Neurobiology and Neuropsychology of HIV

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AUGUST 31, 2017

History

- In the early 1980s, epidemiologists noted sharp increase in two conditions among American homosexual men:
  - Kaposi's sarcoma, a rare cancer
  - Pneumocystis pneumonia, a form of pneumonia that occurs only in people with a compromised immune system
- The failure of the immune system that allowed the growth of rare cancers and the development of rare infections came to be known as AIDS
- Immune system failure was found also in injecting drug users, hemophiliacs, and recipients of blood transfusions as well as in bisexual men.
- Some time later, the syndrome began to occur in heterosexuals who weren't drug users, hemophiliacs, or recipients of blood transfusions

My Experience with AIDS Epidemic: A historical and cautionary perspective – Surviving the pandemic

- 1978: Became a postdoc resident at Kaiser Psychiatry in San Francisco. I am a married heterosexual. San Francisco is a mecca for gay men. Had had only a few interpersonal encounters with gay men historically. Two men on staff were closeted gay men (both eventually die of AIDS). Many gay bath houses in the city.
- Circa 1982, SF Chronicle newspaper begins publishing articles about a mysterious disease among gay men who developed a rare pneumonia (Pneumocystis pneumonia (PCP)) and a rare cancer with red spots (Kaposi's sarcoma). No knew what the cause was. It was labelled the "gay man's" disease. People feared contagion: that you could get it by kissing, saliva, toilet seats, use of poppers (amyl nitrate), casual household transmission, IV drug use, etc.
- Psych dept. held a meeting about staff concerns. Fear of all of the unknowns. Some staff members stated they would not treat anyone who identified as being gay. People were scared and prejudiced.

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A historical and cautionary perspective 2

- Began also appearing in Haitians, hemophiliacs, mother to child transmission. In Africa, the new wasting disease, “slim”. Became clear it was a blood born or sexually transmitted disease. AIDS name adopted in July of 1982. Still lots of fear. Fears about blood supply – homosexual men banned. By end of 1983, 3000 US cases.
- My first experience of shaking hands with a gay male patient was anxiety ridden. Had to overcome my fear of unknown contagion. An explosion of gay men in clinic with fear of disease, anxiety, and depression. Staff would see men who died of PCP after only 2-6 months of tx.
- Closure of gay bath houses in SF as civil rights issue. By 1984, 7900 cases.

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- New virus test announced. Multiple names: LAV, HTLV-III, HIV, AIDS. Issues of confidentiality (in public and medical charts) and telling partners.
- Epidemic of fear: hemophiliacs were seen as the "innocent victims" of AIDS whereas gay men and drug-users were seen as having brought the disease upon themselves. The fear of AIDS caused firemen to ban mouth contact in CPR. HIV kids banned from schools. Actor Rock Hudson dies of AIDS
- 1986: “HIV” name. Gays dismissed from jobs, housing. 38,000 cases.
- 1987: AZT first use. Previously, smuggling drugs from Mexico. Ban on HIV persons entering U.S. 300,000 cases. ACT-UP vs pharmaceuticals.

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- 1987: Universal precautions introduced in hospitals – avoid bodily fluid contact. Use of hand washing in hospitals. Safe sex practices – use a condom. Needle exchange programs
- 1998: 6 million infected; drug companies reduce cost of HIV drugs
- 2000: 34 million infected; 30% of young gay black men were infected with HIV; Kaiser Psych begins hiring gay identified therapists
- 2003: 38% of population of Botswana has HIV. Multiple antiviral meds begin.
- 2008: sale of fake meds in Africa
- 2010: 44 percent reduction in HIV infection risk among HIV-negative participants taking a daily dose of antiretroviral drugs
- 2013: 2 million new infections per year. In Uganda, “Anti-Homosexuality Bill” – kill gays.
- 2015: Gay marriage is legal. 39 million people have died since the first cases were reported in 1981 and 1.5 million people died of AIDS-related causes in 2013. HIV is still the world’s leading infectious killer.

HIV/AIDS: The disease

- Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV).
- Before HIV medication was available, PCP occurred in 70% to 80% of HIV-positive people.
- Following initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the infection progresses, it interferes more and more with the immune system, making the person much more susceptible to common infections like tuberculosis, as well as opportunistic infections and tumors that do not usually affect people who have working immune systems.
- The late symptoms of the infection are referred to as AIDS. This stage is often complicated by an infection of the lung known as pneumocystis pneumonia, severe weight loss, a type of cancer known as Kaposi's sarcoma, or other AIDS-defining conditions.

HIV transmission

- HIV is transmitted primarily via unprotected sexual intercourse (including anal and oral sex), contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Some bodily fluids, such as saliva and tears, do not transmit HIV.
- There is no cure or vaccine; however, antiretroviral treatment (HRT, HAART, cART) can slow the course of the disease and may lead to a near-normal life expectancy.
- While antiretroviral treatment reduces the risk of death and complications from the disease, these medications are expensive and have side effects. Without treatment, the average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype.
- After the diagnosis of AIDS, if treatment is not available, survival ranges between 6 and 19 months.

Pandemic

- Since its discovery, AIDS has caused an estimated 36 million deaths worldwide (as of 2012). In 2013 it resulted in about 1.34 million deaths. As of 2012, approximately 35.3 million people are living with HIV globally.
- HIV/AIDS is considered a pandemic—a disease outbreak which is present over a large area and is actively spreading.
- Genetic research indicates that HIV originated in west-central Africa during the late nineteenth or early twentieth century.
- AIDS was first recognized by the United States Centers for Disease Control and Prevention (CDC) in 1981 and its cause—HIV infection—was identified in the early part of the decade.

Cause of death and Treatment

- The primary causes of death from HIV/AIDS are opportunistic infections and cancer, both of which are frequently the result of the progressive failure of the immune system.
- HRT and appropriate prevention of opportunistic infections reduces the death rate by 80%, and raises the life expectancy for a newly diagnosed young adult to 20–50 years
- Even with anti-retroviral treatment, over the long term HIV-infected people may experience neurocognitive disorders, osteoporosis, neuropathy, cancers, nephropathy, and cardiovascular disease.
- Practice safe sex! Do not be afraid of working with HIV patients.

Developing vs. Developed countries

- HIV is more prevalent in developing countries than developed countries.
- Most (89%) of the 30.6 million of HIV infected people are estimated to live in sub-Saharan Africa and developing countries of Asia
- Treatment is often delayed
- Heavy disease burden persists because of eventual neurological opportunistic infections especially cryptococcal and tubercular meningitis, toxoplasma encephalitis, and progressive multifocal leukoencephalopathy

Prevalence: Global

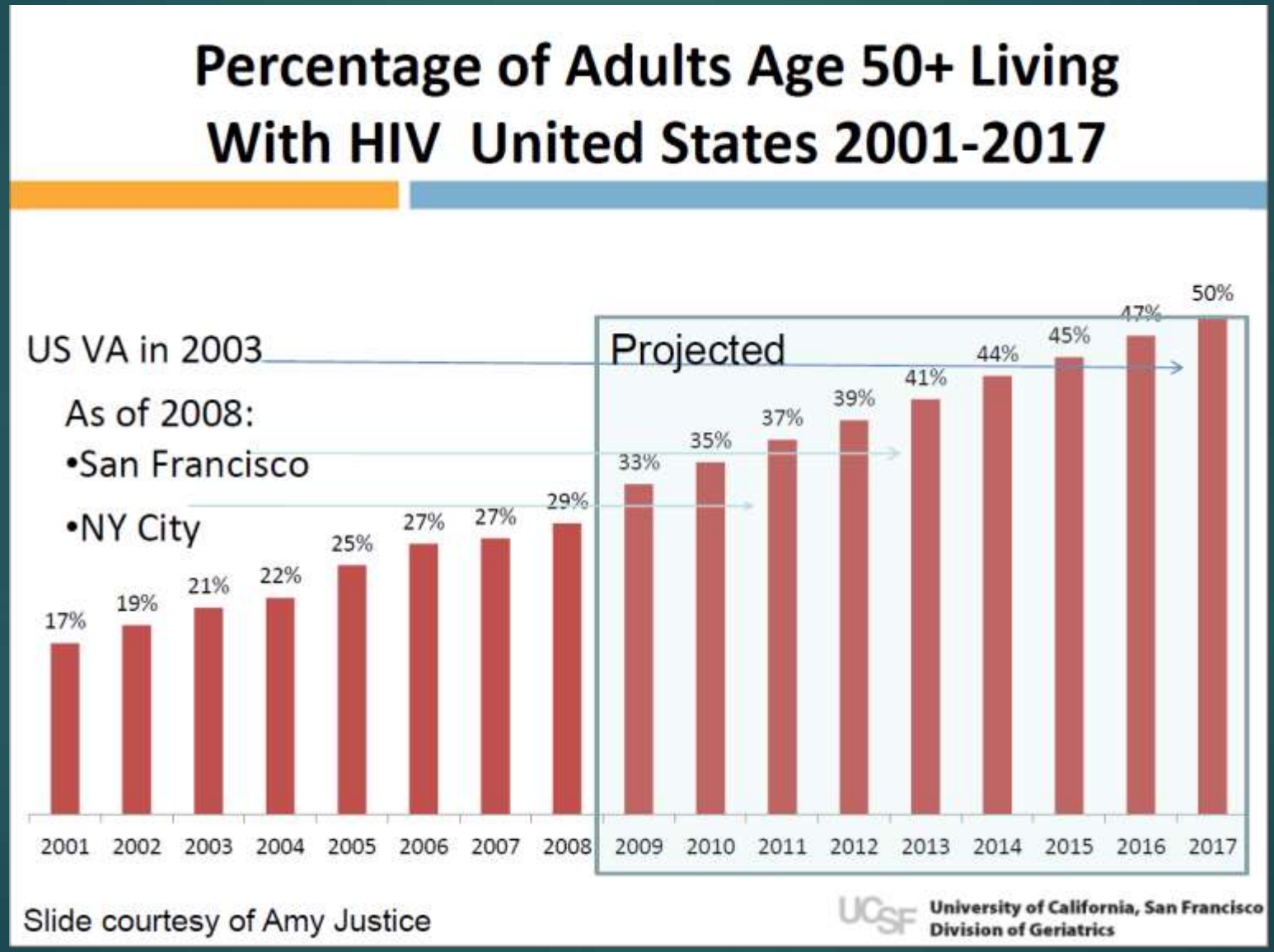
- 35 million individuals live with HIV infection
- Low and middle income countries of Asia and Africa most heavily impacted
  - 1/20 adults w/ HIV is in Sub-Sahara Africa (WHO)
- HIV strands common in United States and Europe may be more neurovirulent than virus in Africa, India and Brazil (Woods et al, 2009).

Prevalence: USA

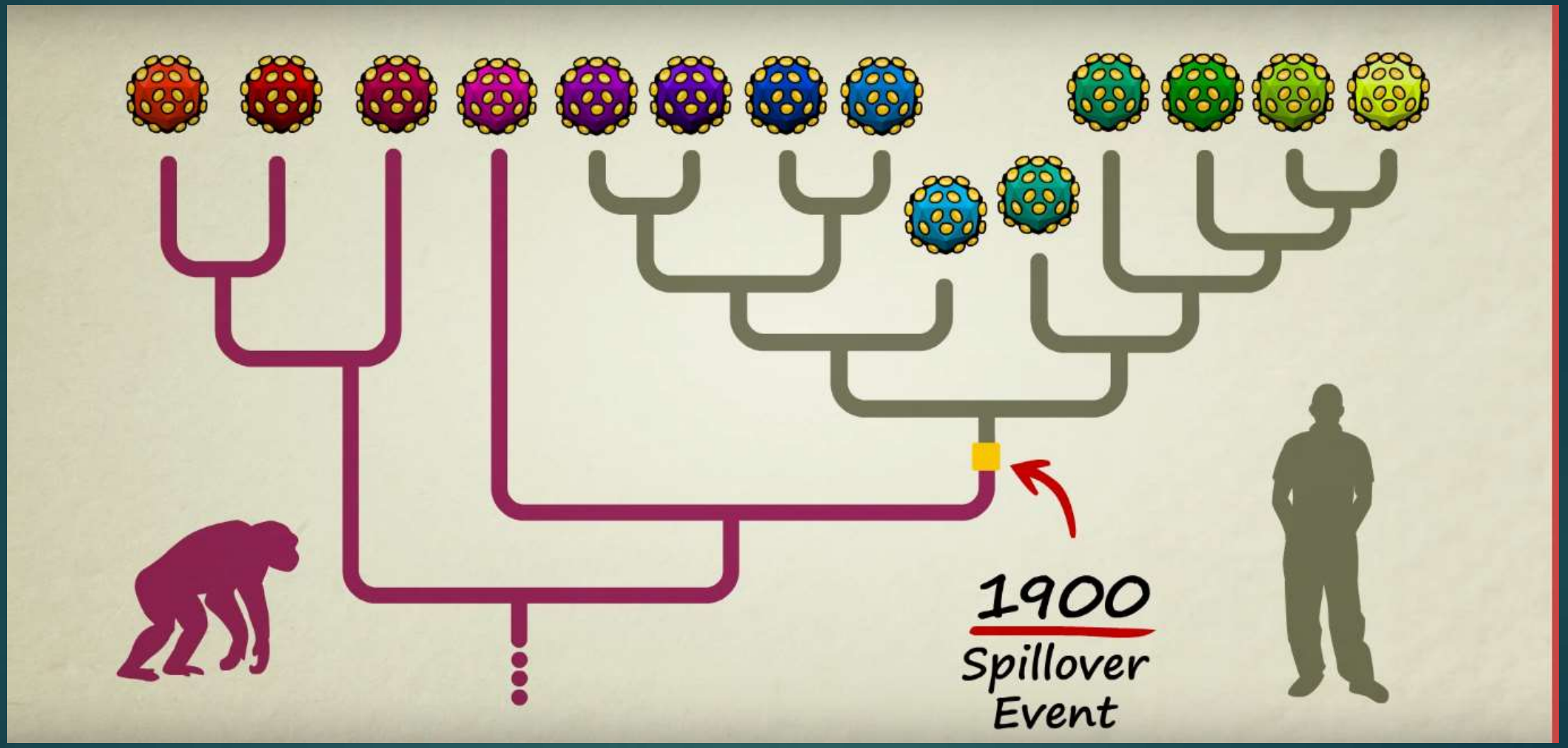
- More than 1.1 million people in the United States are HIV+
- 1 in 5 (18%) are unaware they are infected
- Incidence rate: approximately 50,000 new HIV infections per year
- Most vulnerable populations are MSM (Men having Sex with Men) and African Americans.

From CDC 10/28/13: http://www.cdc.gov/hiv/pdf/statistics_basics_factsheet.pdf

Longer Survival

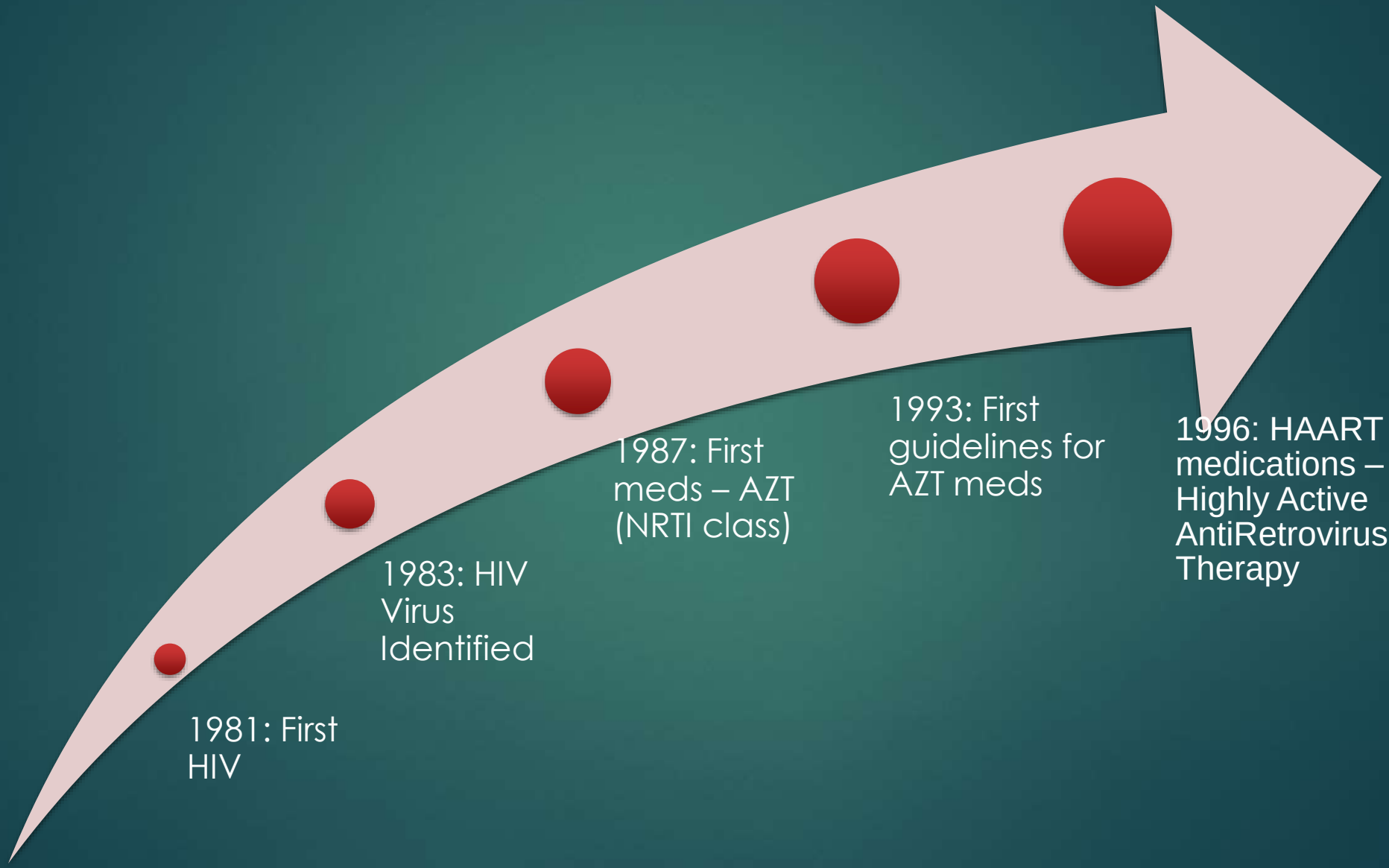


Origin of HIV virus: not patient 0 in 1980s



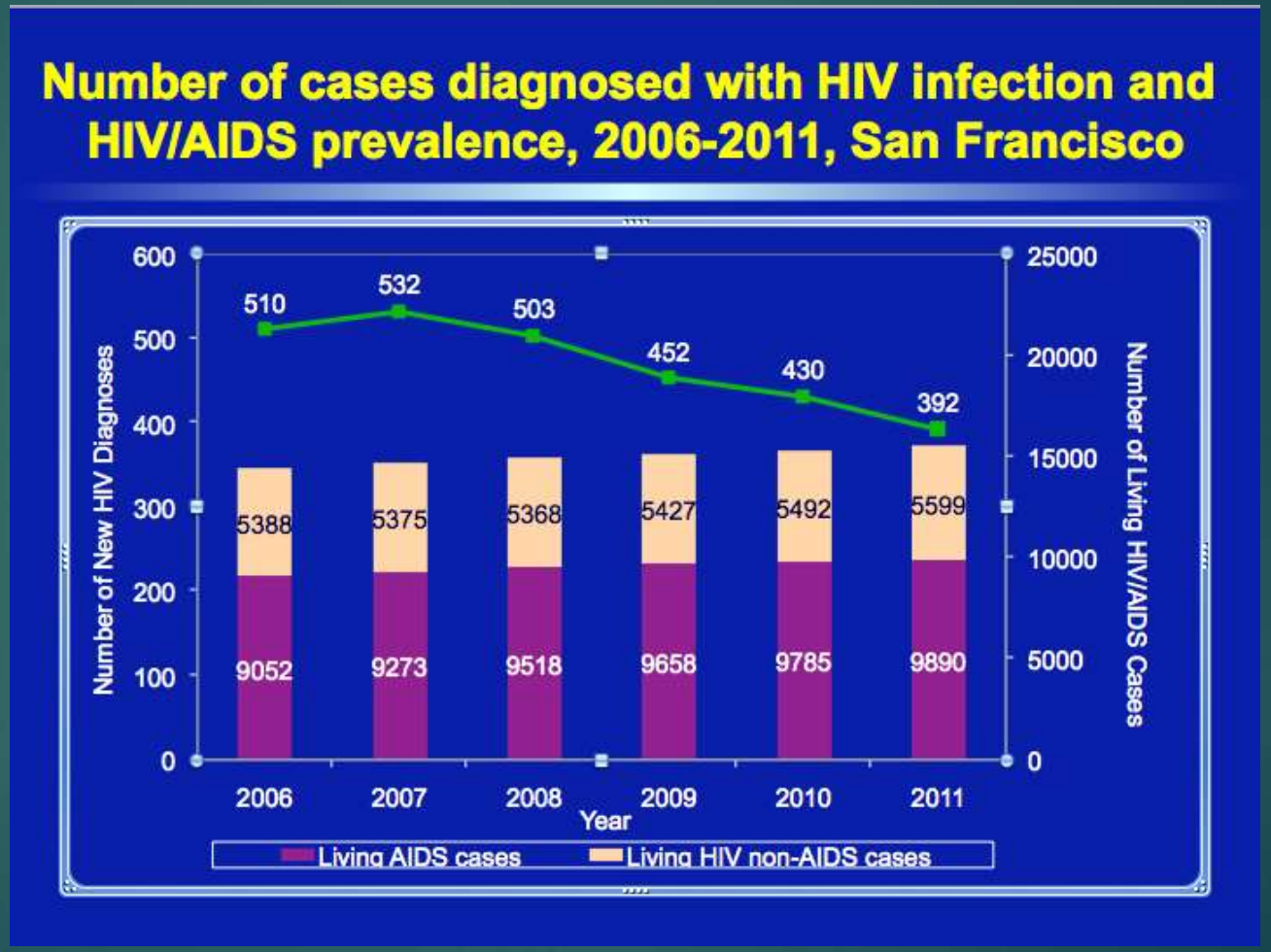
In 1900, African hunter in Cameroon was pt 0

History Timeline



San Francisco HIV infection: 302 new HIV diagnoses in 2014 year, and 177 deaths of HIV-infected people

S.F. 2017=
15,995 people living with HIV.



