Update from the Conference on Retroviruses and Opportunistic Infections

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- Janssen

Pathogenesis – HIV

- HIV Compartmentalization in the CNS Is Associated With Neurocognitive Impairment (401, Bowman)
- Compartmentalized HIV DNA Populations Persist in CSF Despite Suppressive ART (143, Faria de Oliveira)
- CNS Compartmentalization of HIV-1 and Sensitivity to Neutralizing Antibodies (400, Stefic)
- Persistent HIV-1 in the CNS during therapy: evidence of a viral reservoir in the CNS (402, Joseph)
- Chronic low-level HIV-1 tat expression promotes a neurodegenerative phenotype (396, Chin)



Pathogenesis – Host

- Lipid Profiles and APOE4 Allele Impact Midlife Cognitive Decline in HIV+ Men on ART (145, Mukerji)
- CD4/CD8 ratio decline and risk of neurocognitive deterioration (408, Vassallo)
- Mitochondrial DNA Copy Number and Neurocognitive Impairment in HIV-Infected Persons (144, Samuels)
- $(1 \rightarrow 3)$ - β -D-Glucan levels correlate with Neurocognitive Functioning in HIV infection (410, Hoenigl)
- Novel CSF Biomarker Associations with HAND (409, Kallianpur)
- CSF Lymphocyte and Monocyte Activation and Trafficking in Primary HIV Infection (142, Li)
- SIV-Infected Brain Macrophages Leave the CNS (141, Alvarez)
- Peripheral Immune Activation Modulates HIV RNA Entry to CSF in Early Acute Infection (404, Schuetz)
- Neurologic Signs and Symptoms Frequently Manifest in Acute HIV Infection (415, Hellmuth)
- CNS Drug Distribution and CSF Inflammation During Suppressive Antiretroviral Therapy (412, Letendre)

Pathogenesis – Imaging

- Brain MRI Changes Associated with Poorer Cognitive Function in Treated HIV (148, Underwood)
- Advanced MRI predict cognition at 1 year follow-up in mildly impaired HIV+ patients (381, Perrotta)
- Topographies of cortical and subcortical volume loss in HIV and aging in the cART era (382, Guha)
- New Method Measuring Intracranial Vessel Caliber Reveals Arterial Remodeling In HAND (389, De Alwis)
- Effect of cART on functional connectivity in cART naïve HIV infected Individuals (392, Schiffito)
- Cardiovascular risk factors and the rate of change in brain structure in HIV disease (388, Becker)
- Brain Volumetric Changes After Two Years of ART Initiated During Acute HIV Infection (384, Kallianpur)
- NeuroHIV: A Novel High-Resolution Subcortical Shape Analysis (386, Ching)
- Regionally Specific Cortical Thinning in HIV+ Patients in the cART Era (385, Sanford)
- Isolated cingulate correlates with reduced executive function in HIV (390, Jiang)

Stroke

- Persistently Increased Ischemic Stroke Risk in HIV-Infected Women (638, Chow)
- Stroke in HIV-Infected Patients in the Combination Antiretroviral Therapy Era (639, Berenguer)
- Incidental Carotid Plaque in HIV is Associated With Subsequent Cerebrovascular Events (640, Janjua)
- Differences in Predictors for Ischaemic and Haemorrhagic Strokes in HIV+ Individuals (637, Hatleberg)
- Incremental Association Between CD4:CD8 Ratio and Incidence of Non-AIDS Events (710, McGettrick)



Treatment

- Paroxetine and Fluconazole Therapy for HAND: A Double-Blind, Placebo-Controlled Trial (146, Sacktor)
- MVC and TDF Reduce Neurocognitive Impairment in Initial ART: ACTG A5303 (147, Robertson)
- Week-48 Cognitive Improvement in HAND After Switch to HAART based on CHARTER score +3 (420, Force)
- HIV associated neurocognitive impairment: a randomized controlled trial of lithium (419, Decloedt)
- CNS Safety of Simplification to ATV/r+3TC in Virologically Suppressed HIV+ Patients (417, Ciccarelli)



