HIV Dementia and Sensory Neuropathy in Uganda

(R21 MH083465)

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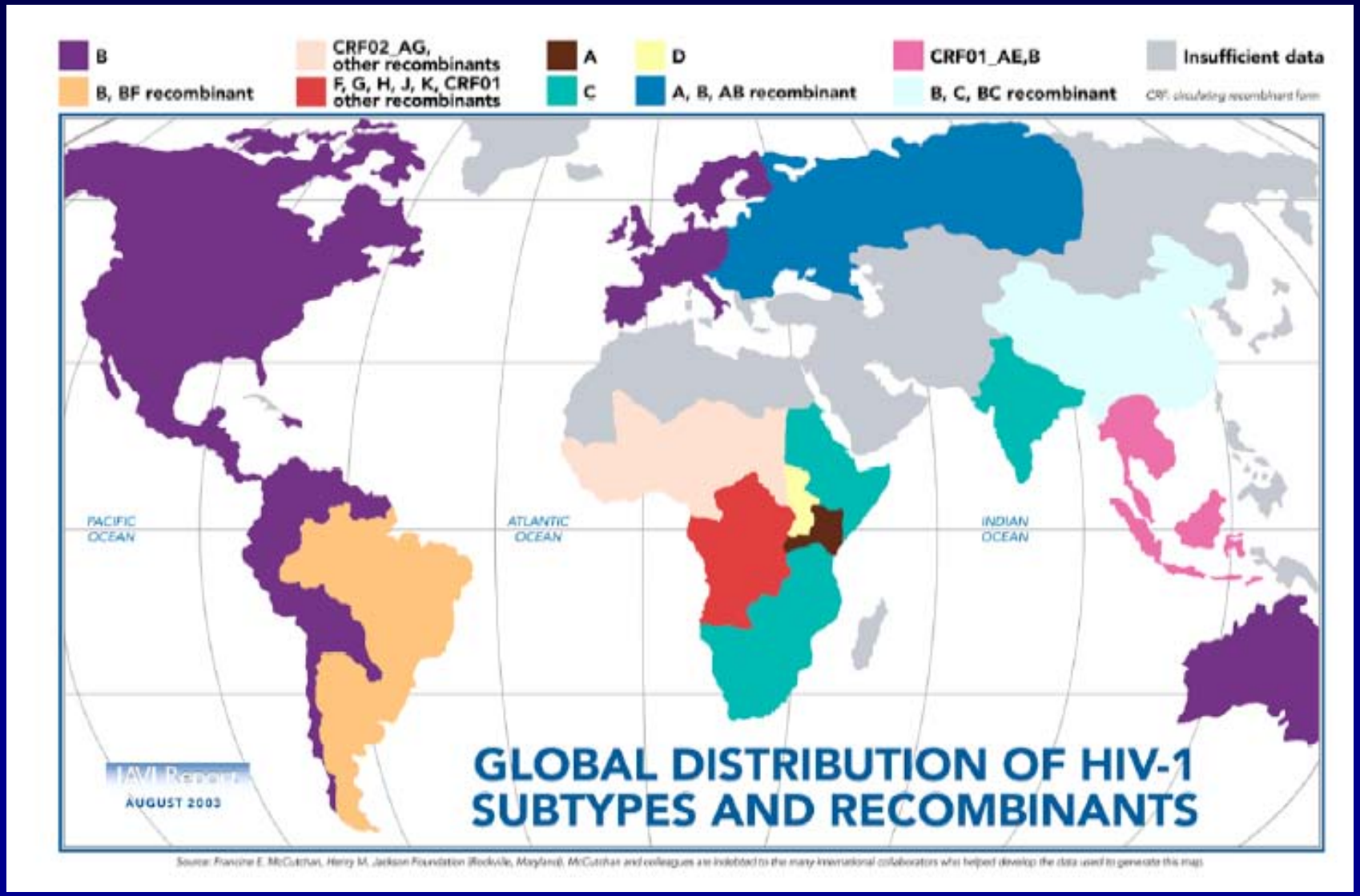
Adults and children estimated to be living with HIV as of end 2011

