HIV and Neurological complications

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CENTERS FOR DISEASE CONTROL

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MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

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.

1981

Pneumocystis pneumonia and Kaposi's sarcoma reported in 26 men in NYC and California

CENTERS FOR DISEASE CONTROL

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MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

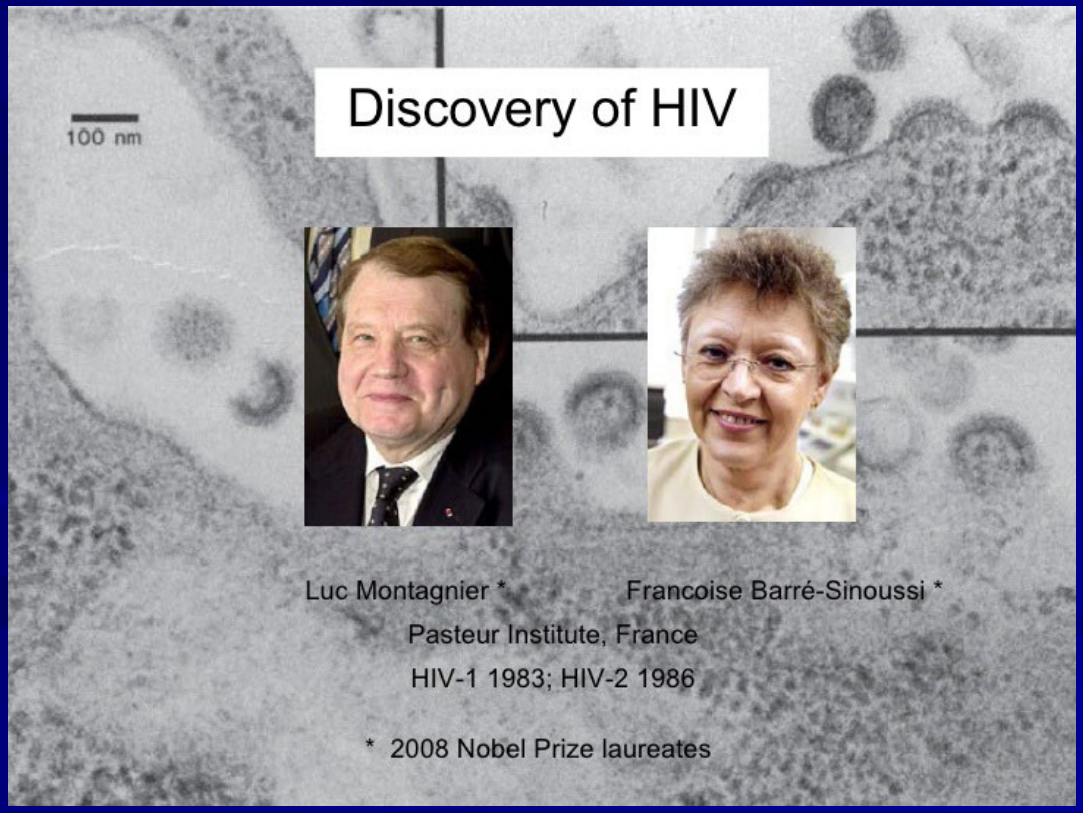
Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men — New York City and California

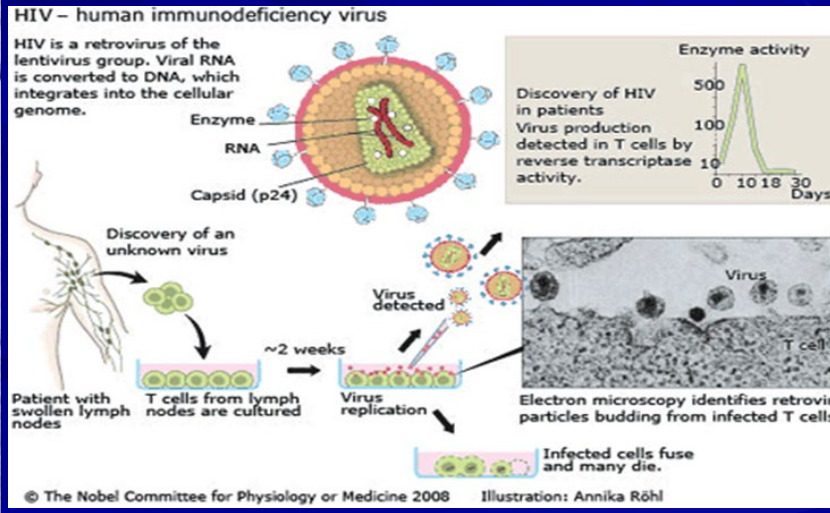
During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malig-nancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC], 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in 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





- HIV is a major global public health issue
  - Claimed 36.3 million lives so far.
- Worldwide at the end of 2020
  - Estimated 37.7 million people living with HIV
  - Two thirds (25.4 million) are in the Africa
- USA
  - Estimated prevalence of HIV infection among persons > 13 years in the US-0.4%
    - **Males- 0.7% (1/150 male Americans)**
    - Females-0.2%

Global ART Rollout

- Since 2016, WHO has recommended that **all people living with HIV be provided with lifelong ART**
  - Regardless of clinical status or CD4 cell count.
  - By June 2021
    - 187 countries had already adopted this recommendation, covering 99% of all people living with HIV globally
- WHO also recommends a **rapid ART initiation for all people living with HIV**
  - **I**ncluding offering ART on the same day as diagnosis
  - By June 2021
    - 82 low- and middle-income countries had adopted this.

