitive impairment in older HIV+ individuals has been reported to correlate with vascular risk factors such as diabetes mellitus and dyslipidemia, but the relationship of cognitive impairment to Framingham stroke risk in HIV+ has not been characterized.

Methods: Younger (18-40 years) and older (50-71 years) HIV+ and HIV- research volunteers group-matched on age, education and race/ethnicity underwent standardized, well-validated, comprehensive neurological and neuropsychological evaluations. Five-year stroke risk was estimated based on data from the Framingham registry. Prospective memory, a cognitive ability often impaired in HIV, was assessed by the Memory for Intentions Screening Test (MIST).

Results: Framingham 5-year stroke risk estimates were elevated in HIV+ (n=117) compared to age- and ethnicity-matched HIV- individuals (n=100) (median [IQR] 1.2 percent [0.5, 2.2] vs. 0.8 [0.3, 1.6]; Wilcoxon p <0.0054). Evaluation of age subgroups (older versus younger) revealed that this difference was primarily due to higher stroke risk scores in older HIV+ (OH; n=75) vs older HIV- (ON; n=52) (1.9 [1.1, 2.7] vs. 1.6 [0.8, 2.5]; p = 0.086), but not younger subjects (0.4 [0.3, 0.6] vs 0.4 [0.1, 0.6]; p=0.34). The principal determinants of differences in stroke risk scores for OH vs ON were ongoing treatment for hypertension (40.0% vs 15.4% of subjects; OR 3.7 [95% CI 1.52, 8.9]; p=0.002) and diabetes mellitus (17.3% vs 5.7%; OR 3.4 [0.9, 12.7]; p=0.044). Demographically-adjusted global neurocognitive performance was more frequently impaired (NPI) in HIV+ vs HIV- individuals, with the highest rates of impairment evident in OH (OH 39%; ON 23%; YH 29%; YN 21%). The excess prevalence of NPI in OH was not related to stroke risk score. After adjusting for age, the association between increasing stroke risk and worse prospective memory (MIST summary score) produced a partial r=0.12 (p=0.08). The relationship of stroke risk to MIST was similar in HIV+ and HIV- subjects.

Summary: Stroke risk estimated by the Framingham risk calculator was modestly increased in older HIV+ as compared to HIV- individuals, principally due to an excess of hypertension and diabetes mellitus. However, cognitive impairment was not independently related to stroke risk in HIV+, beyond consideration of HIV infection and age.

New Evidence of Vascular-related Metabolic Injury in the Brain of HIV+ Individuals

OC4

L.A. Cysique[1,2,3], J. Myung-Lee[2], T. Lane[3,4], K. Moffat[3], N. Davies[3], A. Carr[3], B.J. Brew[1,3] and C. Rae[1,2]

1 University of New South Wales, Brain Sciences, Sydney, Australia
2 Neuroscience Research Australia, Sydney, Australia
3 St.Vincent's Hospital; Sydney, Australia
4 Macquarie University, Department of Psychology, Australia

Background: The impact of cardio-vascular diseases on brain metabolic functions has not been evaluated in aging HIV+ individuals.
Methods: We present the baseline results of a prospective study investigating the effects of HIV and aging on brain functions in a cohort of clinically stable HIV+ individuals aged 45+. Sixty-one HIV+ individuals were enrolled with historically advanced disease (nadir CD4 lymphocyte count ≤ 350 cells/µl; and current stable cART ≥ 6 months. The median HIV duration was 19 years. Sixteen HIV-negative (HIV-) aged 45+ were enrolled as controls. In the HIV+ group, 97% had virus controlled (HIV RNA <50 copies/ml) in the plasma and 96% in the cerebrospinal fluid among the patients who had a lumbar puncture (N=28).
All participants underwent a standard neuropsychological evaluation to assess attention/working memory; verbal learning and memory, verbal generativity; fine-motor coordination; mental flexibility and speed of information processing. Spectra were acquired from the right frontal white matter (FWM), posterior cingulate cortex (PCC) and right caudate nucleus area (Caud) at 3T.
Brain metabolite concentrations were compared between HIV- and HIV+ group using t-test (ß = 0.05). Cohen's d effect sizes (ES) were computed and ES >.40 were included in subsequent analyzes. On brain metabolites with ES>.40, standard linear regression models were built to test biomarkers of HIV (nadir CD4; Blood current CD4 & CD8 counts, HIV duration, adjusted for current cART duration) and cardiovascular risk (Framingham score).
Results: 23% of the HIV+ sample was neurocognitively impaired (Global Deficit Score >.05) versus 0% in the HIV- individuals. In HIV+ individuals, NAA concentration was reduced (p<.02) in the PCC (d=.55) and Caud (d=.57); mIo/Cr was increased (p<.02; d=.59) and Glx is decreased (p=.12; d=.44) in the PCC. mI/Cr comprised lower Cr/H2O and higher mI/H2O in HIV+. Reduced PCC NAA was associated with lower PCC Glx (p<.0001) and higher mI/Cr (p<.03). Regression models showed that a greater HIV duration was predictive of reduced Caud NAA (ß=-.34, SE = .0008; p<.03); a lower nadir CD4 was associated with lower NAA concentration in the PCC (ß=.38, se= .0009; p<.03). And newly a higher Framingham cardio-vascular risks score was associated with reduced NAA in the PCC (ß=-.27, se = .42; p<.03).
Comments: Cardiovascular risks are increasingly impacting the etiology of brain injury in persons with HIV infection.

Distinct Detection of HIV-Associated Neurocognitive Dysfunction According to Clinician and Patient Perception: Findings from the NEU Study

OC5

J.A. Muñoz-Moreno[1,2], A. Prats[1,2], I. Nieto-Verdugo[1,2], E. Negredo[1,2], C.R. Fumaz[1,2], N. Pérez-Álvarez[1,3], M. Bernaus[4], J. Blanch [5], E. Deig[6], L. Force[7], À. Massabeu[8], A. Raich[9], M.J. Ferrer[1,2], M. Garolera[10,11], B. Clotet[1,2,12] and the NEU Study Group

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Background: Assessing self-reported cognitive complaints (CC) might be an easier and more feasible method than undergoing comprehensive neuropsychological testing to identify HIV-associated neurocognitive impairment (NCI). We aimed to study the predictor value of CC existence in patients to detect NCI, also considering clinician and neuropsychologist perceptions.

Methods: The NEU Study is an ongoing seven-site cross-sectional study aimed to validate a brief and reliable instrument for the assessment of HIV-associated NCI. A preliminary sample of 102 HIV-infected patients was considered for this abstract, and data about demographic, medical and neurocognitive variables were included. A comprehensive neuropsychological battery covering 7 areas was applied to determine NCI. Additionally, three dichotomy variables (yes/no) were collected based on impairment detection: self-reported patient CC, perception of the clinician in charge, and estimation of the neuropsychologist evaluating neurocognitive functioning.