Total: 34 million

UNAIDS/WHO 2011 report

HIV clades


B
B, BF recombinant
CRF02_AG, other recombinants
F, G, H, J, K, CRF01 other recombinants
A
C
D
A, B, AB recombinant
CRF01_AE,B
B, C, BC recombinant
Insufficient data
PACIFIC OCEAN
ATLANTIC OCEAN
INDIAN OCEAN
IAVI Report
AUGUST 2003
GLOBAL DISTRIBUTION OF HIV-1 SUBTYPES AND RECOMBINANTS

R21 MH083465 HIV Dementia and Sensory Neuropathy in Uganda Specific Aims

1) To determine the prevalence of and risk factors for HIV dementia and neuropathy in a cohort of untreated HIV+ individuals with a CD4 count $\leq$ 350 in Uganda

2) To determine whether untreated HIV+ individuals (without dementia) with a CD4 count < 350 decline from baseline in neuropsychological test performance and PNS function over a 12 month period

3) To determine whether HIV subtypes differ with respect to the risk of dementia and neuropathy and progression of cognitive impairment and neuropathy

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- Inclusion criteria (selected): CD4 < 200, Age > 18 years, no active or prior CNS OI, afebrile, no prior chronic neurologic or severe medical illness interfering with study evaluation performance

- Clinical assessments- Medical and neurologic history and exam, neuropsychological test battery, functional assessment (Karnofsky), CD4, plasma HIV RNA

Uganda Neuropsychological Test Battery

- Motor Speed – Grooved Pegboard, Timed Gait
- Psychomotor speed – Symbol-Digit, Color Trails 1
- Memory – WHO-UCLA Auditory Verbal Learning Test
- Attention/Executive – Digit Span – Forward and Backward, Color Trails 2

Schedule of Events

Evaluation	Baseline	6 Months	12 Months
Medical/Neurological History	X	X	X
Antiretroviral Drug Use	X	X	X
Neurological Examination	X	X	X
Neuropathy Pain Symptoms Scale	X	X	X
Functional Assessments	X	X	X
Uganda Neuropsychological Test Battery	X	X	X
CD4 Count	X	X	X
Plasma HIV RNA	X		X
Cognitive Impairment Screening Evaluations	X		
Adherence Questionnaire		X	X
Lumbar Puncture (Optional)	X		X

R21 M083465 Cohort Update

- Grant notification-September, 2008
- Enrollment began-February, 2009
- All 125 HIV+ individuals enrolled by April, 2010
- By April 2011, 77 HIV+ received 12 months of follow-up

Demographics and medical history

Variable	Value
Demographic	
Men, %	32.0
Age, mean (SD)	37.14 (7.38)
Main language English, %	4.0
Left handed, %	6.4
Years of education, mean (SD)	8.08 (3.85)
Medical history	
Diabetes, %	0.8
Hypertension, %	4.0
Syphilis, %	24.8
Head trauma, %	4.8
Neuropathy, %	35.0

Diagnostic status, immune status, functional status, and symptomatic complaints

VARIABLE	VALUE
Diagnostic status	
Normal, %	11.2
Asymptomatic neurocognitive impairment, %	17.6
Mild neurocognitive disorder, %	29.6
HIV-associated dementia, %	41.6
Immune Status	
CD4 cells/uL, mean (SD)	241.54 (119.12)
CD4 Nadir cells/uL mean (SD)	240.21 (75.04)
Functional Status	
Karnofsky mean (SD)	89.52 (3.07)
Symptomatic complaints	
Memory, %	22.4
Concentration %	8.8
Depression, %	27.2
Balance, %	4.8
Slowing of hand movement, %	4.0
Numbness, %	34.4
Headache, %	30.4
Stiffness, %	8.8