AIDS Memorial Quilt 1987

HIV- Cure?- not yet!

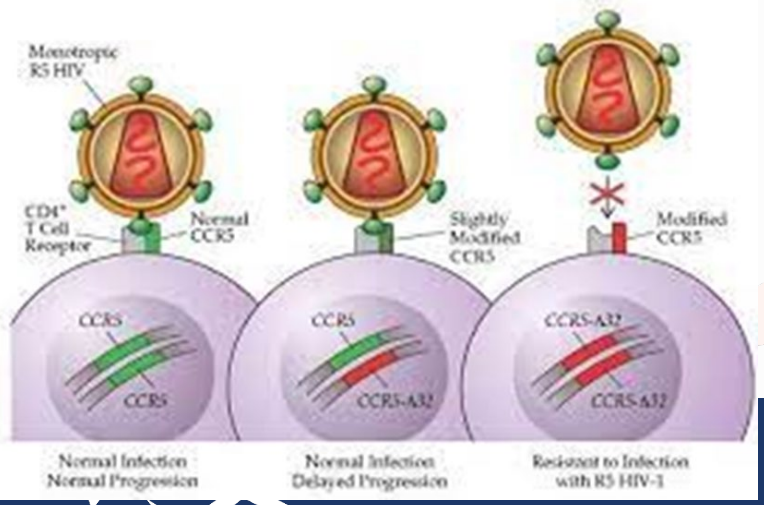
- A woman in New York City “New York Patient” has no detectable HIV 14 months after stopping antiretroviral therapy
  - She received a transplant of HIV-resistant stem cells transplant to treat leukemia
  - Both her cancer and HIV are in remission
  - Too soon to declare that she is cured of HIV
  - But she may join the 'Berlin patient' and the 'London patient' as the third person to be free of HIV over the long term after stem cell transplantation.

“New York Patient”

- IMPAACT P1107
- Post-menopausal woman : HIV , acute myeloid leukemia in 2017
  - Received intensive chemotherapy and whole-body radiation prior to the transplant.
  - Then received previously umbilical cord blood with the double CCR5-delta-32 mutation AND partially matched adult donor stem cells without the CCR5 mutation.
  - Within 100 days, she achieved full engraftment with 100% CCR5-delta-32 immune cells derived from the cord blood cells.
- She remained on antiretroviral therapy for three years after the transplant.
  - Undetectable plasma viral load, undetectable HIV DNA in immune cells (reflecting the latent viral reservoir) and no evidence of replication-competent HIV
- ART stopped in 2020 and she remains undetectable after 14 months

What is CCR-5-delta 32

- CCR5 is the most common mode of entry, “the door” that allows entry of HIV into cells.
- CCR5-delta 32 mutation causes the CCR-5 receptor to develop smaller or no longer sit outside the cell.
- It is believed that the original mutation of CCR5-Delta 32 appeared > 2500 years ago.
  - Persistent epidemics of hemorrhagic fever assisted to reinforce the frequency of the mutation
- 1% of people descended from Northern Europeans are immune to HIV infection.
  - They are homozygous carriers of CCR-5 Δ 32 gene
- Another 10-15% of European heritage are heterozygous
  - But just one copy of the mutation does not prevent against infection.
    - It does reduce the likelihood of infection and progression to AIDS



IAS-USA Guidelines- 2004
Wait before starting ART

Table 1. Recommendations for Initiating Therapy in Treatment-Naive Individuals*

Disease Stage	Recommendation	Evidence Rating†
Symptomatic HIV disease	Antiretroviral treatment	IA
Asymptomatic HIV disease		
≤200 CD4 cells/μL	Antiretroviral treatment	II
>200 CD4 cells/μL but ≤350 CD4 cells/μL	Antiretroviral treatment should be considered‡	II
>350 CD4 cells/μL but ≤500 CD4 cells/μL	Continued monitoring; counseling for HIV transmission prevention§	II
>500 CD4 cells/μL	Continued monitoring; counseling for HIV transmission prevention	II

Abbreviation: HIV, human immunodeficiency virus.
*Excludes pregnant women with specific regard to prevention of HIV transmission to the infant.
†See Box for explanation of evidence ratings.
‡The closer to 200 CD4 cells/μL, the stronger the recommendation for treatment, particularly if the plasma viral load is high (>50 000-100 000 copies/mL) or if the CD4 cell count is declining rapidly (>100/μL per year).
§Consider treatment for patients with high plasma viral load or with rapid decline of CD4 cell count.

Yeni et al. *JAMA.* 2004;292:251-265.

2021- Initiate ART immediately (or as soon as possible)

DHHS[1]	WHO[2]	IAS-USA[3]
▪ Initiate ART immediately (or as soon as possible) after HIV diagnosis	▪ Recommended where feasible	▪ Start ART as soon as possible**, including immediately after diagnosis,** if patient is ready

1. DHHS Guidelines. 2019. 2. WHO Guidelines. July 2017. 3. Saag. JAMA. 2018;320:379.

Global ART Transition

- Ellimination of suboptimal regimens such as nevirapine and efavirenz based ARVs
- Transition to dolutegravir-based regimens (TLD)
- PEPFAR partner countries
- > 98% of on optimal regimens
- WHO-preferred first-line ARVs such as dolutegravir- and efavirenz-based triple therapy regimens
  - **$60 per patient per year**