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Neurobiology of HIV

(Human Immunodeficiency Virus)

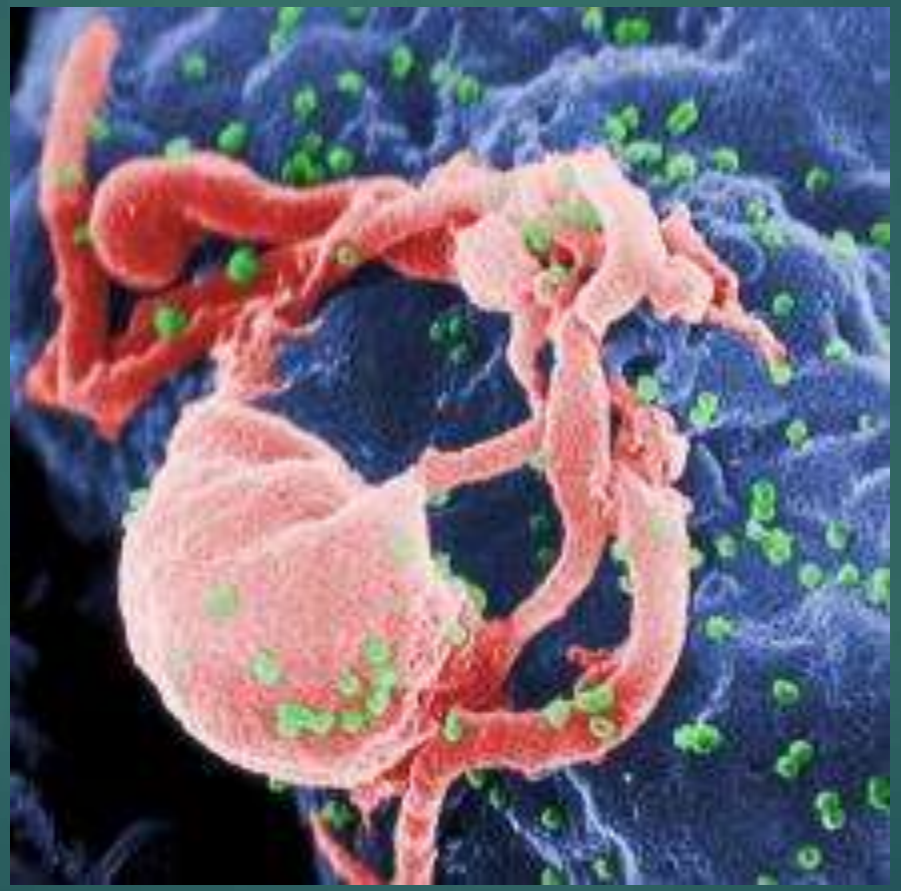
- HIV is a lentivirus (slow incubation) that can severely compromise immune function by damaging CD4 lymphocytes, thereby increasing the risk of opportunistic infections and cancers.

- It is highly neurovirulent.

- It can penetrate the blood brain barrier early in course of infection via white blood cells (monocytes), replicating in macrophages and microglia.

- It also triggers a cascade of neurotoxic molecular events.

Scanning electron micrograph image of HIV-I budding from cultured lymphocyte

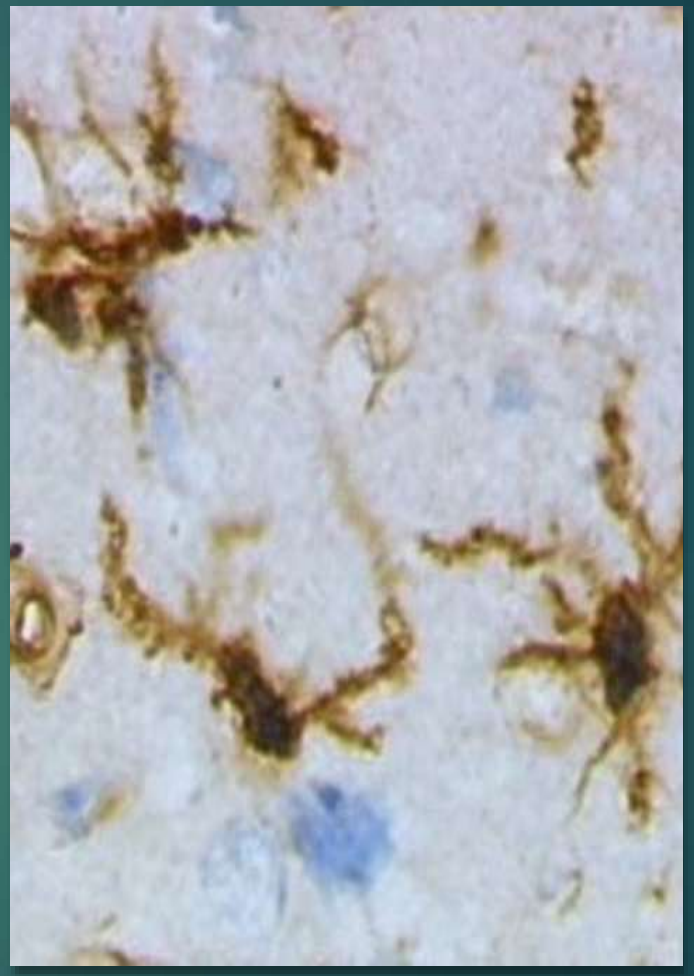


Green = HIV

Centers for Disease Control and Prevention/Cynthia Goldsmith)

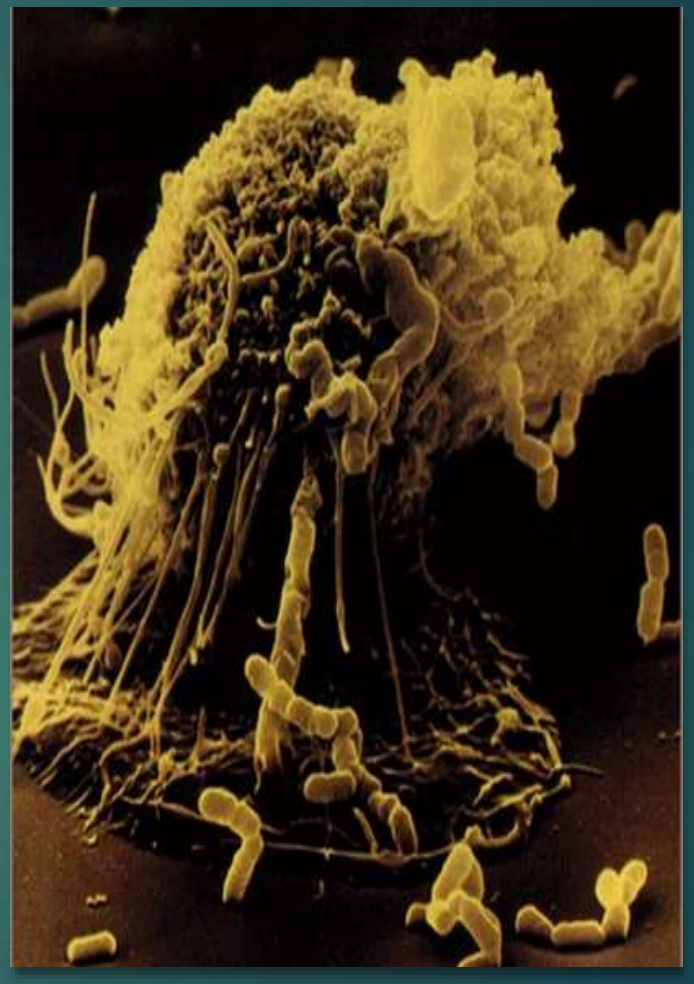
Microglia

Main form of active immune defense in CNS



Macrophage

Large cells that destroy target cells.



Biology of HIV Infection

- Human Immunodeficiency Virus (HIV) infection is an infection by one of two (retro) viruses that progressively destroy white blood cells called lymphocytes, causing Acquired Immunodeficiency Syndrome (AIDS) and other diseases that result from suppressed immune system.
- **Types**
  - *HIV-1* : Most common in the Western Hemisphere, Europe, Asia, and in Central, South, and East Africa
  - *HIV-2 :* Most common in West Africa, although HIV-1 also exists

Biology of HIV infection

Virus enters lymphocytes

Viral genetic material incorporated into the DNA of an infected cell

The virus reproduces itself inside the cell, eventually destroying the cell and releasing new virus particles.

The new virus particles infect other lymphocytes and may destroy them as well

The destruction of helper T lymphocytes weakens the body's immune system

The Human Immunodeficiency Virus

- Lentivirus (lente- Latin for ‘slow’)
  - A genus of viruses characterized by long incubation period.
- Damage cluster of differentiation 4+ (CD4) lymphocytes (T-helper cells)
- Thereby increase risk of opportunistic infections and cancers

1. • Normal CD4+ : 800 to 1,300 cells per microliter of blood
2. • Seroconversion (2 weeks to 3 months?): Possible flu-like sxs
3. • In the first few months CD4+ may decrease by 40-50%
4. • w/in first year, rapid viral replication and neuroinflammatory response before viral load stabilizes
5. • Possible years w/ slow decline to below normal CD4+
6. • 1 to 2 years before AIDS, CD4+ may drop rapidly
7. • Risk of infection increases as CD4+ falls below 200 cells per microliter of blood

The Virus

- **Highly Neurovirulent**
  - Penetrates the blood-brain barrier (BBB) early in the course of infection
    - Likely due to trafficking infected circulating white blood cells (e.g. monocytes) across BBB
  - HIV in most regions of brain, but predilection for frontal, subcortical regions, and particularly basal ganglia

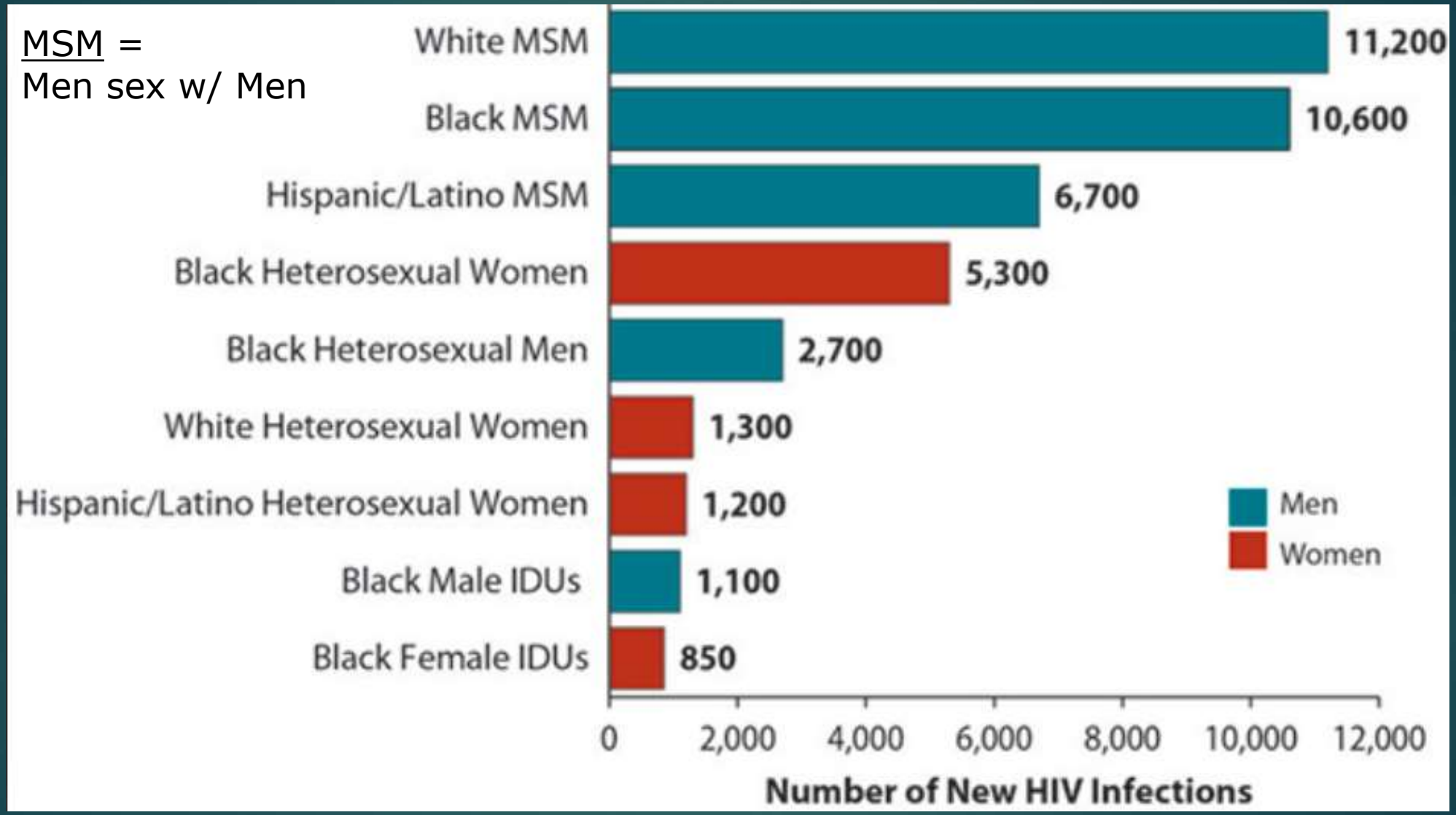
Infection

- 1 in 100 infected if semen recipient
- 1 in 1000 if semen donator

- Risk for HIV infection
  - anyone who engages in unsafe sex (unprotected sex with an infected partner)
  - Male to male sexual contact (61%); ethnic minorities (64% of MSM)
  - Heterosexual contact (21%); women 86%
  - Injection drug use (8%)
  - 50% are unaware they are infected; being poor is a risk factor

Risk for HIV Infection

MSM =
Men sex w/ Men



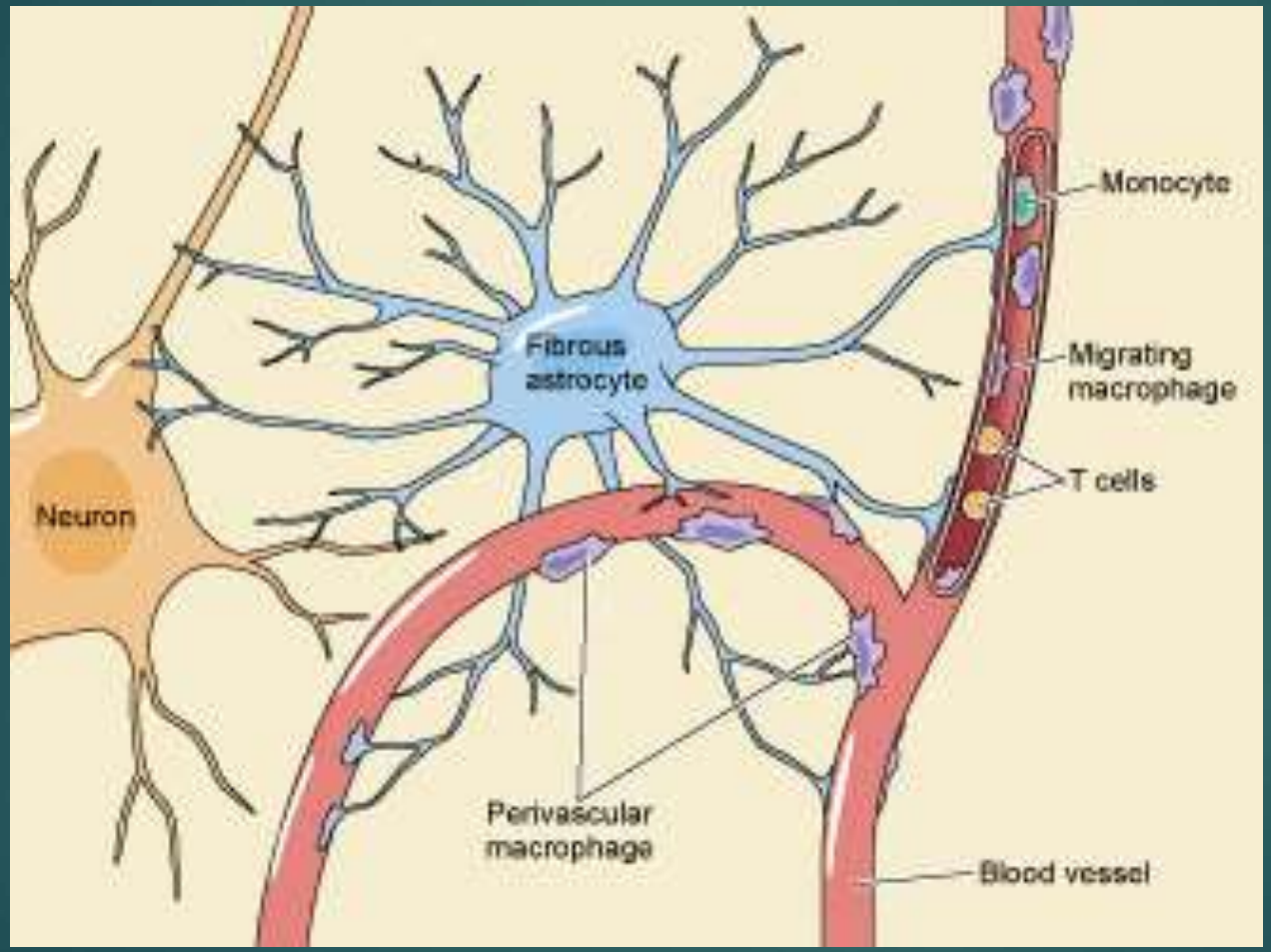
IDU = injecting drug user

How Does HIV Affect the CNS

- HIV is a neurotropic virus
- HIV crosses blood-brain barrier
- HIV infects macrophages and microglia, but not neurons, although neurons are injured and die by apoptosis.
- HIV has *indirect* effect on neurons
- HIV has the potential to cause disease at all CNS levels
- CSF viral loads tend to be higher in individuals with NP impairment

How Does HIV Affect the Nervous System?