Pathogenesis – HIV



HIV Compartmentalization in the CNS Is Associated With Neurocognitive Impairment





- 28 ART naive adults, CD4 < 400
- 10 (36%) had compartmentalization of HIV in CSF
- After ART initiation, compartmentalization was associated with worse GDS at 24 (p=0.04) and 54 weeks (p=0.05)

Bowman et al, CROI 2016, Abstract 401

Compartmentalized HIV DNA Populations Persist in CSF Despite Suppressive ART

 Samples: Paired blood and CSF samples were prospectively collected from 16 HIV-infected participants with continuous suppressed levels of HIV-1 RNA:

n = 9 Early ART (≤ 4 months from EDI)





Faria de Oliveira et al, CROI 2016, Abstract 143

Lower Levels of Inflammation in Early vs. Late ART Group



 No differences for levels of other inflammatory markers, NFL or GDS for early versus later ART start

Faria de Oliveira et al, CROI 2016, Abstract 143

HIV-1 DNA: No Differences Between Early and Late ART Groups

- PCR detectability: 93.8% (15/16) of PBMC and 62.5% (10/16) of CSF cellular pellets: 5 early ART
- No differences in detectability: early versus later ART start



Viral Diversity Possibly Greater in Late ART Group

- Deep sequencing:
 - 14 participants: PBMCs
 - 9 participants: CSF cell pellets



Sequences Only Found in CSF can Persist over Time



Broadly Neutralizing Monoclonal Antibodies Reduce HIV RNA and DNA



Barouch et al. Nature 2013, 503: 224-9

CNS Compartmentalization of HIV-1 and Sensitivity to Neutralizing Antibodies

- Near full-length HIV-1 envelope variants from paired CSF and blood plasma samples of 9 adults by SGA
- CSF compartmentalization in 5 of 9 (55%)
- <u>Autologous neutralization</u>: No significant differences in sensitivity between CSF and blood viruses
- <u>BNAbs</u>: Large differences between CSF and blood viruses with both compartmentalized and equilibrated CSF populations

	Compartmentalized HIV						
	Participant KU			Participant KP			
	Blood	CSF	Ratio	Blood	CSF	Ratio	
CD4s	0.526	2.264	4	1.31	28.57	22	
PGT121	0.023	0.201	9	> 10	> 10	-	
PG16	0.06	2.597	43	> 10	> 10	-	
PGT145	4.267	0.539	8	> 10	> 10	-	
8ANC195	> 10	> 10	-	> 10	> 10	-	
10E8	1.37	1.626	1	0.656	1.111	1	



Pathogenesis – Host



Lipid Profiles and APOE4 Allele Impact Midlife Cognitive Decline in HIV+ Men on ART

- Higher total cholesterol levels or a hypercholesterolemia diagnosis have been associated with lower cognitive scores in HIV+ subjects and worsening of HIVassociated neurocognitive disorder (HAND; Wright 2010, Sacktor 2016).
- The main cholesterol transporter in the central nervous system is Apolipoprotein E.
- The APOE gene exists as three polymorphic alleles (E2, E3, E4).
- APOE E4 allele is associated with Alzheimer's Disease and faster rates of agerelated cognitive decline in the general population.
- APOE E4 allele is associated with hypercholesterolemia, and increased risk for cardiovascular disease.



Higher Total Cholesterol Associated with More Rapid Cognitive Decline in HIV+ Men



Figure: The estimated slope for a 50 year old nonsmoker, IQ score 108, baseline CES-D score 9 and CD4 count 800cells/ul



Cognitive Decline Rapidly Accelerates in APOE E4 Carriers





Cholesterol and APOE E4 Genotype Independently Contribute to Cognitive Decline





CD4/CD8 Ratio & Cognitive Decline

	Stable or Improved	Worsened	p value
Age	46.7	45.6	0.66
Sex (Men)	83%	73%	0.29
Education (< high school)	28%	18%	0.14
Nadir CD4	256	275	0.65
HIV DNA	598.2	390.4	0.46
CD4/CD8 Ratio at Entry	0.67	0.84	0.07
CD4/CD8 Ratio at Follow-up	0.76	0.75	0.87
CD4/CD8 Ratio Trajectory	+0.09	-0.09	0.001
CPE at Entry	8.0	7.1	0.003
CPE Follow-up	7.8	7.2	0.08