Neuropathy Assessment

- Numbness 30%
- Pain or paresthesias (tingling) 21%
- Neuropathy (either of above symptoms) 35%

- Decreased reflexes 7%
- Decreased vibration 3%
- Decreased pin 2%

Lumbar Puncture Feasibility

- **Optional LP's performed in 23/125 (18%) cohort**

- **1st CSF specimens was collected for HIV+ individuals with detailed neuropsychological test assessments in Africa performed on voluntary basis**

Longitudinal Results

- 31 of the 125 HIV+ individuals were able to receive HAART after baseline
- Among HIV+ individuals not on HAART, 28% worsened HAND stage, 43% improved, and 29% remained unchanged
- Univariate predictors of worsening HAND stage at 6 months (logistic regression) were

  Advanced age [OR (C.I.) = 1.15 (0.99, 1.32)]; p= 0.05

  Low education [OR (C.I.) = 0.64 (0.42, 0.99);] p= 0.04

  CD4 Nadir [OR (C.I.) = 0.98 (0.97, 1.00)]; p= 0.08

Impact of HAART

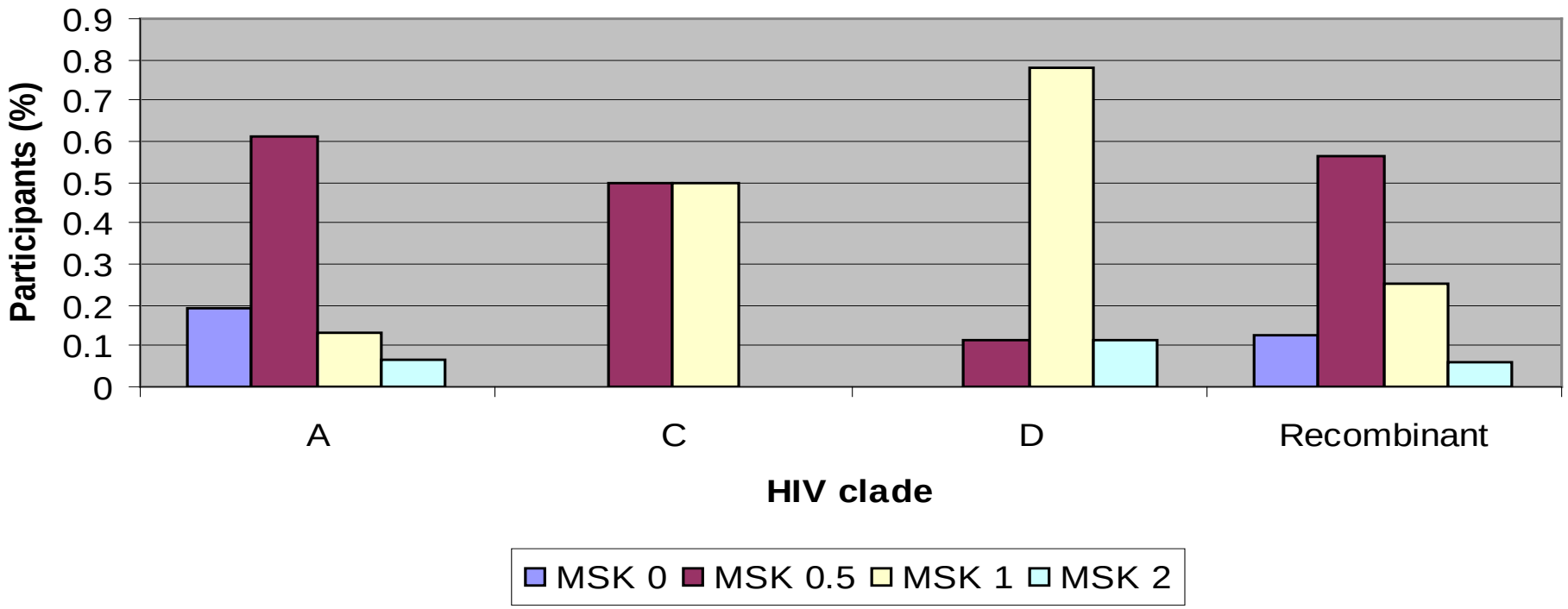
- At 12 months of follow-up, HIV+ individuals showed improvement in verbal memory [WHO-UCLA AVLT total score ($p=0.003$) and delayed score ($p=0.008$)], executive functioning [(Color Trails 1 ($p=0.015$) and Color Trails 2 ($p<0.001$)], and motor performance [Grooved pegboard dominant and non-dominant ($p=0.003$ for each test)].