Results: Subjects were mostly middle-aged (mean 43 years) men (86%), treatment-experienced (86%), HCV seronegative (66%), with undetectable plasma viral load (82%), a median CD4 cell count of 601 cells/µL and nadir CD4 cell count of 200 cells/µL. Thirty-three (52%) patients showed NCI, and sixty (59%) individuals reported CC, being 27 (51%) from those with NCI. According to clinician perception, 33 (32%) subjects had impairment, detecting correctly 18 (34%) out of them. Neuropsychologist perception estimated 54 (53%) patients with NCI and this identified optimally 42 (79%) out of them. Additional logistic regression determined that variables mostly associated with correct detection were being female regarding CC (p=0.04), and higher depression and quality of life scores regarding clinician opinion (p=0.26 and p=0.13, respectively). Other demographic or medical variables were not found in association with correct detection considering neuropsychologist estimation.

Conclusions: These data illustrate differences between clinician and patient perceptions regarding existence of HIV-associated NCI. Neuropsychologist estimation appears to be the highest accurate report detecting HIV-associated NCI, although this emphasizes the use of comprehensive neurocognitive testing.

Progressive Brain Injury among Neurologically Asymptomatic Subjects in the Setting of Chronic HIV Infection and CART: The HIV Neuroimaging Consortium Cohort Study

OC6

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Introduction. Recent studies suggest that brain injury and neurocognitive impairment (NCI) can persist in the setting of chronic HIV infection and stable combination antiretroviral therapy (CART) disease. We hypothesized that neurologically asymptomatic (NA) individuals, despite CART, such individuals can continue to show metabolite changes suggestive of progressive neuronal injury, as measured by proton magnetic resonance spectroscopy (MRS), and these changes would be associated with declines in cognitive function. Furthermore, one or more host or disease related factors would contribute to specific patterns of brain injury.
Methods. Longitudinal MRS and clinical assessments were performed over two years in 226 HIV-infected individuals on stable CART, including 138 NA individuals. N-acetylaspartate (NAA), creatine (Cr), Choline (Cho), myoinositol (MI), and glutamate+glutamine (Glx) were measured in the midfrontal cortex (MFC), frontal white matter (FWM) and basal ganglia (BG). Changes in metabolite levels were examined using linear mixed models, and related to neurocognitive changes. The following baseline covariates were assessed as possible predictors of change using linear mixed models: ADC stage, duration of infection, duration of treatment, CPE score, age, nadir CD4 count, current CD4 count, plasma HIV RNA levels.
Results. Significant metabolite decreases were found annually in the whole group, even among NA subjects, including NAA, WM-3.2%, MFC-1.5%; Cr in MFC-1.9%; Glx in MFC-5.3% and Cho in FWM-2.7%. Analyses in subjects with virologic suppression in plasma and CSF (N=51) showed similar patterns, including significant decreases in NAA and Glx. Decreases in NAA and Glx in the MFC showed significant associations with declines in verbal fluency, learning, memory and executive function. Factors contributing to injury included: duration of infection (Glx-MFC, Cho-MFC, Cr-MFC); duration of CART (Glx-FWM and MFC; Cho-MFC); high current CD4 (Cho-MFC); detectable plasma RNA (NAA-MFC, Cho-FWM) and nadir CD4 (Glx-BG and FWM). No associations were found with age or CPE.
Conclusions. Progressive brain injury continues to unfold in the setting of stable infection and suppression. Mechanisms other than residual viral activity may contribute to pathogenesis and likely involve complex relationships among several host and disease-related factors.

Low Nadir CD4+ Counts and disrupted MRS Brain Metabolite Levels are associated with reduced brain volume in HIV/AIDS

OC7

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Introduction: Around 40% of HIV/AIDS patients experience minor to severe cognitive impairments, but the brain changes underlying this cognitive decline are still poorly understood. We used tensor-based morphometry (TBM) to map 3D patterns of relative brain volume reduction in 210 patients with HIV. We hypothesized that regional brain volumes would be associated with nadir CD4+ counts and with brain metabolite levels measured by proton magnetic resonance spectroscopy.

Methods: T1-weighted 3D brain MRI scans were acquired from 210 patients with HIV/AIDS enrolled into the HIV Neuroimaging Consortium study (mean age: 48.6±8.4 years; 175 men/35 women). A high-resolution average brain template was created to represent common anatomical features for the study group. Individual brain images were non-linearly aligned to the brain template, using an inverse-consistent registration algorithm. Maps were created to show regions of volume deficit or excess relative to the brain template, reflecting, in part, profiles of neurodegeneration. At each voxel in the brain, multiple regression was used to assess associations between regional brain volumes and (1) demographic variables: age, sex, and race; (2) immune system measures: current and nadir CD4+ T-cell counts (cells/µl); and (3) brain metabolite levels: absolute concentrations of *N*-acetyl aspartate (NAA), Creatine (Cr), Choline (Cho), *myo-inositol* (MI), glutamate and glutamine (Glx), and ratios of NAA/Cr, Cho/Cr, MI/Cr, Glx/Cr in the frontal white matter, basal ganglia, and medial frontal cortex. Maps of associations were declared significant if they controlled the false discovery rate at 5%.

Results: We did not detect an age effect in this cohort, but both sex (FDR q=0.05, critical P=0.006) and race (critical P=0.03) were significantly associated with regional brain volumes. After controlling for age, sex and race, lower nadir CD4+ count, but not current CD4+ count, was associated with reduced brain volumes (critical P=0.02). Lower levels of NAA measured in the frontal white matter or the basal ganglia, and increased level of Glx in basal ganglia, were associated with lower brain volumes (FDR q=0.05, critical P=0.01 for NAA in frontal white matter; critical P=0.01 for NAA in basal ganglia; critical P=0.02 for Glx in basal ganglia). Additionally, regional brain volumes were associated with the ratios of Cho/Cr in frontal white matter (critical P=0.002), MI/Cr in frontal white matter (critical P=0.01), NAA/Cr in basal ganglia (critical P=0.003), and Glx/Cr in basal ganglia (critical P=0.01).

Conclusion: Brain atrophy was associated with immunosuppression and alterations in brain metabolites that reflect neuronal integrity. Disruption in these metabolites may lead to subsequent structural loss. This supports a model of brain injury that implicates frontal/striatal pathways in the pathogenesis of HIV-associated cognitive impairment.

Antiretroviral Regimen Efficacy in Monocyte/Macrophages Associated with Cognitive Function

OC8

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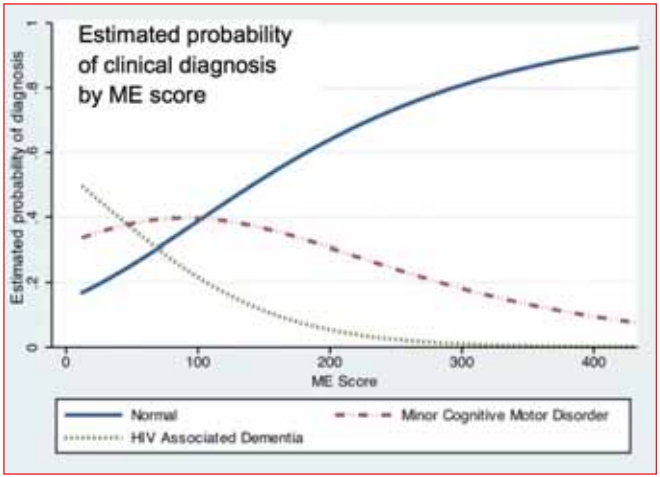
Background: Monocytes/macrophages (M/Ms) play a key role in HIV neurocognitive impairment (NCI), and high levels of HIV infected M/Ms in the bloodstream (HIV DNA in CD14$^+$ cells) correlate to NCI. We hypothesize that NCI despite combination antiretroviral therapy (cART) is due, in part, to the inability of current cART to clear HIV DNA from this M/M reservoir. We devised a M/M efficacy (ME) score based on each cART regimen's anticipated efficacy against M/Ms, examined its association with cognitive status, and assessed its performance relative to the central nervous system (CNS) penetration effectiveness score (CPE) to compare our hypothesis against an alternative but not mutually exclusive hypothesis that NCI is related to poor penetration of cART into the CSF.