- CD4/CD8 ratio declined in 60% of patients with worsened NP tests vs. 31% of those who were stable or improved (p=0.008)
- CPE at entry and CD4/CD8 change were independently associated with NC decline

Vassallo et al, CROI 2016, Abstract 408

Mitochondrial DNA

Cellular mtDNA

- The number of mtDNA per cell
- Low values: problems with mtDNA replication
- High values: problems with mitochondrial function/stress

Free mtDNA

- mtDNA released from cell rupture
- Can trigger immune system (TLR activation)
- Generally related to cell damage or inflammation

Samuels et al, CROI 2016, Abstract 144





PBMC mtDNA and Cognitive Outcomes



Covariates:

platelets/WBC, age, gender, genetic ancestry, duration of HIV, comorbidities, nadir CD4, detectable plasma HIV RNA

mtDNA levels higher in participants with impaired GDS but only <u>incidental</u> comorbidities

Samuels et al, CROI 2016, Abstract 144



CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH



CSF mtDNA and CSF Viral Load

CSF free mtDNA was lower in patients on ART

CSF free mtDNA positively correlated with CSF HIV viral load



CSF free mtDNA was not significantly associated with cognitive outcomes

Samuels et al, CROI 2016, Abstract 144



CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH



SCHOOL OF MEDICINE VANDERBILT UNIVERSITY®



Persistent Inflammation



Dyslipidemia Visceral Fat



Brain

Disease

Vascular

Disease

$(1 \rightarrow 3)$ - β -D-Glucan levels Correlate with Neurocognitive Functioning in HIV



Ancuta et al, PLoS ONE 2008, 3(6): e2516

Novel CSF Biomarkers of HAND

• Iron transport

- Influences immune activation and angiogenesis, which may compromise the BBB
- Linked to neurodegenerative disorders
- Ceruloplasmin: Copper ferroxidase involved in iron and copper transport and angiogenesis
- Haptoglobin: an iron-binding protein and ligand for the macrophage-monocyte scavenger receptor CD163
- **VEGF:** well-described angiogenesis factor



Novel CSF Biomarkers of HAND

Odds Ratio for Neurocognitive Impairment



Primary Infection CNS Events Study (PISCES) Design

- Prospective, observational study in San Francisco
- Enrolled participants with laboratory-confirmed primary HIV infection (<1 yr from HIV transmission), cART-naïve
- Some participants independently initiated cART during follow up
- Multiparameter flow cytometry was used to define phenotypes of CD4⁺ and CD8⁺ T-cells and monocytes in CSF and blood at each visit
- Longitudinal data was analyzed using linear mixed models



T-cell Activation in CSF Increased Over Time in Untreated Primary HIV



CD4+ T-cell Activation Correlated with CSF HIV RNA (not CD8+)

Independent	Univariate	Analysis	Multivariate Analysis		
Variable	Regression Slope	Significance	Regression Slope	Significance	
CSF CD4 ⁺ activation	0.044	<0.001	0.038	0.005	
CSF CD8 ⁺ activation	0.027	0.01	0.009	0.45	
	CSF HIV RNA (1	· ·			

Monocyte α4 Integrin Expression Correlated with T-cell Activation in Blood (off ART)

- Monocyte α4 expression (% and MFI) did not significantly change with time or correlate with CSF viral load
- In blood but not CSF, α4 expression (MFI) correlates with T-cell activation





Monocyte α4 Integrin Expression Correlated with T-cell Activation During ART





Imaging



Brain MRI Changes Associated with Poorer Cognitive Function in Treated HIV





Diffusion Tensor Imaging



White matter tract based spatial statistics group comparison. Areas of significantly (p < 0.05) lower fractional anisotropy (FA), higher mean diffusivity (MD) and higher radial diffusivity (RD) are coloured by t-statistic red-yellow, light blue and dark blue respectively - corrected for multiple comparisons (TFCE) and adjusted for age, intracranial volume, sex and scanner. Overlaid on the white matter skeleton (green) and the mean FA image (greyscale).