- However, there was no additional improvement in the HAART treated group compared to the HAART untreated group likely due to improvement in depression symptomatology ($p=0.003$ for the no HAART group), practice effects, and the impact of ongoing medical follow-up and quality clinical care.

Sacktor et al. Longitudinal neuropsychological test performance among HIV seropositive individuals in Uganda. 2012 Under review. J Neurovirology

HIV SUBTYPE D IS ASSOCIATED WITH AN INCREASED RISK OF DEMENTIA COMPARED TO SUBTYPE A AMONG HIV+ INDIVIDUALS WITH ADVANCED IMMUNOSUPPRESSION

N=31 N=2 N=9 N=16



- 89% HIV+ individuals with D had dementia vs 24% with A, (p = 0.004), (Sacktor et al, Clin Inf Dis, Sept 2009)

Follow-up HIV subtype study among HIV+ adults in Uganda (R21 MH083465)

- To characterize the HIV subtype among HIV+ individuals (n= 111) with moderate immunosuppression

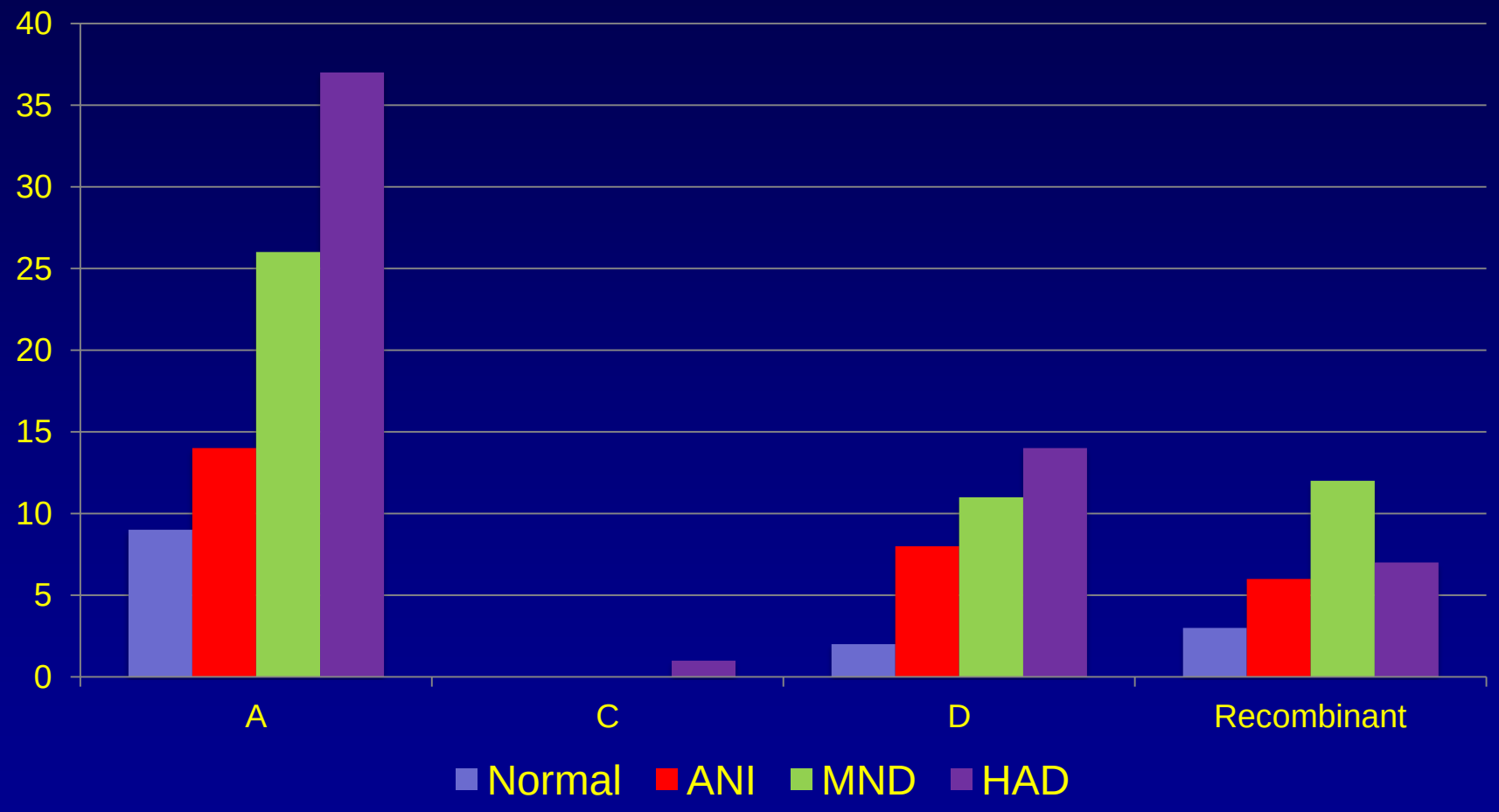
- To evaluate whether any HIV+ individuals had evidence for compartmentalization of HIV subtype between the CSF and blood (n=13 with detectable CSF HIV RNA levels)

