Central Nervous System Complications of HIV

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AWACC
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HIV Neurology

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Nothing to disclose.
Professor Yunus Moosa
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Roadmap

• Spectrum of neurological syndromes in HIV
• General diagnostic patterns of CNS syndromes
• Cases with syndromic differential diagnosis and treatment
• Role of ART in CNS
• Questions and discussion
HIV Neurology: 
Overview

• Neurological complications are common
• All stages of infection/immune status
• All parts of the nervous system affected
• Diverse syndromes
• Multiple pathologies often coexist
• Cumulative neurological burden – the limited ability of recovery in CNS is unique and raises the stakes for early treatment
Case 1

27M with advanced HIV presents with vomiting, HA, neck pain, and mental status change worsening over weeks.
Case 2

38M with HIV presents with 1 day of N/V followed by generalized tonic clonic seizure.
Case 3

52M with HIV presents with 5 weeks of right arm clumsiness, unsteady gait.)
Case 4

64M with HIV presents with gradually worsening mental function over 1-2 years.
HIV Neurology: Diagnostic Principles

- Epidemiology
- Host factors
- Clinical symptoms and signs
- Serological and other non-CNS studies
- CSF studies
- Imaging where available
- Response to treatment
Epidemiology

- Limited data in resource-limited settings
- Little confirmatory evidence of definitive diagnosis
- Malaria, tuberculosis, and neurocysticercosis increased in sub-Saharan Africa
- HIV prevalence impacts CNS infectious epidemiology
Epidemiology

• Meningitis in Johannesburg, South Africa\textsuperscript{1}
  – Tuberculous meningitis (TBM) 25.4%
  – Bacterial meningitis (BM) 22.5%
  – Viral meningitis 14.1%
  – Cryptococcal meningitis (CM) 13%

• Meningitis in Harare, Zimbabwe\textsuperscript{2}
  – CM 45%
  – Mononuclear meningitis (aseptic) 27%
  – BM 16%
  – TBM 12%

\textsuperscript{1}Bergemann 1996; \textsuperscript{2}Hakim 2000.
Immune Status

- **CD4 count > 500** – “normal host”*
  - Dysimmune syndromes: Guillain-Barre, polymyositis
  - Chronic low-grade meningitis
- **CD4 200-500**
- **CD4 < 200** – differential expands
Immune Status

- CD4 count > 500 – “normal host”
- **CD4 200-500**
  - Tb, syphilis, VZV
  - Dementia, neuropsychiatric syndromes
  - Rarely PML
- CD4 < 200 – differential expands
Immune Status

• CD4 count > 500 – “normal host”*
• CD4 200-500
• **CD4 < 200 – differential expands**
  – Moderate: Toxoplasma, cryptococcus, PML
  – Severe: PCNSL, CMV
CD4 count over time showing various conditions:
- GBS
- Polymyositis
- Chronic HIV meningitis
- TB, syphilis, VZV
- Dementia
- Neuropathy
- Toxoplasmosis, Cryptococcosis
- PML, PCNSL
- CMV encephalitis

Infection occurs at time zero, with conditions developing over 10 years.
Viral Status/Prophylaxis

- High viral load, even with preserved CD4 count, carries increased risk for neurological complications
- ART effectiveness and timing changes differential, including IRIS
- Prophylaxis with TMP-SMX lowers risk of toxoplasmosis
- Prophylaxis with fluconazole lowers risk cryptococcal meningitis (but not mortality)\(^1\)

\(^1\)Parkes-Ratanshi 2009
Clinical Localization

Localization within nervous system

• Meninges
• Diffuse brain lesions
• Focal brain lesions
• Spinal cord
• Nerve root and peripheral nerve
• Muscle
Clinical Localization

Localization within nervous system

- *Meninges*
- *Diffuse brain lesions*
- *Focal brain lesions*
- Spinal cord
- Nerve root and peripheral nerve
- Muscle
Clinical Localization

Localization within nervous system

• **Meninges**
  – Headache, nuchal rigidity, photophobia, confusion (may overlap with encephalitis)

• Diffuse brain lesions

• Focal brain lesions
Clinical Localization

Localization within nervous system

- Meninges
- *Diffuse brain lesions*
  - Encephalopathy, dementia, neuro-psychiatric
- Focal brain lesions
Clinical Localization