- HIV easily crosses the blood-brain barrier



Dave R, Pomerantz RJ. (2005). HIV neuropathogenesis: persistent infection, persistent questions. Science & Medicine.

Indirect neuronal damage

- The predominant pathway to neuronal injury is indirect through release of macrophage, microglial and astrocyte toxins, although direct injury by viral proteins might also contribute.
- These toxins overstimulate neurons, resulting in the formation of free radicals and excitotoxicity.

HIV has high affinity for the CNS

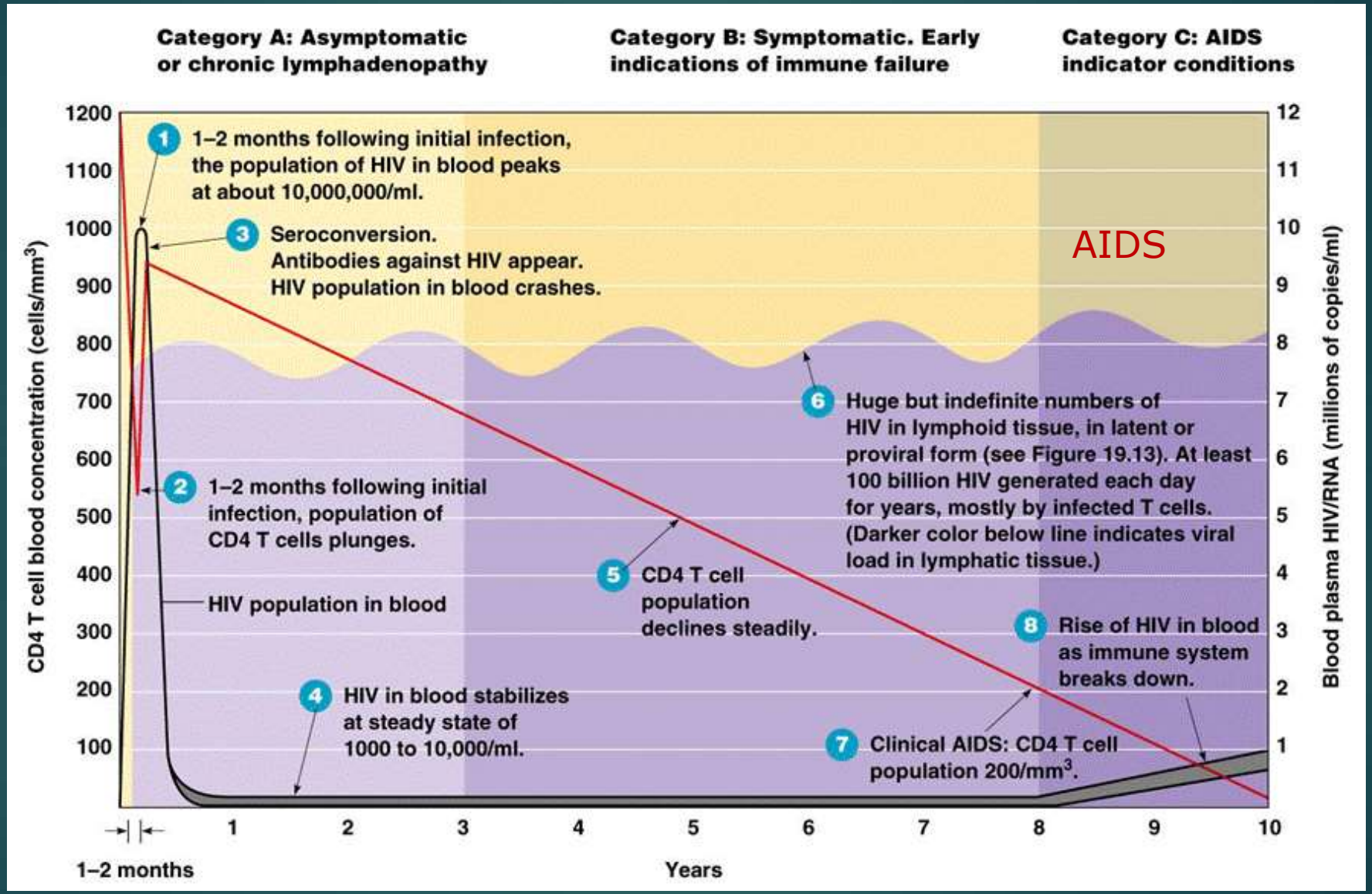
- HIV causes brain encephalitis (inflammation)
- Neurochemical changes
- Structural Damage:
  - Neuronal loss in the frontal, temporal, and parietal lobes
  - Dendritic injury
  - Decreased connections between brain cells
  - Esp. effects cerebral white matter & fronto-striato-thalamic circuits.

Major et al., 2000; Goudsmit et al., 1986; Ellis et al., 1997; Stankoff et al., 1999; Masliah et al., 1992; 1994; 1997

Course of HIV increase & CD4 decrease

Red = CD4

Black = HIV



http://classes.midlandstech.edu/carterp/Courses/bio225/chap19/Slide20.GIF

HIV variability

- HIV has very high genetic variability. This diversity is a result of its fast replication cycle, with the generation of about 10^{10} virions (10 Billion) every day, coupled with a high mutation rate of approximately 3×10^{-5} per nucleotide base per cycle of replication and recombinogenic properties of reverse transcriptase.
- Causes generation of many variants of HIV in a single infected patient in the course of one day.
- This variability is compounded when a single cell is simultaneously infected by two or more different strains of HIV.
- Modern HIV testing is extremely accurate. A single screening test is correct more than 99% of the time

Classification of HIV Nervous System Disease

- Primary Disease (caused by HIV alone)
  - NCD due to HIV
- Secondary (opportunistic infections associated with immunodeficiency)
  - Fungal, Parasitic, Viral, TB, Bacterial, Cancer
- Tertiary (treatment complications)
  - Immune Reconstitution Inflammatory Syndrome (IRIS): inflammation

“Trojan horse” theory of HIV entrance into the CNS

- HIV enters CNS within 2 weeks of primary infection, crosses BBB by infected monocytes which differentiate into macrophages

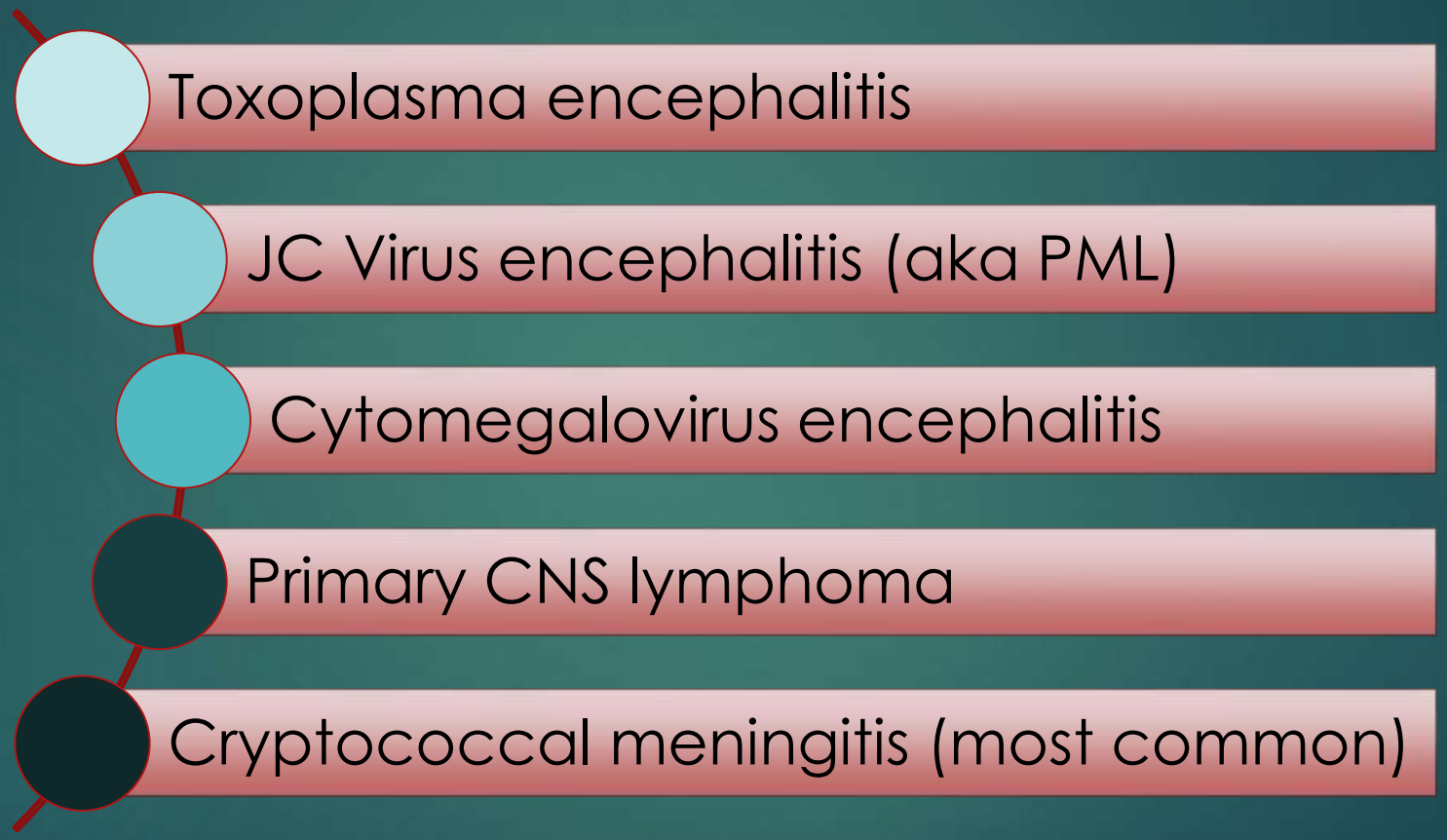
Trojan Horse 2

- Cell-free virus also enters by infecting endothelial layer of cells that line interior surface of blood and lymphatic vessels of BBB and diffusing into CNS
- Macrophages infect other cells in CNS by direct contact.
- Neurons do not become directly infected
- Cognitive impairment is caused by gradually increasing neuronal damage due to toxic effect of viral proteins, chronic inflammatory process and production of cytokines (a small protein released by cells that has effect on interactions, behavior, or interaction between cells)

HIV-associated Neurocognitive Disorder

- Neurocognitive ability is impaired in most patients with HIV
- Severe Major NCD rarely develops in pts on HRT
- Most patients with mild neurocognitive impairment are clinically stable
- Comorbid disorders contribute to neurocognitive impairment but do not fully explain it
- Typical HIV disease biomarkers (viral load or CD4) are no longer closely associated with impairment
- Cardiovascular disease and inflammatory markers are associated with impairment.

CNS Opportunistic Infections



Less common in cART era
Most common during periods of immunosuppression (CD4 <200 cells/μL)

Bio-Markers of HIV-Associated Neurocognitive Disorders

CD4 Lymphocyte Count

- Primary target of HIV are CD4 lymphocytes
  - Type of white blood cell (leukocytes)
- Normal CD4 = 800-1200 cells/μL
- Nadir CD4 (lowest known CD4 count) predictive of HAD even if current CD4 count is OK

Viral Load: HIV RNA

- Quantified in blood plasma or CSF
- Plasma viral load important to monitor tx efficacy BUT
  - Not reliably predictive of HIV-associated NP impairment
- Viral compartmentalization in the CNS

Viral Load Continue

- Ellis et al (2002) found that CSF HIV RNA levels (≥200 copies/mL) predicted progression to NP impairment even if presently no significant impairment.
  - Particularly worsening attention, learning and motor functioning.
  - They suggest monitoring CSF viral load BEFORE you note any cognitive issues.

Biomarkers

- Chemokines (small signaling proteins (aka cytokines) often associated with inflammatory response)
- Neuroprotective factors
- Markers of neuroinflammation
- Markers of oxidative stress
- Markers of neuronal damage

Lab results: What do they mean?

- CD4 count:
  - CD4 cells are helper T-cells that destroy infected cells
  - HIV targets and kills CD4 cells
  - Significant decline in CD4 cells signals that the immune system is losing the battle with HIV
  - Nadir count (lowest ever of CD4 cells): significantly predicts Major NCD (difference of 100 cells associated with 40% increased risk of Major NCD)
  - CD4 declines correlate with Caudate atrophy
  - Normal: above 450; most people have >500-1500
  - <200 = AIDS (acquired immunodeficiency syndrome)
  - <50 = opportunistic infections likely

Lab results #2

CD8: suppress the action of other immune cells

CD4%: percentage of T-cells that are CD4 cells

CD8%: percentage of T-cells that are CD8 cells

HIV-1 RNA Quant: viral load in the blood. Should be less than 500 copies.

CD4 count seems to be a better marker for cognitive decline than viral load; but ?? remain

HIV-associated Neurocognitive Disorder

- Optimum HIV therapy is necessary, but not sufficient, to avert cognitive impairment
- Neither higher CNS-penetrating combined antiretroviral therapy nor adjuvant treatments have proven to be effective to reverse HIV-associated neurocognitive disorder
- http://www.cats.org/gallery/160158/HIV

CV risk in HIV infection

- Chronic inflammation, which persists during effective antiretroviral therapy, is directly and causally associated with vascular dysfunction and the accelerated development of atherosclerosis.
- Most maintain plasma levels of human immunodeficiency virus (HIV) RNA that are undetectable by conventional assays.
- Treatment-mediated suppression of HIV replication results in immune reconstitution, less morbidity, and a prolonged life span.
- Despite these unquestioned successes of therapy, HIV-infected adults treated with antiretrovirals have excess risk of morbidity and, perhaps, mortality.

CV risk in HIV infection

- Complications include cancer, liver disease, renal disease, neurocognitive decline, and osteoporosis.
- Another important cause of premature morbidity and mortality appears to be cardiovascular complications.

- For reasons that have not yet been fully defined, long-term–treated patients have a greater prevalence of atherosclerosis and vascular dysfunction than age-matched uninfected adults.

- They also have increased risk of myocardial infarction, heart failure, and other vascular diseases.

Cardiovascular effects

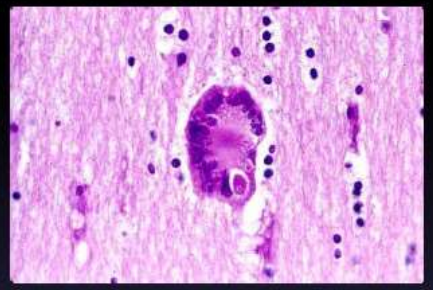
- Asymptomatic case: 79 yo male with broad atrophy and WM decline
- Ischemic stroke increase (F. Chow, 2011); worse in women
- 50% small vessel disease with HIV protease inhibitors, eps. Lipids
- WM lesion increase correlated with CV risk factors and smoking
- WM decrease correlated with EF decline

Brain pathology from HIV

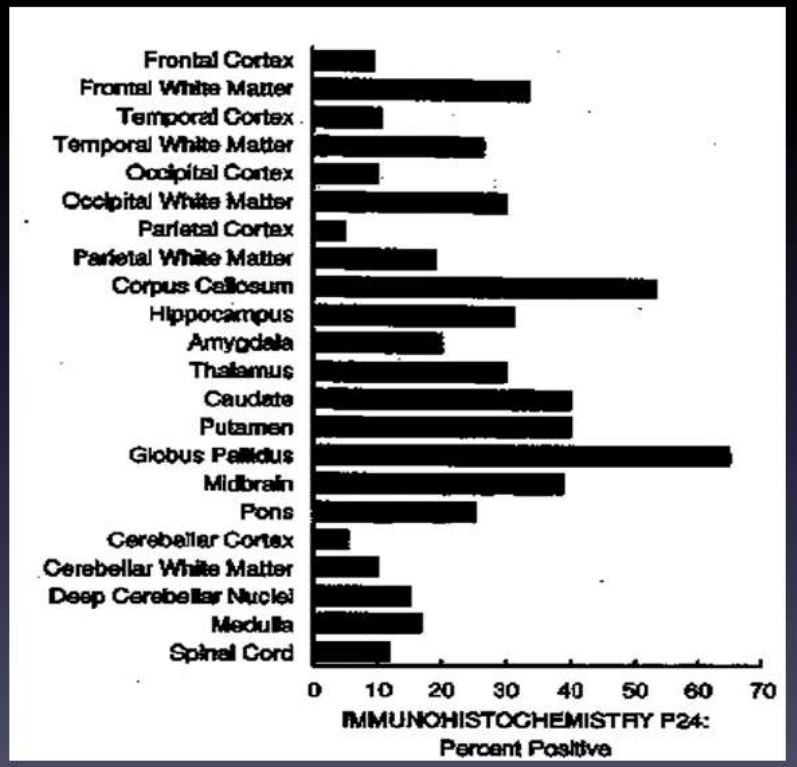
- HIV replicates in perivascular region in macrophages and microglia which can later fuse to form multinucleated giant cells – a hallmark of HIV Encephalitis (i.e. inflammation of the brain due to the HIV virus)
- Widespread axonal, dendritic and synaptic damage – particularly decrease in dendritic complexity
- Myelin pallor, microglial activation, neuronal loss by apoptosis

HIV is a white matter and deep grey disease: slow motor and processing speed deficits

HIV Neuropathology



- Perivascular monocytes and multinucleated giant cells (above)
- High frequency in white matter & deep grey matter



Neuropathology of AIDS 1998

R. Price, 1998

Brain Imaging findings

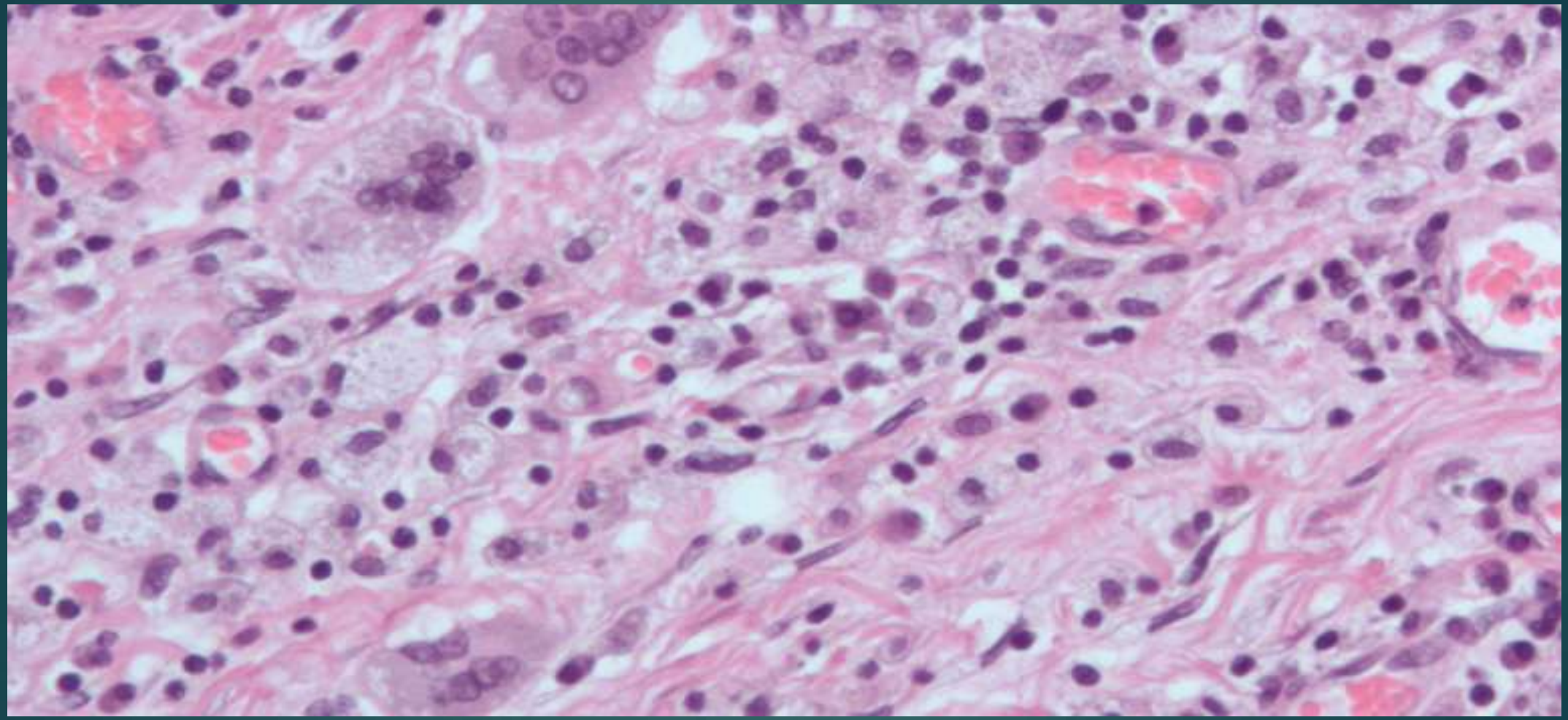
- Increased ventricular and sulcal spaces
- White and gray matter atrophy
- White matter signal abnormalities
- More prominent findings in basal ganglia and white matter

1996: HART

Pre- / Post HAART Medication

- HAART (highly active antiretroviral therapy) became standard of care in US in 1996 (Scott and Marcotte, 2010)
- HAART medication has variable penetrance of the BBB
- Post- HAART: Continue to observe signs of inflammation, possibly unchanged (Tate et al, 2010).
- Site of inflammation may have shifted to hippocampus and surrounding regions of temporal cortex
- Also note elevated levels of hyperphosphorylated paired helical filament (PHF) Tau and beta amyloid proteins associated with Alzheimer's pathology in hippocampus
- May suggest accelerated neuro-aging

HIV Encephalitis: Multinucleated Giant Cells



HIV Encephalitis

- Cognitive deficits associated with HIV – neuropathological causes suspected is HIV Encephalitis
  - Sub-acute inflammatory response in brain related to infection of brain cells with HIV-1
    - HIV-1 always infects brain, however, does not always trigger same level of inflammatory response – may be related to CSF viral load
  - No characteristic anomaly although mild brain atrophy may be present

Portegies and Berger, 2007

HIV Encephalitis: Histological Findings

- Hallmark: Multinucleated Giant Cells
- Most common in perivascular sector of brain white matter
- macrophages and microglia fused by HIV-1 glycoprotein 41 (gp41)
- multiple microglial nodules (loosely aggregated clusters of activated microglial cells)
- loss of white matter (likely loss of axons, not just myelin like in MS)
- General sxs of inflammatory response.

