NEUROLOGICAL COMPLICATIONS OF HIV

Dr P.T KUMIRE
Neurological complications of HIV infection

Justin C McArthur, Bruce J Brew, Avi Nath

Cognitive disorders, vacuolar myelopathy, and sensory neuropathies associated with HIV are the most common disorders in patients with HIV AIDS, and are the focus of this review. These disorders are treatable and of those associated with HIV AIDS the pathogenic mechanisms are the most understood. Although triggered by productive HIV macrophage infections, aberrant immune activation plays a major role in inducing the CNS disorders. Novel therapies aimed at these inflammatory mechanisms can be effective. The sensory neuropathies associated with HIV infection are a major cause of morbidity; incidence may be increased by the toxic effects of specific antiretroviral drugs within the peripheral nervous system.

Biology of HIV infection
HIV-1 is a retrovirus that produces profound CD4 depletion, possibly through an initial massive depletion of gut-associated memory T cells, and then chronic immune activation, leading to fatigue of homoeostatic T-cell responses and progressive immunodeficiency. The CD4 receptor is the main target for HIV-1, however, specific chemokine receptors are important secondary cellular receptors. Additionally, specific lectins on dendritic cells may stabilise HIV for presentation to susceptible cells. HIV can infect CD4 negative cells, including astrocytes. HIV-1 strains are grouped according to preferred site of replication; T-tropic viruses prefer replication in T lymphocytes and M-tropic viruses in macrophages. Use of chemokine receptors differs for each subgroup: CD4 and CXCR4 (or fusin, the receptor for SDF-1) for T-tropic viruses, CCR5 (the receptor for RANTES) for M-tropic viruses. Of the HIV-1 viruses in the brain, M-tropic viruses are the most common.

After the HIV provirus has been integrated into the proinflammatory cytokines and chemokines within the CNS and peripheral nervous system. This progression is crucial for the onset of both HIV-associated dementia (HIV-D) and sensory neuropathies (panel 1).

Neurological symptoms of HIV infection
HIV may affect the nervous system directly, producing distinct neurological syndromes, or indirectly, by causing immunodeficiency with a resultant susceptibility to opportunistic infections. Nervous system infection with HIV-1 can produce a range of clinical disorders, but only dementia, myelopathy, and sensory neuropathies will be discussed here. These debilitating disorders generally do not develop until advanced stages of HIV infection. Typically, other AIDS-defining illnesses or immunosuppression occur before these neurological syndromes. Little is known of these disorders in Asia and Africa.

HIV-D
NeuroAIDS in sub-Saharan Africa: a clinical review.

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Abstract
NeuroAIDS affects half of the 22 million people currently living with HIV/AIDS in sub-Saharan Africa, where cryptococcal meningitis alone is responsible for 504,000 deaths annually. A good understanding of NeuroAIDS may help improve disease-free survival in patients at risk and optimize resource utilization by caregivers. In this review, we aimed to provide a summary of major NeuroAIDS syndromes of relevance in Africa. We searched Medline for English language literature to identify relevant publications, using the search terms "NeuroAIDS" and "HIV and nervous system.

The most common NeuroAIDS syndrome is HIV-associated neurocognitive disorders (HAND), which affects over 1.5 million Africans yearly. While incidence of HAND has decreased with the use of highly active antiretroviral therapy, prevalence has increased due to longer life expectancy. Other NeuroAIDS syndromes include tuberculous meningitis and intracerebral tuberculoma, cryptococcal meningitis, toxoplasma encephalitis, progressive multifocal leukoencephalopathy, primary central nervous system lymphoma, stroke, and distal sensory polyneuropathy. NeuroAIDS care and research in Africa are hindered by resource limitations. Inadequate neuroimaging and laboratory facilities result in diagnostic delays and confusion, while limited access to drugs leads to inappropriate treatment. However, the situation may be improving. Better funding of HIV care by African governments and donor agencies have resulted in decreasing HIV prevalence and prolonged survival. Yet, central nervous system opportunistic infections remain important causes of death and disability among African patients with HIV/AIDS. There is the need for additional funding to improve access to antibiotics and to facilitate further research into NeuroAIDS and its treatment.