Localization within nervous system

- Meninges
- Diffuse brain lesions
- **Focal brain lesions**
  - Hemiparesis, ataxia, aphasia, visual field deficit, seizure
Clinical Localization

Localization within nervous system

- Meninges
- Diffuse brain lesions
- Focal brain lesions

- **In practice, there is often overlap of syndromes (meningoencephalitis)**
  - Seizures, altered mental status, CSF abnormalities may be seen in each syndrome
Etiology

• Meninges: *acute*
  – Aseptic meningitis
  – Pyogenic
  – HIV seroconversion
  – HSV-2, VZV, neurosyphilis
  – HIV rebound
  – HIV IRIS
Etiology

- Meninges: *subacute*
  - Cryptococcal meningitis
  - Tuberculous meningitis
  - Other fungal (histoplasma, coccidioides)
  - Neurosyphilis
  - Neoplastic (lymphomatous)
  - HIV (usu asymptomatic)
Etiology

- Diffuse brain lesions: acute
  - HIV encephalitis
  - CMV encephalitis
  - VZV encephalitis
  - Post-infectious encephalitis (ADEM)
  - Toxic (efavirenz, illicit drugs, EtOH)
  - Neurosyphilis
  - Cerebral malaria (HIV or non-HIV)
Etiology

• Diffuse brain lesions: *subacute*
  – HIV-associated dementia
  – HIV rebound meningoencephalitis
  – Neuro-IRIS
  – Neurosyphilis
Etiology

• Focal brain lesions *with mass effect*
  – Toxoplasmic encephalitis
  – Primary CNS lymphoma
  – Fungal abscess (crypto, aspergillus)
  – Bacterial abscess (including atypical organisms, e.g. Nocardia)
  – Tuberculosis
  – Neurocysticercosis
Etiology

• Focal brain lesions *without mass effect*
  – PML (except in IRIS, when inflammation can cause mild mass effect and enhancement on imaging)
  – HIV-associated stroke (usually no mass effect except at ~4 days w/peak cytotoxic edema)
  – Neurosyphilis (including optic neuritis)
Diagnostic Studies: non-CNS

- Serum CrAg 98% sens, 99% spec
  - May precede clinical symptoms by 22 days
- Serum Toxo IgG 84-93% sensitive
- Malarial smear
- Chest x-ray abnormal in up to 50% of patients with CNS TB
## Diagnostic Studies: CSF Profiles

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<thead>
<tr>
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<th>Aseptic</th>
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<tbody>
<tr>
<td>Opening Pressure (mmH₂O)</td>
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<td>Normal to elevated</td>
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<td>Glucose (mg/dL)</td>
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<tr>
<td>Protein (mg/dL)</td>
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<td>WBC (cells/mm³)</td>
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<tr>
<td>Culture</td>
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<td>≤70%</td>
<td>Gold standard</td>
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<tr>
<td>Other</td>
<td>Latex agglutination+ ~ 60-100%</td>
<td>PCR+ ~60%, IGRA+ ~ 50%</td>
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Diagnostic Studies: CSF Clues

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- High protein: TB with CSF block
- All lymphocytes: aseptic after 24 hours, TB, LCMV
- Elevated PMNs: bacterial, early TB, HSV
- Hemorrhagic: HSV, other rare viruses (Hantavirus, Ebola, Dengue), and ameba
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<td>Aseptic meningitis &gt; 24h, TB, LCMV</td>
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### Diagnostic Studies: CSF PCR

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<th>HSV</th>
<th>VZV</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Var (74-92%)</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Var (70-80%)</td>
<td>H (94-100%)</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
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<th>TB</th>
<th>EBV/PCNSL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>L (44-81%)</td>
<td>L (60%)</td>
<td>H (80-98%)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>H (100%)</td>
<td>H</td>
<td>H (88-100%)</td>
</tr>
</tbody>
</table>
Resource-Limited CNS Infection

- Mortality much higher than in resource-rich countries
- Definitive diagnosis elusive
- Presentation delayed
- LP often delayed
- Treatment delayed
Resource-Limited CNS Infection

• Reasons for LP delay
  – No equipment available
  – Limited laboratory hours
  – Patient response to empiric therapy prior to LP
  – Patient mortality prior to LP
  – Patient refusal
  – Concern for herniation
Resource-Limited CNS Infection

