



HIV and Neurological complications

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MNWR

MORBIDITY AND MORTALITY WEEKLY REPORT

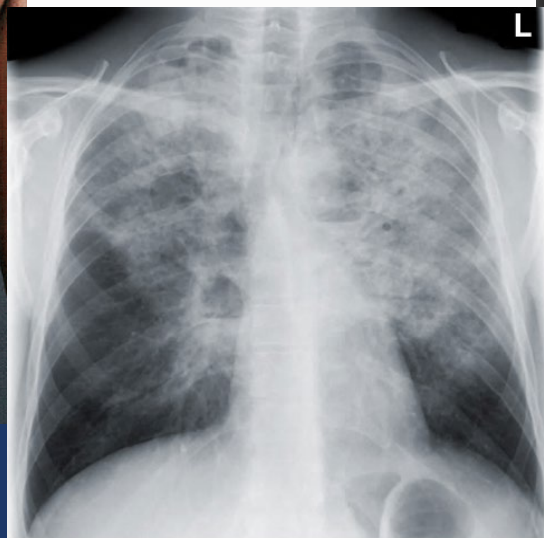
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1981

Epidemiologic Notes and Reports

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.



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MORBIDITY AND MORTALITY WEEKLY REPORT

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Epidemiologic Notes and Reports

Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men — New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)—all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are shown in Table 1.

Skin or mucous membrane lesions—often dark blue to violaceous plaques or nodules

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

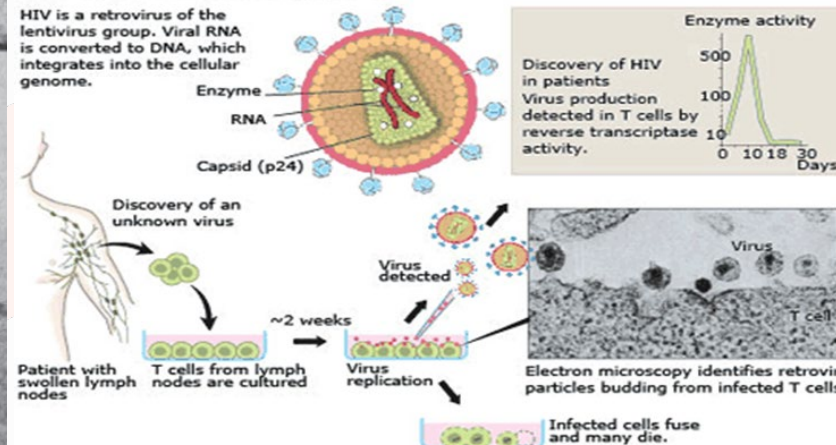


Françoise Barré-Sinoussi *

* 2008 Nobel Prize laureates

HIV – human immunodeficiency virus

HIV is a retrovirus of the lentivirus group. Viral RNA is converted to DNA, which integrates into the cellular genome.



© The Nobel Committee for Physiology or Medicine 2008 Illustration: Annika Röhl

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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 - 1. 1 out of 150
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 - 3. 1 out of 10000
 - 4. 1 out of 27000

 - 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).

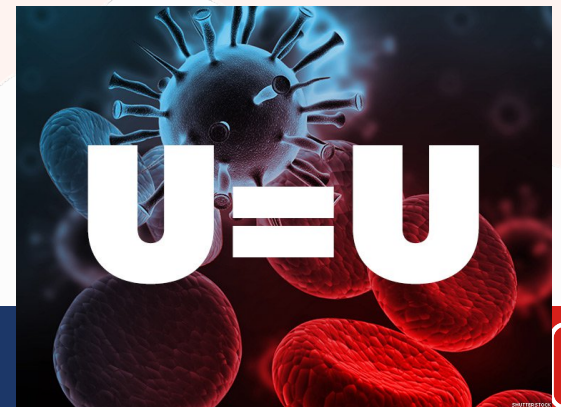
4. Respond : quickly to outbreaks



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



Genvoya



Complera



Juluca



Triumeq



Odefsey



Biktarvy

Stribild



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)

Immune Activation of the Central Nervous System Is Still Present after >4 Years of Effective Highly Active Antiretroviral Therapy

Arvid Edén,¹ Richard W. Price,³ Serena Spudich,³ Dietmar F. Lars Hagberg,¹ and Magnus Gisslén¹