Demographic Characteristics: Follow-up R21 Study

N = 111	Normal 8%	ANI 19%	MND 32%	Dementia 41%
Age-years (mean)	35.5	33.6	36.7	39.7
Education-years (mean)	9.5	10.0	8.1	7.0
Gender (%male)	54.6	40.0	39.5	20.4
CD4 count (mean)	254	260	239	233
Log plasma HIV RNA (mean)	4.2	4.7	4.8	4.9

- **HIV+ individuals with dementia were older (p = 0.003) and had less education than less impaired subgroups**
- **Follow-up study patients had less immunosuppression (mean CD4 count = 254) compared to initial study (mean CD4 count = 127), (P < 0.001).**

HIV subtype and risk of dementia among HIV+ individuals with moderate immunosuppression



Phylogenetic analysis for HIV subtype in CSF and blood: possible evidence for compartmentalization

- Subtype assignments (using gp41 and gag sequencing) for most individuals matched between the CSF and blood

- However, there were 2 individuals with HIV subtype A/D in blood, 1 with subtype D in CSF (MND) and the 2nd with subtype A in CSF (dementia)

- 1 individual with HIV subtype A in blood had HIV subtype A/D in CSF (dementia)

- HIV subtype may show evidence for compartmentalization which could contribute to risk for dementia

- HIV+ individuals in Uganda may have been infected with multiple strains (D and A)

- Pyro-sequencing and specimen linkage currently underway to confirm these data suggesting HIV subtype compartmentalization

Research Capacity Building

- Ugandan researchers now trained in neurological assessment, LP techniques, neuropsychological test administration, and clinical research methods
- Computerized algorithm to classify HAND stage based upon neurological symptoms, signs, and functional assessments
- These data represent the first 12 month longitudinal results of the natural history of neurocognitive performance in an HIV+ cohort in Africa

Barriers in conducting research

- Multiple protocol reviews (University IRB's, National AIDS Council, National Science Council, etc).
- Laboratory capacity for HIV subtyping in Uganda
- Quality control in neuropathy assessment

Abstracts/Papers

- Sacktor, N, Nakasujja, N., Skolasky, R., Robertson, K., Musisi, S., Ronald, A., Katabira, E., Clifford, D. B. Benefits and risks of stavudine therapy for HIV associated neurological complications in Uganda. Neurology 2009;72:165-170.