Portegies and Berger, 2007

Virus in the brain

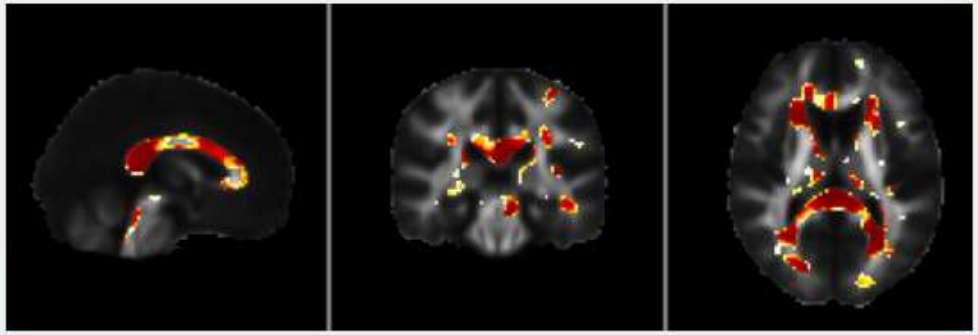
- Many opportunistic infections impact the brain. However, even without infection, virus has impact on the brain.
- Presented as nonspecific evidence of neurodegeneration on MRI
  - Diffuse white matter abnormalities
    - White matter hyperintensities (correspond with postmortem markers of synaptodendritic injury severity)
  - Enlarged ventricles
  - Enlarged subarachnoid spaces
- **Most vulnerable: cerebral white matter and fronto-striato-thalamo-cortical circuits**

WM fiber integrity decline correlates with NP, esp. EF, deficits

Imaging

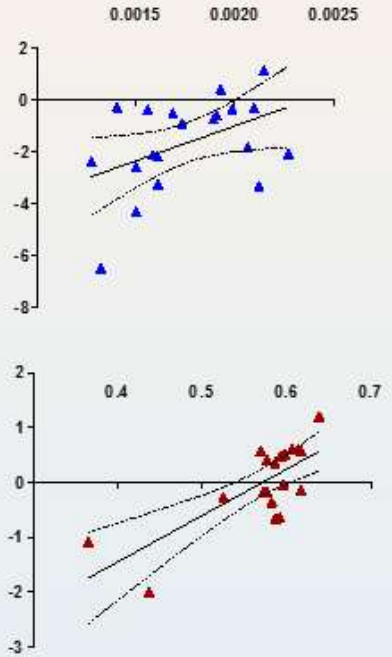
- Corpus Callosum volume and Fractional Anisotropy (FA) correlate to functional performance on the NAB

Regions of significant difference in fractional anisotropy (FA) correlated to NAB z-scores, controlling for age



Top panel: Correlation between NAB t-scores (y-axis) and corpus callosum volume as a fraction of ICV.

Bottom panel: Correlation between NAB t-scores (y-axis) and splenium FA.



From VG Valcour, MD, at Washington, DC: June 18, 2013, IAS-USA.

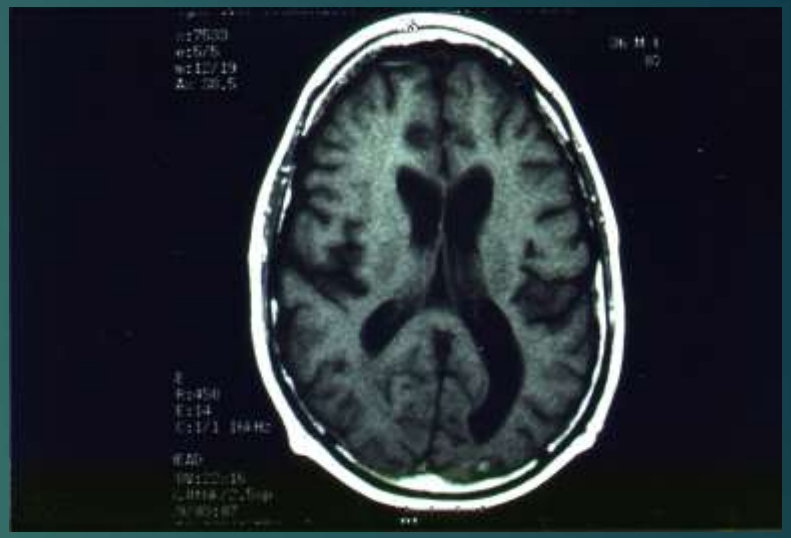
HIV-associated pathologies CNS

- Evident throughout the CNS including temporolimbic system
- However, research focus on frontal cortex and striatum (caudate nucleus, putamen)
  - Wiley et al (1998) HIV RNA viral load in caudate nucleus higher than in other brain regions for patients with HIV encephalitis
- HIV infection associated with structural abnormalities in frontal cortices (e.g. lower volume, and neocortical thinning)

(from Woods et al, 2009)

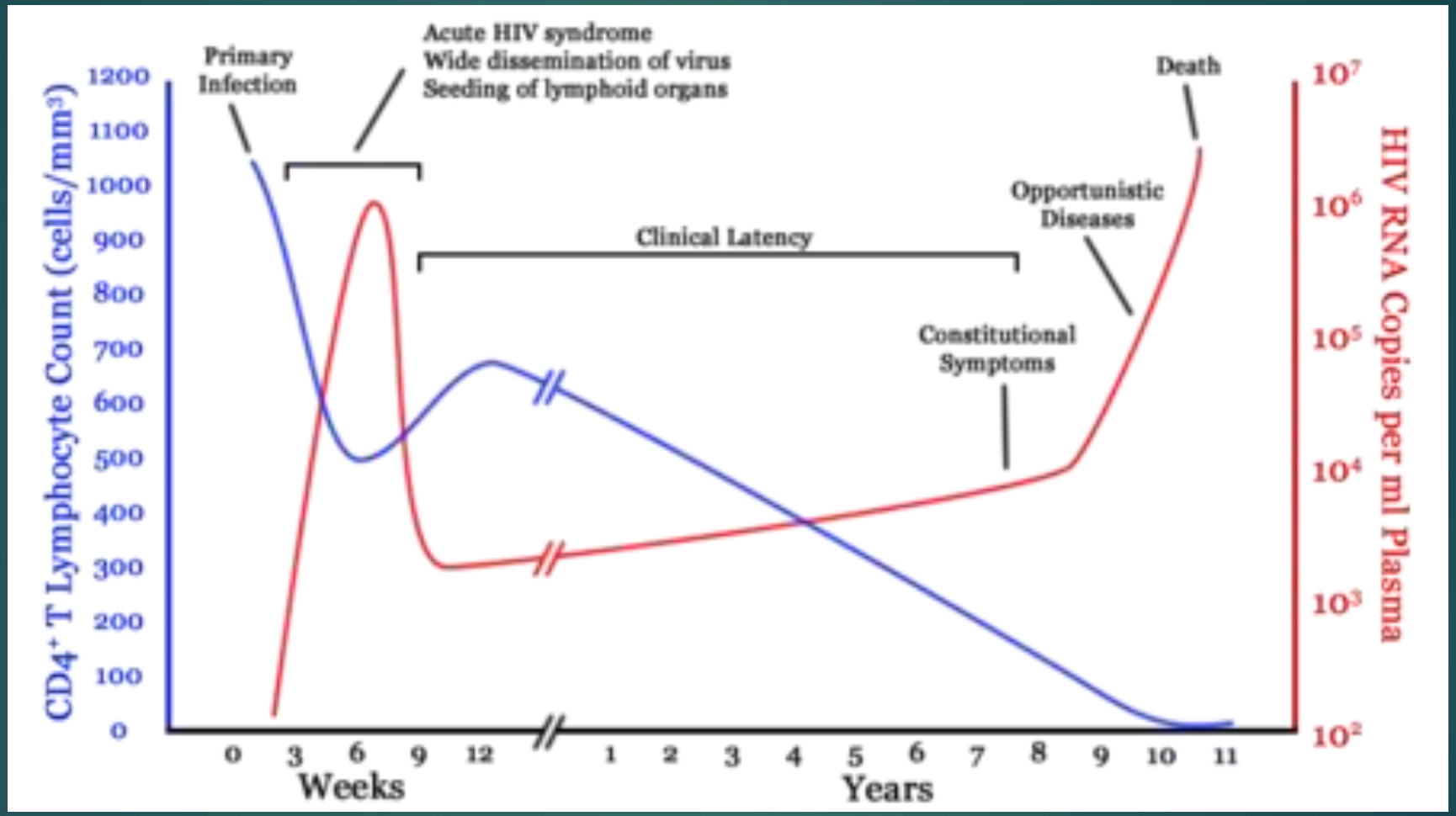
How Does HIV Affect the Nervous System?

- Primary HIV Disease can lead to:
  - Major NCD due to HIV (brain)
  - Vacuolar Myelopathy (spinal cord)
  - Peripheral Neuropathy (nerve)
  - Meningitis (acute and chronic)



Progression of Untreated HIV Infection

Blue = CD4



Red = HIV & other diseases

Simplified course of untreated HIV infection; there is considerable variability across individuals.

---- CD4+ T Lymphocyte count (cells/mm³) ---- HIV RNA copies per mL of plasma

Neuroanatomy of HIV: a primarily subcortical disease

- Nonspecific white matter changes
- Globus pallidus and other parts of basal ganglia
  - Caudate
  - Putamen (caudate + putamen = neostriatum, part of corpus striatum)
  - Midbrain
- Thalamus
- Corpus callosum
- Frontal lobes
- Also described as affecting the fronto-striato-thalamo-cortical circuits

How Does AIDS Affect the Nervous System?

- 10-15% of AIDS patients present with neurologic symptoms only (5% with NCD).
- 35-50% of AIDS patients have neurologic symptoms during life (35% develop minor cognitive/motor disorder; 15-20% progress to NCD)
- 75-90% have neuropathologic abnormalities at death

1) Brouwman et al, Neurology. 1998 ; 50:1814-20.
2) McArthur J Neuroimmunol 2004; 157 : 3-10
3) Vago et al., AIDS. 2002;16:1925-8.

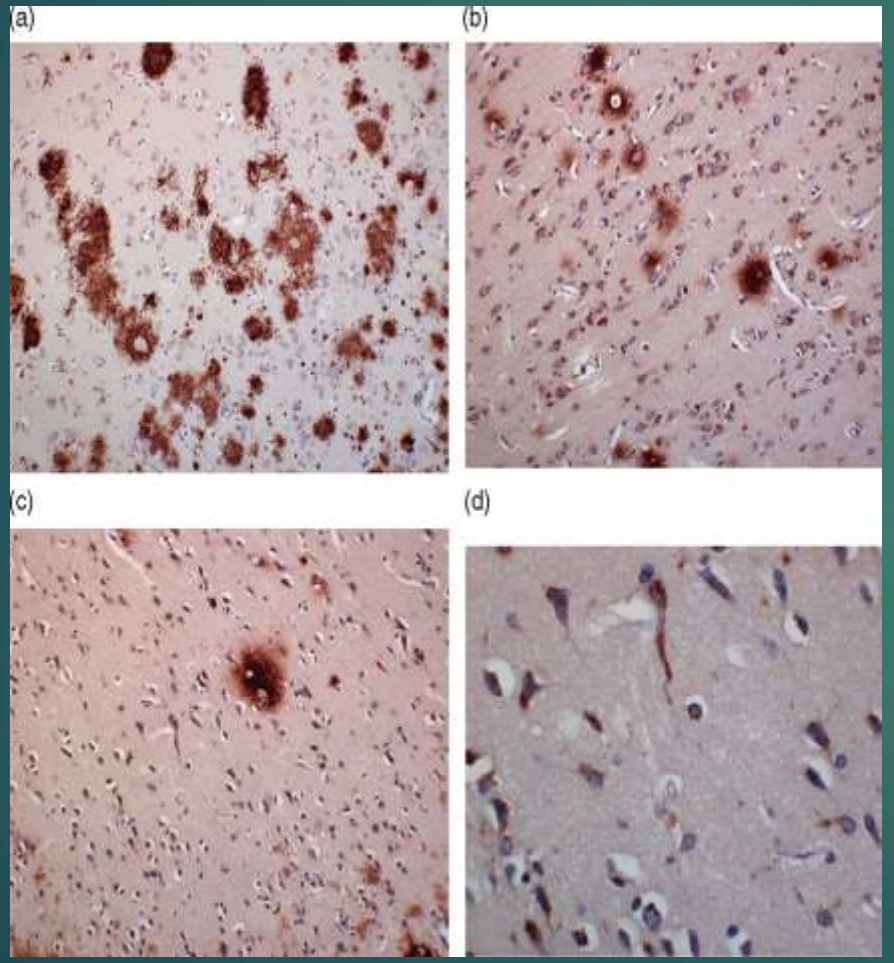
HIV Neuropathogenesis

Neuropathology in HIV:

- Sustained CNS inflammation
- Accelerated vascular disease
- Amyloid deposition

Brain deposition of beta-amyloid is a common feature in HIV+ patients (age 31-58 years) (Green et al AIDS 2005)

AD



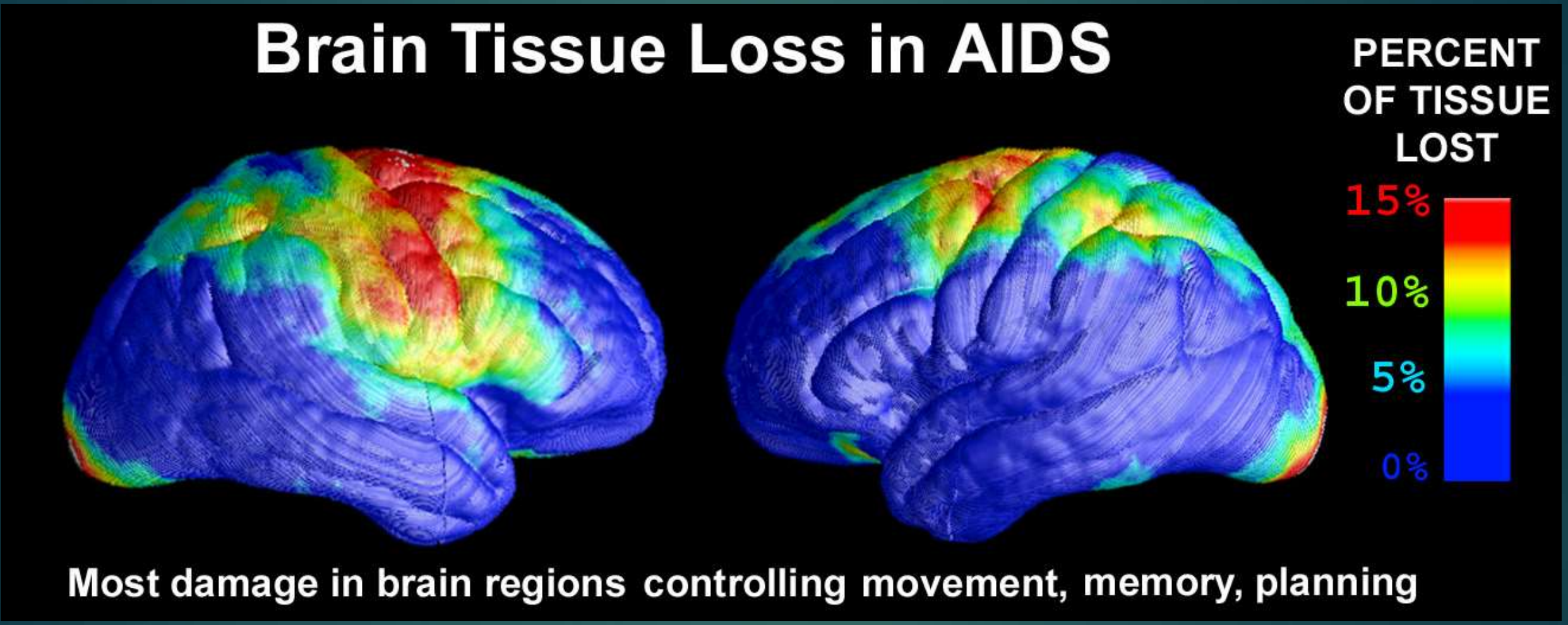
HIV

HIV

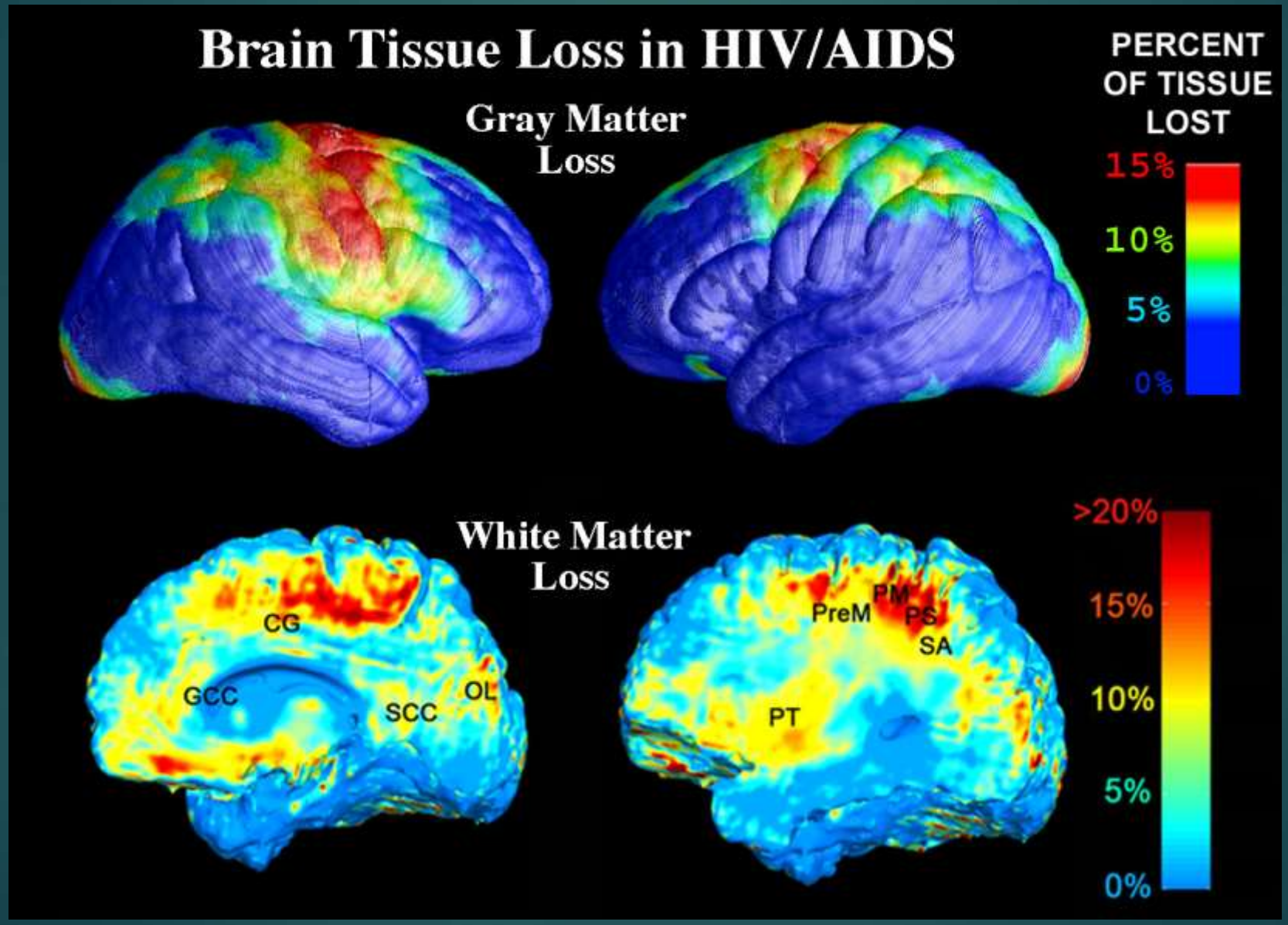
HIV

- Amyloid is increased in diffuse non-neuritic plaques in HIV+ brains
- An increase in diffuse plaques suggest early aging with HIV infection and may be enough to cause cognitive impairment