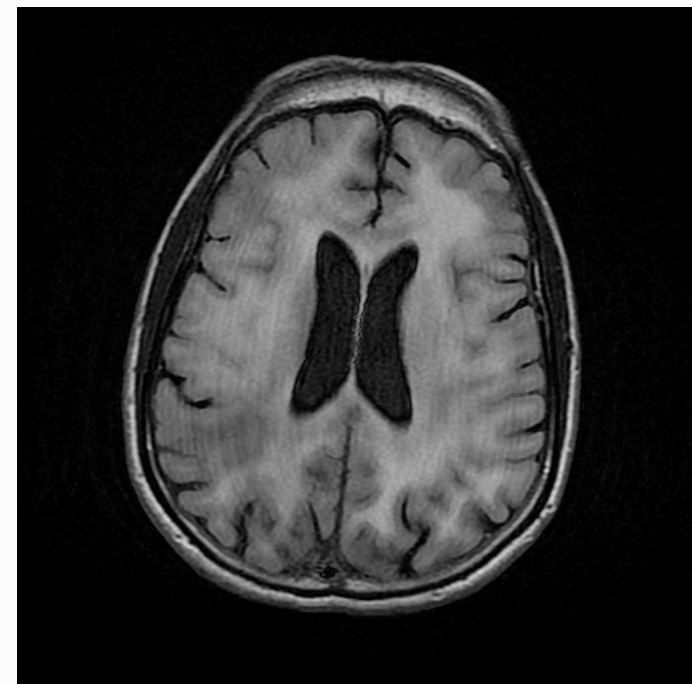
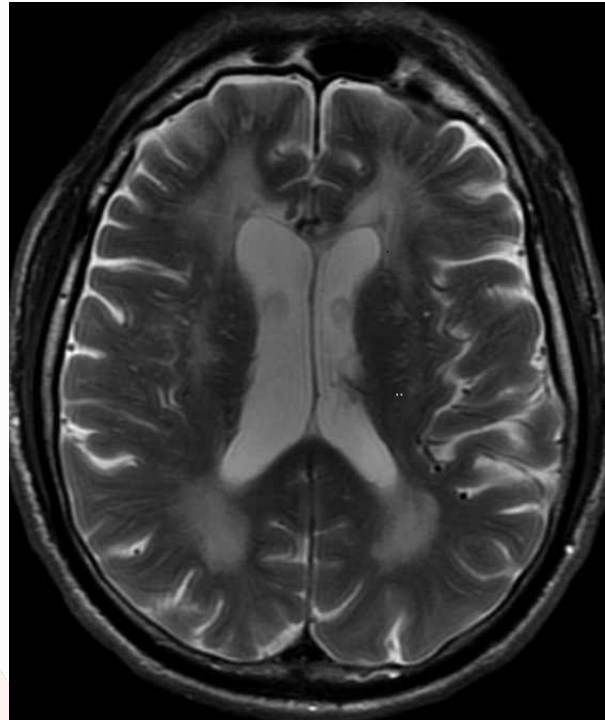
October 30, 2007; 69 (18) ISSUES IN NEUROLOGIC PRACTICE

Updated research nosology for HIV-associated neurocognitive disorders

A. Antinori, G. Arendt, J. T. Becker, B. J. Brew, D. A. Byrd, M. Cherner, D. B. Clifford, P. Cinque, L. G. Epstein, K. Goodkin, M. Gisslén, I. Grant, R. K. Heaton, J. Joseph, K. Marder, C. M. Marra, J. C. McArthur, M. Nunn, R. W. Price, L. Pulliam, K. R. Robertson, N. Sacktor, V. Valcour, V. E. Wojna

First published October 3, 2007, DOI: <https://doi.org/10.1212/01.WNL.0000287431.88658.8b>

- 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 3. Clinical signs and symptoms of HIV dementia

| | Symptoms | Signs |
|-----------|--|--|
| Cognitive | Poor Concentration Forgetfulness | Slowness of thought Executive cognitive dysfunction |
| Motor | Gait instability Urinary urgency/ hesitation | Saccadic ocular pursuit movements Slowing of repetitive movements |
| Behavior | Loss of interest in friends, hobbies | Apathy |

HIV and opportunistic infections

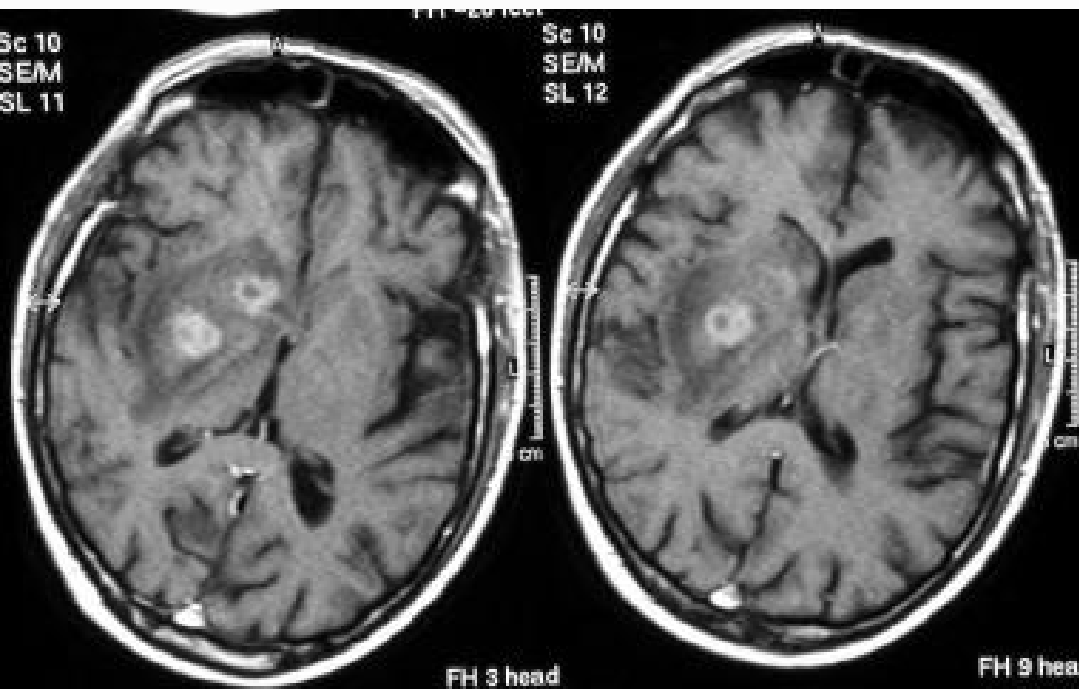
- The most important factor is the degree of immunosuppression in the host.
- Patients with CD4 cell counts $>500/\text{microL}$
 - benign and malignant brain tumors and metastases
- Patients with CD4 cell 200 - 500/ microL
 - HIV-associated cognitive and motor disorders are common, but usually do not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