Methods: Analyses utilized a subset of subjects on stable antiretroviral (ARV) medications unchanged for > 6 mos. on entry into the Hawaii Aging with HIV Cohort, a cognitively well-characterized HIV cohort conducted between 2001-2008. Composite neuropsychological scores [NPZ8] and clinical cognitive diagnoses by 1991 AAN criteria were available. ME scores, determined for each cART regimen, was defined as the summed reciprocal score (x 100) of each of the regimen's drug's median effective concentration (EC_{50}) [acute infection] published value in primary cells. We applied Pearson's



Correlations, multiple linear regression, Kruskal-Wallis Test and multinomial logistic regression.

Results: The selected cohort (n=139) had a mean current CD4 of 494 cells/µl, nadir CD4 of 197 cells/µl with HIV RNA < 50 copies/ml in 87.1%. Better NPZ8 performance was observed with

higher ME score (r=0.24, p<0.01) but not with CPE score (r=0.12, p=0.17). By multiple linear regression (adjusted R^2=0.12), ME score (ß=0.003, p=0.02), CD4 nadir (ß=0.001, p<0.01) and gender (ß=-0.456, p=0.02) were significant predictors of NPZ8 whereas CPE score was not (ß=0.001, p=0.98). Distributions of ME scores differed by clinical cognitive classification with a pattern of lesser ME correlating to more severe impairment (p=0.001). With a range in ME score of 12.5 to 433 units seen in this study, a 100 unit increase in ME score resulted in a 6.6 times increase in OR of diagnosis of dementia (p=0.001).

Conclusions: In this cohort, ARV regimen efficacy against M/Ms (ME) correlates to cognition whereas CPE score does not. If validated, use of ARV medications with better efficacy against M/Ms may be warranted to improve HIV NCI.

Poster

Current Prevalence and Clinical Impact of HIV-Associated Neurocognitive Disorders in a London Cohort with High ART Coverage

P1

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Background: HIV-associated neurocognitive disorders (HAND) that interfere with function (Minor Neurocognitive Disorder [MND] or HIV-Associated Dementia [HAD]) have an estimated prevalence of 20-40%. The current clinical impact in UK cohorts is unknown.
Objective: To estimate documented clinical burden of HAND in a London HIV clinic.
Methods: From patients attending in 2009/10 (n=3129), we first selected a random sample of 150 (4.8%). Notes were reviewed by hand to estimate the proportion who (1) were ever diagnosed with HAND, AIDS dementia complex, or HIV encephalopathy, or (2) reported recent symptoms of cognitive impairment, e.g. memory, concentration, attention, language. Second, we reviewed all referrals to HIV neurology, psychology and inpatient services with suspected cognitive impairment in the same 1-year period.
Results: The random sample (n=150) was representative of the entire clinic: median age was 43 years (IQR 38–49 yrs); 125 were male (83%); ethnicity was white (98, 65%), black African (20, 13%) or other (32, 21%); route of infection was sex between men (106, 71%), heterosexual sex (36, 24%), IVDU (2, 1.3%) or vertical (1, 0.7%); current CD4 count was median 540 cells/μL (IQR 400–720 cells); nadir CD4 was median 195 cells/μL (IQR 130–280 cells); 129 patients (86%) were on ART, of whom 123 (95%) had plasma VL<50 copies/mL. Relevant comorbidity included depression (41, 27%), schizophrenia (1, 0.7%), substance misuse (14, 9%), hepatitis C (10, 7%), and toxoplasmosis (2, 1.3%).
Two patients (1.3%; 95% CI 0.2–4.7%) had documented HAD and no patients (95% CI 0–2.4%) had MND. Eleven patients (7.3%; 95% CI 3.7–12.7%) including the 2 with HAD had cognitive symptoms recorded within the past year, of whom 6 had depressive symptoms and 2 were attributable to efavirenz.
In the second analysis, there were 37 referrals (1.1%) to HIV neurology clinic, clinical psychology or inpatient unit with chronic symptoms of cognitive impairment +/- neurological symptoms, caused by HAND (9, 24%), anxiety/depression (12, 32%), and new or past OIs (5, 14%).
Conclusions: Using 2 sampling methods, we found that cognitive symptoms were rare, based on routine clinical records, and often attributable to psychiatric illness. This study may have underestimated true prevalence, indicating the need for well-evaluated HAND screening and studies of subclinical HAND. Our clinic may differ from published cohorts with higher prevalence; this could be evaluated by prospective studies.

Antiretroviral Therapy-Related Increases in CD4 are Associated with More White Matter Abnormalities and Increased Gray Matter Volume Over Time in HIV: The CHARTER Study

P2

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Background: Abnormalities in the cerebral white matter (WM) on MRI (e.g., T2 hyperintensities) are common in HIV infection, even during successful combination antiretroviral therapy (CART), but their pathophysiology and clinical significance are unclear. Successful CART yields virologic suppression and immune recovery, indexed as rises in blood CD4 count over months to years. Occasionally, robust CD4 recovery results in paradoxical worsening of neurological deficits known as immune recovery CNS disease. Subclinical CNS changes of an inflammatory nature have been postulated, and predicted MR correlates include WM abnormalities and potentially increased subcortical gray matter (GM) volume.

Methods: HIV+ volunteers in the multi-site CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study underwent non-contrast structural brain MR imaging at 2 time points (median 1.0 year apart [IQR 0.99, 1.1]). Multi-channel morphometry yielded volumes of total cerebral WM, abnormal WM, cortical and subcortical gray matter (GM), and ventricular and sulcal CSF. Multiple linear regressions were used to predict change in each volume. Variables included age, scanner, ethnicity, gender, education, time between scans, cranial vault volume, status of hepatitis C infection, and primary variables of interest: nadir CD4 and change in CD4.

Results: The 75 participants had a mean age of 45.2 (+/-7.8) years and 83% were male. At the initial visit, 79% took CART and among these 43 (56%) had achieved virologic suppression in plasma. Lower nadir CD4 was associated with structural damage at first visit (less WM $t=2.2$, $p<.05$; more abnormal WM $t=-1.7$, $p=.10$; larger CSF spaces $t=-2.7$, $p<.05$). As expected, at the second visit, subjects with virologic suppression on ART had greater CD4 recovery (me-

dian [IQR] +35 [-37, +98]) than those not on ART (-50 [-126, +18]) or those without virologic suppression on ART (-8 [-172, +103]; K-W p=.03). Greater CD4 recovery was associated with increased volumes of abnormal WM (t=2.4, p<.05) and subcortical GM (t=2.3, p<.05). Current CD4 levels increased >50 cells/mm3 (from median of 360 [176, 518] to 514 [379, 672]) in 33% of the sample, and this group showed increased abnormal WM (t=2.9, p<.01) and subcortical GM (t=2.8, p<.05) over time. Those decreasing by >50 points (35% of the sample) had smaller subcortical GM (t=-2.2, p<.05) but no change in abnormal WM (t<1.0, p>.05).