HIV: Single Tablet Regimens

Atripla

Genvoya

Complera

Juluca

Stribild

Triumeq

Odefsey

Biktarvy

Case

- 38 year woman, 2 day H/O fever, headache, neck stiffness, sexually active with husband.
- Has 2 children at home
- T-99.8, meningismus, alert, oriented
- CSF:
- **WBC-70, 80% lymphocytes, glucose-60**, Protein-70, gram stain negative,

Aseptic Meningitis

- Viral
- Parasitic
- Mycobacterial- TB meningitis- high protein, low glucose
- Bacterial
  - Syphilis- usually secondary syphilis but can present at any stage
  - Lyme meningitis- late summer, mild fever , may include CN palsies
- Neoplasm
- Fungal- Cryptococcus and coccidiomycoses
- Drug induced- sulfa drugs, phenytoin, IVIG, OKT3 antibodies,

Viral Meningitis

- Commonest aseptic meningitis
  - Enteroviruses- summer or fall, PCR is a good test
  - Mumps- Most frequent extrasalivary complication (10-20%)
  - Herpes virus (Including HSV, VZV)
  - Measles
  - Influenza (Non Polio Enteroviruses)
  - EBV
  - Lymphocytic choriomeningitis virus
  - **HIV- primary HIV (Fever, rash, lymphadenopathy, pharyngitis)**

Viral Meningitis

- **Viral Meningitis**
  - Not distinguishable from bacterial meningitis based on symptoms
  - Duration usually less than 1 week
  - Most commonly caused by enteroviruses, HSV-2, and arboviruses

Treatment

- Empiric antimicrobials until CSF profiles and cultures finalize
- Symptomatic and supportive management

CSF Parameter	Viral Meningitis[a]
Opening pressure	≤250 mm H_2O
Leukocyte count	50-1000/µL (50-1000 × 10^6/L)
Leukocyte predominance	Lymphocytes[d]
Glucose	>45 mg/dL (2.5 mmol/L)
Protein	<200 mg/dL (2000 mg/L)
Gram stain	Negative
Culture	Negative

Case

- 56 year female presented with a 2 day history of fever, chills headache confusion
- Headache, stiff neck, fever, purpuric rash
- Platelets 20 K, WBC 30K
- CSF
  - **WBC 2800, 99% Neutrophils, Glucose 20**

Treatment for Community acquired Bacterial meningitis

- Dexamethasone + PCN G
- Dexamethsone + ceftriaxone
- Dexamethasone + vancomycin + ampicillin
- Dexamethasone + vancomycin + ceftriaxone
- Vancomycin + ceftriaxone +rifampin

Bacterial Meningitis

- Fever, HA, meningismus, cortical dysfunction are hallmarks
  - Most have 2/4
- Absence of all four almost rules out meningitis
- **Lab evaluation**:
- Culture
  - positive in 70% to 85% (if no previous antibiotics)
- Gram stain
  - positive in 30% to 90%(Listeria 30% and pneumococcus 90%)
- Latex agglutination
  - May help in culture negative or pretreated meningitis but not routinely recommended
- PCR:

CSF- PCR Panel

Meningitis Encephalitis Panel

Sample Type: Cerebrospinal Fluid (CSF)

14 TARGETS IN ONE TEST

The FilmArray Meningitis/Encephalitis (ME) Panel tests for a comprehensive set of 14 bacteria, viruses and yeast. The FilmArray ME Panel identifies the most common viral, bacterial and yeast pathogens that cause infections in the central nervous system which in some cases can be life-threatening. The diagnosis of meningitis and encephalitis can allow faster decisions on appropriate therapy to be made to prevent complications.

ME PANEL MENU

BACTERIA:

- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

VIRUSES:

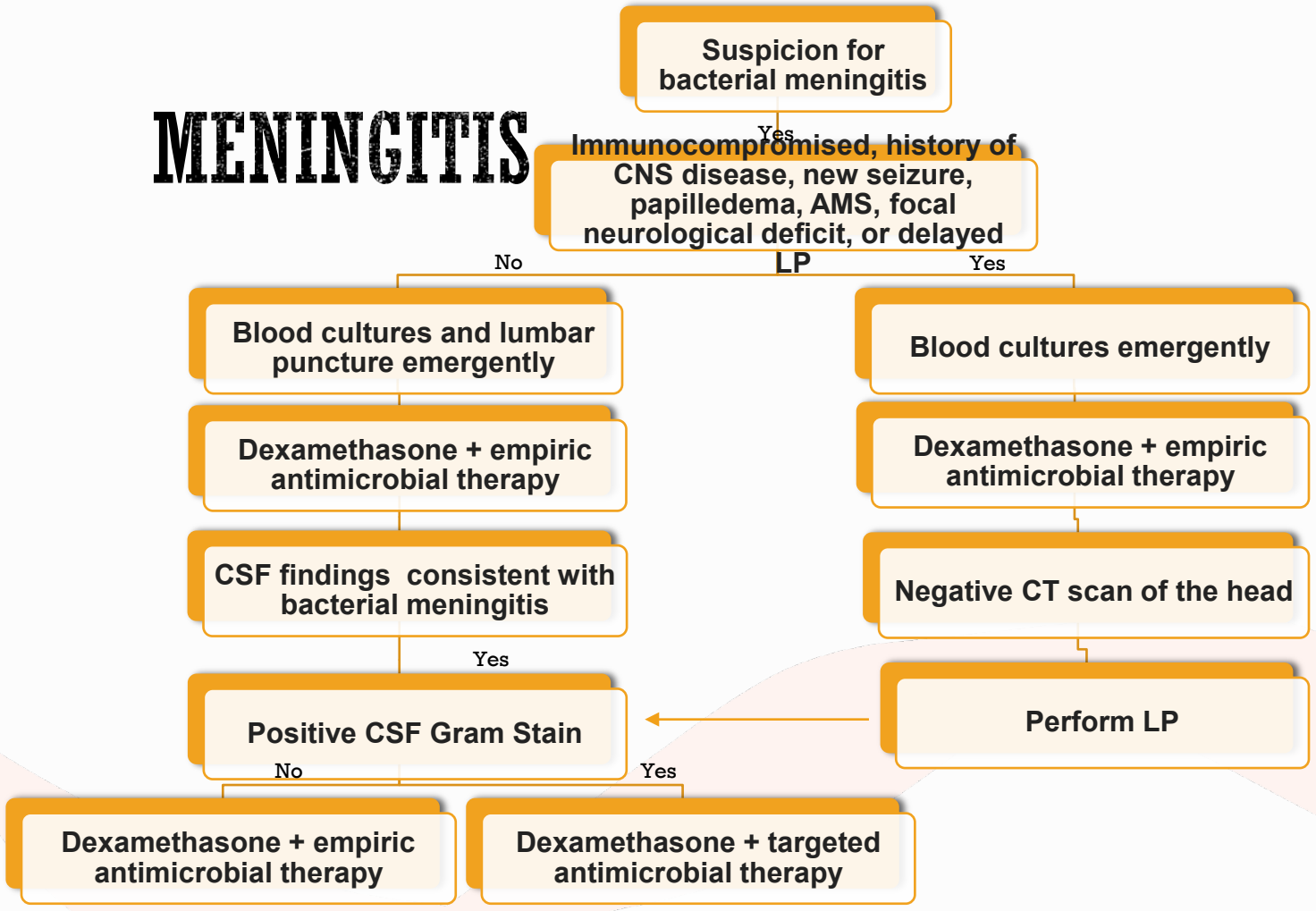
- Cytomegalovirus (CMV)
- Enterovirus
- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Human herpesvirus 6 (HHV-6)
- Human parechovirus
- Varicella zoster virus (VZV)

YEAST:

- *Cryptococcus neoformans/gattii*

http://www.biofiredx.com/products/the-filmarray-panels/

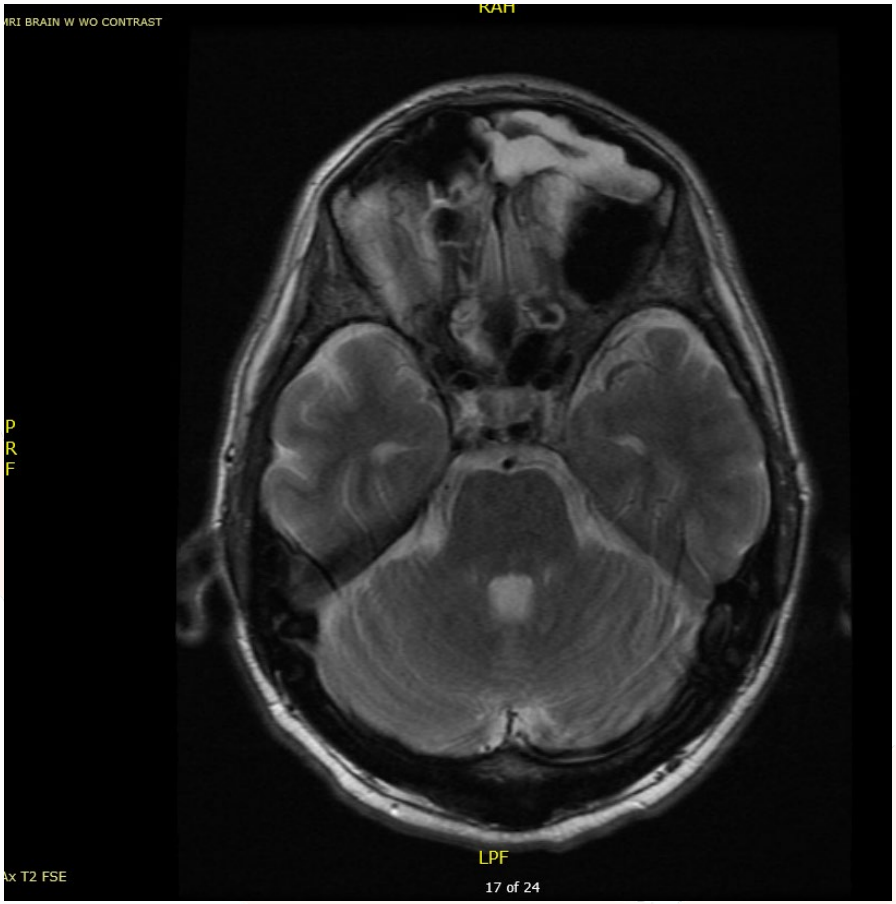
MENINGITIS

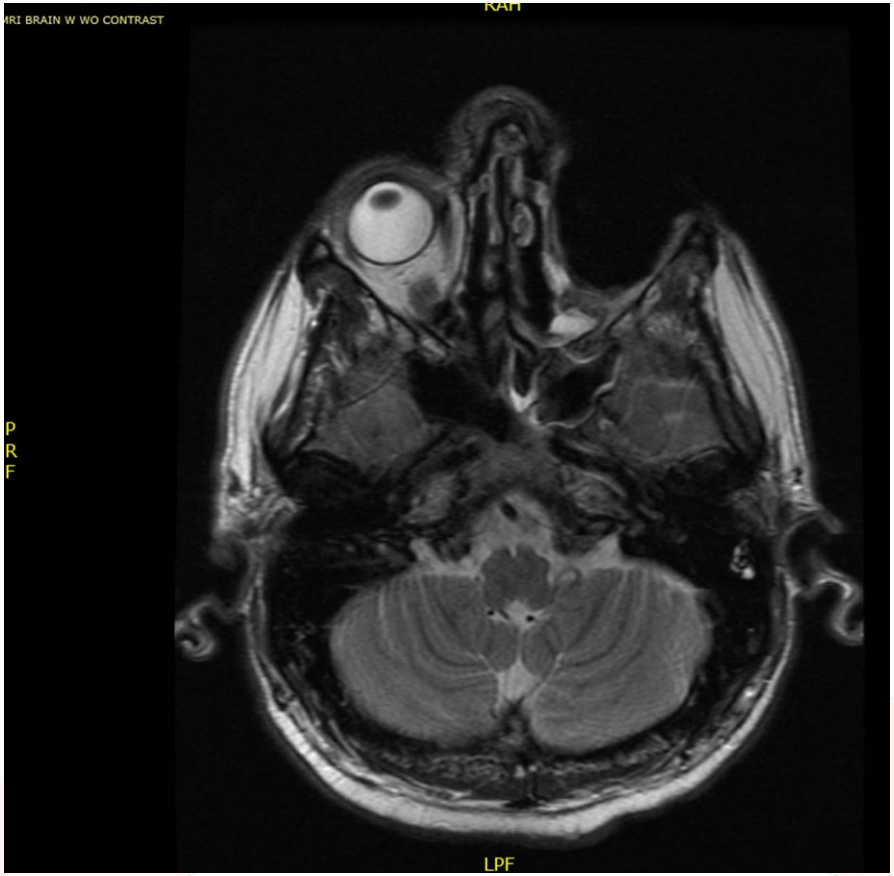

Suspicion for bacterial meningitis
Yes
Immunocompromised, history of CNS disease, new seizure, papilledema, AMS, focal neurological deficit, or delayed LP
No
Yes
Blood cultures and lumbar puncture emergently
Dexamethasone + empiric antimicrobial therapy
CSF findings consistent with bacterial meningitis
Yes
Positive CSF Gram Stain
No
Yes
Dexamethasone + empiric antimicrobial therapy
Dexamethasone + targeted antimicrobial therapy
Blood cultures emergently
Dexamethasone + empiric antimicrobial therapy
Negative CT scan of the head
Perform LP

Mucor infections

- 50 year old healthy male
- COVID-- received steroids and tocilizumab
- 3 weeks later developed fungal sinusitis
- Progressive orbital involvement led to left eye exenteration

- This is not his picture but similar!
- 3 months later is getting his 5th sinus surgery


RAH
MRI BRAIN W WO CONTRAST
P
R
F
LPF
Ax T2 FSE
17 of 24


RAH
MRI BRAIN W WO CONTRAST
P
R
F
LPF

HIV and opportunistic infections

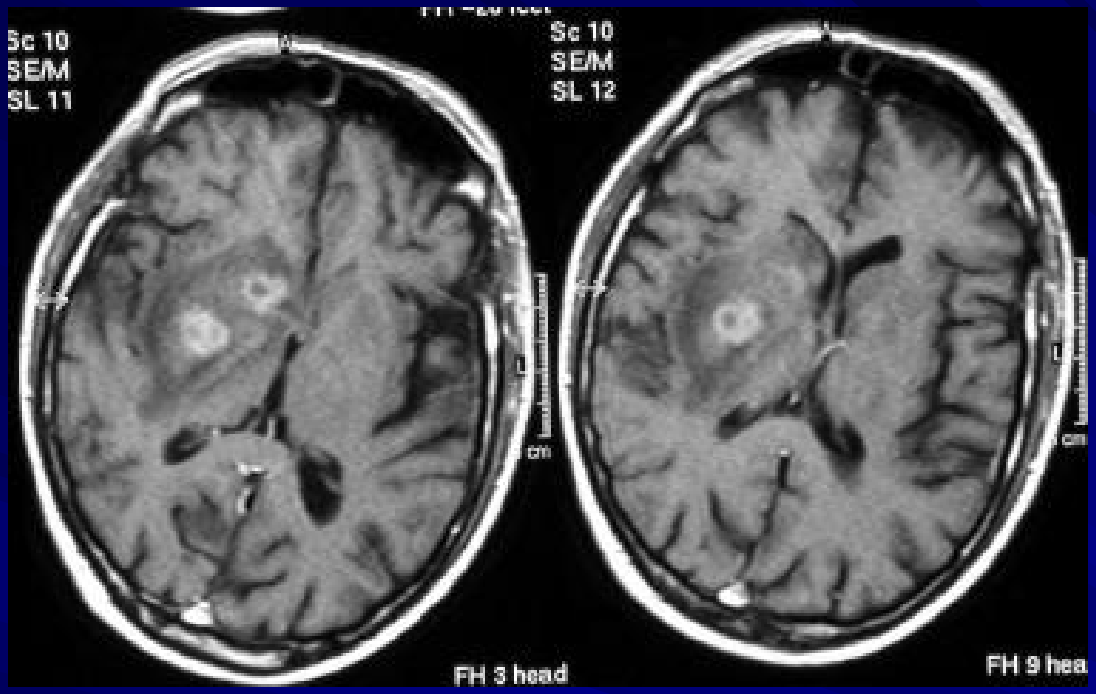
- The most important factor is the degree of immunosuppression in the host.
- Patients with CD4 cell counts >500/microL
  - benign and malignant brain tumors and metastases
- Patients with CD4 cell 200 - 500/microL
  - HIV-associated cognitive and motor disorders are common, but usually do not present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