CSF Characteristics of HIV associated OIs

| | White-blood-cell count | Glucose concentration | Protein concentration | Other |
|---|--------------------------------------|-----------------------|-----------------------------------|--|
| Toxoplasmic encephalitis ^{21,22,36} | Normal or increased lymphocytes | Decreased or normal | Normal or increased | <i>Toxoplasma gondii</i> PCR nearly 100% specific and 50–80% sensitive |
| PML ^{23,24} | Normal, rarely increased lymphocytes | Normal | Normal or increased | JC-virus PCR sensitivity variable at 50–90%, but specificity 90–100% |
| Primary CNS lymphoma ^{25,26} | Normal or increased lymphocytes | Normal | Normal | Epstein-Barr virus PCR nearly 100% sensitive and about 50% specific |
| Cytomegalovirus encephalitis ^{27,28} | Normal, rarely increased neutrophils | Normal | Normal or increased | PCR >90% sensitive and specific and <25% culture positive |
| Cryptococcal meningitis ^{29,30,37} | Normal, rarely increased lymphocytes | Decreased or normal | Normal or increased ³⁶ | 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 |
| Tuberculous meningitis ³²⁻³⁴ | Increased lymphocytes | Decreased | Normal or increased | <i>Mycobacterium tuberculosis</i> culture has variable sensitivity, but use of microscopy for acid-fast bacilli and CSF NAAT can increase sensitivity to >80% |
| Herpes simplex virus ³⁵ | Usually increased lymphocytes | Normal or increased | Increased | CSF PCR sensitivity 100%, specificity 99.6% |

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 > = 150 IU/ml.
 - *Derouin F, et al. AIDS. Nov 1996;10(13):1521-1527*
 - 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/ μ L should receive prophylaxis against TE
 - Primary Prophylaxis can be safely discontinued in patients with CD4 100 -200 cells/mm³ and HIV plasma RNA < 400