K-means Cluster Analysis: HIV+



Discriminant coordinate plot showing the separation of the clusters based on the k-means cluste analysis of parcellated grey matter and mean fractional anisotropy data. Each individual number represents a participant with the number representing their cluster assignment



Combining Imaging and Cognitive Data





Topographies of cortical and subcortical volume loss in HIV and aging in the cART era

- MRI has typically focused on subcortical regions of interest (ROIs) but more recently cortical changes have been detected
- Relative contribution of cortical & subcortical atrophy to HAND remains unclear
- 146 HIV+ and 51 HIV- adults
- PCA was applied to regional volumes to reduce dimensionality & account for colinearity between regions for the entire sample. Each principal component yielded a factor loading that represents a particular neural topography



Guha et al, CROI 2016, Abstract 382

Advanced MRI Predicts Cognition at 1 year Follow-up in Mildly Impaired HIV+ Patients

- 36 aviremic HIV+ adults
- Cross-over randomized clinical trial of rivastigmine for MND
- 3T MRI with T1/T2* relaxometry and Magnetization Transfer Imaging at entry and 6 & 12 months
- 6 months: T1/T2* in basal ganglia and thalamus associated with cognitive performance
- **12 months:** T1/T2* in global WM and GM associated with cognitive performance
- Results suggest that:
 - Integrity of the cortico-striatalthalamic loop highly influence executive function, working memory and reaction time
 - WM integrity plays a major role in processing speed



	Df	Pillai	approx F	num Df	den Df	Pr(>F)
Age	1	0.25	11.39	6	204	5.69E-11 ***
Gender	1	0.20	8.54	6	204	2.75E-08 ***
Arm of study	1	0.47	30.80	6	204	< 2.2E-16 ***
Group	1	0.26	12.09	6	204	1.30E-11 ***
MRI sequence	2	1.72	211.55	12	410	< 2.2E-16 ***
Time-point	2	0.06	1.12	12	410	0.3431

Perrotta et al, CROI 2016, Abstract 381

New Method Measuring Intracranial Vessel Caliber Reveals Arterial Remodeling in HAND

- T2* weighted MRI measured cross-sectional areas of the A1 segment of anterior cerebral arteries and M1 branch of middle cerebral arteries
- 13 HAND, 43 HIV+ without HAND, 23 HIV-
- HAND had higher M1 crosssectional areas
- HIV may cause vessel wall thinning, loss of plasticity, and lumen expansion, which may reflect arterial remodeling



Cardiovascular risk factors and the rate of change in brain structure in HIV

- 122 HIV+ or HIV- men in MACS
- 2 brain MRI scans 3.2 years apart
- Annualized rate of change of 3 brain compartments (GM, WM, CSF) was calculated
- HIV was not related to change in any of the 3 brain compartments after adjusting for age and race
- Among HIV+ men, nadir CD4+ cell count was associated with changes in GM and WM volumes

Table 3: Standardized Regression Coefficients (β) of Adjusted Models						
Predicting Change in GM and WM Volumes						
	Change in GM Change in WI					
Age > 60	.18*	005				
Race (Caucasian)	11	.11				
Cohort	17	.01				
Baseline Volume	45*	45*				
HDL	16*	.10				
Creatinine	.20*	21*				
UPCR ¹	03	005				
Hemoglobin A1c	16	06				
HIV Infection	.01	.03				
1-Urine Protein Creatine Log ₁₀ ; * p<.05						



Stroke



Persistently Increased Ischemic Stroke Risk in HIV-Infected Women



Model A: Unadjusted Model B: Demographics Model C: +Traditional Risk Factors Model D: +Sex-specific Risk Factors



Chow et al, CROI 2016, Abstract 638

Treatment



Paroxetine and Fluconazole Therapy for HAND: Double-Blind, Placebo-Controlled Trial