- Reasons for treatment delay
  - Limitations on empiric use of antimicrobials
  - Overlap of syndromes
  - Delay in presentation
  - Delay in diagnosis
Resource-Limited CNS Infection: Proposed Algorithm

- Immediate CXR and malarial smear
- HIV +/-
- CRAG +/-
- Empiric Rx based on CSF profile
- Concurrent adjunct studies: toxo IgG (focal signs), VDRL, lymph node biopsy (lymphadenopathy), CSF AFB & mycobacterial culture, head CT, transfer
- Reassess based on response

Trachtenberg 2007
Suspected Central Nervous System Infection.
1. If focal neurological deficit, mental status change or recent seizure is present, then consider a CT scan prior to lumbar puncture if possible. If a CT scan is not available, then consider the risks versus benefits of the LP, and make a decision with the patient or family members.
2. CXR and malaria smear (if applicable) on admission if possible.

**HIV status** by rapid test or suggestive physical exam: thrush, wasting, Kaposi's sarcoma, etc.

**Positive**

Cryptococcus by India ink of CSF or serum or CSF antigen.

**Negative**

Lumbar puncture: If this will be delayed more than 30 minutes, treat for bacterial meningitis by local or national standard of care or guidelines.

CSF: cell count, glucose, Gram stain. If possible consider adding CSF: protein, culture, AFB stain, VDRL, cryptococcal antigen (if not already done).

**Positive**

Treat for Cryptococcus by local or national standard of care or guidelines.

Therapeutic lumbar puncture for signs of increased intracranial pressure.

**Bacterial meningitis:** neutrophilic predominant, low glucose. Treat by local or national standard of care or guidelines.

**Tuberculous meningitis:** lymphocytic predominant, low glucose. Treat by local or national standard of care or guidelines. CXR should be taken if this has not already been done.

**Viral meningencephalitis:** lymphocytic predominant, normal glucose. Treat by local or national standard of care or guidelines.

**Diagnostic suggestions:**
1. Repeat CSF analysis. If glucose is still low consider bactericidal failure or misdiagnosis (i.e., Tb instead of BM).
2. CXR if not already done.
3. Toxoplasma IgG if HIV positive and focal deficit or encephalitis.
4. CSF culture and/or AFB stain.
5. Lymph node biopsy if lymphadenopathy is present.
6. CT scan.
7. VDRL (CSF and/or serum).
8. Transfer to referral hospital if possible.

**Improvement within 24–48 hours or confirmed diagnosis?**

- Yes → Continue treatment
- No
27M with advanced HIV (CD4 17, VL 63K) not on ART presents with vomiting, HA, neck pain, and mental status change worsening over weeks. Taking TMP-SMX and azithromycin.

**PE:** T 39, poorly responsive, CN intact, moving all 4 equally (GCS 11).

**Labs:** Toxo IgG+; CMV Ag -, CMV Ab + CXR clear; head CT no mass lesions, edema, or abnormal enhancement.
Case 1

27M with advanced HIV (CD4 17, VL 63K) not on ART presents with vomiting, HA, neck pain, and mental status change worsening over weeks. Taking TMP-SMX and azithromycin.

PE: T 39, poorly responsive, CN intact, moving all 4 equally (GCS 11).

Labs: Toxo IgG+; CMV Ag -, CMV Ab +

CXR clear; head CT no mass lesions, edema, or abnormal enhancement
Case 1

**LP**: opening pressure > 500 mmH2O; glucose 45, protein 77, WBC 91 (50%N, 17%L, 28%M); India ink stain shows encapsulated yeast; cryptococcal Ag+ at 1:500K
Meningitis

Differential:

- In pts with CD4<200: CM, TBM, BM, and syphilis
- **CM** usu occurs when CD4<100
- CM is often AIDS defining illness
- Typically symptoms progress over 1-2 weeks before presentation
- Most common symptoms are fever, malaise, and headache
Meningitis

Differential:

- Like CM, **TBM** is more subacute than BM
- TBM often associated with cranial nerve palsies
- Prior or concurrent pulmonary TB
- CSF glucose classically low
- Protein may be extremely high
- Initial worsening may occur with TB treatment and/or with ART (IRIS)
Meningitis

Differential:

• **BM** more often acute, higher WBC count, PMN predominance

• Associated stroke should suggest meningovascular syphilis (or TBM)