CSF Characteristics of HIV associated OIs

	White-blood-cell count	Glucose concentration	Protein concentration	Other
Toxoplasmic encephalitis[21,22,36]	Normal or increased lymphocytes	Decreased or normal	Normal or increased	*Toxoplasma gondii* 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	*Mycobacterium tuberculosis* 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


Sc 10
SE/M
SL 11
Sc 10
SE/M
SL 12
FH 3 head
FH 9 hea


DECAMP
RIX
msGP:

Toxoplasma gondii

- Obligate intracellular parasite
- Forms cysts in mammalian tissues
  - Transmission from ingestion of food or water
  - 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, seizures
- 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
  - 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 (Serum 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/mm^3 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

- Broad Differential
  - Anemia, uremia, electrolyte abnormalities,
  - Drug toxicity (recreational) or Bactrim
  - Other causes of encephalopathy/encephalitis
  - PML
  - Cryptococcal meningo-encephalitis
  - Disseminate Mycobacterium avium

Next Steps

- History, Examination
- Labs: CBC, CMP, Serum Toxo IgG, Serum Cryptococcal Antigen, RPR
- Imaging: MRI better than CT
- Subsequently Lumbar Puncture, especially if Serum Cryptococcal antigen is positive
- CSF studies:
  - Cell count with diff, protein, glucose, CSF cryptococcal antigen, VDRL, May need to send CSF EBV PCR and JC Virus PCR if MRI abnormal

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

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%)

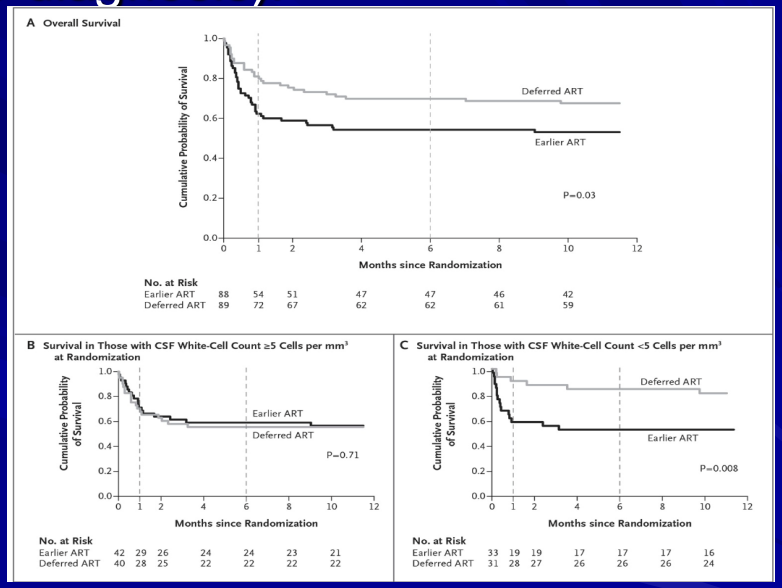
Treatment in HIV infected patients

- Management of cryptococcal meningoencephalitis includes all of the following:
  - Antifungal therapy: Liposomal amphotericin and Flucytosine X 2-4 weeks followed by fluconazole

  Control of 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
  - ART
    - antiretroviral therapy (ART) should be started between 2 and 10 weeks after antifungal therapy has

COAT Trial- timing of ART with Cryptococcal meningoencephalitis

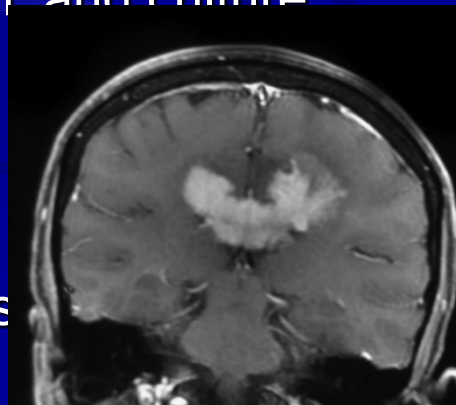
- South Africa and Uganda
- assigned study participants to undergo
  - earlier ART initiation (1 to 2 weeks after diagnosis)
  - Or deferred ART initiation (5 weeks after diagnosis).
  - Rx: Amphotericin B and fluconazole.