Brain Tissue Loss in AIDS



Brain Tissue Loss 2



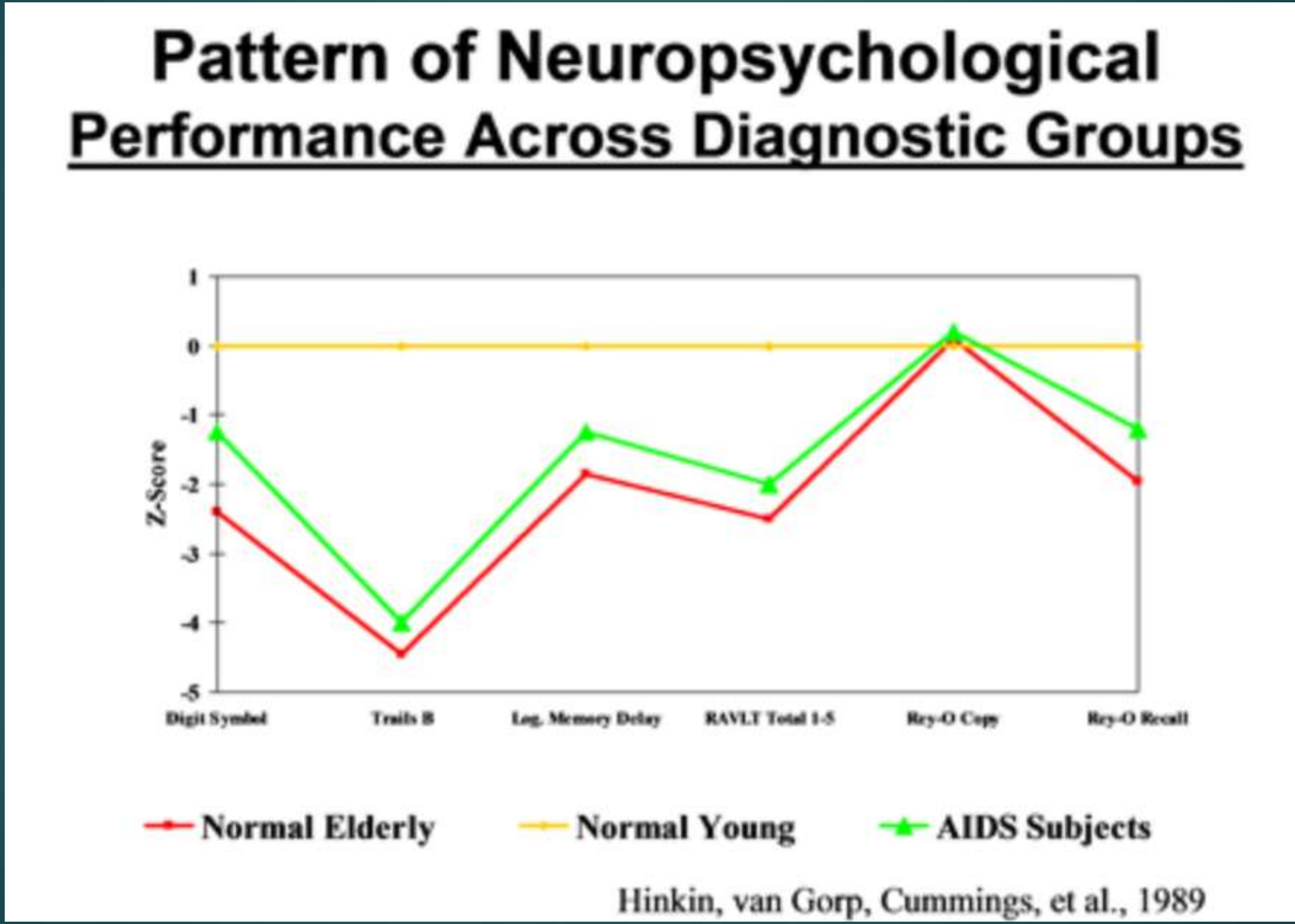
HIV and the Nervous System

- Multiple areas of the nervous system may be involved simultaneously or sequentially.
- Without anti-retroviral treatment, up to 80% of patients are symptomatic and for 30%, neurologic symptoms are the initial clinical problem.
- Neurologic syndromes may be the sole clinical problem or cause of death.

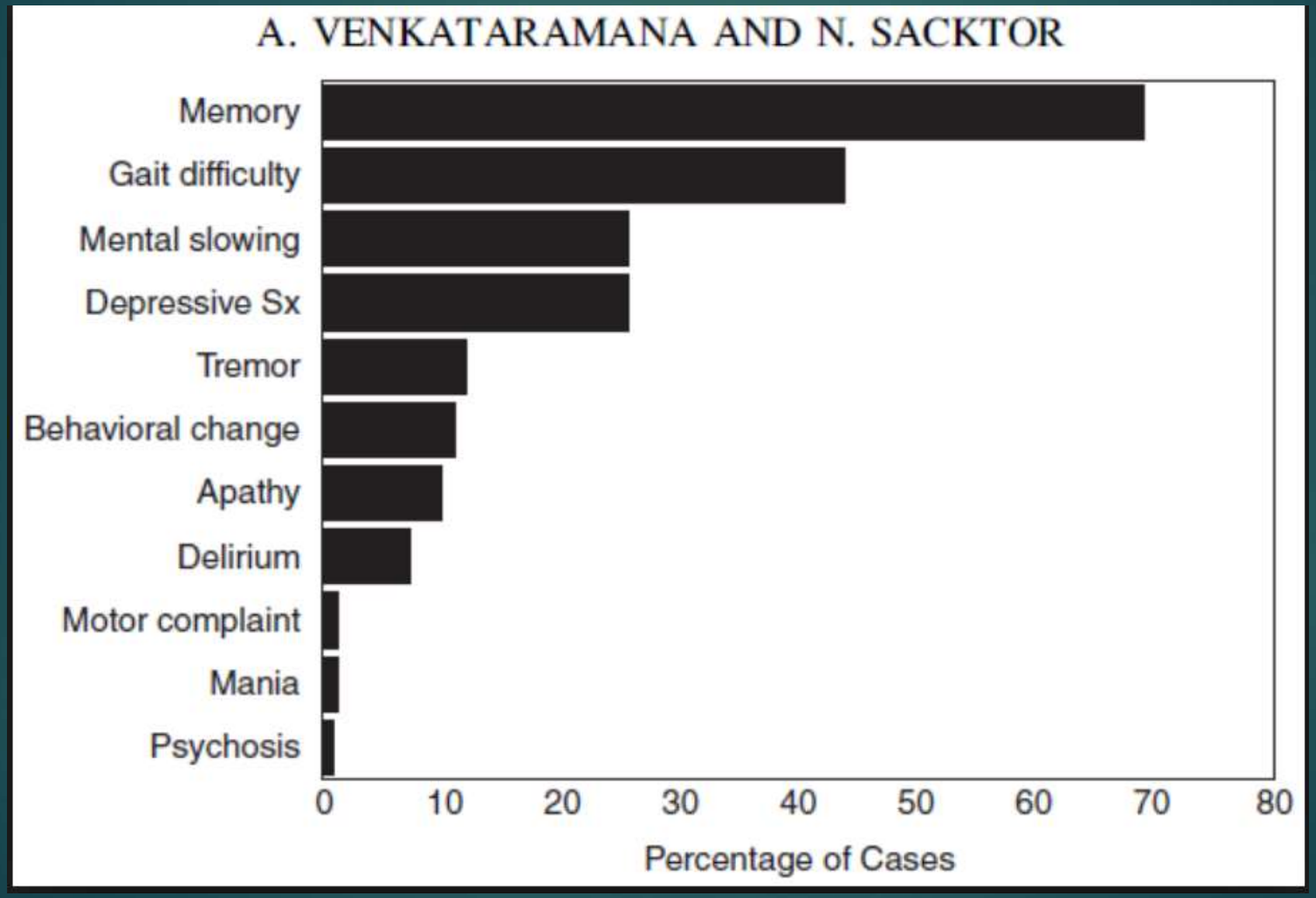
Grant, 1987

- Neuropsychological evaluations of 55 ambulatory homosexual men revealed abnormalities in:
  - 13 of 15 with AIDS,
  - 7 of 16 with AIDS-related complex,
  - 7 of 13 with HIV-seropositivity only,
  - 1 of 11 with HIV-seronegativity.
  - Common neuropsychological problems included impaired abstracting ability, learning difficulties, and slowed speed of information processing.

1989: Elderly, Young, AIDS



2003: Frequency of symptoms in HIV dementia among 300 pts



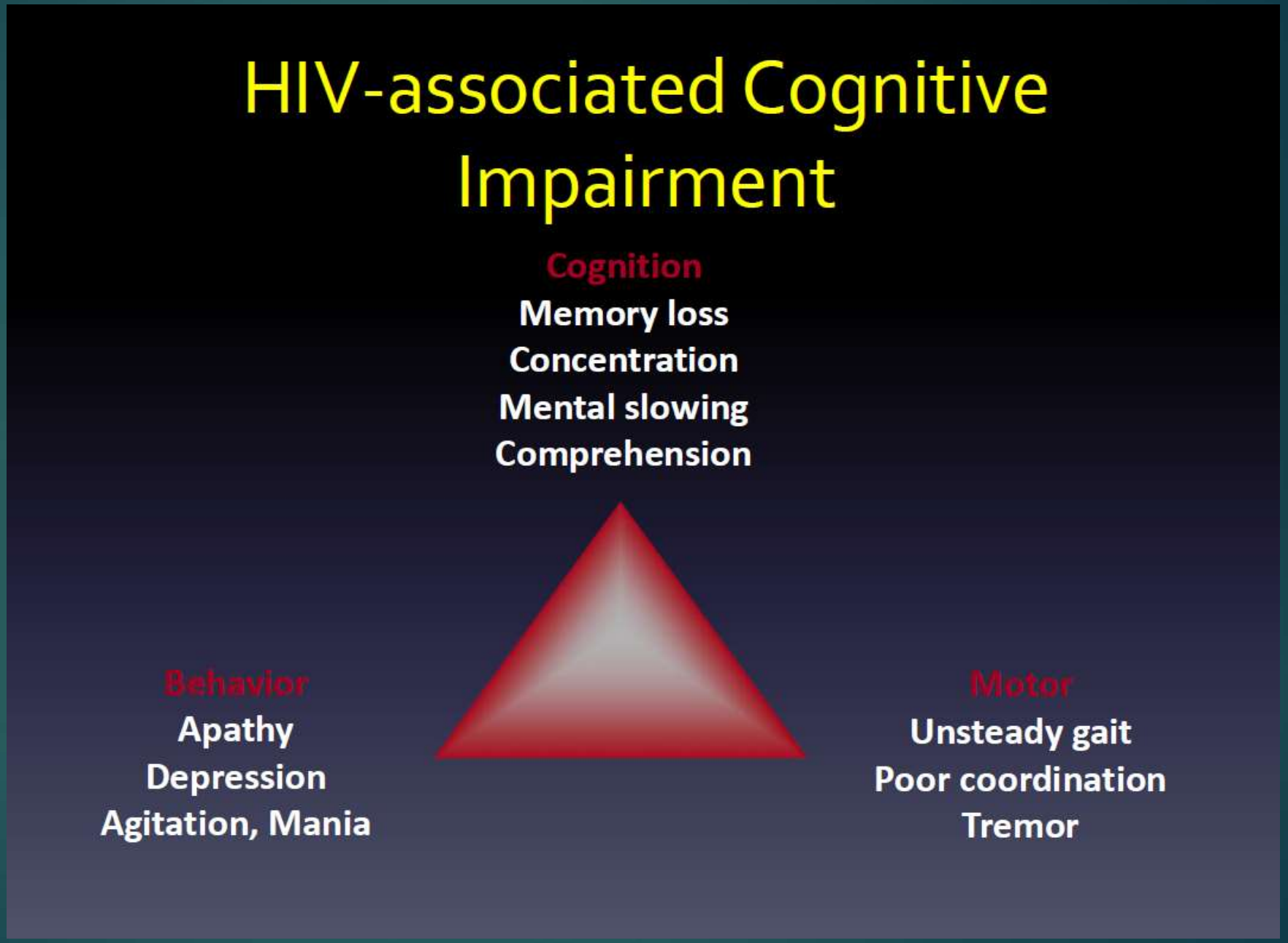
HIV Neurological disease and death

- Of 1,651 HIV-infected patients assessed in 2010,
  - 25% were identified as having one or more neurologic disorders,
  - 41% of AIDS-affected persons exhibited neurologic disease.
  - Symptomatic distal sensory polyneuropathy (10%)
  - HIV-associated neurocognitive disorder (6 %) represented the most prevalent disorders among 53 recognized neurologic disorders.
- Patients with at least one neurologic disorder exhibited higher mortality rates (18%), particularly AIDS-related deaths (10%).
- The highest mortality was associated with opportunistic infections of the brain, followed by HAND, and the presence of any neurologic disorder. increment in plasma viral load.

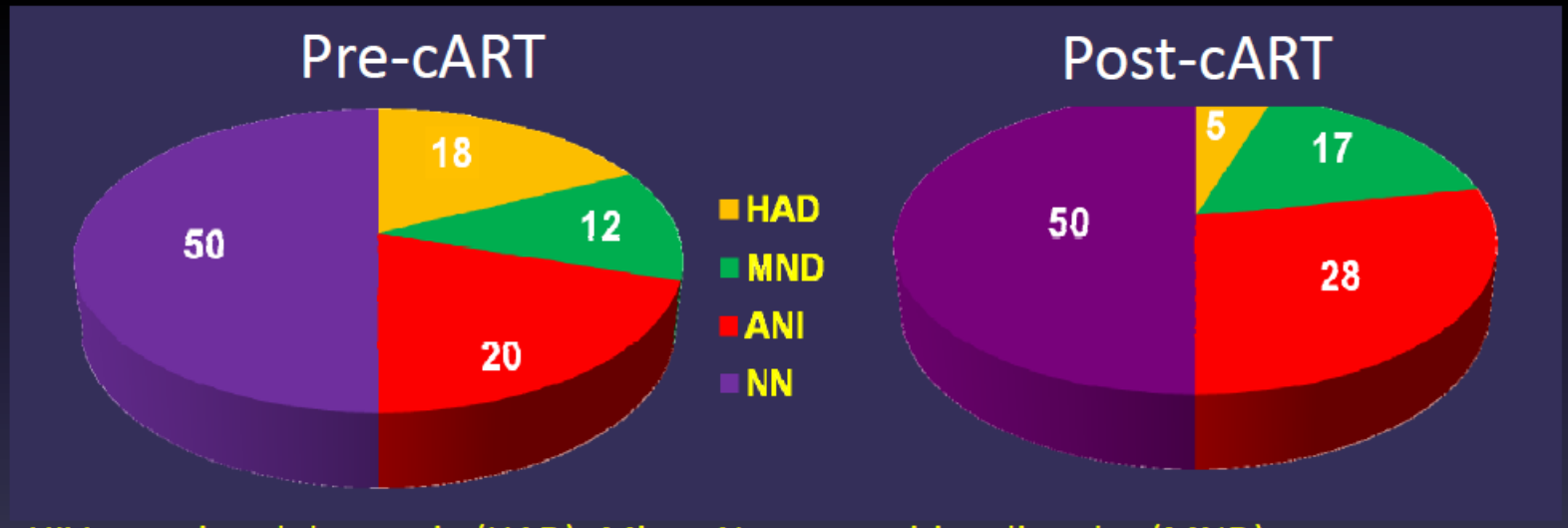
P. Vivithanaporn, 2010

<u>High Psych Sxs</u>
burden in HIV 60+:
Mood, restless,
Agitation

<u>Cognition</u>:
Attention,
Mental slowness,
Not just reactive
depression



Cognitive Diagnoses
Pre-cART vs. Post-cART



HIV-associated dementia (HAD); Minor Neurocognitive disorder (MND); Asymptomatic Neurocognitive Impairment; (ANI) Neurocognitively normal (NN)

n=1555 from US; subjects attending academic centers and have access to cART

Modified from Ellis et al, 2007 Nat Rev Neurosci & Grant et al., 2009 CROI

Updated research terminology for HIV-associated NCDs

- 1991: American Academy of Neurology (AAN) criteria –
  - HIV-associated Major NCD (HAD) (also AIDS Dementia Complex)
  - Minor cognitive motor disorder (MCMD)

- 2007: Current standard nomenclature: A. Antinori, et al., *Neurology*, 2007:
  - HIV Neurobehavioral Research Center at UCSD
  - Types of HAND (HIV Associated Neurocognitive Disorders):
    - ANI, MND, HAD

- 2013: DSM-5

Symptoms of HIV Associated Neurocognitive Disorders (HAND)

- Confusion
- Forgetfulness
- Behavioral changes
- Headaches
- Gradual weakening and loss of feeling in the arms and legs
- Problems with cognition or movement
- Pain due to nerve damage.

HIV associated asymptomatic neurocognitive impairment (ANI)

- a. Acquired impairment in cognitive functioning with performance at least 1.0 SD below the mean in 2 domains for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
- b. Cognitive impairment does not interfere with daily functioning.
- c. The cognitive impairment does not meet criteria for delirium or Major NCD.
- D. No evidence of another preexisting cause.