• HIV “aseptic” meningitis occurs at seroconversion

• HIV viral breakthrough (rebound) occurs with ART failure or non-adherence
Meningitis

Differential considerations:

- HIV pts are susceptible to the same causes of meningitis as the normal population, especially where bacterial meningitis is endemic.
- In advanced HIV, symptoms typical for meningitis may be mild due to lack of appropriate inflammatory response; CSF may be bland or minimally inflamed.
Meningitis

Diagnosis:

- Blood cultures; serum CrAg, RPR/TPPA
- CXR to look for pulmonary Tb
- LP for opening pressure (typically high in CM); glucose, protein, WBC with differential; bacterial and fungal cultures, India ink, CrAg, AFB and mycobacterial culture
Meningitis

Diagnosis:

- CT is helpful as many pts with advanced HIV have multiple infections
- Presence of mass lesions would change differential
- Mass lesions causing downward pressure increase risk for herniation with LP
- In practice, CT is limited in resource-limited settings
Cryptococcal Meningitis

Treatment:

• Induction: IV amphotericin 0.7-1 mg/kg/d IV plus flucytosine 25 mg/kg PO q6 ≥ 14d

• Alternative: amphotericin B lipid formulation 4 mg/kg/d IV plus flucytosine 25 mg/kg PO q6 ≥ 14d

• Consolidation: fluconazole 400 mg daily ≥ 8wks (or until CSF sterile)

• Maintenance: fluconazole 200 mg daily
Cryptococcal Meningitis

Alternative Treatment (less effective):

- Induction: IV amphotericin 0.7-1 mg/kg/d IV x 14d
- Induction: IV amphotericin 0.7-1 mg/kg/d IV plus fluconazole 800mg daily x 14d
- Induction: Fluconazole 1200mg daily + flucytosine 100 mg/kg daily for 6 weeks
- Induction: Fluconazole >1200mg daily for 10-12 weeks
- Maintenance: fluconazole 200 mg daily
Cryptococcal Meningitis

Treatment:
- May need repeat LP to relieve ICP
- No benefit to acetazolamide
- IRIS is common in CM
- Initiate ART 2 weeks after starting crypto-specific therapy to avoid confusion over medication toxicity*
- Can consider discontinuing fluconazole after 12 months at CD4>100 but often must prophylax indefinitely
Case 2

38M with HIV (CD4 31, VL 112K) presents with 1 day of N/V followed by generalized tonic clonic seizure. Non-compliant with TMP-SMX prophylaxis.

PE: afebrile, white plaques on tongue, mild right hemiparesis.
Case 2

38M with HIV (CD4 31, VL 112K) presents with 1 day of N/V followed by generalized tonic clonic seizure. Non-compliant with TMP-SMX prophylaxis.

PE: afebrile, white plaques on tongue, mild right hemiparesis.
Focal Brain Lesion

Differential:

- *Toxoplasma gondii*
- Primary central nervous system lymphoma (PCNSL)
- Progressive multifocal leukoencephalopathy (PML)
- Tuberculosis
- Cysticercosis
- Bacterial abscess
Focal Brain Lesion

**Differential:**

- All commonly present with fever, headache, confusion
- Symptoms in toxo generally develop rapidly over days, as opposed to PCNSL (over a few weeks) and PML (over weeks to months)
- Focal tuberculous lesions can present similarly over days to weeks
- NCC often presents first with seizure
Focal Brain Lesion

**Diagnosis:**

- Most patients with toxo are serum IgG positive, so a negative serology makes toxo doubtful (7-16% false negative)
- If patient is adherent to TMP-SMX prophylaxis for PCP, toxo is less likely.
- Gold standard for diagnosis is brain biopsy
Focal Brain Lesion

Diagnosis:

- Therapeutic trial.
- Approximately 70-80% of pts have clinical and radiographic response.
- Vast majority have at least 50% improvement from baseline at 14 days of treatment.
- If no improvement within three weeks, other diagnoses should be pursued and treated.
Case 2

Diagnostic studies:

• Serum toxo IgG+, IgM-
• Chest X-ray clear
• CSF normal; EBV and JCV PCR negative
• Empiric toxo treatment lead to rapid clinical and radiographic improvement
• Continued on anti-epileptic for one year and then tapered off
Case 2

Pre-Rx

Post-Rx
Toxoplasmosis

Treatment:

- Pyrimethamine 200 mg PO x1, then 50 mg (for <60 kg body wt) or 75 mg (for >60 kg body wt) PO qd
- Plus folinic acid 10 mg PO qd
- Plus sulfadiazine 1000 mg (for <60 kg body wt) or 1500 mg (for >60 kg body wt) PO q6h
- Treat for 6-8 weeks until good response
Toxoplasmosis

Treatment:

- Alternative to sulfadiazine: Clindamycin 600 mg IV or PO q6h
- Suppressive therapy: Pyrimethamine 50 mg PO qd + sulfadiazine 0.5-1 g PO q6h + folinic acid 10 mg PO daily
- May be discontinued when CD4 $>$ 200 for at least 6 months
- Recovery is variable; may have lifelong epilepsy
Case 3

52M with HIV (CD4 130, VL 803K) presents with 5 weeks of right arm clumsiness, unsteady gait. Not on TMP-SMX.

**PE:** afebrile and well-appearing, right upper extremity dysmetria.

**Labs:** toxo IgG (-)

**CXR:** clear

**CSF:** OP, glucose, protein normal; 10 WBC (lymphocyte predominance); CrAG (-); AFB, fungal & mycobacterial cultures (-)
Case 3

52M with HIV (CD4 130, VL 803K) presents with 5 weeks of right arm clumsiness, unsteady gait. Not on TMP-SMX.

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Case 3
Case 3
Focal Brain Lesion

Differential:

• Subacute (weeks to months) onset of focal neurological symptoms
• Without contrast-enhanced imaging, differential remains broad
• Toxo IgG (-), moderate CD4 count make toxo and PCNSL less likely
• PML, PCNSL, tuberculous abscess or tuberculoma, bacterial abscess all possible
Focal Brain Lesion

**Diagnosis:**

- For PML, CSF JCV PCR 72-92% sensitive and 92-100% specific in the pre-ART era (less sensitive w/cART).
- Diagnosis in resource-rich countries usually based on clinical and radiographic patterns combined with CSF PCR studies and (lack of) response to other treatments.
Focal Brain Lesion

Treatment:

• ART is only effective therapy for PML (or PCNSL)

• Survival in PML with ART has improved from 10 to 50% in resource-rich countries

• PML-IRIS may have enhancement, edema

• Steroids controversial but may be considered for severe cases
Case 3

The patient is started on cART and TMP-SMX. Over 2-4 weeks he develops worsening symptoms.

**PE**: new brainstem signs.

**Labs**: stable CD4 count, decrease in VL from 803K to 4K.

Repeat MRI w/worsening, enhancement

Treated with prednisone 60mg tapered over 2 weeks, with stabilization but poor recovery.
Case 3
Case 4

64 RHM h/o HIV 3 years prior in setting of PCP with initial CD4 in 30s and viral load 180K; wild-type HIV genotype. Started emtricitabine/tenofovir/efavirenz 2 months later. One month later he developed behavioral changes and had GTC seizure. **MRI** showed bilateral moderate atrophy and confluent subcortical T2 hyperintensities without enhancement or mass effect:
Case 4
Case 4

**Serum**: CD4 had risen from 34 to 115; viral load had dropped from 180K to 9K.

**CSF**: glucose 72, protein 140, WBC 4 (65L, 25M); JCV, VDRL, mycobacterial culture neg; **CSF HIV viral load > 750K**.

Uncontrolled CNS viral replication vs. IRIS. ART changed to efavirenz + lamivudine/zidovudine for better CNS penetration, later changed to atazanavir/ritonavir, lamivudine/ zidovudine and tenofovir.
Case 4

He continued to have behavioral changes including apathy, requiring skilled nursing facility care for about a year but then he moved into a supported living facility with his own apartment.

His serum viral load was undetectable and was doing well for about a year.
Case 4

Two years after diagnosis he gradually developed poor hygiene and had several falls. He reported a "limp" in his left leg and endorsed some "slowing down" and "not taking care of myself." He also had incontinence and weight loss and was admitted to the hospital.