Summary: While CD4 nadir was associated with greater pathology at first visit, individuals who had the greatest increases in CD4 counts while on effective CART during this time period had the greatest increases in volumes of abnormal WM and subcortical GM. The association of increasing CD4 counts with expanding volumes of subcortical gray and abnormal white matter is consistent with immune recovery phenomena, such as immune recovery inflammatory syndrome (IRIS), possibly directed at HIV infection in the brain.

Neuroimaging Morphometric Correlates of Metabolic Variables in HIV: The CHARTER Study

P3

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Background: Body mass index (BMI) and other metabolic variables correlate with the size of brain structures in HIV-uninfected populations. Since HIV infection is often accompanied by metabolic abnormalities, we examined brain volumetric correlates of metabolic factors in HIV+ patients.

Methods: Of 223 HIV+ participants in the CHARTER study, most were male (80%), currently on antiretroviral therapy (78%), and relatively young (mean age of 44). MRI exams used a multi-channel protocol and semi-automated segmentation to measure total cerebral and abnormal white, cortical and subcortical gray, and ventricular and sulcal CSF volumes. Metabolic factors included BMI, total blood cholesterol (C), low- and high-density lipoprotein C (LDL-C and HDL-C), blood pressure (diastolic and systolic), random blood glucose levels and diagnosis of diabetes. Multiple linear regression models, which controlled for scanner, age, gender, ethnicity, cranial vault, and nadir CD4, allowed us to examine each metabolic variable separately and in combinations to predict each brain volume.

Results: Examining each metabolic variable separately, greater BMI was associated with smaller cortical gray ($p<.001$) and larger cerebral white ($p<.001$) volumes. Higher total cholesterol (C) levels were associated with smaller cortical gray volumes ($p<.05$); higher LDL-C was associated with larger cerebral white volumes ($p<.05$), while higher HDL-C levels were surprisingly associated with increased sulcal CSF ($p<.05$). Higher glucose levels were associated with increased volumes of abnormal white matter ($p<.01$). Similarly diabetes predicted larger abnormal white volumes ($p<.05$) as well as increased ventricular size ($p<.05$). Multivariate models including multiple metabolic factors confirmed most of these findings.

Summary: Elevated BMI, cholesterol, and glucose (and diabetes) correlated with altered brain volumes in these HIV patients. Atherogenic metabolic factors (hyperglycemia and diabetes) were associated with more white matter abnormality (? ischemia) suggesting cerebral atherosclerosis as a mechanism. Alternatively, initiation of ART could both increase these metabolic variables and cause white matter inflammation through immune recovery inflammatory syndrome (IRIS). Either of these mechanisms of brain damage could accelerate the onset and severity of brain injury in HIV infection. Further investigation of the effects of antiretroviral treatment on these associations is planned.

Predictors of HIV-Associated Neurocognitive Decline in the Era of CART: The HIV Neuroimaging Consortium Cohort Study

P4

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Introduction. Over 25 years have passed since the initial description of AIDS Dementia Complex (ADC) and although combination antiretroviral therapy (CART) can benefit neurocognitive impairment (NCI), recent studies suggest this complication as well brain injury persist among medically stable patients. We postulated that despite the effectiveness of treatment, neurologically asymptomatic subjects (NA) would develop NCI and that decreases in neuronal function as measured by magnetic resonance spectroscopy (MRS) would be an important predictor. Age, nadir CD4 and HIV RNA levels would also contribute to this complication.

Methods. Neurocognitive assessments, including AIDS dementia complex (ADC) staging, and MRS were performed over two years in 167 NA HIV-infected persons with stable HIV disease on CART. Metabolites over creatine (Cr) included N-acetyl aspartate (NAA), choline (Cho), myoinositol (MI) and Glutamine/glutamate (Glx) from the midfrontal cortex (MFC), frontal white matter (FWM), and basal ganglia (BG). Probability of conversion to ADC >0.5 was estimated by the Kaplan-Meier method. Univariable associations were first identified by Cox proportional hazards model and the best multivariable predictive model was then selected based on the model comparisons via an Akaike Information Criterion (AIC).

Results. Probability of conversion to ADC≥0.5 was 13.6% in Year 1 and cumulatively, 35.2% in Year 2; conversion to ADC≥1 was 3.9% in Year 1 and 12.3% in Year 2. Plasma HIV RNA, low current CD4 (<350 cells/ mm3), decreases in NAA/Cr, Glx/Cr and Cho/Cr and an increase in MI/Cr were significant predictors of conversion to ADC≥0.5. Subjects with a low CD4, detectable HIV RNA showed an increased risk in conversion (HR=3.55, p=0.001) while subjects with low CD4 and undetectable plasma RNA had a less significant risk (HR 2.40, p-value=0.02). In the multivariable analysis, however, only the decrease in BG NAA/Cr and increase in MFC MI/Cr remained significant factors. The decrease in BG NAA/Cr was the only significant predictor for conversion to ADC>1 (HR=3.53, p=0.0006).

Conclusions. NA subjects are at significant risk for converting to cognitive impairment in the setting of CART. Further, this is the first prospective study to show that decreases in NAA in the basal ganglia is a significant predictor of declines in cognitive function and may therefore serve as a useful prognostic biomarker.

Chronic HIV Infection and Aging in Neuro-AIDS (CHAIN): a Pilot Study Using Novel Evaluations

P5

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Background: Emerging data suggest that frailty may occur earlier in HIV-infected patients. We report a pilot study to evaluate this in younger and older HIV-infected adults with traditional and objective measures of frailty.

Methods: Participants were 20-40 years old (younger; n=21), and > 50 years old (older; n=20).

Participants underwent a history and physical examination; neuropsychological (NP) battery to assess executive function, motor skills, verbal learning, memory, and speed of processing; assessment of grip strength; balance assessed using a Wii balance board; actigraph monitoring for 2 weeks; and surveys for depression, fatigue, loneliness and activities of daily living.

Where applicable, a two-sample t-test or Wilcoxon rank sum test, was used to compare means for continuous variables between the two age groups. Exact Chi-Square tests were applied to compare proportions between the groups. Raw NP scores were standardized to z scores and adjusted for age and education, and a total z score was computed.

Results: The mean age of younger subjects was 31.5 years, 14 were men, 7 women, and white/black/Hispanic = 15/4/2. The mean age of older subjects was 56.5 years, 15 were men, 5 women and white/black/Hispanic = 13/5/2. There was no difference between groups for income, education, tobacco/substance abuse, CD4 count, viral load, depression, fatigue or loneliness. Older patients had more diagnoses (mean 2.2 vs 0.76, P=0.004), more concomitant medications (mean 4.3 vs 1.1, P=0.03), longer duration of HIV disease (mean 14.53 vs 6.2 years, P<0.001), longer antiretroviral therapy exposure (mean 11.3 vs 3.8 years, P<0.001), and lower CD4 nadir (mean 161 vs 315.2 cells/mm^3, P=0.004). Overall, there was a trend to lower scores in the older age group for NPZ (p=.11) and for verbal learning (p=0.09). Functioning in the memory domain was significantly lower in older subjects (p=0.007). There was no difference in executive function, speed of processing, memory, motor skills or total activity. 6 older and 2 younger subjects had low grip strength, and 4 older and 3 younger met the definition of frailty. Total activity by actigraphy did not correlate well with self-reported activity or frailty.