- Sacktor, N**.,** Nakasujja, N., Skolasky, Rezapour, M., Robertson, K. Musisi, S., Katabira, E., Ronald, A., Clifford, D. B., Laeyendecker, O., Quinn, T.C. HIV subtype D is associated with dementia compared with subtype A in immunosuppressed individuals at risk of cognitive impairment in Kampala, Uganda Clin Inf Dis 2009;49(5):780-786.

- Nakasujja, N., Skolasky, R.L., Musisi S., Allebeck, P., Robertson, K., Ronald, A., Katabira, E., Clifford, D.B., Sacktor, N. Depression symptoms and cognitive function among individuals with advanced HIV infection initiating HAART in Uganda. BMC Psychiatry 2010 10(1): 44.

- Okonkwo O, Nakasujja N, Robertson K, Sacktor N. "Risk factors for Dementia among HIV+ individuals in Uganda", Poster presentation at International Society of Neurovirology, Milan, IT; October 14, 2010, J Neurovirology 2010 16; S1: 64

- Okonkwo O, Nakasujja N, Robertson K, Skolasky, R., Musisi, S., Katabira, E., Sacktor N. "Longitudinal cognitive functioning and antiretroviral therapy use among HIV+ persons in Uganda", American Academy of Neurology Annual Meeting, April 2012.

- Nakasujja, N., Miyahara, S., Evans, S., Lee, A., Musisi, S., Katabira, E., Robertson, K., Ronald, A., Clifford, D.B., **Sacktor, N.** A randomized trial of minocycline in the treatment of HIV-associated cognitive impairment. Neurology 2012, (in press).

- Sacktor, N., Nakasujja, N., Okonkwo, O., Skolasky, R., Robertson, K., Musisi, S., Katabira, E. Longitudinal neuropsychological test performance among HIV seropositive individuals in Uganda. Under review. J Neurovirology

- Sacktor, N., Nakasujja, N., Laeyendecker, O., Manucci. J., Skolasky, R., Okonkwo, O., Robertson, K., Musisi, S., Katabira, E., Quinn. T. HIV subtype compartmentalization among individuals with HIV-associated neurocognitive disorders. Draft form awaiting submission.

Grant Submissions

- P.I. Maria Wawer. “Health functional status and, long-term combined ART, Rakai, Uganda”. R01 submitted to NIMH, 30th percentile, not funded-7/10

- P.I. Ronald Gray. “Training in non-communicable disease in Uganda and Malawi” PAR-10-257- Fogarty International Research Training Award. 10/10 submitted, unscored

- Co-PI’s Ned Sacktor, Maria Wawer. Neurological sequelae of HIV subtype A and D infection and HIV treatment, Rakai, Uganda. RO1 submitted 2012, 22nd percentile. To be resubmitted, 2013

Neurological sequelae of HIV subtype A and D infection and HIV treatment, Rakai, Uganda.

Co-PI's Ned Sacktor, Maria Wawer

Specific Aims

1. To assess whether, and to what degree, ART naïve HIV+ adults aged ≥ 20 years with moderate immunosuppression (CD4 ≥350-500), and advanced immunosuppression (CD4 ≤ 200) experience key neurocognitive co-morbidities, and associated depression symptoms and reduced functional status, compared to HIV- adults.

2. To assess whether the trajectory of morbidity over two years of follow up differs by HIV subtype and by level of immunosuppression prior to ART initiation, controlling for the period of time on ART.

3. To define the level of compartmentalized virus in the CSF of HIV+ individuals with and without dementia, stratified by HIV subtype.

Collaborators

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