HIV and Neurological complications

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1981

Pneumocystis pneumonia and Kaposi’s sarcoma reported in 26 men in NYC and California.
Discovery of HIV-1

- 2 French researchers discovered HIV in 1983; both received the Nobel Prize in 2008

**Discovery of HIV**

Luc Montagnier  
Pasteur Institute, France  
HIV-1 1983; HIV-2 1986

Françoise Barré-Sinoussi  
* 2008 Nobel Prize laureates
HIV

What is the prevalence of HIV in males >13 years in the United States?

1. 1 out of 150
2. 1 out of 450
3. 1 out of 10000
4. 1 out of 27000
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The estimated prevalence of HIV infection among persons > 13 years in the US-0.4%

- Males- 0.7% (1/150 male Americans)
- Females-0.2%

Columbia, SC is # 6 in the country for AIDS cases per capita
End the HIV Epidemic: 10 year initiative

Federal initiative will focus efforts in 48 counties, Washington, DC, San Juan and seven states with substantial rural HIV burden:

1. **Diagnose**: as early as possible

2. **Treat**: HIV rapidly

3. **Prevent**: including HIV Pre-Exposure Prophylaxis (PrEP) and syringe service programs (SSPs).

4. **Respond**: quickly to outbreaks

**Geographic locations**: The 48 counties, plus Washington, DC, and San Juan, PR, where >50% of HIV diagnoses occurred in 2016 and 2017, and an additional seven states with a substantial number of HIV diagnoses in rural areas. [View the list](PDF - 44 kb)
Recommendations for Initiating ART for an HIV infected person

- ART (Antiretroviral therapy or HIV medications) is recommended for all HIV-infected individuals to reduce the risk of disease progression.
- Effective ART reduces transmission to almost “0”
- HIV is easier to treat than Diabetes, COPD, CHF
- Undetectable = Untransmissible
HIV: Single Tablet Regimens

- Atripla
- Complera
- Genvoya
- Juluca
- Triumeq
- Odefsey
- Biktarvy
Mental disorders seen with HIV

Mental disorders associated with HIV:
- Delirium
- Minor cognitive-motor disorder (MCMD)
- HIV-associated dementia
- Major depression
- Bipolar disorder (including AIDS mania)
- Schizophrenia
- Substance abuse or dependence
- Posttraumatic stress disorder (PTSD)
- HIV disseminates to the CNS early
- ART has been associated with a marked decrease in the incidence of more severe neurocognitive deficits
- Three broad categories of neurocognitive disorders
  - Asymptomatic neurocognitive impairment (ANI)
    - There is continued prevalence of milder cognitive impairment
    - Biomarker evidence of mild immune activation within the CNS even after years of durable viral suppression
  - HIV-associated mild neurocognitive disorder (MND)
  - HIV-associated dementia (HAD)
HIV Dementia/Encephalopathy

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor Concentration</td>
<td>Slowness of thought</td>
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<tr>
<td></td>
<td>Forgetfulness</td>
<td>Executive cognitive dysfunction</td>
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<tr>
<td>Motor</td>
<td>Gait instability</td>
<td>Saccadic ocular pursuit movements</td>
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<tr>
<td></td>
<td>Urinary urgency/hesitation</td>
<td>Slowing of repetitive movements</td>
</tr>
<tr>
<td>Behavior</td>
<td>Loss of interest in friends, hobbies</td>
<td>Apathy</td>
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HIV and opportunistic infections

- The most important factor is the degree of immunosuppression in the host.
- Patients with CD4 cell counts >500/microL
  - benign and malignant brain tumors and metastases
- Patients with CD4 cell 200 - 500/microL
  - HIV-associated cognitive and motor disorders are common, but usually do not present with focal lesions.
- Patients with CD4 cell < 200/microL
  - CNS mass lesions
  - Opportunistic infections
  - AIDS-associated tumors
## CSF Characteristics of HIV-associated OIs

<table>
<thead>
<tr>
<th></th>
<th>White-blood-cell count</th>
<th>Glucose concentration</th>
<th>Protein concentration</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmic encephalitis</td>
<td>Normal or increased lymphocytes</td>
<td>Decreased or normal</td>
<td>Normal or increased</td>
<td>Toxoplasma gondii PCR nearly 100% specific and 50–80% sensitive</td>
</tr>
<tr>
<td>PML</td>
<td>Normal, rarely increased lymphocytes</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>JC-virus PCR sensitivity variable at 50–90%, but specificity 90–100%</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>Normal or increased lymphocytes</td>
<td>Normal</td>
<td>Normal</td>
<td>Epstein-Barr virus PCR nearly 100% sensitive and about 50% specific</td>
</tr>
<tr>
<td>Cytomegalovirus encephalitis</td>
<td>Normal, rarely increased neutrophils</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>PCR &gt;90% sensitive and specific and &lt;25% culture positive</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>Normal, rarely increased lymphocytes</td>
<td>Decreased or normal</td>
<td>Normal or increased</td>
<td>Opening pressure frequently raised; India ink stain 75% sensitive; CSF cryptococcal antigen sensitivity 92% and specificity 83%; high CSF antigen titre associated with poor prognosis, but change of titre with treatment has little correlation with prognosis</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>Increased lymphocytes</td>
<td>Decreased</td>
<td>Normal or increased</td>
<td>Mycobacterium tuberculosis culture has variable sensitivity, but use of microscopy for acid-fast bacilli and CSF NAAT can increase sensitivity to &gt;80%</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Usually increased lymphocytes</td>
<td>Normal or increased</td>
<td>Increased</td>
<td>CSF PCR sensitivity 100%, specificity 99.6%</td>
</tr>
</tbody>
</table>