Conclusions: Frailty was not common in this pilot study. Objective activity measurements did not correlate with patient self-report and other variables. Further study is needed to better define the appropriate measures to identify frailty and premature aging.

A Diffusion Tensor Imaging and Neurocognitive Study of Clade C HIV Positive Children who are HAART-Naïve 'Slow Progressors'

P6

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In the present study we the examined neuroimaging and neuropsychological signatures of clade C among 10 asymptomatic HIV positive children between the ages of 6 and 11 years. The asymptomatic group is unique as it consists of individuals that meet criteria as "slow progressors". The results indicate that cognitive function and white matter integrity as defined by diffusion tensor imaging (DTI) is altered among asymptomatic HIV positive children when compared to 10 children from low socio-economic status. Specifically, fractional anisotropy (FA) but not mean diffusivity (MD) is altered among asymptomatic individuals in the superior longitudinal fasiculus, the genu of the corpus callosum and the internal capsule ($p=<0.05$). The asymptomatic patients performed poorly on Performances tasks of the WAIS-R and on language measures of verbal fluency, category fluency, and confrontation naming ($ps < .05$). Furthermore, parents or caregivers reported Internalizing behaviours in the clinical range. This study provides an important contribution to the understanding of the neurocognitive and neuroimaging profile of clade C children defined as slow progressors.

Effects of HIV Infection and Cocaine Dependence on Cognitive Processes Related to Impulsivity and Risk Taking

P7

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Cocaine use is prevalent among HIV-infected Americans and is associated with increased rates of risky and impulsive behaviors. Both HIV infection and cocaine dependence affect neurocognitive functioning, yet few studies have empirically examined the effects of comorbid HIV infection and cocaine dependence on neurobehavioral outcomes. To examine this, a sample of 160 patients is being recruited for a 3-group comparison study of HIV-positive, cocaine dependent persons (HIV + cocaine), HIV-positive, non substance users (HIV only), and HIV-negative, cocaine dependent persons (cocaine only). In preliminary analyses from the first 27 participants, HIV + cocaine participants performed more poorly compared to HIV only and cocaine only participants on tests of attention ($T = 42.73$ vs. 51.23 and 52.23, respectively; $t(24) = 1.59$; $p = .12$) and impulse control ($T = 42.20$ vs. 48.21 and 47.14; $t(24) = 1.84$, $p = .08$), and they were more likely to choose smaller immediate rewards over larger delayed rewards on a delay discounting task ($k = 0.59$ vs. 0.10 and 0.12; $t(24) = 2.15$, $p = .04$). HIV was independently associated with greater risk taking propensity on the Balloon Analogue Risk Task (average adjusted pumps = 45.34 vs. 33.57; $t(26) = 2.04$, $p = .05$) and riskier decision making on the Iowa Gambling Task ($T = 39.43$ vs. 50.86; $t(26) = 2.32$, $p = .03$). These results suggest that HIV and cocaine may affect different cognitive processes related to impulsivity and risk taking, and that co-occurring HIV infection and cocaine dependence may have an interactive effect on attention and impulse control. As enrollment continues, a subset will participate in an fMRI experiment to examine differences in brain activity during response inhibition and decision making tasks.

HIV-Related Encephalopathy: First Manifestation of HIV Infection in a Patient with Atypical Imagiological Findings

P8

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Introduction: Central Nervous System (CNS) is a privileged sanctuary for HIV virus which induces neurological manifestations during all stages of infection. In about 17% of the cases, neurological manifestations define the first clinical evidence of HIV infection.

Case report: A 38-year-old male presented to our Emergency Department with a one week history of behavioral change and self-neglect. Patient also stopped going to work for about a week. There was also a history of sore throat, fever (38ºC), pharyngitis and a maculopapular rash. No history of weight loss, genital ulcers or penile discharge was obtained. He was heterosexual and reported sexual intercourse with prostitutes without consistent condom use. There had been no drug abuse. On physical examination, patient had 38ºC of temperature and an erythematous pharynx, without exudates or ulcers. A macular rash over his back and chest was identified, as also a cervical lymphadenopathy. Neurological examination revealed only a slurred speech and a notorious cognitive impairment with slowness of information processing. Laboratory values showed: white blood cell count of 2200/µL, with lymphocytes of 970/µL. An HIV antibody test by ELISA was reactive, confirmed by Western-blot and by a positive p24 antigen. HIV viral load was 679 000 copies/µL and CD4 count was 53 cells/µL. Brain MRI revealed diffuse and symmetrical white matter lesions, involving all cerebral lobes, the left cerebral peduncle, the right pons and the right cerebellar hemisphere, with no contrast enhancement. Some vascular lesions and a discrete cortico-subcortical atrophy were identified. Lumbar puncture revealed high protein content in CSF (112.4 mg/dl [12-60]) and a normal cellular count. CSF Gram and PCR for JC virus were negative. He started HAART with darunavir/ritonavir/emtricitabine/tenofovir with a rapid and dramatic regression of neurological symptoms in about two weeks with CD4 count of 245 cell/µL and viral load of 868 copies/µL. A control MRI performed 4 months later revealed a partial regression of the white matter lesions.

Discussion/Conclusion: In this case, the imagiological properties of the lesions, the dissociation between their exuberance and the soft clinical signs identified, as well as the dramatic improvement under HAART only (with no need of other drugs, namely corticosteroids) support the diagnosis of a HIV-related encephalitis and exclude other frequent clinical entities in these patients.

Neurologic and Psychiatric Safety Profile of Rilpivirine Compared with Efavirenz in Treatment-Naive HIV-1-Infected Patients: Emtricitabine/Tenofovir DF Subset from Pooled Analysis of the Phase III ECHO and THRIVE Trials at 48 Weeks

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Background. Rilpivirine (RPV) is an FDA investigational NNRTI that met the primary objective of non-inferiority to efavirenz (EFV) in confirmed virologic response at week 48 (TLOVR) based on two double-blind, double-dummy Phase III trials, ECHO and THRIVE, in treatment-naïve HIV-infected adults. EFV has been associated with neurologic and psychiatric adverse events (AEs), a pre-planned, pooled analysis of these AEs was performed through 48 weeks. The subset of patients taking emtricitabine/tenofovir DF (FTC/TDF) is presented since a single tablet regimen (STR) of FTC/RPV/TDF is under development.

Methods. Patients received (1:1) RPV 25mg daily or EFV 600mg daily. The subset of subjects that received FTC/TDF in combination with either RPV or EFV from both ECHO (N= 690) and THRIVE (N= 406) are presented. Of these subjects (N=1096), a total of 550 received RPV + FTC/TDF and 546 received EFV+ FTC/TDF.