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HIV RELATED NEUROLOGICAL DISEASES

<table>
<thead>
<tr>
<th>SEROPositive</th>
<th>ARC</th>
<th>AIDS with opportunistic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE ASEPTIC MENINGITIS</td>
<td>PERSISTENT PLEOCYTOSIS</td>
<td>HIV DEMENTIA</td>
</tr>
<tr>
<td>INFLAMMATORY NEUROPATHY</td>
<td>MONONEURITIS</td>
<td>SENSORY NEUROPATHY</td>
</tr>
<tr>
<td>MYOPATHY</td>
<td>MYELOPATHIES</td>
<td>NEUROBEHAVIORAL ABNORMALITIES</td>
</tr>
</tbody>
</table>
HIV associated neurocognitive disorder

- Current nosology published 2007
- HIV-associated asymptomatic neurocognitive impairment
- HIV-associated mild neurocognitive disorder
- HIV-associated dementia
- All are characterized by impairment in at least two cognitive domains
  - Language
  - Abstract-executive function
  - Attention
  - Memory
  - Information processing
  - Sensory perception
  - Motor skills
HIV DEMENTIA: epidemiology

- Prevalence has increased post-HAART era
- Incidence of HAD 3-5%
  - Prevalence ranges from 21% in Cameroon to 53% in Nigeria
- Risk factors:
  - Age
  - Substance abuse - IVI
  - Females
  - Low BMI
  - HCV
- Genetic factors influence development of HAD
  - Apolipoprotein E4 allele
  - Genetic mutations of monocyte chemoattractant F1
HAD: clinical features

- Onset over several months
- Subcortical and cortical dementia
- Mental slowing, reading and comprehension difficulties, apathy
- Gait disturbance-stumbling/tripping
- Postural tremor, impaired fine manual dexterity
- New onset mania in 5%
- Physical exam:
  - Impaired rapid eye movements
  - Hyper-reflexia
  - Frontal release signs
  - Apraxia
  - IHDS- International HIV Dementia Scale
- Congenital infected children present with spastic paraparesis, microcephaly
Neuropsychological test components of the international neurobehavioral battery developed at the human immunodeficiency virus neurobehavioral research centre, University of California, San Diego

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Neuropsychological test</th>
<th>Maximum time limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor speed/attention/concentration</td>
<td>Paced auditory serial addition test</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Trail making test A/colour trails test 1</td>
<td>96 seconds</td>
</tr>
<tr>
<td></td>
<td>Stroop colour and word test</td>
<td>45 seconds×3 trials</td>
</tr>
<tr>
<td></td>
<td>Wechsler adult intelligence scale-III (WAIS-III) Digit symbol</td>
<td>120 seconds</td>
</tr>
<tr>
<td></td>
<td>Wechsler adult intelligence scale-III (WAIS-III) Symbol search</td>
<td>120 seconds</td>
</tr>
<tr>
<td>Attention/working memory</td>
<td>Spatial span</td>
<td>None</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>Trail making test B/colour trails test 2</td>
<td>301 seconds</td>
</tr>
<tr>
<td></td>
<td>Stroop colour and word test</td>
<td>45 seconds×3 trials</td>
</tr>
<tr>
<td>Memory</td>
<td>Hopkins verbal learning test-revised</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Brief visuospatial memory test - revised</td>
<td>None</td>
</tr>
<tr>
<td>Verbal/language</td>
<td>Controlled oral word association test</td>
<td>60 seconds×3 trials</td>
</tr>
<tr>
<td></td>
<td>Category fluency test</td>
<td>60 seconds×2 trials</td>
</tr>
<tr>
<td>Motor skills</td>
<td>Finger tapping test</td>
<td>10 seconds×5 trials, twice</td>
</tr>
<tr>
<td></td>
<td>Grooved pegboard</td>
<td>301 seconds</td>
</tr>
<tr>
<td></td>
<td>Timed gait</td>
<td>90 seconds</td>
</tr>
</tbody>
</table>
HAD: pathophysiology