PML = progressive multifocal leukoencephalopathy. NAAT = nucleic-acid amplification test.

Table 4: CSF characteristics of HIV-associated CNS opportunistic infections
Toxoplasma gondii

- Obligate intracellular parasite
- Forms cysts in mammalian tissues
  - Transmission due to ingestion of food or water contaminated with oocysts
  - eating undercooked or raw meat
  - via transplacental transfer
- Prevalence
  - 11% in the United States
  - 50% to 80% in Latin American & African countries
Cerebral toxoplasmosis

- **Presentation**
  - Fever, altered sensorium, focal neurologic deficits (80%), seizures (20%)

- **Diagnosis**
  - Cerebrospinal fluid may be normal
  - Best “screening” test for cerebral toxoplasmosis in a patient with AIDS and ring enhancing lesions:
    - **Serum Toxoplasma IgG**
      - Positive in > 95% AIDS
        - Higher risk for titers \( \geq 150 \text{ IU/ml} \).
    - CSF Toxoplasma PCR
Treatment for toxoplasma encephalitis (cerebral toxoplasmosis)

- **Therapy**
  - Pyrimethamine plus sulfadiazine plus leucovorin
    - **Pyrimethamine**
      - penetrates the brain parenchyma efficiently
      - Pyrimethamine toxicities: rash, nausea, and bone marrow suppression
      - Can be reversed by increasing the leucovorin dose
    - **Leucovorin**
      - reduces the likelihood of pyrimethamine toxicity
  - **Sulfadiazine toxicities**
    - rash, fever, leukopenia, hepatitis, nausea, diarrhea, renal insufficiency, and crystalluria.
Monitoring

- Clinical response to empirical treatment in 14 days
- MRI usually better in 2-4 weeks
- Acute therapy for TE
  - At least 6 weeks
- Maintenance therapy till CD4 > 100
- Primary Prophylaxis
  - *Toxoplasma*-seropositive patients (Toxo IgG +) and CD4 counts <100 cells/µL should receive prophylaxis against TE
  - Primary Prophylaxis can be safely discontinued in patients with CD4 100-200 cells/mm³ and HIV plasma RNA < 400
Case

- 33 year male.
- AIDS, CD4- 40, Viral Load 102,000
  - Presents with 3 week H/O malaise, headaches, fever.
  - Drove to clinic
- On exam
  - T-99.5, Mild confusion, oral thrush, no neck stiffness or cranial N palsies
  - On occasional Bactrim for PCP prophylaxis
- Next steps??
- Broad Differential
  - Anemia, uremia, electrolyte abnormalities,
  - Drug toxicity (recreational) or Bactrim
  - Other causes of encephalopathy/encephalitis
  - PML
  - Cryptococcal meningo-encephalitis
  - Disseminate Mycobacterium avium
- Labs:
  - CBC, CMP, Toxo IgG, Serum Cryptococcal Antigen, RPR
Case

Similar case
Patient has AIDS and
Cryptococcal Meningoencephalitis

- Cryptococcal meningitis is the largest single cause of neurological mortality in HIV patients worldwide
  - Mortality rates of 25–50%
- The yeast is inhaled and then disseminates hematogenously and then crosses the blood brain barrier
Cryptococcus neoformans

Encapsulated yeast
- Normally found in soil and pigeon droppings
- Causes disease by aerosolization and inhalation
- May be asymptomatic
  - Colonize the respiratory tract in immunocompetent

Cryptococcus on the skin
C. neoformans meningoencephalitis

- Subacute presentation over several days or weeks
- Clinical features
  - Fever
  - Headache
  - Nausea
  - Mild – moderate Meningismus
  - Altered mental status
- CSF
  - Raised opening pressure
  - Minimally raised protein and WBC
  - Positive CSF cryptococcal Ag (98%)
- Blood
  - Positive cultures
  - Positive serum cryptococcal Ag (98%)
Management of cryptococcal meningoencephalitis includes all of the following:

- Antifungal therapy.
- Control of intracranial pressure
  - Can lead to blindness, herniation, persistent headaches, and/or neuropathies if left untreated.