Results. Baseline characteristics were balanced between the 2 groups (RPV vs. EFV): 22 vs. 21% female; 64 vs. 61% Caucasian, 25 vs. 23% Black/African American, 10 vs. 13% Asian. The overall incidence of neuropsychiatric AEs was lower with RPV (40.9%) than EFV (40.9 % versus 58.1%; p<0.0001).

Incidence, %	RPV 25mg qd (n=550)	EFV 600mg qd (n=546)	Difference between groups
Any neuropsychiatric AE	225 (40.9)	317 (58.1)	p<0.0001
Any neurologic AE	145 (26.5)	247 (45.2)	p<0.0001
Headache	77 (14.0)	77 (14.1)	NS
Dizziness	56 (10.2)	152 (27.8)	p<0.0001
Somnolence	15 (2.7)	33 (6.0)	p=0.0077
Disturbance in attention	4 (0.7)	13 (2.4)	p=0.0291
Any treatment-related neurologic AE	91 (16.5)	196 (35.9)	p<0.0001
Headache	34 (6.2)	34 (6.2)	NS
Disturbance in attention	4 (0.7)	13 (2.4)	p=0.0291
Somnolence	14 (2.5)	31 (5.7)	p=0.0095
Any psychiatric AE	135 (24.5)	173 (31.7)	p=0.0088
Abnormal dreams/nightmares	53 (9.6)	82 (15.2)	p=0.0076
Insomnia	41 (7.5)	43 (7.9)	NS
Depression	35 (6.4)	24 (4.4)	NS
Anxiety and anxiety disorder	14 (2.5)	31 (5.7)	p=0.0095
Sleep disorder	6 (1.1)	23 (4.2)	p=0.0012
Any treatment-related psychiatric AE	84 (15.3)	136 (24.9)	p<0.0001
Abnormal dreams/nightmares	49 (8.9)	79 (14.5)	p=0.0047
Insomnia	26 (4.7)	32 (5.9)	NS
Sleep disorder	4 (0.7)	19 (3.5)	p=0.0013
Anxiety and anxiety disorder	5 (0.9)	13 (2.4)	NS

Conclusion. In the subset of the pooled ECHO and THRIVE data, RPV-treated patients reported fewer neurologic and psychiatric AEs overall due to lower incidences of dizziness, somnolence, disturbance in attention, sleep disorders and abnormal dreams/nightmares, compared with EFV + FTC/TDF treated patients. A FTC/RPV/TDF tablet will provide patients with the convenience of a once daily STR with reduced neuropsychiatric AEs.

Paper-Based Tapping Test Is a Good Predictor of Psychomotor Slowing in HIV-Infected Patients: Findings from the NEU Study

P10

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Background: There is a current need to find brief and feasible tools to assess HIV-related neurocognitive decline. Regarding psychomotor function, tests involving boards or electronic mechanisms are generally required to achieve a reliable assessment. We studied whether a test based on paper execution might be an adequate tool to evaluate HIV-related psychomotor slowing.

Methods: A total of 102 HIV-infected patients were assessed in the NEU Study, an ongoing seven-site study aimed to validate a brief and reliable instrument for the assessment of HIV-associated neurocognitive impairment. Demographic and medical variables were recorded, and neurocognitive variables were assessed using a comprehensive neuropsychological tests battery. A paper-based tapping test was included in the battery, and responses by subjects were compared to scores obtained in other 2 motor tools: electronic tapping and grooved pegboard tests, assessing pure and fine motor functions respectively. Pearson's correlations and ROC curves were used to analyze data.

Results: Subjects were mostly middle-aged (mean 43 years) men (86%), treatment-experienced (86%), HCV seronegative (66%), with undetectable plasma viral load (82%). Thirty-three (52%) patients showed neurocognitive impairment and sixty (59%) individuals reported cognitive complaints. Comparing scores in the paper-based tapping test with the other two motor tests, correlation rates were higher in the pegboard test than in electronic tapping for dominant hand (r=-0.73; r=0.33, respectively), and also for non-dominant hand (r=-0.63; r=0.31). Estimating existence of neurocognitive decline, the paper tapping test indicated an optimal cut-off of ≥35 taps to detect impairment in dominant hand (sensitivity=72.2%, 95%CI: 58.1%:83.1%; specificity:17%; 95%CI: 8.1%:31.3%), and ≥29 for non-dominant hand (sensitivity=73.5%, 95%CI: 59.4%:84.3%; specificity: 22.4%; 95%CI: 12.2%:37%).

Conclusions: Our data show good correlation between measures from a paper-based tapping and traditional tests evaluating psychomotor execution in HIV-infected patients, specifically in fine motor function. These findings support possibility to reach higher feasibility and less economical costs in the assessment of HIV-associated neurocognitive decline.

Application of the Framingham Stroke Risk Calculator to a Stroke-Free Sample of HIV+ Adults

P11

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Background: In previous population-based studies of healthy older adults, increasing Framingham stroke risk scores, a potential marker of subclinical cerebrovascular disease, correlate with poorer cognitive performance, regardless of whether a clinical stroke has actually occurred. Cognitive impairment in older HIV+ individuals has been reported to correlate with vascular risk factors such as diabetes mellitus and dyslipidemia, but the relationship of cognitive impairment to Framingham stroke risk in HIV+ has not been characterized.

Methods: Younger (18-40 years) and older (50-71 years) HIV+ and HIV- research volunteers group-matched on age, education and race/ethnicity underwent standardized, well-validated, comprehensive neurological and neuropsychological evaluations. Five-year stroke risk was estimated based on data from the Framingham registry. Prospective memory, a cognitive ability often impaired in HIV, was assessed by the Memory for Intentions Screening Test (MIST).

Results: Framingham 5-year stroke risk estimates were elevated in HIV+ (n=117) compared to age- and ethnicity-matched HIV- individuals (n=100) (median [IQR] 1.2 percent [0.5, 2.2] vs. 0.8 [0.3, 1.6]; Wilcoxon p <0.0054). Evaluation of age subgroups (older versus younger) revealed that this difference was primarily due to higher stroke risk scores in older HIV+ (OH; n=75) vs older HIV- (ON; n=52) (1.9 [1.1, 2.7] vs. 1.6 [0.8, 2.5]; p = 0.086), but not younger subjects (0.4 [0.3, 0.6] vs 0.4 [0.1, 0.6]; p=0.34). The principal determinants of differences in stroke risk scores for OH vs ON were ongoing treatment for hypertension (40.0% vs 15.4% of subjects; OR 3.7 [95% CI 1.52, 8.9]; p=0.002) and diabetes mellitus (17.3% vs 5.7%; OR 3.4 [0.9, 12.7]; p=0.044). Demographically-adjusted global neurocognitive performance was more frequently impaired (NPI) in HIV+ vs HIV- individuals, with the highest rates of impairment evident in OH (OH 39%; ON 23%; YH 29%; YN 21%). The excess prevalence of NPI in OH was not related to stroke risk score. After adjusting for age, the association between increasing stroke risk and worse prospective memory (MIST summary score) produced a partial r=0.12 (p=0.08). The relationship of stroke risk to MIST was similar in HIV+ and HIV- subjects.

Summary: Stroke risk estimated by the Framingham risk calculator was modestly increased in older HIV+ as compared to HIV- individuals, principally due to an excess of hypertension and diabetes mellitus. However, cognitive impairment was not independently related to stroke risk in HIV+, beyond consideration of HIV infection and age.