HIV associated mild neurocognitive disorder (MND) = Mild NCD

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean in 2 domains for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
2. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following): Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning.
3. Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.
4. The cognitive impairment does not meet criteria for delirium or Major NCD.
5. There is no evidence of another preexisting cause for the MND.

HIV associated Major NCD (HAD) = Major NCD

1. Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means in 2 domains
2. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities).
3. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for Major NCD need to have been met on a prior examination when delirium was not present.
4. There is no evidence of another, preexisting cause for the Major NCD (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse compatible with CNS disorder).

Spectrum of HAND

	No alternative cause	Delirium absent	Acquired impairment in ≥ 2 cognitive abilities	Interferes with daily functioning
Asymptomatic Neurocognitive Impairment (**ANI**)	✓	✓	✓	No
Mild Neurocognitive Disorder (**MND**)	✓	✓	✓	Mild
HIV-Associated Dementia (**HAD**)	✓	✓	Marked	Marked

Antinori A, et al. Neurology 2007;69:1789–99

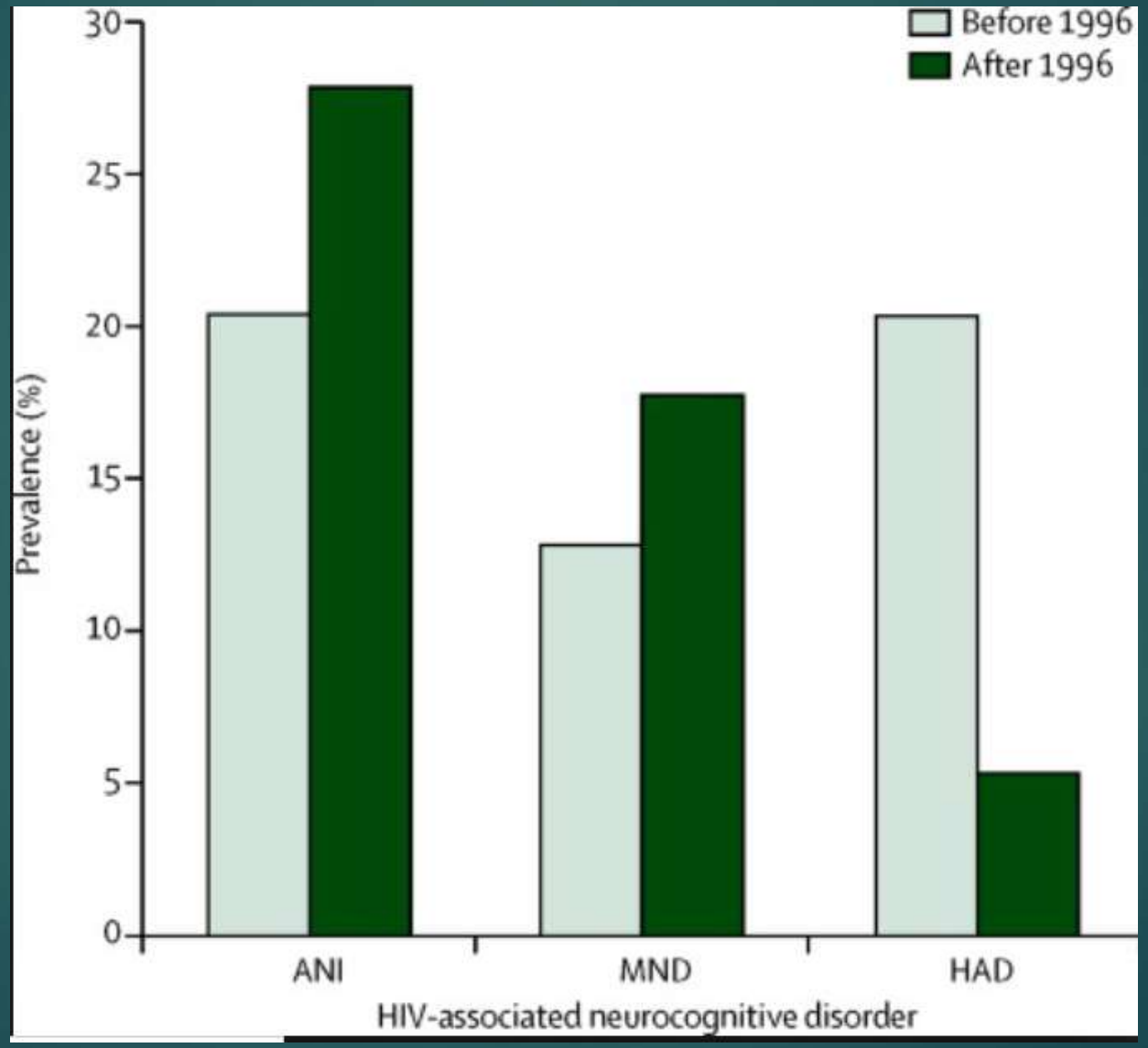
DSM-5 Mild Neurocognitive Disorder due to HIV

- A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains based on;
  - 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function.
  - 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing in the following areas; complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition.
- B. The cognitive deficits do not interfere with capacity for independence in everyday activities
- C. There is documented infection with HIV
- D. NCD not better explained by non-HIV conditions, incl. 2nd brain diseases

DSM-5 Major neurocognitive disorder due to HIV

- A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains.
  - 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function.
  - 2. Substantial impairment in cognitive performance preferably documented by standardized neuropsychological testing in the following areas: complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition.
- B. The cognitive deficits interfere with independence in everyday activities.
- C. There is documented infection with HIV
- D. NCD not better explained by non-HIV conditions, incl. 2nd brain diseases

- HAND: Before and after 1996



Differential Diagnosis of HIV Neurological Syndromes

- The differential diagnosis of a neurologic syndrome is derived from consideration of:
  - History
  - Clinical findings or localization
  - HIV disease stage
    - Seroconversion
    - Early disease
    - Late disease

HIV and the Nervous System

- Causes or etiologic considerations for neurologic disorders include:
  - Primary or HIV-related: Acute or chronic
  - Secondary opportunistic infections or malignancy
  - Metabolic or nutritional derangements
  - Complications of medical therapy
  - Diseases Unrelated to HIV infection

Major NCD due to HIV: Clinical features

- Slowed processing and reaction times (subcortical features indicating white matter involvement)
- Memory loss, subjective if early
- Psychiatric symptoms such as anxiety, psychosis or mania
- May co-exist with myelopathy or peripheral neuropathy

Major NCD due to HIV: Laboratory Findings

- Risk increases with disease severity, i.e., more common in AIDS, CD4 < 200
- CT/MRI: cortical atrophy, ventricular dilatation, white matter rarefaction on CT, T2 signal hyperintensity on MRI
- Cerebrospinal fluid: normal or non-specific pleocytosis, normal glucose and protein. CSF gamma-globulin often elevated

Major NCD due to HIV: Differential Dx

- Toxic/metabolic factors: medication; hypoxia, electrolyte disturbance, B-12 deficiency
- Secondary opportunistic infection
- Secondary malignancy
- Unrelated to HIV

Major NCD due to HIV: Medical Evaluation

- Stage the infection with CD4 and viral load
- CBC, electrolyte and hepatic panel, serum RPR or FTA, B12 level, thyroid function studies, arterial blood gas where indicated
- Lumbar puncture
- Blood culture for MAI, CMV, fungus
- MRI of brain +/- gadolinium

HIV Treatment

- Drugs are effective in suppressing virus
- Drugs attack virus' ability to replicate at different points in the replication cycle
- cART should be started immediately (updated Department of Health and Human Services and WHO recommendations, 2015)
- PrEP Pre-Exposure Prophylaxis treatment available for at-risk, non-HIV individuals, 90% effective: **Truvada**
- Presently – possible no change in life expectancy

HRT (highly active antiretroviral therapy)

- Development of HRT changed HIV to chronic disease with life expectancy approaching population norms for pts complying with treatment.

- Remaining issues for NCD due to HIV include:
  - persistent low levels of HIV,
  - ongoing inflammatory responses,
  - potential therapeutic toxicity
  - interactions between aging and neurodegeneration caused by virus.

HIV in elderly and Alzheimer's

- Post HRT, pattern of NCD due to HIV is more similar to other common degenerative disorders (i.e. Alzheimer's) than to classic HIV associated Major NCD, which could creates challenges in differentiation of disease in the elderly.

Table 1

Differential Features of Alzheimer's Disease and HIV-Associated Dementia

	Population Affected	Motor/Spinal Cord Signs	Clinical Course	CSF Testing
HIV-Associated Dementia	Younger	+	Rapid, +/– progressing atrophy	Mild pleocytosis, protein elevated
Alzheimer's Disease	Older	–	Develops slowly	Normal

CSF: cerebral spinal fluid
Pleocytosis: presence of a greater than normal number of cells in CSF

Source: Reference 3

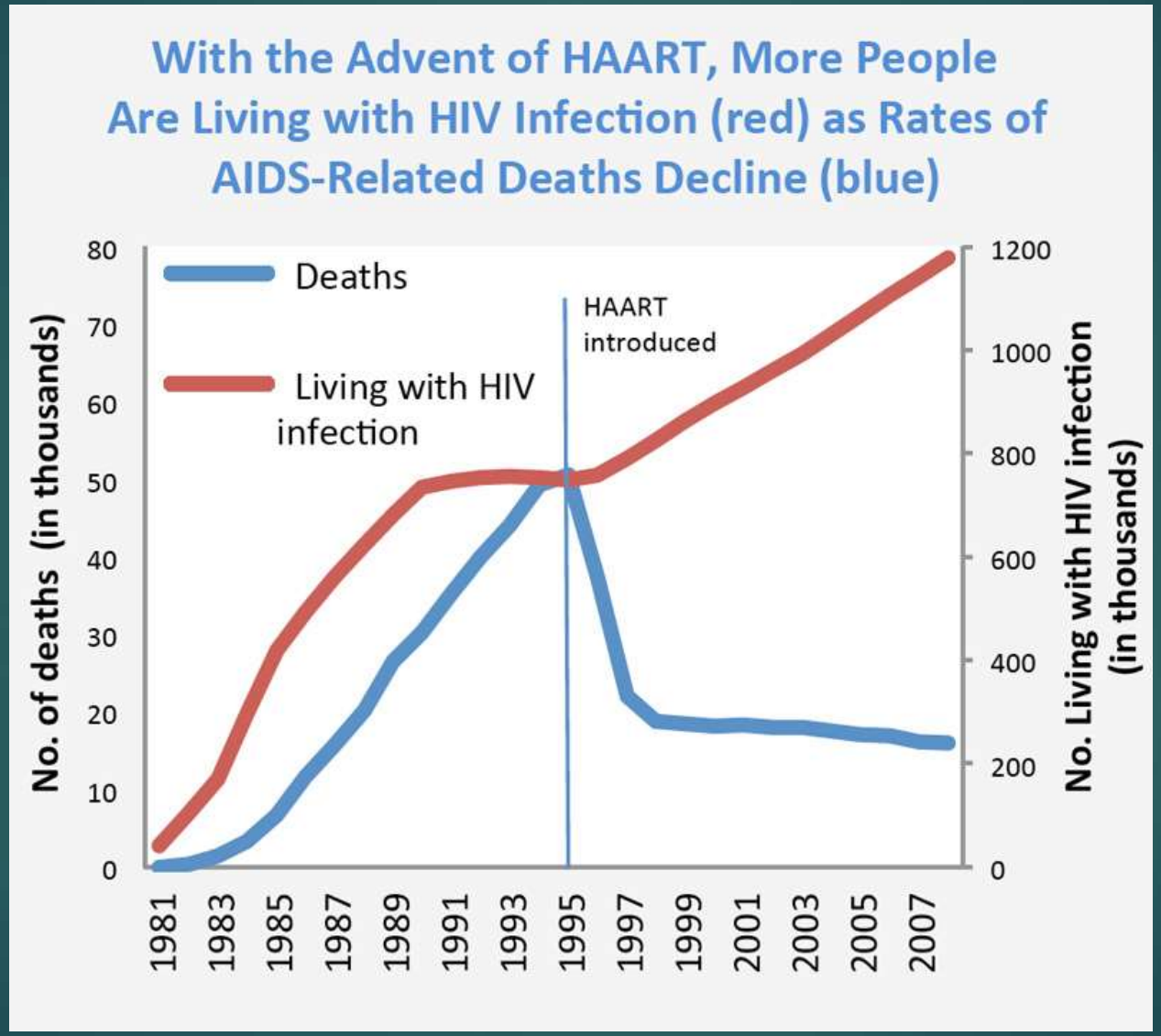
HRT statistics

- Prior to HRT, 20-30% with advanced HIV had sx of HIV associated Major NCD (HAD)
- Since HRT, incidence of Major NCD has dramatically decreased; but up to 40% of HIV patients continue to suffer from mild NCD deficits

- CHARTER study 2003-2007, 1500 patients on HRT: >50% with HAND.
  - 2% Major NCD
  - 25% Mild NCD
  - 25% ANI (NP findings, but totally functional)

http://depts.washington.edu/nwaetc/echo/presentations.html#PID=114

As a result of HRT in 1995, more people living with HIV



http://www.drugabuse.gov/sites/default/files/images/colorbox/drugfactshiv2.jpg

Despite HRT…

- ..there is a concern that neurocognitive disorders are present and will still worsen leading to resurgence of problem in the future.

- Controversy: “I don’t see cognitive impairment in my patients who are adherent to medications”
- Paul Volberding

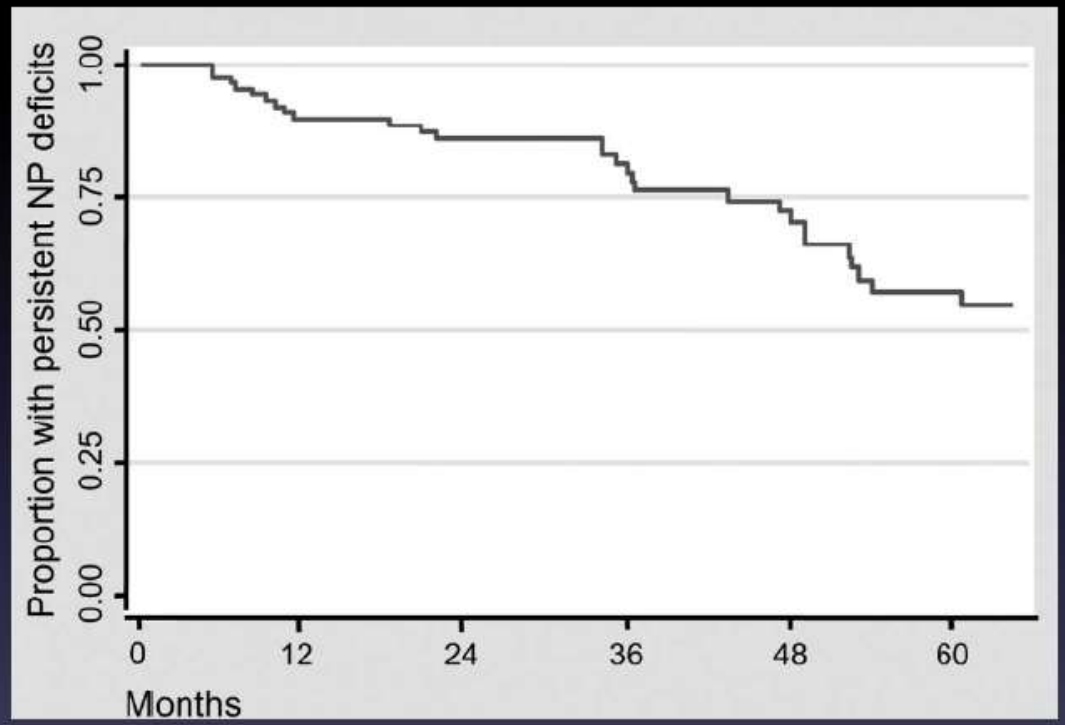
Persistent Cognitive Impairment despite cART

- HAND: HIV-associated Neurocognitive Disorder:
- Why does it persist despite cART?
- Cognitive deficits remain frequent despite effective HIV Tx
- HIV and inflammatory response remnants cause cognitive deficits despite suppression of plasma HIV RNA
- Comorbidities are highly correlated to cognitive deficits
- HIV invades CNS in acute infection within 10 days (95% of CD4 decline in 1st month); damages BBB; insula abnormal
- Acute HIV infection is T cell driven; later, its macrophage driven; lot of inflammation from intracellular infection
- Evidence of monocyte-mediated on-going brain damage despite cART

Continued cognitive impairment despite cART

- HAND remains frequent despite cART
- Asymptomatic impairment may not be that asymptomatic
- Comorbid illnesses are important contributors to impairment, particularly in older age
- There are not enough data to determine if older HIV+ patients will be at increased risk for Alzheimer’s disease; in 2015, only five individuals with HAND who have undergone amyloid PET imaging, and all were negative

Persistent Cognitive Deficits

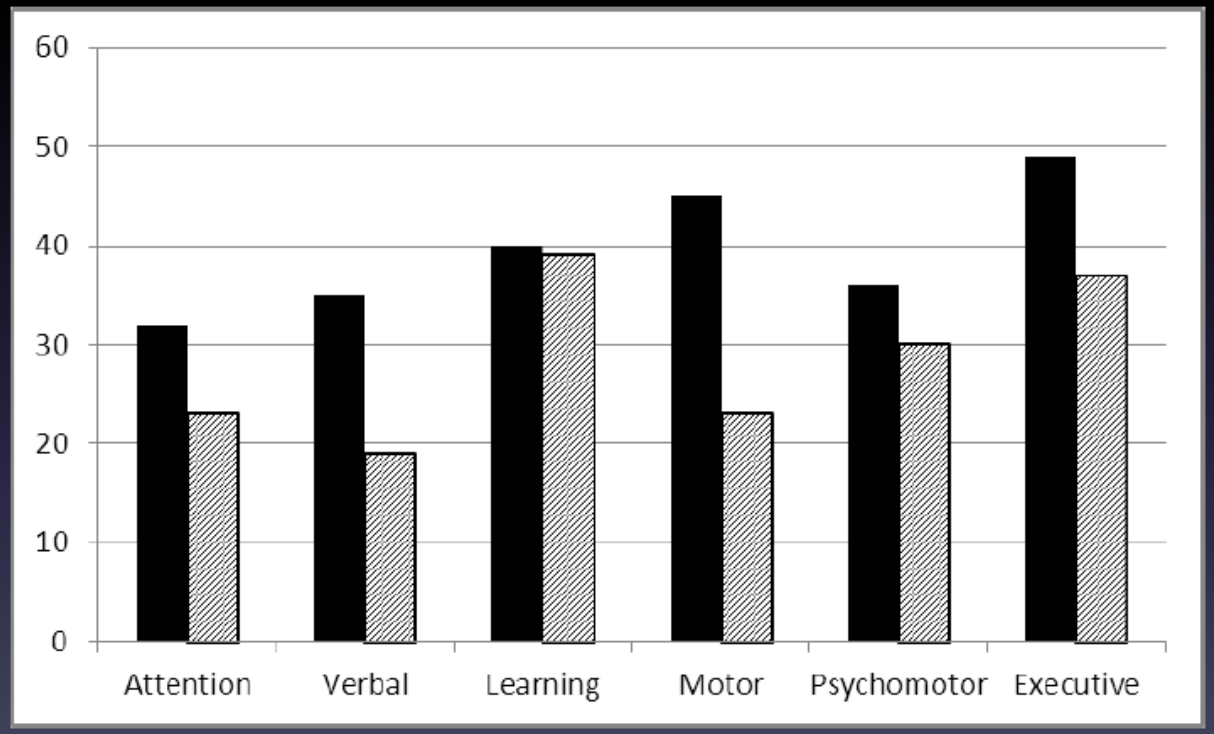


n = 94
Neuropsychological impairment =
(a) -1 SD on two tests
or
(b) -2 SD on one test out of 8

>50% probability of persistent neuropsychological deficits despite 5 years of cART