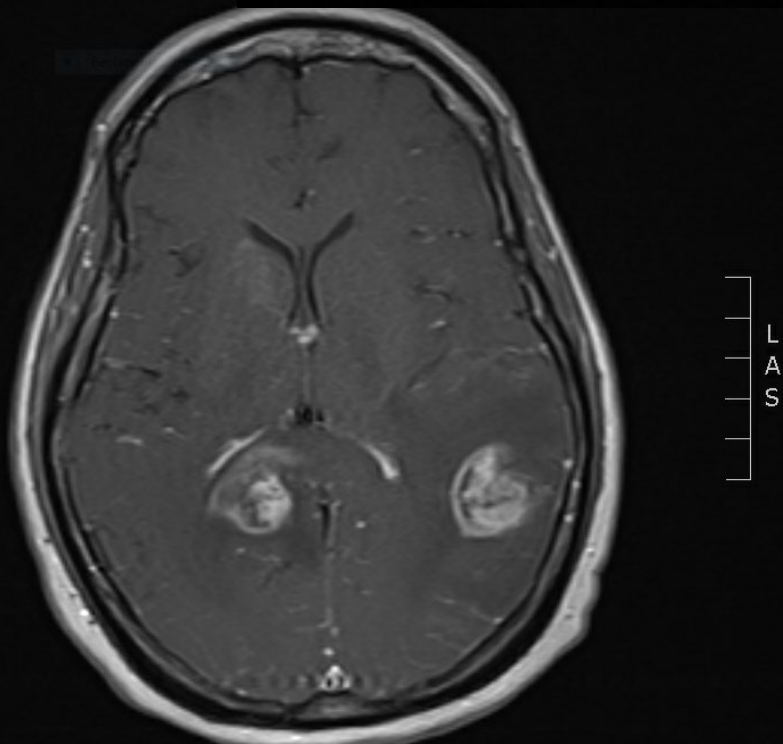
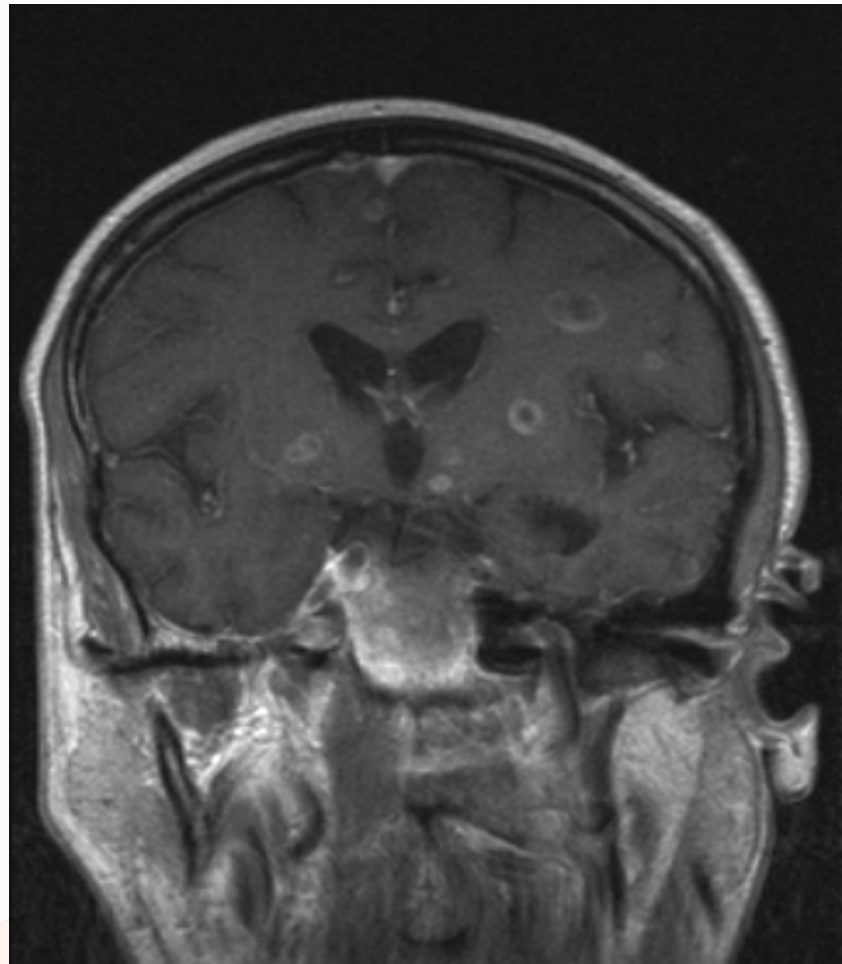
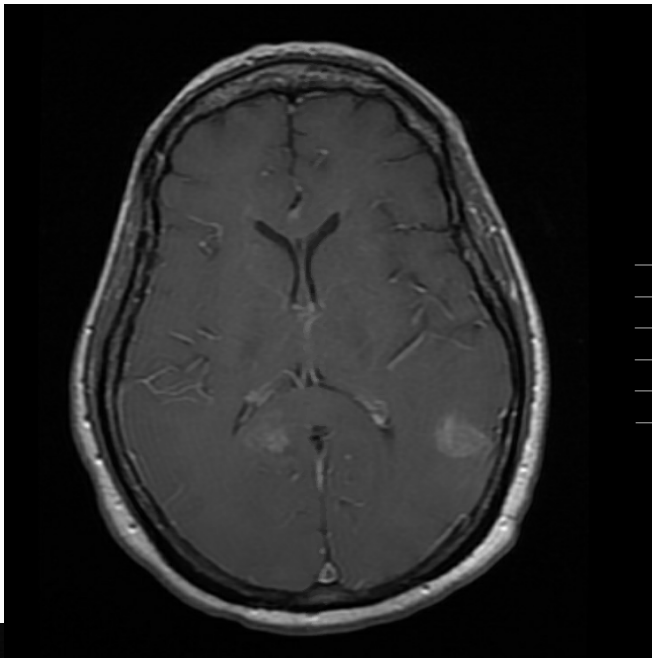
Case