- HIV access through blood stream, infected monocytes penetrate BBB
- Parenchymal release of proinflammatory cytokines impairs cellular functioning and induces neuropathological changes in HAD

- Pathological features:
  - Activation of macrophages and astrocytes
  - Multinucleated giant cell
  - Changes prominent in basal ganglia
**HAD: differential diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>HIV-D</th>
<th>Cytomegalovirus encephalitis</th>
<th>Progressive multifocal leucoencephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features</strong></td>
<td>Memory disturbances, mental slowing, gait disturbances</td>
<td>Delirium, seizures, brainstem signs</td>
<td>Focal neurological signs</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Several months</td>
<td>Days to weeks</td>
<td>Weeks to months</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Diffuse atrophy, symmetrical deep white-matter diffuse hyperintensities</td>
<td>Normal or periventriculitis</td>
<td>Scattered, asymmetrical subcortical white-matter lesions</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td>Non-diagnostic: immune activation less marked in patients treated with HAART</td>
<td>PCR + for cytomegalovirus 90%</td>
<td>PCR + for JC/BK virus 60%</td>
</tr>
</tbody>
</table>

*Table 1: Differentiation of HIV-D from opportunistic infections*
HAD: diagnostic workup

- CSF to exclude opportunistic infections: cryptococcal /TBM/ EBV
- Neither CSF HIV-RNA or plasma HIV RNA correlate with progression of HAD
- Neuropsychological test
  - Impairment in nonverbal memory, psychomotor speed and frontal lobe
- CTB: ventricular enlargement and white matter hypodensities
- MRI-B: subcortical atrophy and central atrophy, signal abnormalities deep within white matter
Diagnostic studies
HAD: treatment

- Objective is to suppress HIV replication in CNS
- ARV penetrates blood-brain barrier
- Abacavir, zidovudine, stavudine, efavirenz, lamivudine
- PI can reverse neurocognitive deficits
- Selegiline preliminary study showed improvement
Antiretroviral Drugs Promote Amyloidogenesis by De-Acidifying Endolysosomes

Liang Hui¹ · Yan Ye¹ · Mahmoud L. Soliman¹ · Koffi L. Lakpa¹ · Nicole M. Miller¹ · Zahra Afghah¹ · Jonathan D. Geiger¹ · Xuesong Chen¹

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Abstract
Antiretroviral therapeutics (ART) have effectively increased the long-term survival of HIV-1 infected individuals. However, the prevalence of HIV-1 associated neurocognitive disorders (HAND) has increased and so too have clinical manifestations and pathological features of Alzheimer’s disease (AD) in people living with HIV-1/AIDS. Although underlying mechanisms are not clear, chronic exposure to ART drugs has been implicated in the development of AD-like symptoms and pathology. ART drugs are categorized according to their mechanism of action in controlling HIV-1 levels. All ART drugs are organic compounds that can be classified as being either weak acids or weak bases, and these physicochemical properties may be of central importance to ART drug-induced AD-like pathology because weak bases accumulate in endolysosomes, weak bases can de-acidify endolysosomes where amyloidogenesis occurs, and endolysosome de-acidification increases amyloid beta (Aβ) protein production and decreases Aβ degradation. Here, we investigated the effects of ART drugs on endolysosome pH and Aβ levels in rat primary cultured neurons. ART drugs that de-acidified endolysosomes increased Aβ levels, whereas those that acidified endolysosomes decreased Aβ levels. Acidification of endolysosomes with the mucolipin transient receptor potential (TRPML) channel agonist ML-SA1 blocked ART drug-induced increases in Aβ levels. Further, ART drug-induced endolysosome de-acidification increased endolysosome sizes; effects that were blocked by ML-SA1-induced endolysosome acidification. These results suggest that ART drug-induced endolysosome de-acidification plays an important role in ART drug-induced amyloidogenesis and that endolysosome acidification might attenuate AD-like pathology in HIV-1 positive people taking ART drugs that de-acidify endolysosomes.