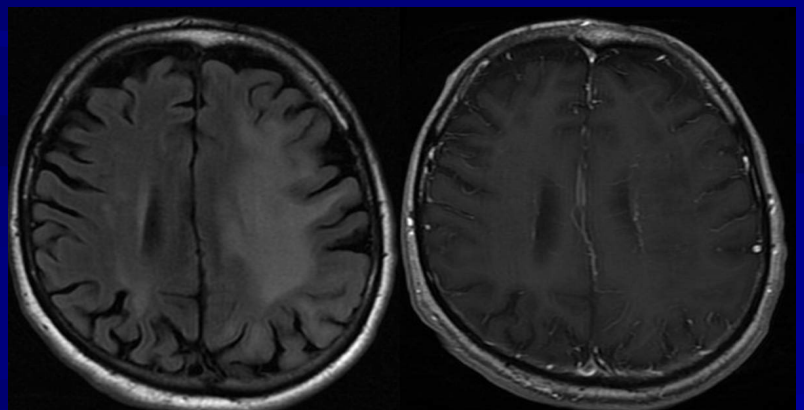
- Results:
- 26-week mortality
  - **Earlier ART -45% [40 of 88 patients]**
  - Deferred ART-30% [27 of 89 patients]
- Excess deaths associated with earlier ART initiation occurred 2 to 5 weeks after diagnosis

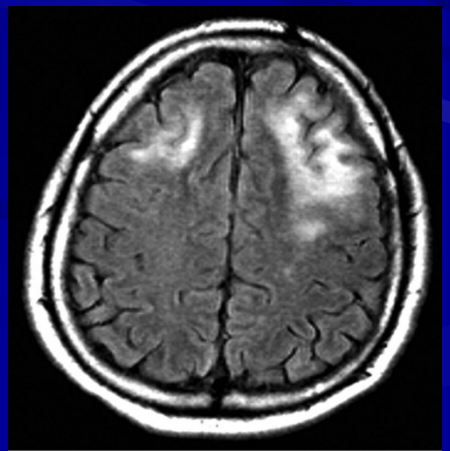
Primary CNS Lymphoma

- 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.
- EBV DNA in CSF is used as a marker of HIV-associated primary central nervous system lymphoma
- 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.
- Radiological findings
  - Single or multiple lesions
  - Involve the corpus callosum or the periventricular areas
  - > 4 cm in size are more likely to be lymphoma.



- **Progressive Multifocal Leukoencephalopathy**
  - Caused by the polyoma virus JC virus
    - Seroprevalence of **39% to 69%** among adults.
      - Primary JCV infection occurs in childhood
- PML manifests as focal neurological deficits
  - Cognitive impairment, focal deficits, ataxia
  - Subacute- weeks to months
- The lesions are
  - hyperintense (white) on T2
  - hypointense (dark) on T1
  - **non-contrast enhancing** and produce **no mass effect**





Diagnosis

- Antibody testing - not reliable for the presence of active PML, as an estimated 86% are seropositive
- CSF
  - Typically normal with absence of leukocytes
  - Protein is mildly elevated, but < 100 mg/dl
- PCR for JC virus - **best non-invasive test for confirmation of PML**
  - PCR based diagnosis has a reported sensitivity of 75% and specificity of 96%.
- 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%.

Bossolasco: CID 2005

Patient , 34 years old, with PML

B/L Dysdiadochokinesia, dysmetria, intention tremor, nystagmus

Cytomegalovirus Retinitis

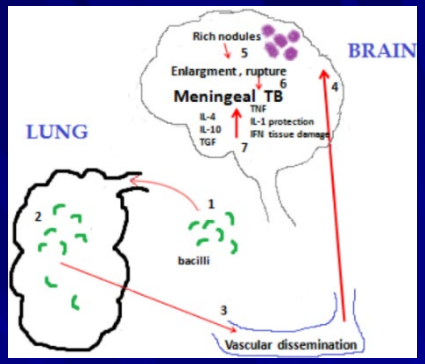
- Usually with CD4< 50
- CMV retinitis is a full-thickness necrotizing retinitis
- In patients with unilateral CMV retinitis and CD4 count <50 cells/mm^3, rates of contralateral disease are high
- Colitis occurs in 5% to 10% : weight loss, anorexia, abdominal pain, debilitating diarrhea

Diagnosis and Treatment of CMV

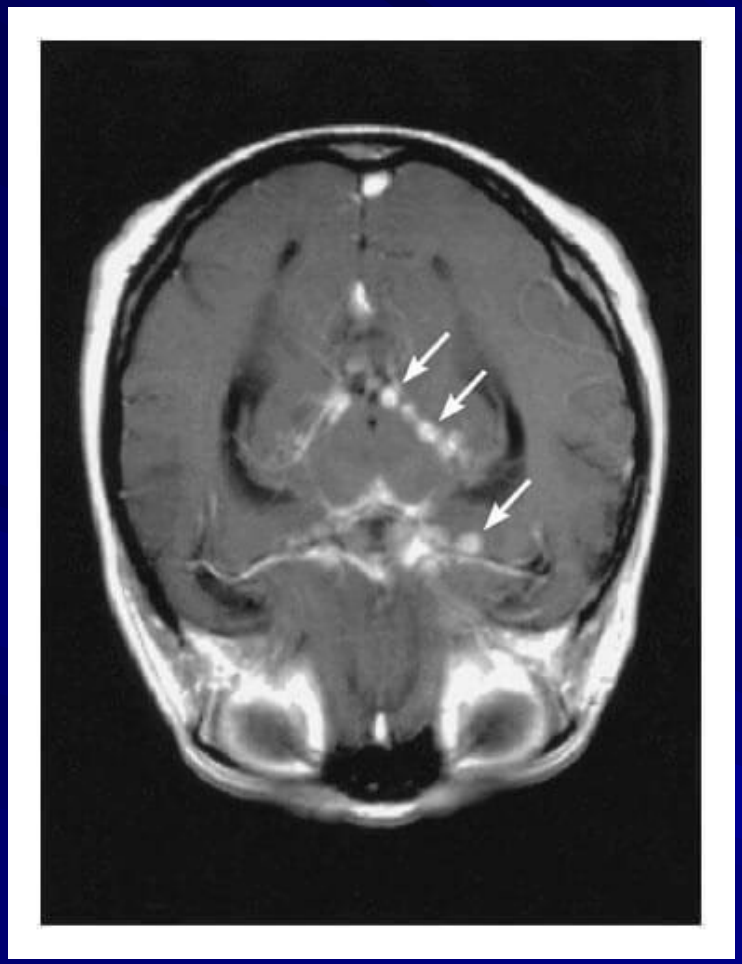
- Diagnosis:
  - NO Role of CMV IgG in HIV infected patients
  - Use PCR: blood and CSF.
  - Tissue biopsy if available is **best** as denotes CMV end-organ disease rather than colonization
- Treatment
  - ART
- Anti-virals:
  - IV ganciclovir
  - OR PO valganciclovir (this is a prodrug with good bioavailability)
  - Intravitreal injections of ganciclovir or foscarnet