- 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

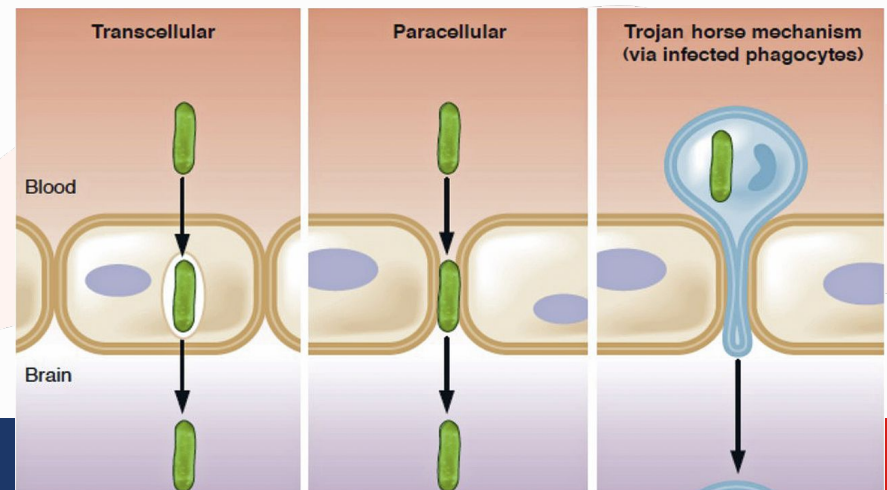
Case



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

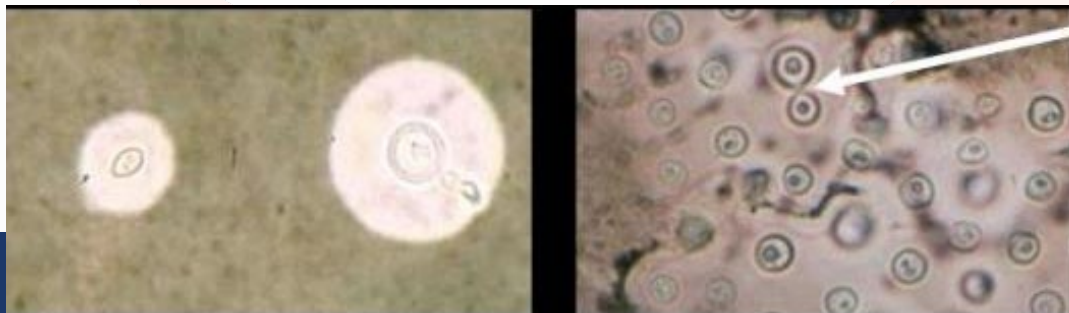


Cryptococcus neoformans

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



Cryptococcus and its capsule

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%)

Treatment in HIV infected patients

- 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.

| Outcome | CSF opening pressure | | |
|---------------------|-----------------------------|-----------------------|-----------------------------|
| | Decrease >10 mm (n = 81) | No change (n = 24) | Increase >10 mm (n = 56) |
| Clinical failure | 2 | 4 | 20 ^a |
| Mycological failure | 33 | 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

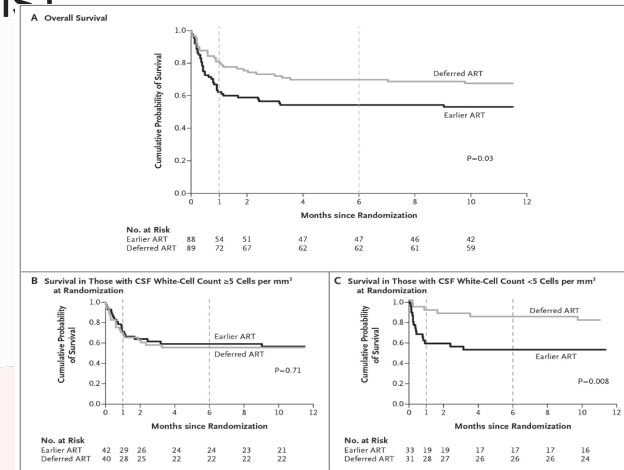
COAT Trial- timing of ART with CM

- 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:

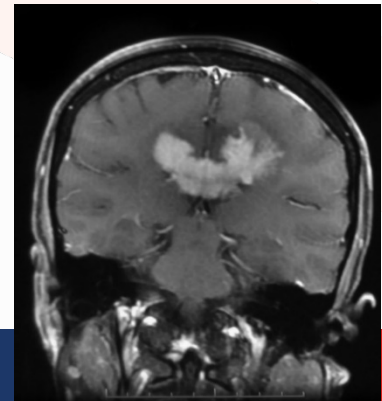
■ 26-week mortality

- **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.



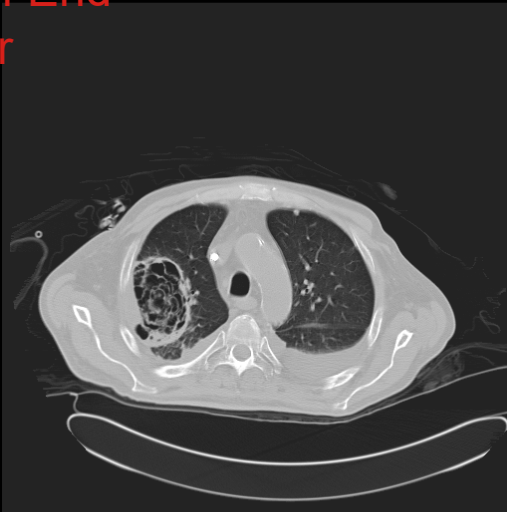
PCNS Lymphoma

- 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 10,000copies/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.