Tozzi et al JAIDS 2007

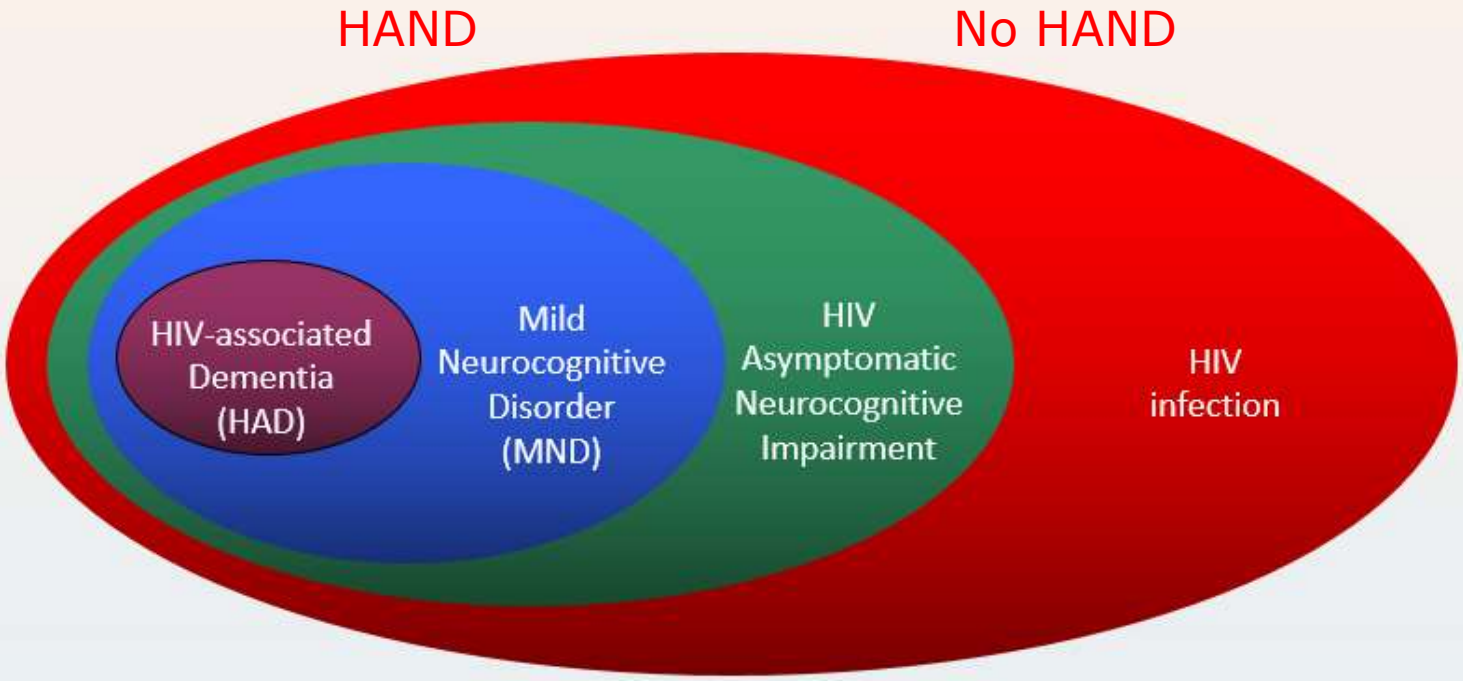
Persistent deficits 12 months after initiation of cART



n=82 from South Africa; Severity of baseline deficits predicts 12 month deficits

Joska et al BMC Infectious Ds. 2012

Cognitive Impairment in HIV



From VG Valcour, MD, at Washington, DC: June 18, 2013, IAS-USA.

CHARTER Study (n=1,555 HIV-infected adults)

52% had NP impairment: Major NCD 2%, Mild NCD 12%, ANI 33%

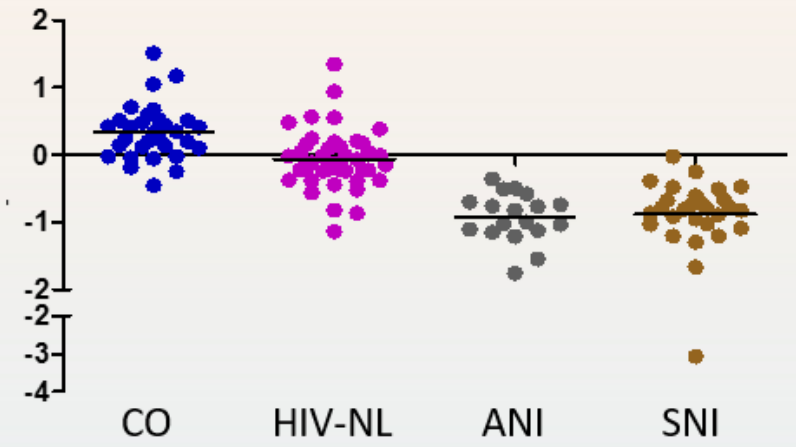
Pre and post cART Cognition: Comorbidities

- Percent with normal cognition has not changed between pre and post cART
- Lower incidence (rate of occurrence of new cases - risk) but not prevalence (proportion of a population at risk that is affected at a given time – how widespread)
- Implies that there are confounding comorbidities (multifactorial brain damage):
  - Concurrent neurological diseases + ApoE4
  - Cumulative CV disease
  - Chronic immune activation
  - Long term exposure to cART: cART toxicity & poor CPE (CNS penetration effectiveness
  - HIV specific factors (uncontrolled plasma/CSF HIV)
  - Drugs
  - Other infections: TBI, Hepatitis C
  - Other lifestyle factors: Cognitive Reserve (education)
  - Age

- Classic risk factors (CD4, viral load) not as predictive as above

No difference in summary NP testing scores between ANI and MND/HAD

Composite neuropsychological testing performance



HIV Negative Controls (CO), HIV Normal Cognition (HIV-NL), asymptomatic impairment (ANI), and symptomatic impairment (SNI = MND + HAD)

From VG Valcour, MD, at Washington, DC: June 18, 2013, IAS-USA.

Neuropsychological Assessment Battery (NAB)

1. Memory
2. Judgment
3. Driving *(Attention/Executive)*
4. Bill Pay *(Language and calculations)*
5. Map *(Spatial ability)*

Edison Electric Company

Statement

Account Number: 661-837-1842 002
Bill Period: January 16 - February 16

Account Summary: *Amount* *Total*

Previous Balance	$60.83
Payment Received (1/23)	$60.83
Balance as of January 23	$0
New Charges	$67.29

Total Amount Due $67.29

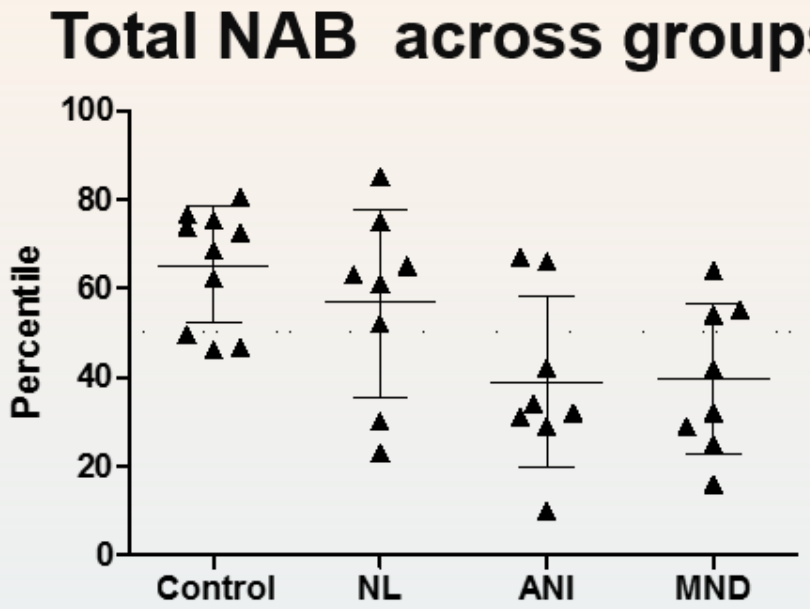
Date of Statement	Payment Due Date	Total Amount Due
February 16	March 2	$67.29

Payment Instructions:
Please make check payable to ***Edison Electric Company****. Please include your account number on the check. Send payment to: Edison Electric Company, 4000 Medway Street, Dennis, MD 21986-4600.*

From VG Valcour, MD, at Washington, DC: June 18, 2013, IAS-USA.

No difference in NP deficits in ANI and MND = 2 SD below

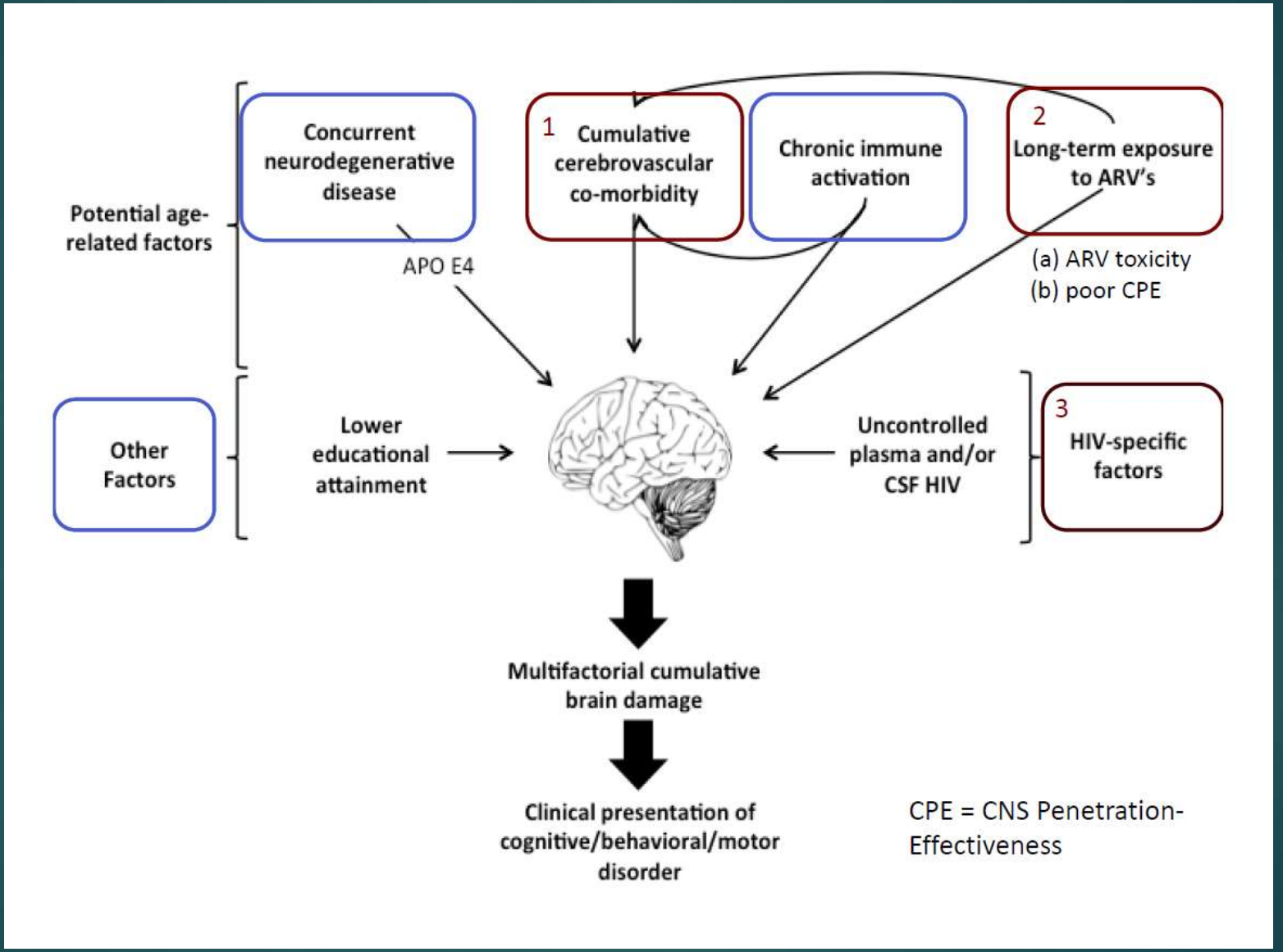
Total NAB Performance



ANI did not differ from MND, but both ANI and MND performed more than 2 SD below controls.

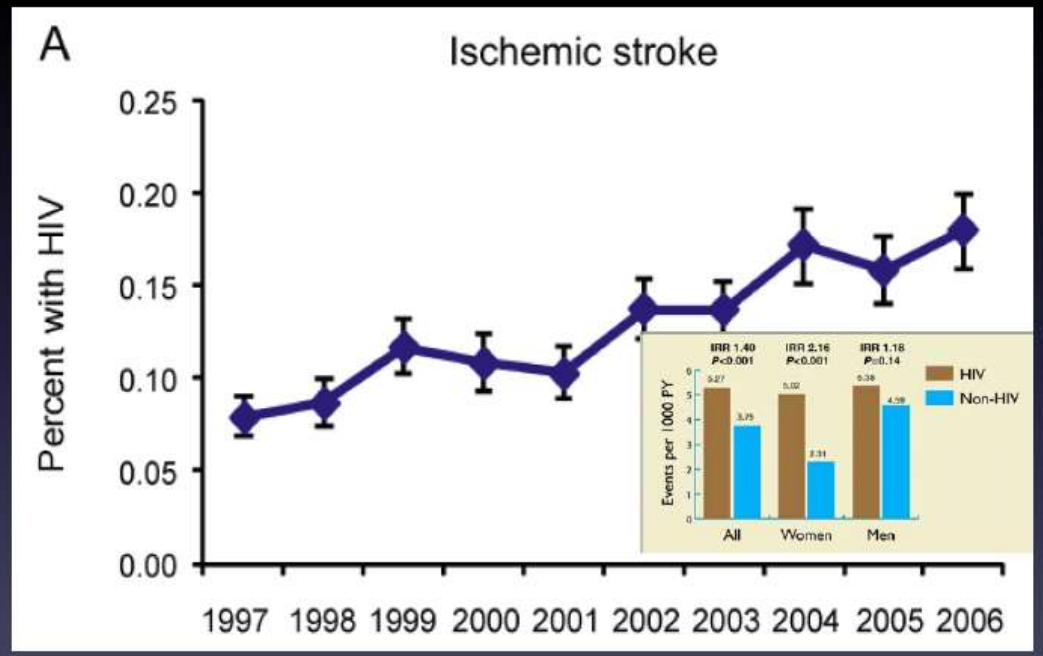
VG Valcour, MD, at Washington, DC: June 18, 2013, IAS-USA.

Comorbid factors in HIV HAND

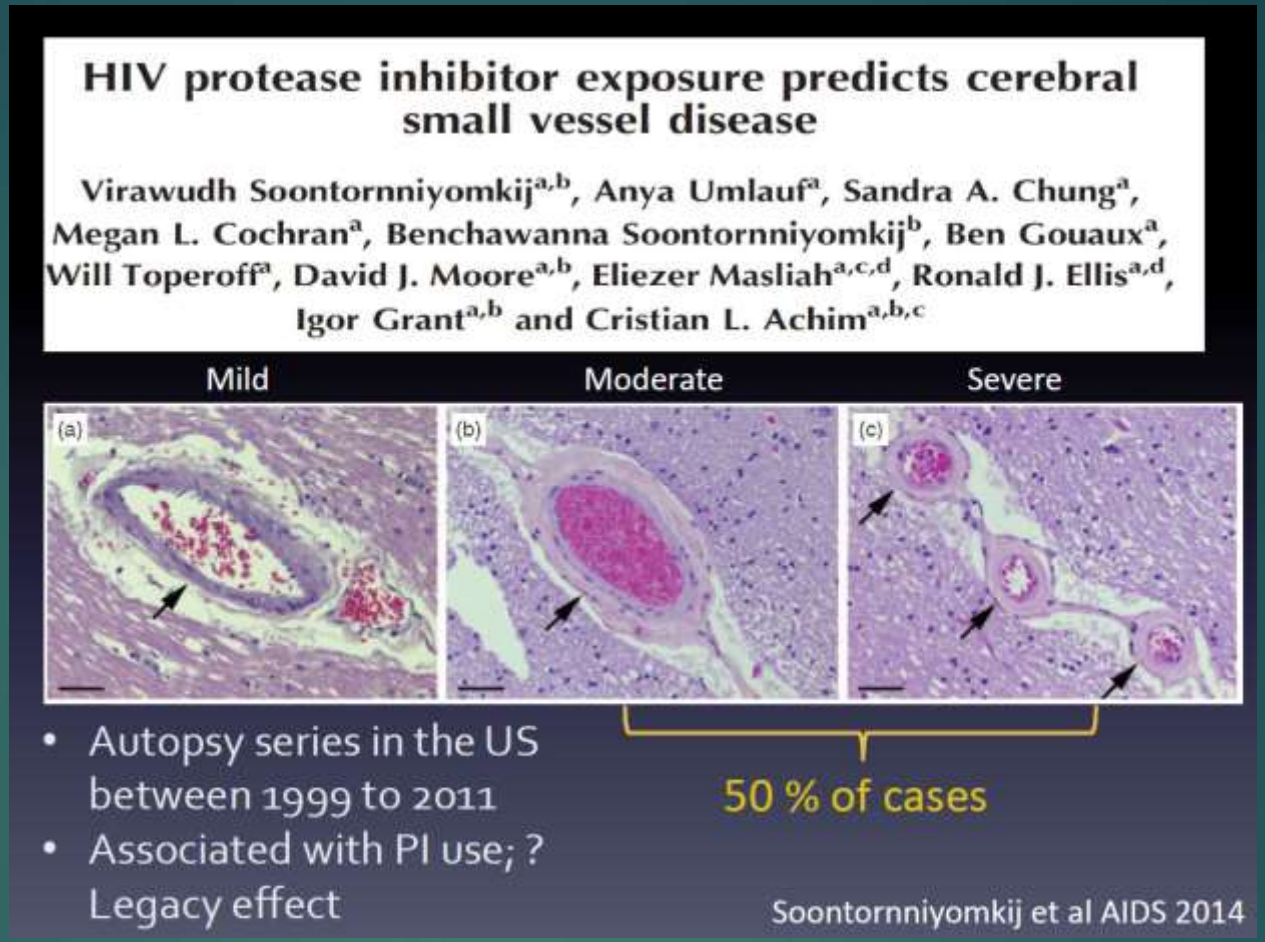


Cumulative CV comorbidity

Increasing Frequency of Ischemic Stroke in HIV



Ovbagle and Nath 2011 Neurology & Chow et al 2011 JAIDS



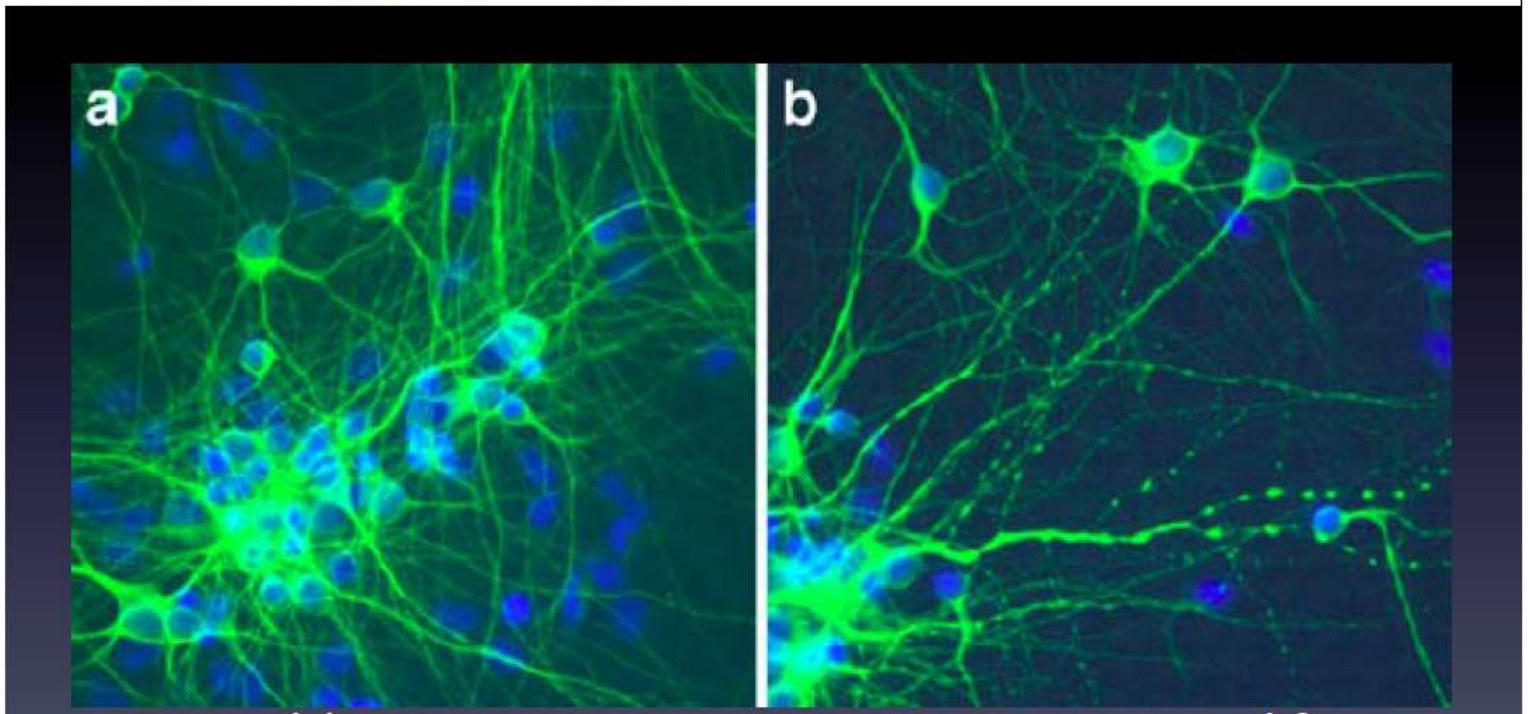
Protease inhibitor-based HAART exposure may increase the risk of CSVD and thereby neurocognitive impairment in HIV-infected adults. Apart from the possible direct toxicity to cerebral small vessels, protease inhibitor-based HAART may contribute indirectly to CSVD by inducing metabolic abnormalities.