Brain Atrophy in Chronic HIV Infection: Longitudinal Analysis of Factors Affecting the Atrophy Rates in the HIVNC Cohort Study

P12

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Introduction. There is mounting evidence that HIV affects the brain of infected people and the nature of HIV-associated brain dysfunction is heterogeneous depending on various host and disease-specific factors. Our previous cross-sectional work has demonstrated a relationship between cortical and white matter volumes and baseline clinical indices as well as prior immunologic compromise, providing a compelling rationale for our current analysis of factors associated with changes in brain volume over time.

Method. We studied 167 HIV-infected patients with a total of 463 observations. Patients were stable on combination antiretroviral therapy (cART) with baseline median age 47 years; infection duration 12 years; nadir CD4: 43 cells/µl; current CD4: 322 cells/µl and ADC stage: neuroasymptomatic (101), subclinical (44), ADC (22). Repeated MRI evaluations were obtained on 1.5T scanners over 3 year period for morphometric analysis. Total cortical grey matter (GM), total white matter (WM), and ventricular volume were analyzed. A novel combination of Classification and Regression Trees (CART) and linear mixed models (LMM) was used to find subgroups, defined by a combination of baseline factors, associated with the most rapid change in brain volumes.

Results. GM volume decreased on average by 0.49% per annum, WM volume decreased by 0.51%, while ventricular volume increased by 2.5%. Besides gender and age, the most important factors identifying patients with most rapid volumetric changes were the infection duration and current CD4 count. Other factors included nadir CD4 count and race. Males 55 years and older exhibited 2.0% decrease in GM volume, while females infected for 7 or fewer years exhibited 0.1% decrease. The atrophy of WM was the greatest in patients infected for 19 or more years (1.9%). Ventricular volume in females infected for 7 or fewer years increased by 1.4%, while the increase in older males infected for 7 or more years was 5.4%.

Discussion. It is particularly noteworthy that subgroups with different rates of volumetric change can be found in this middle-aged cohort using a novel statistical technique combining CART and LMM. The results point to a complex interactions of host (gender, age) and disease-related factors (HIV duration, CD4 count) in determining specific patterns of structural change. . Heterogeneity in the evolution of brain atrophy appears to be the norm rather than the exception among HIV-infected patients in the setting of stable disease and treatment.

Soluble Neural Cell Adhesion Molecule (NCAM) and CX3CL1 (fractalkine) Systemic Levels Might Predict ART Efficacy in HIV-1 Infected Patients: NCAM Prevents gp120 Neurotoxicity in Cortical Neurons ¨In Vitro¨ Exposed to CX3CL1

P13

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Introduction: The Cognitive impairment is one of the most important complications of HIV-1 infection and may affect adherence to treatment. The human immunodeficiency virus type 1 (HIV-1) external envelope glycoprotein gp120 presents conserved binding sites for binding to the primary virus receptor CD4 as well as the major HIV chemokine coreceptors, CCR5 and CXCR4. The appropriate chemokines have been shown to inhibit viral replication by blocking interaction of the gp120 glycoprotein with theses coreceptors On the other hand, Neural Cell Adhesion Molecule (NCAM) plays a role in neural plasticity, axonal elongation, neurogenesis and memory formation, which colocalizes with CXCR4 in the CNS (Merino et al., 2008).

Aim, Material and methods: CX3CL1 (Fractalkine) and NCAM soluble levels were quantified by ELISA in a subset of naïve HIV-1 infected patients starting antiretroviral therapy (ART) during 24 and 48 weeks of treatment. Base line characteristic were: (ART: 65% of NNRTI –Non Analog Nucleoside Reverse Transcriptase Inhibitor, HIV-1 Duration: 2 years; CD4 Nadir: 249; CD4: 260; Viral Load: log 4.5+-0.7; Mean CD4 Increment at 48 week is 193 cells/mm 3 and all patients (100%) show undetectable viral load (<50 copies/ml; 1.7 Log).

In addition, we evaluated whether Neural Cell Adhesion Molecule might promotes neuroplastic effects NCAM dependent levels in cortical neurons exposed to gp120 III Beta neurotoxine (200 pM, o/n) and/or chemokines (CXCL12 - 20 nM o/n or CX3CL1 -20 nM o/n) at 7 DIV - *Days in Vitro* -. For this aim, neurite lenght and cortical dendrite branching was quantified with these treatment in cortical neurons ¨*in vitro*¨.

Results and conclusions: Our findings indicates that ART treatment reduces CX3CL1=fractalkine and increases soluble NCAM protein levels after 48 weeks of treatment, suggesting that NCAM may predicts ART efficacy in HIV-1 infected patients. In addition, NCAM is a target of gp120 neurotoxicity in cortical neurons at 7 DIV. Interestingly, CX3CL1 was able to prevent gp120 III Beta neurotoxicity by promoting dendrite branching PSA-NCAM dependent levels in cortical neurons at 7 DIV.

(Proyect: to JIM: ¨Neuroprotective effects of chemokines and Neural Cell Adhesion Molecule against gp120 neurotoxicity¨, Spain)

Neuroprotective Effects of Platelet-Derived Growth Factor: Implications for HAND

P14

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Platelet-derived growth factor-BB (PDGF) has been reported to provide tropic support for neurons in the central nervous system. The protective role of PDGF on dopaminergic neurons, especially in the context of HIV-associated neurodegenerative disorder (HAND), however, remains largely unknown. Here, we show that exogenous PDGF was neuroprotective against toxicity induced by HIV-1 Tat in primary midbrain neurons. Furthermore, we report the involvement of transient receptor potential canonical (TRPC) channels in PDGF-mediated neuroprotection. TRPC channels are Ca2+-permeable, nonselective cation channels with a variety of physiological functions. Blocking TRPC channels with either a blocker or short-interfering RNAs (specific for TRPC 5 and 6) in primary neurons resulted in suppression of both PDGF-mediated neuroprotection as well as elevations in intracellular Ca2+. PDGF-mediated neuroprotection involved parallel but distinct ERK/CREB and PI3K/Akt pathways. TRPC channel blocking also resulted in suppression of PDGF-induced Pyk2/ERK/CREB activation, but not Akt activation. Relevance of these findings in vivo was further corroborated by intrastriatal injections of PDGF and HIV-1 Tat in mice. Administration of PDGF was able to rescue the dopaminergic neurons in the substantia nigra from Tat-induced neurotoxicity. This effect was attenuated by pre-treatment of mice with the TRP blocker, thus underscoring the novel role of TRPC channels in the neuroprotection mediated by PDGF.

In addition to midbrain neurons, in the rat hippocampal neurons PDGF also regulated the expression of Arc/Arg3.1 gene that has been implicated in both synapse plasticity and long term potentiation. Relevance of these findings was confirmed in vivo by injecting mice with intracerebral inoculations of PDGF, which resulted in a rapid induction of Arc in the hippocampus of the injected mice. PDGF induced long term potentiation in rat hippocampal slices, which was abolished by PDGF receptor-tyrosine kinase inhibitor STI-571. We also present evidence that PDGF-mediated induction of Arc/Arg3.1 involved activation of the MAPK/ERK (MEK) pathway. Additionally, induction of Arc/Arg3.1 also involved the upstream release of intracellular calcium stores, an effect that could be blocked by thapsigargin but not by EGTA. Pharmacological approach using inhibitors specific for either MAPK/ERK phosphorylation or calcium release demonstrated that the two pathways converged downstream at a common point involving activation of the immediate early gene Egr-1. These findings point to the neuroprotective role of PDGF-BB in treating neurodegenerative diseases such as HAND.