Corcoran C, J Clin Virol. 2008;42(4):433–436. doi: 10.1016/j.jcv.2008.03.017



Cryptococcus pneumonia in a patient with End Stage Liver Disease



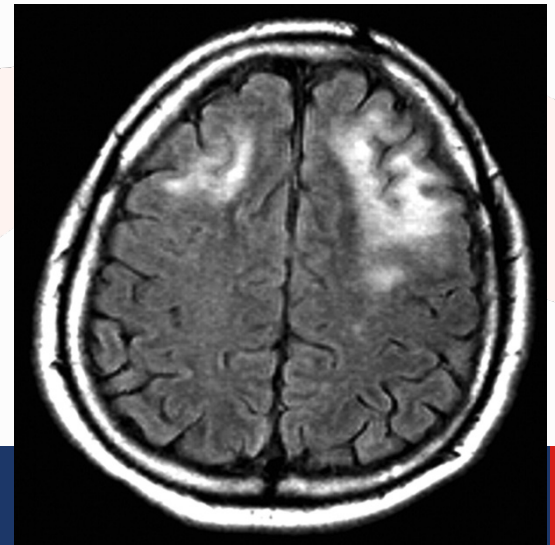
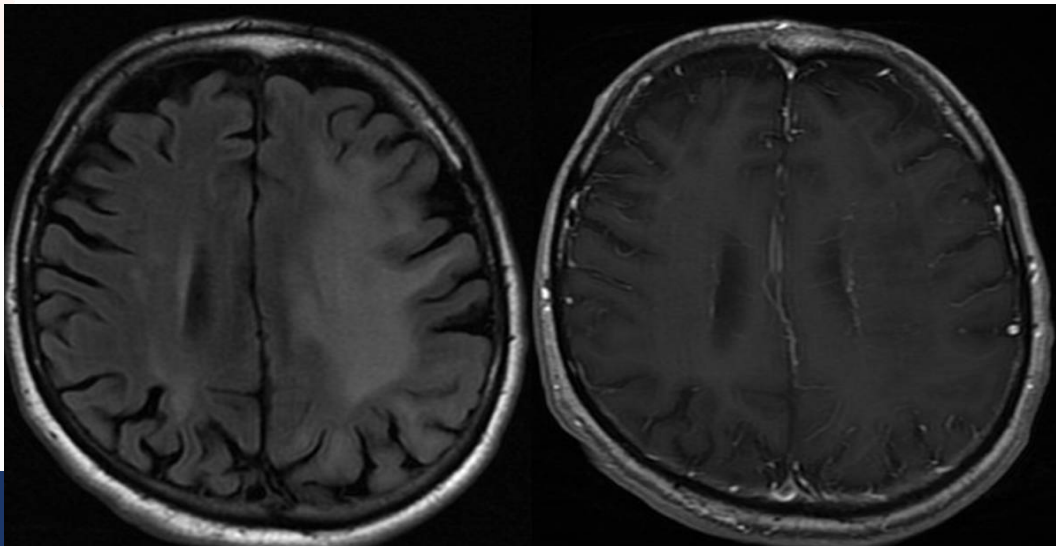
Cerebral Cryptococcoma in a non-HIV patient