Keywords Antiretroviral therapy · Alzheimer’s disease · Amyloid beta · Endolysosome pH
Materials and Methods

Reagents Zidovudine, abacavir, lamivudine, efavirenz, nevirapine, ritonavir, and nelfinavir were obtained from Sigma. Emtricitabine, tenofovir disoproxil fumarate, darunavir, dolutegravir and elvitegravir were obtained from MedChem Express. LysoSensor (DN160) was obtained from Fisher Thermo Scientific. Aβ_{1-40} and Aβ_{1-42} ELISA kits were obtained from Wako. ML-SA1 was obtained from Tocris Bioscience.

Primary Cultures of Rat Hippocampal Neurons As previously described (Buscemi et al. 2007; Hui et al. 2012b), primary cultured hippocampal neurons were prepared from Sprague-Dawley rats. Pregnant dams at embryonic day 18 were sacrificed by asphyxiation with CO_{2}. After the fetuses were removed and decapitated, meninges-free hippocampi were isolated. trypsinized. and seeded onto 35-mm^{2} nolv-D-lvsine
Course of HAD

- Pre-HAART era mean survival 6 months without treatment. (Int Review Psych 2008)
- Post-HAART mean survival is 2 years with low CD4
- Course of HAD has changed with HAART and subtypes proposed:
  - Subacute progressive D-untreated, severe progressive dementia
  - Chronic active D- HAART, incomplete virological control, slowly progressive dementia
  - Chronic inactive D- virological suppression on HAART, some recovery from neurological deficit and stable
  - Reversible D- HAART initially progressive but neurological deficits reversed with effective virological suppression
HIV associated sensory neuropathy: DSP

- Appears late in stage of HIV
- Aetiology: HIV infection and ARV
- 30% of patients with AIDS hospitalised had DSP without ARV toxicity
- Risk factors:
  - Age
  - Nutritional deficiency
  - Ethanol abuse
  - Low CD4 count
  - Pre-existing peripheral neuropathy
- Studies have not shown relation between these factors and development of DSP
Pathophysiology of DSP

- Pathogenesis incompletely understood and multifactorial
- Length dependent axonal degeneration of sensory fibres with little evidence of nerve-fibre degeneration
- Large myelinated and unmyelinated fibres are lost
- HIV likely immune-mediated, activation of macrophages infiltration in peripheral nerves and dorsal root ganglia-neuronal hyperexcitability
- ARV due to mitochondrial toxicity
Clinical features of DSP

- Distal painful dysesthesias
- Pain—severe burning, aching, worse at night
- Pins and needles sensation
- Hyperalgesia and allodynia
- Symptoms bilateral, gradual onset
- Predominantly distal involves feet and legs
- Disease progression distal involvement of hands “stock-glove distribution’
- Weakness if present confined to intrinsic foot muscles
- Physical exam:
  - Distal sensory loss of all modalities
  - Decreased/absent ankle reflex
Diagnosis DSP

- Primarily a clinical diagnosis
- Blood: TSH, s-B12, electrolytes, glucose
- NCS not routinely required
  - Length dependent axonal sensory polyneuropathy
  - Low sensitivity for detection of small fibre neuropathy, can be normal
- EMG usually normal
- Nerve biopsy rarely necessary, considered if there are unusual features: asymmetric distribution or associated weakness
Differential diagnosis

- Progressive polyradiculopathy
  - Asymmetrical weakness in legs, low back pain
  - Bladder and bowel involvement
  - Flaccid paraplegia

- IDP acute/chronic
  - Motor findings predominate with less sensory symptoms

- Mononeuritis multiplex asymmetrical, multifocal, motor and sensory
Treatment DSP

- Stop neurotoxic drug
- Assess risk factors
- Pain modifying treatment
- Antidepressants: amitriptylline not effective in DSP
- Lamotrigine - well tolerated ant effective for DSP, 2 separate studies
- Gabapentin 1 single small placebo trial effective in HIV-DSP
- Pregabalin
- Opioids only in severe HIV-DSP, consider dependence
- Topical high dose capsaicin patch double-blind trial showed efficacy in HIV-DSP
HIV associated CIDP/AIDP

- HIV-GBS present at time of seroconversion
- HIV-GBS more frequent recurrent episodes
- Clinical presentation similar to HIV seronegative
- Relapsing motor and sensory symptoms