Concomitant treatment with systemic anti-CMV therapy

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.

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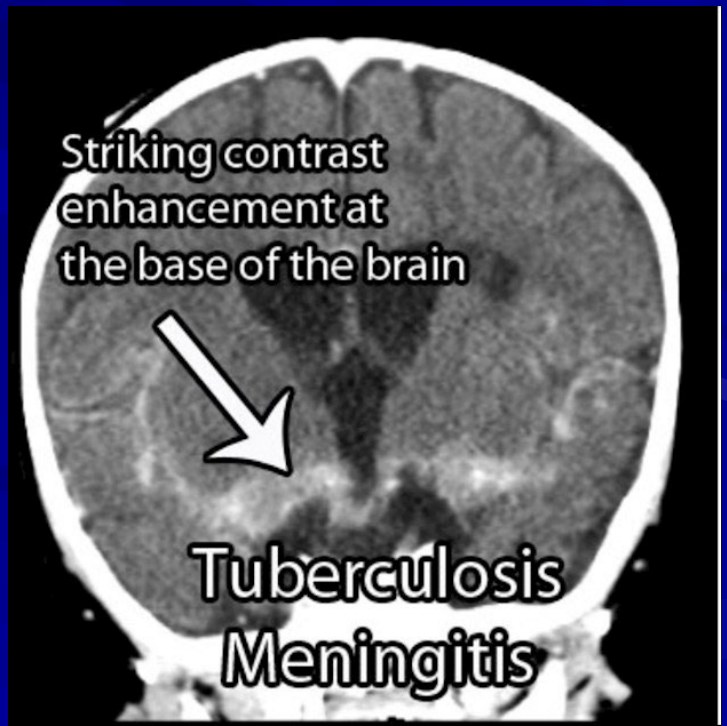
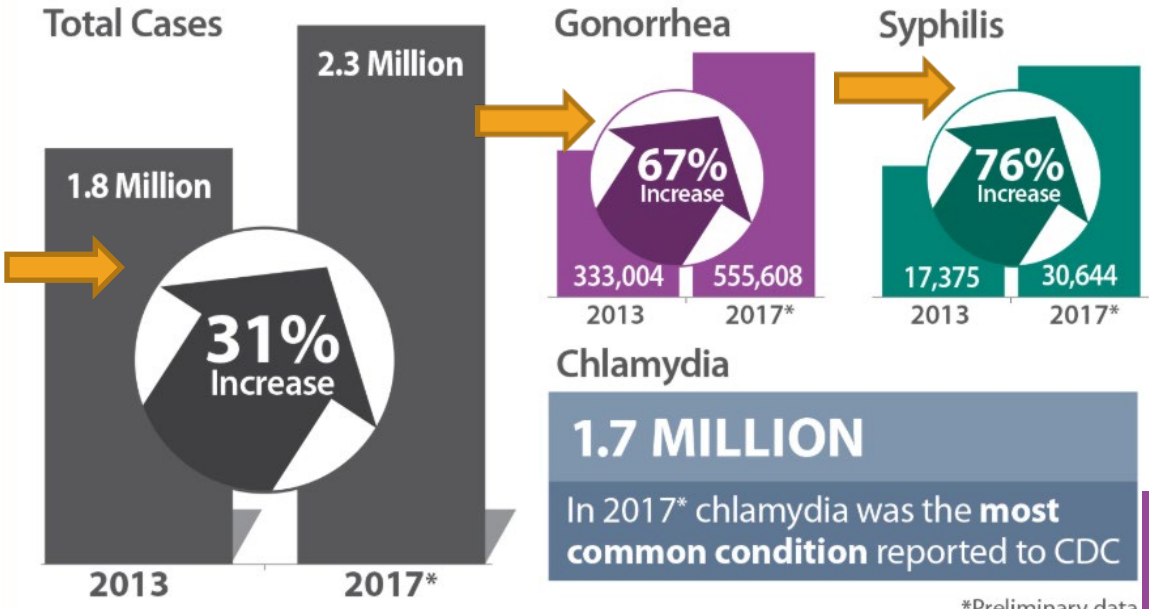

Striking contrast
enhancement at
the base of the brain
Tuberculosis
Meningitis

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**



Chlamydia

1.7 MILLION

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

- infertility
- ectopic pregnancy
- increased HIV risk

AETC AIDS Education & Training Center Program Southeast

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