PE: frontal dysfunction (grasp, Meyerson, verbal fluency), bradykinesia, rigidity, hyper-reflexia, and marked gait instability.
Case 4
Diffuse brain lesion

Differential: subacute to chronic mental status changes in a patient with HIV

- HIV-associated dementia (HAD)
- Neurosyphilis
- HIV rebound meningoencephalitis
- Neuro-IRIS
- Cytomegalovirus (CMV) encephalitis
- PML (usu with focal deficits)
Diffuse brain lesion

**CMV Clinical:**

- CMV encephalitis occurs with profound immunosuppression (usu CD4 < 50)
- Can manifest with progressive dementia similar to HAD, but is a rare cause of dementia
- Imaging may show inflammation around the ventricles and meninges, but this is not specific
CMV Diagnosis:

- PCR for CMV DNA from the CSF is both sensitive and specific.
- CMV also infects the retina (retinitis), ventricles (ventriculitis), spinal cord (myelitis), nerve roots (lumbosacral polyradiculopathy), or peripheral nerves (mononeuritis multiplex).
HIV-associated dementia:

- Subacute to chronic subcortical dementia
- Early cognitive deficits in short-term memory, mental slowing, reading and comprehension problems, concentration problems, and apathy.
HIV-associated dementia:

- Early motor deficits are often subclinical but can be detected on examination as slowing of rapid movements.
- Later patients have a more diffuse dementia, frontal release signs, and more obvious extra-pyramidal symptoms.
HIV-associated dementia:

- Diagnosis of exclusion.
- Minimal focal findings compared to PML.
- CSF findings are nonspecific, but often mild lymphocytic pleiocytosis; HIV RNA viral load is often detectable and may even be elevated above that in the blood; with cART, however, CSF viral load correlates poorly with severity of dementia.
HAD Diagnosis:

- Neuropsychological testing can help distinguish HAD from other causes of dementia, which is becoming more important as patients are living longer and are thus at risk for AD and vascular dementia.

- In Uganda, older age and lower CD4 count were associated with increased risk for HAD.
Case 4

**Serum:** viral load < 50, macrocytic anemia. HIV genotype: TAM (41L) [6-fold decreased potency of zidovudine].

**CSF:** glucose 79, protein 76, WBC 4 (90L); JCV neg; HIV viral load 5,270; CSF HIV genotype same as serum.
Case 4

ART regimen ultimately changed to lopinavir/ritonavir, emtricitabine/tenofovir, zidovudine; nevirapine later added for optimal “Neuro-HAART”. Donepezil added.

As of last visit, his mental status was improved (no apathy, normal verbal fluency, continued grasp), improved speed of movements, and significant improvement in gait. Viral load remained < 50 although CD4 still 160s. MRI was stable.
Neuro-ART

• Incidence of HIV-associated dementia (as well as toxo and PCNSL) has decreased with effective ART
• Even with good immune and viral response, however, neurocognitive impairment is common
• Emerging evidence that early ART is more neuro-protective
Neuro-ART

<table>
<thead>
<tr>
<th>Year</th>
<th>1992</th>
<th>2002</th>
<th>2003</th>
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</thead>
<tbody>
<tr>
<td># per 100 persons living with AIDS</td>
<td>3.71</td>
<td>0.34</td>
<td>0.24</td>
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</table>

Fig. 1. Incidence of central nervous system diagnoses among AIDS cases 1991–2003. 

- dementia; 
- toxoplasmosis; 
- cryptococcosis; 
- brain lymphoma; 
- progressive multifocal leukoencephalopathy.

*Incidence per 100 individuals living with AIDS per year.

*Likelihood ratio for trend, $P < 0.001$ for all central nervous system diagnoses.
HAART becomes widespread in 1995
Neuro-ART

• Weight of evidence suggests that control of HIV in periphery = control of HIV in CNS
• To date, no convincing and reproducible evidence that CNS-penetration matters if regimen is effective in periphery
CNS Penetration Effectiveness Score

- Classification of ARVs into 3 categories
  - 0 = low penetration
    - Chemical properties with poor CNS penetration
    - Unmeasurable in CSF or IC\(_{50}\) in CSF is low
    - Clinical data for poor CNS penetration
  - 0.5 = medium penetration
  - 1 = high penetration