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Rise in Neurocognitive Deficits in HIV-Positive Patients in a Big German Neuro-AIDS Cohort

P15

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Introduction: After the introduction of modern cART in 1996, HIV-infection became a chronic disease and HIV-associated neuro-cognitive disorders declined in incidence and prevalence. A few years later, prevalence of HIV-associated brain disease rose again and a new nomenclature was established (asymptomatic neuro-cognitive impairment = ANI, mild neuro-cognitive deficit = MNCD and HIV-associated dementia = HAD). But to date, it remains unclear how many patients suffer from ANI and MNCD and whether these are precursor stages of HAD or diseases on their own.

Methods: In a cohort of 4029 consecutively and unselectively recruited HIV-positive patients cognitive and motor tests, CD4+cell count and plasma viral load were evaluated in three time periods: from 1996 – 2000, 2001-2004 and 2005-2009).

Results: The analysis showed that from 2005-2009 - as could be expected because of the constantly improved therapeutic options - CD4+-cell count was significantly higher and plasma viral load significantly lower than before. In contrast, motor performance revealed during the first two periods in up to 60% pathological results, but up to almost 100% in the last period. This was independent from duration of HIV-positivity and CDC-stage as well as not due to a decline in the performance of the cohort growing older or to a higher percentage of patients with advanced disease over time, but obviously to the new patients entering the cohort. The cognitve tests showed also a decline, but not to the extent of the motor tests (20-60%).

Conclusions: Nowadays, systemic HIV infection is obviously treated more successfully than in former years. Unfortunately, this doesn´t seem to be true for virus-associated brain disease. The reasons for this development are unclear. But they are not based on the aging of the cohort, possible toxic effects of cART or in a therapeutic failure of cART with respect to the brain, because the rise in neurocognitive deficits is due the patients newly entering the cohort. Thus, it is important to find out whether this might be due to a change of HIV itself (f. ex. selection of neurotropic strains due to the fact that therapy exclusively refers to systemic HIV-infection?).

Chronically Active VZV-Infection of the Brain - a Co-Factor of HIV-Associated Dementia?

P16

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Introduction: Since the early years of this century, neurological complications of HIV-infection are rising again after having declined in incidence and prevalence as a consequence of the introduction of highly active antiretroviral therapy (HAART) in 1996. This is especially true for HIV-associated dementia (HAD) and its precursor stages (HIV-associated asymptomatic neuro-cognitive impairment = ANI and mild neuro-cognitive deficit = MNCD). Besides searching for the reasons of this development, researchers focus more and more on so-called "cofactors" (age, metabolic syndrome, psychiatric co-morbidity and chronic co-infections). In contrast to hepatitis virus C, varicella zoster virus (VZV) has not been examined in this context.

Methods: Out of a cohort of more than 3500 HIV-positive patients, three subgroups have been selected:

1: HIV-positive patients without dementia or VZV-coinfection, n = 187

2: HIV-positive patients without dementia, but with chronically active VZV-infection), n = 167

3: HIV-positive patients with dementia and chronically active VZV-infection, n = 33

Chronically active VZV-infection was identified by an antibody index in CSF. Patients were comparable with respect to age and CDC-stage. Group 3 patients had the longest duration of HIV-positivity (90.59 months). Whereas almost all of the group 1 patients have been treated antiretrovirally, this was true for only 52% of group 2 and 25% of group 3 patients. Additionally to a neurological examination, plasma HI-viral load, CD4+-cell counts, CSF routine parameters (cell count, protein content, glucose, lactate, IgG and CSF-HI-viral load) have been determined.

Results: As expected, group 1 patients had the lowest HI-viral load in plasma and the highest CD4+-cell count; with respect to these parameters difference between group 2 and 3 was statistically significant. The highest inflammatory CSF reaction (lymphcytic pleocytosis, elevated protein content, high IgG) was found in group 1. But surprisingly, CSF-HI-viral load was highest in group 3 in comparison to both of the other groups.

Conclusions: These results support the hypothesis that "opportunistic" viruses may trigger HIV-activity in the human brain and thus, could be cofactors of HIV-associated brain disease.

Detection of HIV-Associated Neurocognitive Disorders (HAND) Using the Montreal Cognitive Assessment (MoCA) and the International HIV Dementia Scale (IHDS)

P17

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Background: There is currently no data about HIV-associated Neurocognitive Disorders (HAND) in Singapore. This study had the objectives of estimating the prevalence of HIV-associated neurocognitive disorders (HAND) among HIV patients in Singapore, and describing the pattern of neurocognitive impairment in HAND, and the factors associated with HAND.

Methods: This was a cross-sectional survey of a sample of HIV-positive outpatients and inpatients attending the Communicable Disease Centre in Singapore over a 4-week period. The Montreal Cognitive Assessment (MoCA), International HIV Dementia Scale (IHDS) and Instrumental Activities of Daily Living (IADL) scale were administered to the study participants. A chart review was conducted to retrieve sociodemographic data and various clinical factors. Cognitively impaired patients were categorized using the 2007 updated research nosology for HAND (Antinori et al. 2007).

Results: Data from 132 subjects were analyzed. The prevalence of HAND was 22.7% of which 70% were Asymptomatic Neurocognitive Impairment (ANI), 23.3% were Mild Neurocognitive Disorder (MND) and 6.7% were HIV-Associated Dementia (HAD). Increasing age (OR 1.104, $p < 0.001$), less education (OR 0.782, $p< 0.001$) and severe stage of illness at diagnosis (OR 4.09, $p=0.002$) increased the risk of HAND. Delayed recall, verbal skills, abstract thinking, motor speed and psychomotor speed were the domains most commonly affected. Logistic regression showed that impairment in domains of visuospatial and attention were most strongly associated with HAND. Baseline and current CD4 counts, and duration of illness were not associated with prevalent HAND.

Conclusion: HAND is common among HIV patients in Singapore, most of whom are asymptomatic. Older patients with less education and severe illness at diagnosis are at highest risk of HAND. Delayed recall is most commonly affected in HAND but visuospatial dysfunction is most strongly associated with prevalent HAND.

The authors do not know of other studies to have used a combination of standardized mental status examinations to detect HAND.

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ORAL COMMUNICATIONS

POSTER

HIV

Roberto è sieropositivo. In mancanza di una cura definitiva per debellare l'infezione da HIV, il paziente è costretto ad una terapia cronica i cui effetti collaterali riducono la qualità di vita.

Come per l'AIDS, esistono molte altre malattie alle quali la medicina non è ancora in grado di dare una risposta: la nostra missione è quella di aiutare milioni di pazienti, sviluppando trattamenti innovativi per patologie gravi come schizofrenia, morbo di Alzheimer, epatite C, tubercolosi, disordini metabolici, malattie onco-ematologiche, psoriasi e altre patologie immunitarie.

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