Diagnosis
- CSF: elevated protein, mild lymphocytic pleocytosis

Treatment
- Similar to that of HIV seronegative patients
- IVIG/ plasmapharesis- GBS
- CIDP- oral prednisone until clinical improvement
Diagnosis of HIV-myelopathy

- US studies pre-HAART estimates of 22-35%
- Post HAART fewer than 10%  (Muscle Nerve 2009:40)
- Commonly parallels development of dementia
- Risk factor: high number of AIDS defining illness
- Pathogenesis
  - Intrallamellar vacoulation in spinal white matter particularly lateral and posterior columns of thoracic spinal cord
  - Vascular changes in ascending and descending spinal tracts of thoracic spinal cord
Clinical features myelopathy

- Slowly progressive painless spastic paraparesis
- Sensory ataxia
- Neorogenic bladder
- Increased reflexes
- Relapsing and remitting course
Diagnosis of HIV-myelopathy

- CSF to exclude other causes
- S-vit B12, folate
- Electrophysiological studies can confirm diagnosis
- CT and MRI are typically normal or may show nonspecific tract hyperintensities and cord atrophy

**Treatment**
- Studies of ARV have not been proven effective
- Physiotherapy and OT
HIV associated Myopathies

- Most common HIV myopathy is polymyositis
- Clinically similar to autoimmune polymyositis in HIV negative patients
- Occurs in all stages of HIV disease
- Slowly progressive
- Proximal and symmetrical muscle weakness

Classical diagnostic criteria
- Objective muscle weakness
- Elevated s-CK
- Myopathic findings on EMG
- Myopathic muscle biopsy

Aetiology HIV infection and ARV-zidovudine

Treatment corticosteroids
Neurological complications of HIV infection in pre-HAART and HAART era: a retrospective study.

Matinella A1, Lanzafame M, Bonometti MA, Gajofato A, Concia E, Vento S, Monaco S, Ferrari S.