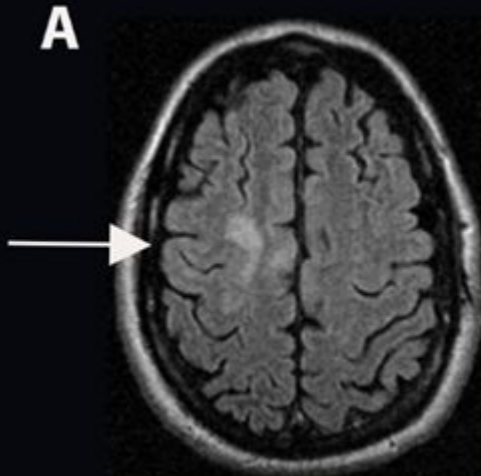
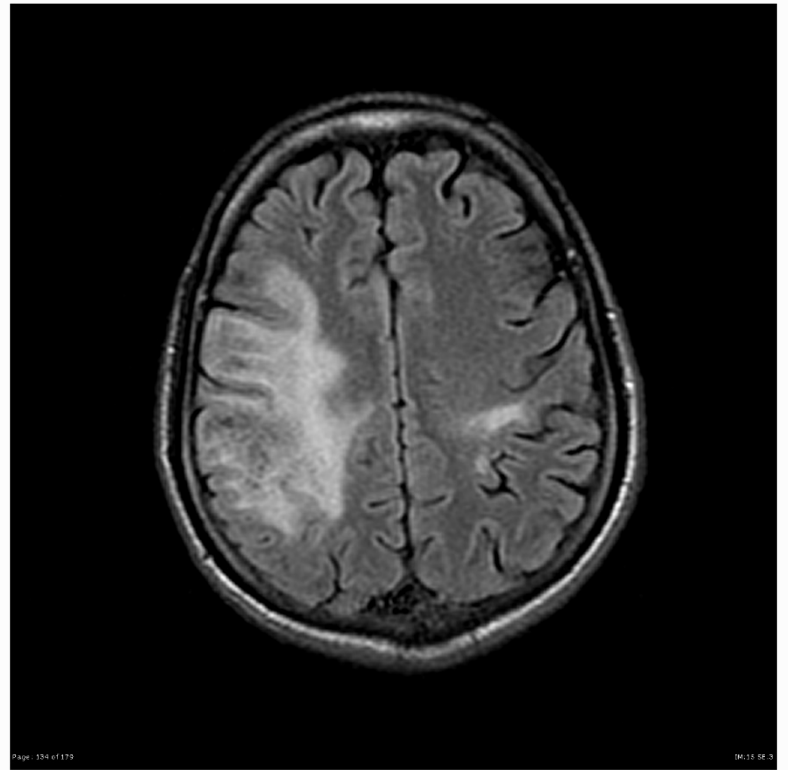
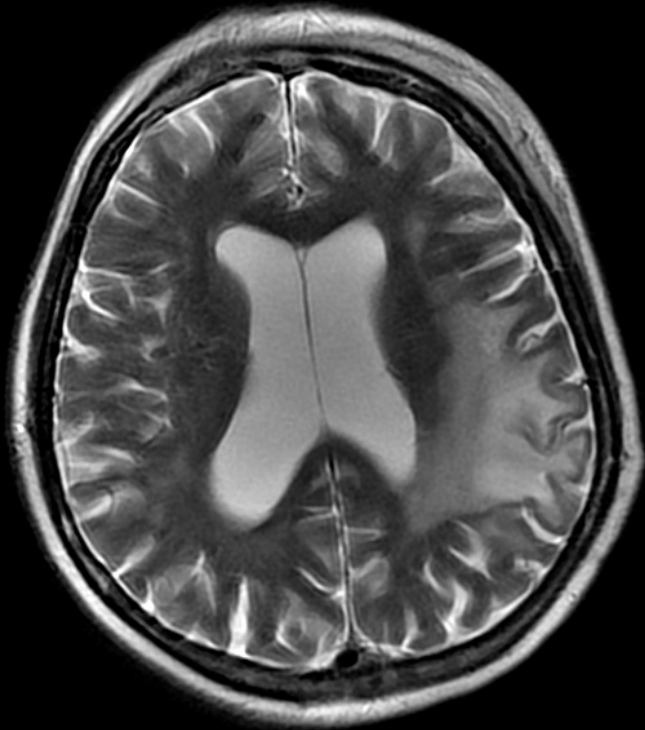
Progressive multifocal leukoencephalopathy (PML)

- 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%.

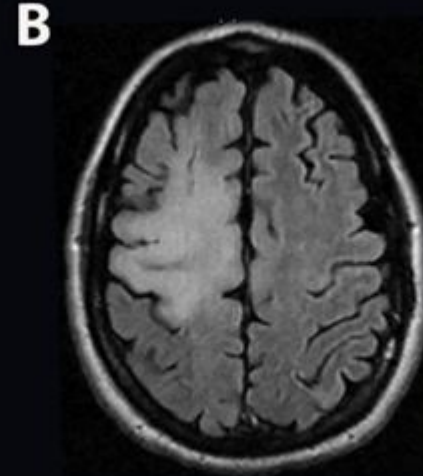
Prognostic Significance of JC Virus DNA Levels in CSF of Patients with HIV-Associated Progressive Multifocal Leukoencephalopathy ; Bossolasco: CID 2005