- cART CPE: sum of CPE for ARVs in regimen

Letendre 2008
<table>
<thead>
<tr>
<th>ART CNS Penetration Effectiveness Scores</th>
<th>Higher (1)</th>
<th>Intermediate (0.5)</th>
<th>Lower (0)</th>
</tr>
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<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td>Abacavir</td>
<td>Emtricitabine</td>
<td>Didanosine</td>
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<tr>
<td></td>
<td>Zidovudine</td>
<td>Lamivudine</td>
<td>Tenofovir</td>
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<tr>
<td></td>
<td></td>
<td>Stavudine</td>
<td>Zalcitabine</td>
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<tr>
<td><strong>NNRTIs</strong></td>
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<td>Efavirenz</td>
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<td>Nevirapine</td>
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<td>Atazanavir</td>
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<td>Enfuvirtide</td>
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<tr>
<td><strong>Integrase Inhibitor</strong></td>
<td>Raltegravir</td>
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</table>

Adapted from Letendre 2009
Neuro-ART

- In cross-sectional study, higher CPE associated with lower CSH viral load
- Clinical outcomes have been mixed
  - Some evidence of benefit in cognitive function
  - Some evidence of no difference
  - Most recently some evidence of *worsening* cognitive function
- Limited by small observational studies, incomplete toxicity data, poor understanding of CSF to CNS relationship
Acknowledgements

“We must try to form and strengthen synapses with other neurons (medical colleagues) as much as possible, to make the neural network stronger.”

-Nagagopal Venna
Case 2b

67M with a history of leukopenia dating to at least 1989 presents with several weeks of progressive confusion and gait problems. PE: encephalopathic, left arm weakness. MRI...
Case 2b
Case 2b

Diagnosis:

- Clinical course of subacute focal deficits
- MRI characteristic of PCNSL (mass effect, patchy ring enhancement, cross corpus callosum)
- CSF cytology insensitive but highly specific
- CSF EBV PCR 80-98% sens, 88-100% spec
Diagnosis:

- Metabolic imaging (SPECT, PET) suggestive but not reliable
- Gold standard remains biopsy
- Should consider when Toxo IgG neg, no response to Toxo Rx or presents while on TMP-SMX
Case 2b

Treatment:

- No standard approach
- Surgery offers no benefit
- Radiation reduces burden but is often poorly tolerated
- High dose methotrexate may be used but may also be limited by profound immunosuppression and renal function
- cART has improved outcomes and may sensitize to radiation
Case 5

49M with recent HIV dx, pulmonary and cardiac Tb diagnosed by retroperitoneal biopsy, complicated by inflammatory myocarditis w/4 drug Rx, recently started on ART now presents with left arm weakness. Treated with TMP-SMX prophylaxis (serum levels of TMP-SMX low due to Tb meds).

PE: left face and distal>proximal arm weakness
Case 5

49M with recent HIV dx, pulmonary and cardiac **Tb** diagnosed by retroperitoneal biopsy, **complicated by inflammatory myocarditis w/4 drug Rx, recently started on ART** now presents with left arm weakness. Treated with **TMP-SMX prophylaxis** (serum levels of TMP-SMX low due to Tb meds).

PE: *left face and distal > proximal arm weakness*
Case 5

Labs: CD4 44, viral load 961K, toxoplasma IgM-/IgG+, CMV IgG+, Urine histo Ag -. 

CSF: (for ? seizure) normal protein and glucose with 3 WBC. CSF AFB and mycobacterial culture, EBV and CMV PCR, and crypto Ag were negative. 

Baseline MRI (for ? seizure): right pre/post-central T2 lesion, no enhancement.
Case 5

Follow-up MRI at time of neurological symptoms:
Case 5

Due to concern for toxo, bactrim changed to treatment dose sulfadiazine and pyrimethamine. LP was deferred due to concern for mass effect. Given his concurrent use of rifabutin and bactrim, serum sulfamethoxazole level was checked and was low.

Baseline eval had shown serum toxo IgG+, CSF EBV-, and systemic Tb as above.
Case 5

The plan was to give toxo Rx for two weeks, then reassess for improvement. Due to the development of continuous partial seizures, however, dexamethasone and antiepileptics were given. He improved over several days with increased strength in his left arm but developed myoclonus of the left wrist. He was continued on toxo and Tb treatment with slow steroid taper. Follow-up MRI showed…
CNS tuberculosis vs. toxoplasmosis IRIS?

- Significant edema and previous Tb-related inflammation suggest CNS Tb IRIS
- Low sulfa level, + serum toxo IgG, and quick response could support toxoplasmosis
- While toxoplasmosis is the most common focal CNS OI in HIV, there are few reports of Toxo-IRIS (possibly because it resolves quickly with treatment)