- 2000 compounds for human use were screened for neuroprotective effects in an in vitro model of oxidative stress-mediated cytotoxicity against HIV proteins
- Rat mixed hippocampal cultures pre-incubated with increasing concentrations of drugs for 1 hour before exposure to multiple toxins including HIV tat







Paroxetine and Fluconazole Therapy for HAND: Double-Blind, Placebo-Controlled Trial

 Paroxetine and fluconazole protected macaques from SIV-induced neurodegeneration, as measured by NFL and APP accumulation in neurons





Sacktor et al, CROI 2016, Abstract 146

Paraflu Study Design

- 24-week, double-blind, placebo-controlled, Phase I/II study in 45 HIV+ adults with HAND
- Participants randomly assigned to 1 of 4 groups
 - Paroxetine 20 mg orally every evening
 - Fluconazole 100 mg orally every 12 hours
 - Paroxetine plus Fluconazole
 - Placebo



Sacktor et al, CROI 2016, Abstract 146

Paroxetine and Fluconazole Therapy for HAND: Double-Blind, Placebo-Controlled Trial

- Paroxetine: Cognitive improvement on NPZ8 (+0.16 vs. -0.33, p = 0.023 after adjusting for baseline NPZ8 and depression symptoms)
- Fluconazole: Cognitive worsening on GDS (+0.12 vs. -0.13, p = 0.05 after adjusting for baseline GDS and depression symptoms)



Sacktor et al, CROI 2016, Abstract 146



ACTG A5303: MVC and TDF Reduce Neurocognitive Impairment in Initial ART

- Prospective, double-blind, placebo-controlled, randomized, multicenter, 48-week clinical trial
- 262 HIV+ ART-naive participants
- Plasma viral load > 1,000 cp/mL and R5 tropism on Trofile
- MVC 150 mg or TDF 300 mg plus:
 - Darunavir 800 mg once daily
 - Ritonavir 100 mg once daily
 - Emtricitabine 200 mg once daily



ACTG A5303: MVC and TDF Reduce Neurocognitive Impairment in Initial ART





Robertson et al, CROI 2016, Abstract 147

Week 48 Cognitive Improvement in HAND After CPE-Guided Switch

- 31 HIV+ adults on ART with virologic suppression > 1 year
- ART changed to new regimen with CPE improved ≥ 3 points and total CPE ≥ 9 (open-label)
- Initial median CPE of 6 was improved to 10 with addition of NNRTI, II or CCR5 inhibitor



• After 48 weeks, significant improvement in standardized NP tests and in cognitive complaints, without evidence of neurotoxicity





CNS Therapeutic Window





CNS Therapeutic Window



Acknowledgements & Conflicts Study Volunteers



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(Very) Brief Summary of the Symposium

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Thursday, 26 May



 Asymptomatic patients with potential CNS toxicity



 CNS Safety of Current ART Drugs



 Neurocognitive impairment and cardiovascular disease



 CNS Efficacy of Current ART



Friday, 27 May (Morning)



 Neuroinflammation in depression: microglia activation and dysfunction



 Impact of ART on the CNS: Two sides of the same coin



- Overall and CNS Safety of
 Integrase Inhibitors
- Natalia Gil Prevalence of psychiatric comorbidities among HIV Patients
 - Isabel Ramos Communication of the HIV Diagnosis: Experiences and Preferences

Friday, 27 May (Afternoon)



 CNS as a Reservoir for HIV: Why it happens and what can be done



Differential diagnosis between depression and neurocognitive impairment in HIV



 Emerging neurological toxicities in HIV

Saturday, 28 May





- Substance abuse in HIV patients: what the clinicians should know
- Sexuality, substance use, and HIV



Transdermal rivastigmine for HIVassociated neurocognitive impairment



 Update from the Conference on Retroviruses and Opportunistic Infections

Isabel Ramos

Neurocognitive disorders in patients with HIV virological suppression

• Elisabetta Teti

New EEG Technique (LORETA) to Early Detect and Monitor HAND

Guida Da Ponte

What do Psychiatrists need to know when treating HAND?

Fins l'any vinent Hasta el próximo año 10th Neuropsychiatry