- ART
  - antiretroviral therapy (ART) should be started between 2 and 10 weeks after antifungal therapy has
Management of increased intracranial pressure

- Increased ICP in patients with cryptococcal meningoencephalitis should be managed aggressively to decrease mortality
- LP should be performed to reduce the opening pressure to <20 cm CSF
  - In symptomatic patients with extremely high CSF pressures (eg, ≥30 cm CSF), the goal is to reduce the ICP by 50%
  - Daily LPs
  - Occasionally Lumbar Drain
Outcomes for 161 patients with AIDS and cryptococcal meningitis after 2 weeks of therapy, according to the change in their CSF opening pressure at follow-up lumbar puncture.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CSF opening pressure</th>
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|                       | Decrease >10 mm  
|                       |  (n = 81)           |
|                       | No change            |
|                       | (n = 24)             |
|                       | Increase >10 mm    |
|                       |  (n = 56)            |
| Clinical failure      | 2                    |
| Mycological failure   | 33                   |
|                       | 4                    |
|                       | 20^a                 |
|                       | 21                   |
|                       | 43                   |

NOTE. Data are % of patients. Data are limited to 161 patients who had measurements of opening pressure at baseline and at 2 weeks. Early deaths may bias this comparison. Mycologic failure is defined as positive culture of CSF at 2 weeks of treatment. Data are not related to pressure quartiles at initial lumbar puncture but to change in pressure during therapy.

^a P < .001.
Antifungal therapy

- Induction therapy X 2 weeks
  - IV Liposomal Amphotericin B plus PO flucytosine
    - Liposomal amphotericin B-3 to 4 mg/kg/day
- Followed by consolidative therapy X 8 weeks
  - Fluconazole
    - 400 mg -800 mg PO daily
      Maintenance therapy- Fluconazole 200 mg PO daily till CD4 reconstitutes and > 100
COAT Trial- timing of ART with CM

- South Africa and Uganda
- assigned study participants to undergo
  - earlier ART initiation (1 to 2 weeks after diagnosis)
  - Or deferred ART initiation (5 weeks after diagnosis)
- Rx: Amphotericin B and fluconazole.

- Results:
  - 26-week mortality
    - Earlier ART -45% [40 of 88 patients]
    - Deferred ART-30% [27 of 89 patients]
  - Excess deaths associated with earlier ART initiation occurred 2 to 5 weeks after diagnosis
  - Mortality highest among patients with CSF WBC < 5
Primary CNS Lymphoma

- Primary central nervous system lymphoma (PCNSL)
  - Confusion, lethargy, memory loss, hemiparesis, aphasia, seizures
  - Fever, night sweats, and weight loss, occur in > 80 percent of patients.

- Radiological findings
  - Single or multiple lesions
  - Some enhancement
  - Involve the corpus callosum or the periventricular areas
  - > 4 cm in size are more likely to be lymphoma.
PCNS Lymphoma

- Epstein-Barr virus infects over 90% of the world
- EBV DNA in CSF is used as a marker of HIV-associated primary central nervous system lymphoma
  - Using a cut-off of 10,000 copies/ml improved the specificity and positive predictive value (PPV)

- Lumbar puncture
  - Should be performed in all patients
    - unless contraindicated by mass effect or midline shift
  - CSF studies
    - Routine cell count, differential, glucose, total protein, and culture, cytology, flow cytometry, EBV PCR, JC virus PCR.

Cryptococcus pneumonia in a patient with End Stage Liver Disease

Cerebral Cryptococcomia in a non-HIV patient
Progressive multifocal leukoencephalopathy (PML)

- Caused by the polyoma virus JC virus
  - Seroprevalence of 39% to 69% among adults.
    - Primary JCV infection occurs in childhood

- CSF JCV assay in HIV infected patients
  - Positive in 70% - 90% of patients not taking ART
  - Quantitative assay had a diagnostic sensitivity of 76% and specificity of 100%.

Prognostic Significance of JC Virus DNA Levels in CSF of Patients with HIV-Associated Progressive Multifocal Leukoencephalopathy ; Bossolasco: CID 2005
- PML manifests as focal neurological deficits, usually with insidious onset and steady progression.
  - Cognitive impairment, focal deficits, ataxia
  - Subacute- weeks to months
- The lesions are
  - hyperintense (white) on T2
  - hypointense (dark) on T1
  - typically involve white matter rather than gray matter
  - non-contrast enhancing and produce no mass effect
Neurological CMV in HIV

- Retinitis: 85%
- Ventriculo-encephalitis
  - Acute onset
  - CSF pleocytosis and ventriculomegaly
- Polyradiculopathy and myelitis
  - Subacute presentation with ascending flaccid paralysis, variable sensory loss
- Mononeuritis multiplex
- Diffuse micronodular encephalitis
  - periventricular or diffusely scattered