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Abstract
The introduction of highly active anti-retroviral therapy (HAART) led to a radical change in the natural history of HIV infection and of the associated neurological opportunistic infections. However, the mortality of central nervous system (CNS) complications and opportunistic infections is still high in untreated HIV-infected individuals or in patients unaware of their HIV infection. We describe the outcome of HIV-infected patients followed at a single center for AIDS-related neurological syndromes in the 16 years following the introduction of HAART, and compare the findings with those in patients admitted up to 1996. We have conducted a retrospective study of patients with HIV infection or AIDS (based on WHO criteria and classified according to the 1993 CDC criteria) admitted during 20 years (January 1992 to March 2012) to the Infectious Diseases Unit of the University of Verona for the presence of focal or widespread CNS lesion on neuroimaging. Clinical history, CD4 cell count, HIV-RNA level, neurological examination, imaging, cerebrospinal fluid examination and eventual cerebral biopsy results were reviewed as well as the final neurological diagnosis and the treatment. The survival time from the clinical onset of the neurologic syndrome to death was calculated for each patient who died. A statistical analysis was performed comparing data collected up to and after 1996, i.e., before and after HAART introduction. Among 1043 patients with HIV infection or AIDS admitted to the Infectious Diseases Unit of the University of Verona between January 1992 and March 2012, 114 had a CNS lesion. The following diseases were observed: neurotoxoplasmosis (NT), progressive multifocal leukoencephalopathy (PML), primary central nervous system lymphoma (PCNSL), the severe form of HIV-associated neurocognitive disorder, cryptococcal encephalitis (CE) and lesions of undetermined origin. The follow-up period was 4 weeks to 72 months both in the pre-HAART and HAART era. Cerebral lesions were detected in 59/240 patients (21.8%) in the pre-HAART era and in 61/601 patients (7.6%) in the HAART era (p < 0.001). Most patients who developed a neurological complication in the HAART period (40/59, 67.8%) were untreated or did not know to be HIV-infected, in particular, 27.9% of patients with a CNS lesion in the HAART era were unaware of their HIV infection vs 13.2% in the pre-HAART era (p < 0.05). Some patients were not virologically suppressed (14/59, 23.7%) or were immunological non-responders (undetectable viral load, with CD4 count < 200 cells/μL; 4/59, 6.8%). Other statistically significant data were the mean age at the onset of neurological complications (32.6 ± 5.4 years in the pre-HAART, 40.3 ± 9.5 in the HAART group, p < 0.001) and the mean CD4 cell count at the onset of illness (median of 38 cells/μL (2-215) in the pre-HAART, 77 cells/μL (2-752) in the HAART group, p < 0.001). In the HAART era a reduction of PCNSL and NT was observed. Our results, while confirming a decrease in the incidence of opportunistic infections of the CNS in the HAART era, show that late presentation of patients with HIV infection remains an important issue in our catchment area.
<table>
<thead>
<tr>
<th>Feature</th>
<th>All cases (N = 114)</th>
<th>Pre-HAART (N = 53)</th>
<th>HAART (N = 61)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M</td>
<td>39/75</td>
<td>13/40</td>
<td>26/35</td>
<td>0.071</td>
</tr>
<tr>
<td>Age—years, mean ± SD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36.6 ± 8.7</td>
<td>32.6 ± 5.4</td>
<td>40.3 ± 9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neurological diagnosis, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurotoxoplasmosis</td>
<td>42 (36.8 %)</td>
<td>21 (39.6 %)</td>
<td>21 (34.4 %)</td>
<td>&lt;0.001</td>
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<td>PML</td>
<td>27 (23.7 %)</td>
<td>8 (15.1 %)</td>
<td>19 (31.1 %)</td>
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<tr>
<td>PCNSL</td>
<td>15 (13.1 %)</td>
<td>14 (26.4 %)</td>
<td>1 (1.6 %)</td>
<td></td>
</tr>
<tr>
<td>HAD</td>
<td>14 (12.3 %)</td>
<td>1 (1.9 %)</td>
<td>13 (21.3 %)</td>
<td></td>
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<tr>
<td>Undetermined origin lesions</td>
<td>14 (12.3 %)</td>
<td>9 (17 %)</td>
<td>5 (8.2 %)</td>
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<td>Cryptococcal encephalitis</td>
<td>1 (0.8 %)</td>
<td>0</td>
<td>1 (1.6 %)</td>
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<tr>
<td>Herpetic encephalitis</td>
<td>1 (0.8 %)</td>
<td>0</td>
<td>1 (1.6 %)</td>
<td></td>
</tr>
<tr>
<td>Brain biopsy performed, N (%)</td>
<td>34 (29.8 %)</td>
<td>27 (50.9 %)</td>
<td>7 (11.5 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIDS, N (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>51 (44.7 %)</td>
<td>28 (52.8 %)</td>
<td>23 (37.7 %)</td>
<td>0.056</td>
</tr>
<tr>
<td>New HIV diagnosis (%)</td>
<td>24 (21 %)</td>
<td>7 (27.9 %)</td>
<td>17 (13.2 %)</td>
<td>0.055</td>
</tr>
<tr>
<td>Risk category, N (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Substance abuser</td>
<td>59 (51.7 %)</td>
<td>34 (64.2 %)</td>
<td>25 (40.9 %)</td>
<td>0.002</td>
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<tr>
<td>Homosexual</td>
<td>10 (8.8 %)</td>
<td>7 (13.2 %)</td>
<td>3 (4.9 %)</td>
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</tr>
<tr>
<td>Heterosexual</td>
<td>28 (24.5 %)</td>
<td>10 (18.9 %)</td>
<td>18 (29.5 %)</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>17 (14.9 %)</td>
<td>2 (3.8 %)</td>
<td>15 (24.5 %)</td>
<td></td>
</tr>
<tr>
<td>Anti-retroviral therapy, N (%)</td>
<td>46 (40.3 %)</td>
<td>27 (50.9 %)</td>
<td>19 (31.1 %)</td>
<td>0.044</td>
</tr>
<tr>
<td>CD4 count, median (range)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>53.5 (2–752)</td>
<td>38 (2–215)</td>
<td>77 (2–752)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Thank you