- 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**

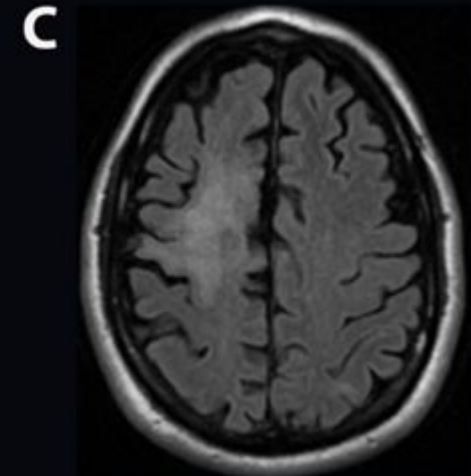




PMI



IRIS



Resolution

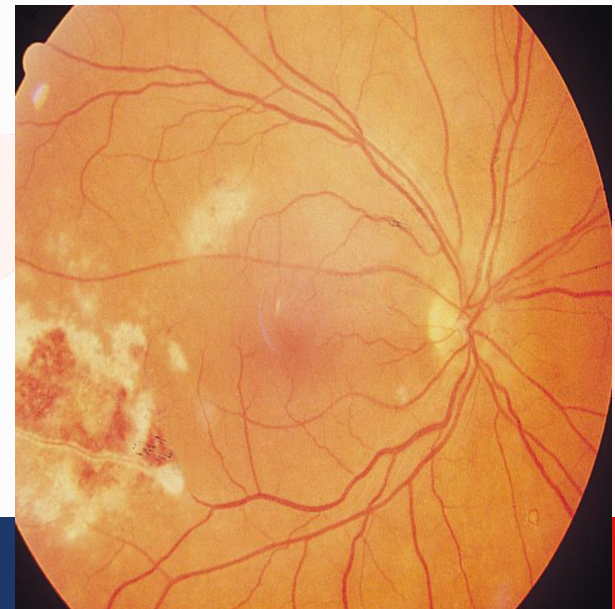
Neurological CMV in HIV

- 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

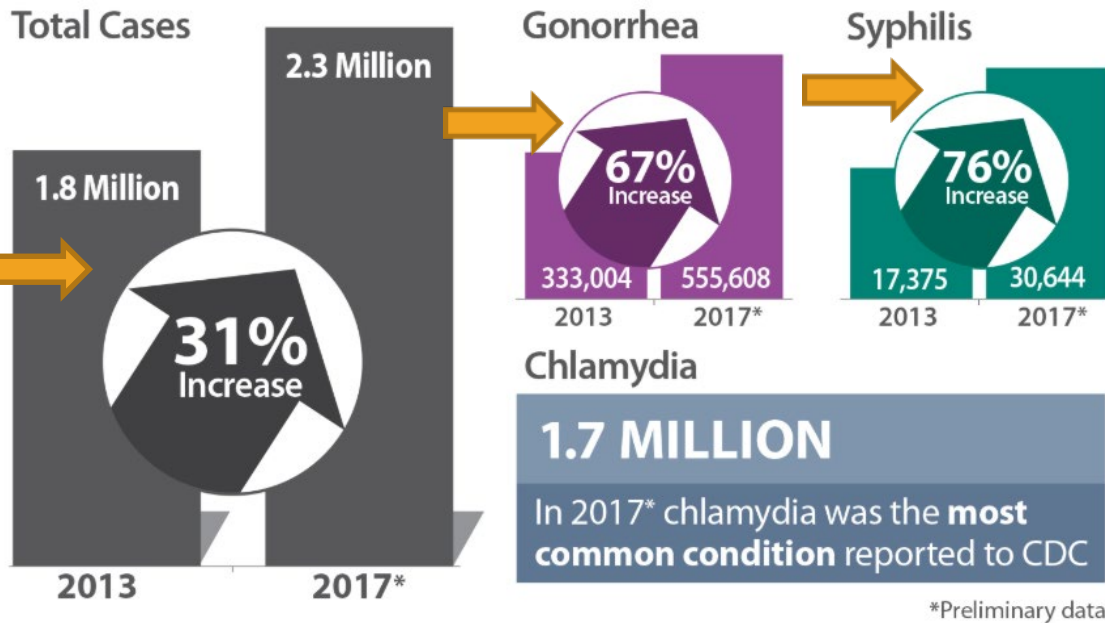
- Anti-virals:

- 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**



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

infertility *ectopic pregnancy*
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**

Untreated Syphilis in the Male Negro

Twenty-Two Years of Serologic Observation in a Selected Syphilis Study Group

SIDNEY OLANSKY, M.D., Durham, N. C.
AD HARRIS
JOHN C. CUTLER, M.D.
and
ELEANOR V. PRICE, Chamblee, Ga.

Since 1932 there has been carried on a study of the outcome of untreated syphilis in the male Negro.* Although the primary objective of this study is the determination

to 22 years. The initial sero- tion in 1932-1933 was based on complement fixation and flocculation tests for syphilis the National Institute of Health 1938-1939 and subsequent testing has been done by the ease Research Laboratory Staten Island, N. Y., and Chamblee, Ga.) Although

(Aus der Dermatologischen Universitätsklinik in Oslo.)

Über das Schicksal der nicht spezifisch behandelten Luetiker.

Von
E. Bruusgaard.

(Eingegangen am 23. Oktober 1928.)

Aus den pathologisch-anatomischen Instituten in Eppendorf sowie aus denen der Charité und des Rudolf Virchow-Krankenhauses sind eine Reihe größerer Statistiken über die syphilitischen Arterienaffektionen

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

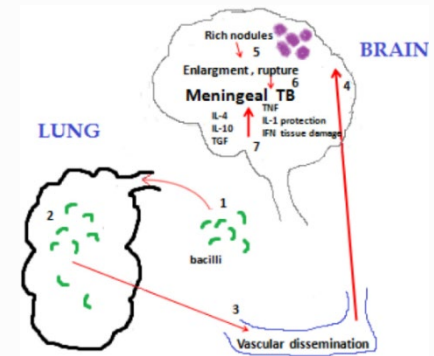
Case

- 43-year old Puerto Rican female
- HIV pos since 1988, CD4-43
- CSF, 350 protein, 50 white cells, 10 000 RBCs, 52% neutrophils, 17% lymphs and 37% eosinophils, 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.