*CID 1995*
Cytomegalovirus Retinitis

- Usually with CD4< 50
- CMV retinitis is a full-thickness necrotizing retinitis
- In patients with unilateral CMV retinitis and CD4 count <50 cells/mm³, rates of contralateral disease are high

Colitis occurs in 5% to 10%: weight loss, anorexia, abdominal pain, debilitating diarrhea
Diagnosis and Treatment of CMV

- **Diagnosis:**
  - NO Role of CMV IgG in HIV infected patients
  - Use PCR: blood and CSF.
  - Tissue biopsy if available is **best** as denotes CMV end-organ disease rather than colonization

- **Treatment**
  - **ART**
  - **Anti-virals:**
    - IV ganciclovir
    - OR PO valganciclovir (this is a prodrug with good bioavailability)
    - Intravitreal injections of ganciclovir or foscarnet

Concomitant treatment with systemic anti-CMV therapy
THE U.S. IS EXPERIENCING STEEP, SUSTAINED INCREASES IN SEXUALLY TRANSMITTED DISEASES

Combined diagnoses of chlamydia, gonorrhea, and syphilis increased sharply over the past five years.

**Total Cases**
- 2013: 1.8 Million
- 2017*: 2.3 Million
  - Chlamydia: 31% Increase
  - Gonorrhea: 67% Increase
  - Syphilis: 76% Increase

**Chlamydia**
- 2013: 333,004
- 2017*: 555,608

**Gonorrhea**
- 2013: 17,375
- 2017*: 30,644

**Syphilis**
- 2013: 2013
- 2017*: 2017

In 2017* chlamydia was the most common condition reported to CDC.

*Preliminary data

UNDIAGNOSED STDs CAN LEAD TO SEVERE HEALTH PROBLEMS

Diagnosed cases of chlamydia, gonorrhea, and syphilis represent just a small fraction of the true disease burden.

Left untreated, these STDs can produce severe, adverse effects:
- ectopic pregnancy
- infertility
- increased HIV risk
Primary Syphilis Chancre
Syphilis

- "It has been estimated that approximately ten per cent of the adult population is infected with syphilis"

*The Management of Syphilis in Elderly Persons* Cleveland Clinic Journal of Medicine. 1936 July;3(3):205-211, E. W. Netherton, M. D.

- Published in 1928, a study reported on the natural history of untreated syphilis in a group of white males.
- Clinical secondary relapse seen in 23.6% within five years
- Late syphilis occurred in 14.4 per cent of males and 16.7 per cent of females
Neurosyphilis

- CNS invasion in early disease – occurs in about 50% of patients
- Majority are asymptomatic
- 80% will clear the CNS infection spontaneously
- 20% develop tertiary syphilis in 10-20 years
- Serum RPR (VDRL) positive in
  - 70-80% of primary
  - 99% of secondary
  - 56-70% of late syphilis
Neurosyphilis

- Diagnosis of neurosyphilis
  - Presence of any of the following in the CSF
    - Elevated protein
    - Pleocytosis
    - VDRL

- Presentations:
  - Syphilitic meningitis; 5% of Early neurosyphilis is symptomatic-meningitis, cranial N palsy (within 1-10 years)
  - Meningo-vascular- focal signs due to infarction
  - Parenchymatous- combination of vascular and ischemic changes-GPI, Tabes dorsalis

- Treatment
  - Aqueous crystalline penicillin G, 18-24 million units IV in divided doses a day for 10-14 days
Case

- 43-year old Puerto Rican female
- HIV pos since 1988, CD4-43
- CSF, 350 protein, 50 white cells, 10 000 RBCs, 52% neutrophills, 17% lymphs and 37% eosinophills, opening pressure normal, glucose 102
- Peripheral eosinophils 52%
Eosinophilic Meningitis

- Defined by the presence of more than 10 eosinophils in the CSF or more than 10% in CSF
- Commonest cause worldwide is Angiostrongylus cantonensis followed by Baylisascaris procyonis and Coccidioides immitis
CNS TB

- Central nervous system (CNS) tuberculosis (TB) includes three clinical categories
  - tuberculous meningitis
  - intracranial tuberculoma
  - Spinal tuberculous arachnoiditis
- Bacillemia leads to scattered tuberculous foci (tubercles) in the brain, meninges, or adjacent bone.
  - Subependymal tubercle progresses and ruptures into the subarachnoid space
- Meningitis develops most commonly as a complication of progressive primary infection in
  - Infants and young children
  - In older adults with immune deficiency
- Risk of death in children with tuberculous meningitis can be almost 20% and neurological sequelae occur in more than 50% of patients.
Striking contrast enhancement at the base of the brain

Tuberculosis Meningitis