cARTs are neurotoxic

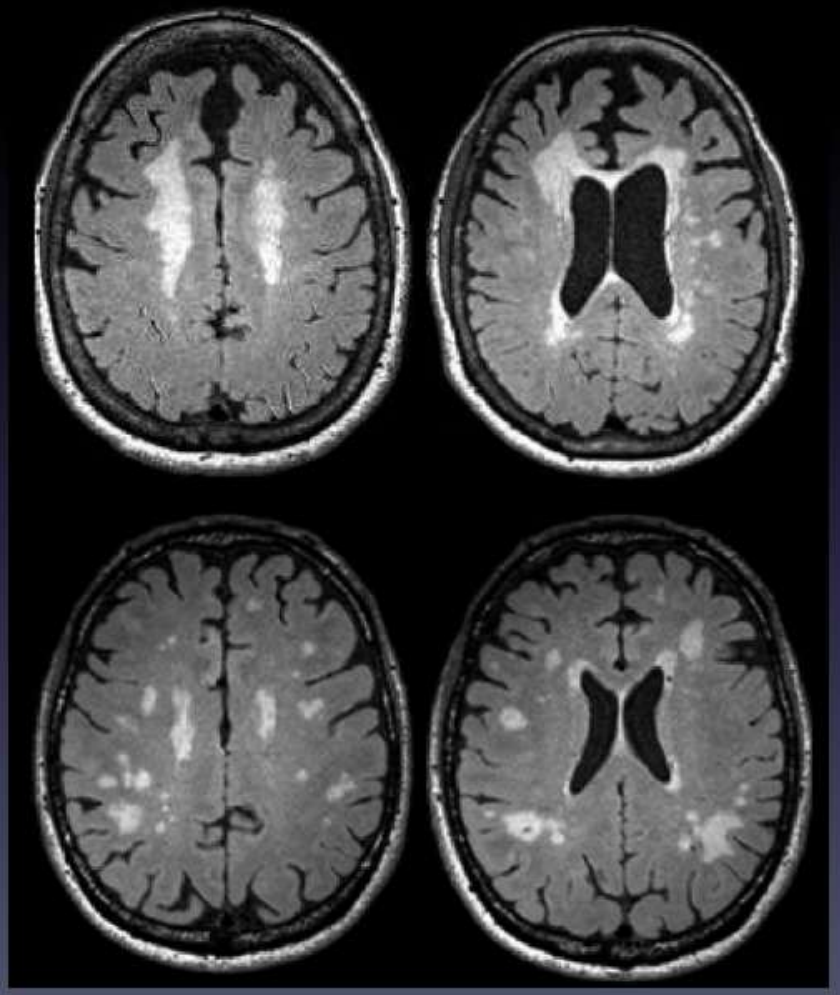
J. Neurovirol. (2012) 18:388–399
DOI 10.1007/s13365-012-0120-3

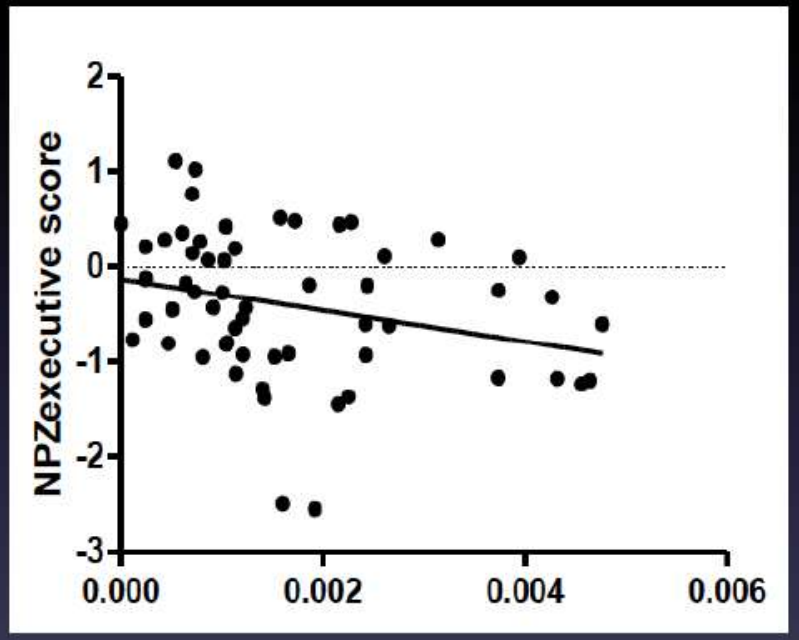
Antiretroviral neurotoxicity

Kevin Robertson · Jeff Liner · Rick B. Meeker



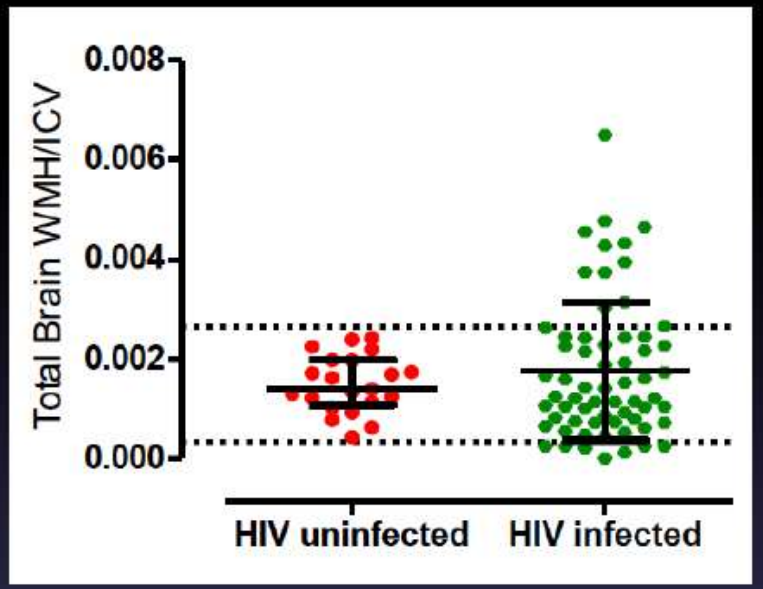
White Matter Injury

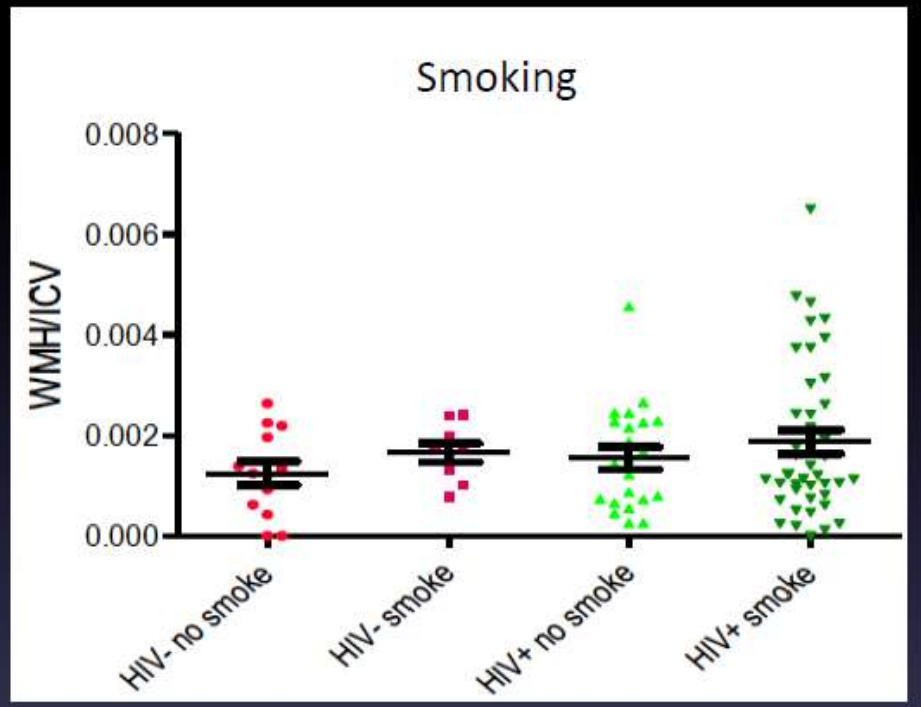




Subjects over the age of 60 in the US who are living with HIV as a chronic illness

White Matter Lesions

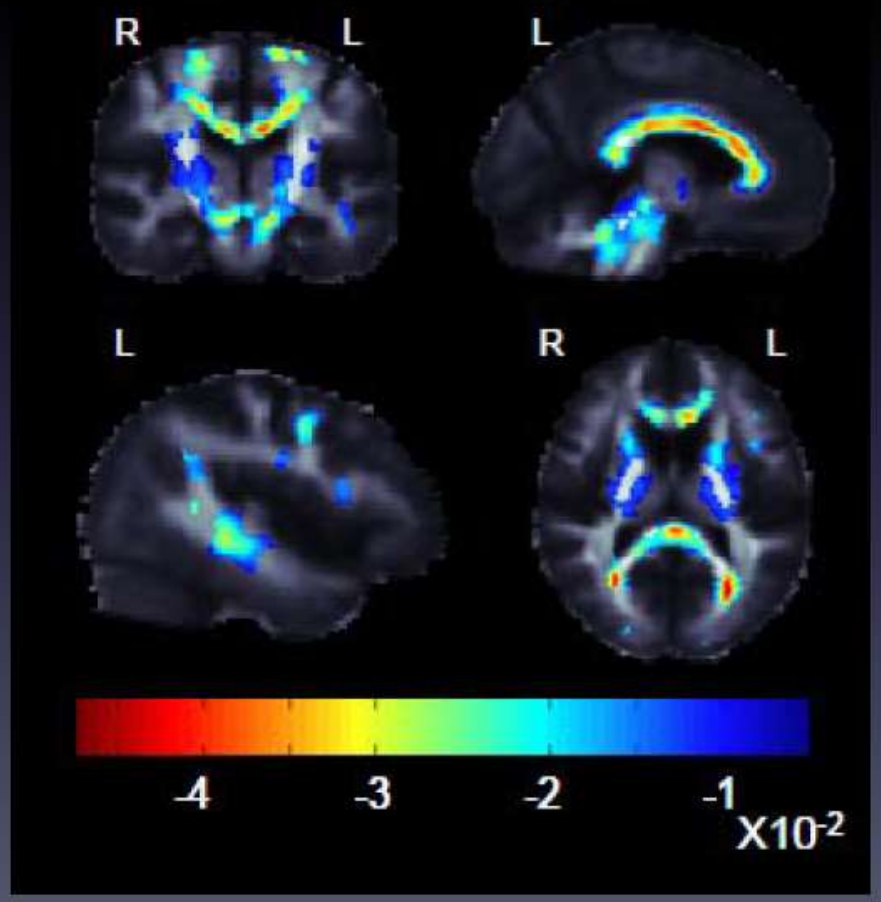




- Higher white matter lesion volume in HIV compared to age-matched controls
- Smoking impacts total WML volume in HIV

Valcour et al, ISNV 2013

Broad Abnormalities in Fractional Anisotropy in HIV



Exacerbated by APOE4

Nir et al, Human Brain Mapping 2013

Prevalence of HIV Associated Neurocognitive Disorders

- HIV-associated Major NCD (HAD): 6-66% of HIV individuals
- On HRT (highly active antiretroviral therapy): 10%
- In asymptomatic HIV pts, <1%
- In AIDS pts: 10-20%
- Neurological involvement of HIV infection (HAND): up to 65% of adults with HIV & majority of children with HIV

- Prevalence in countries without HRT is much higher (1st or 2nd most common Major NCD after AD); recent sub-Saharan estimate: 31% (HAD), & 46% had NP impairments

Risk factors for HAND

- HIV infection; HIV genes in CSF
- Lower CD4 counts and/or higher CSF HIV viral load
- Low CD4 count (<200)
- Level of plasma viremia (presence of a virus in the blood), CSF viral load
- Lower nadir (lowest point) CD4 count
- Hepatitis C co-infection
- Drug abuse/dependent (meth)
- Aging
- Diabetes
- Cardiovascular risk factors

http://depts.washington.edu/nwaetc/echo/presentations.html#PID=114

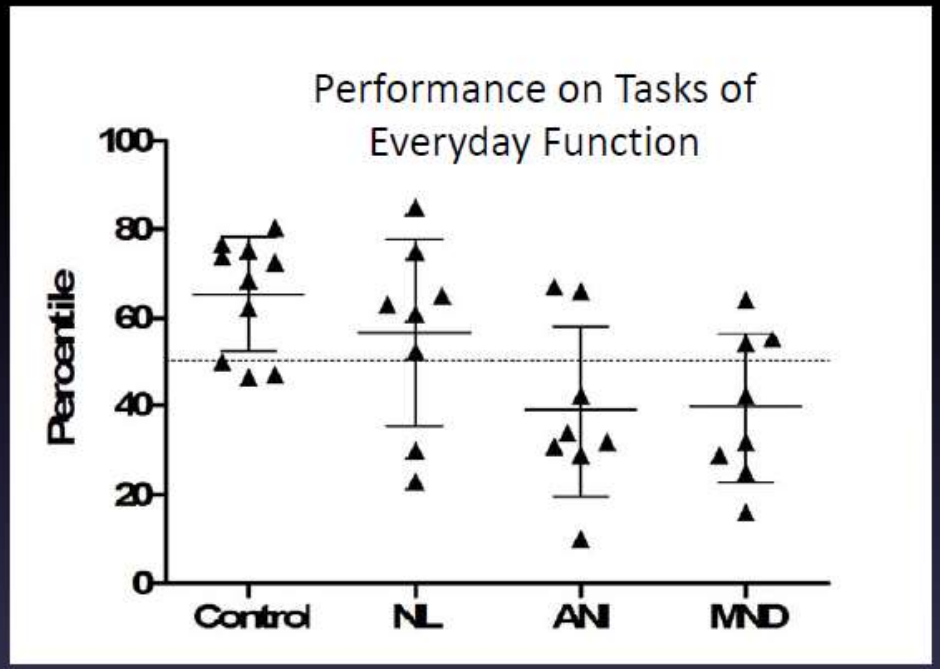
Risk Modifiers

- Demographic Factors (age, education, etc.)
  - Brain reserve capacity
  - Socioeconomic status and access to health care
- Substance Abuse
- Genetic Factors
- CNS responsiveness to HRT

NCD due to HIV Course

- NCD due to HIV can resolve, improve, slowly worsen, or have fluctuating course.
- Rapid progression to profound NCD is uncommon with HRT.
- Subcortical NP pattern of deficits (motor, retrieval memory, PS, EF deficits)
- NCD due to HIV has considerable heterogeneity, esp. in older pts.
- NCD due to HIV has not declined significantly with advent of HRT, although most severe presentations (Major NCD) have decreased sharply

Is ANI Really Asymptomatic?

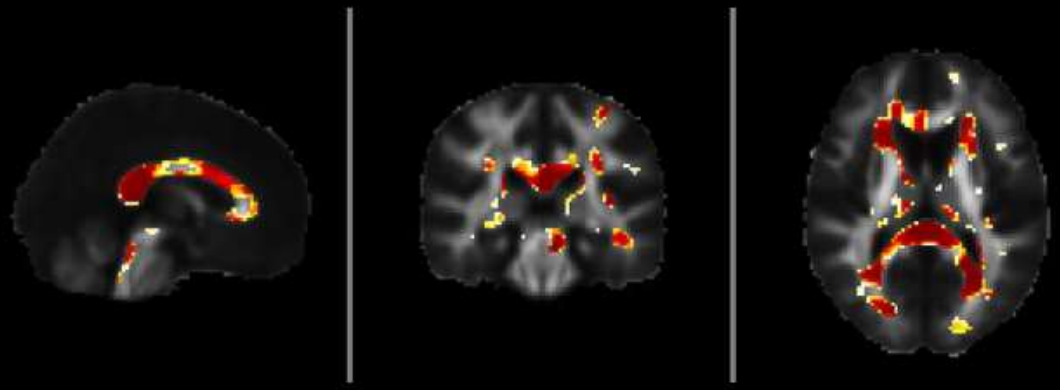


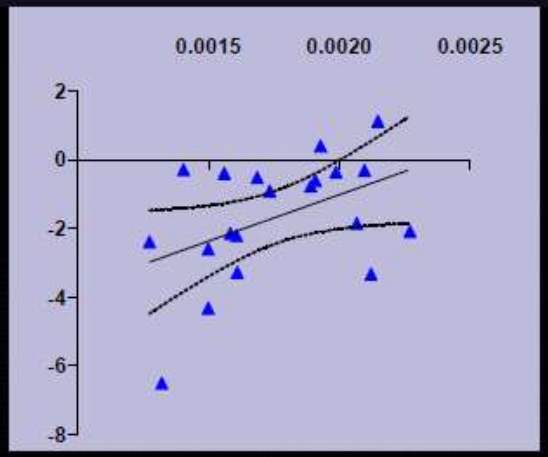
Patients with Asymptomatic Neurocognitive Impairment (ANI) perform just as poorly on tasks of everyday functioning as do symptomatic subjects (MND)

Chiao et al AIDS Res Hum Retro 2013

DTI and Morphometry Correlate to Tests of Everyday Functioning

Everyday functioning correlates to DTI and morphometry





NAB t-scores (y-axis) and corpus callosum volume as a fraction of ICV.

Course of HIV Associated Neurocognitive Disorders

- Onset & progression varies, but generally tends to be slow with long period (2-20 years) of relative asymptomatic problems followed by increasing physical & neurocognitive morbidity as HIV infection evolves into AIDS, eventually leading to mortality.

- Neurocognitive deficits present in up to 65% of people with HIV, but neurological involvement may be very mild;

- Up to 44% of cases of asymptomatic HIV infection present with neurocognitive sxs (10-30% is generally accepted). HIV Major NCD rare in asymptomatic HIV pts

- Course is usually progressive

Behavioral Symptoms/Clinical Presentation of HIV Associated Neurocognitive Disorders

- Motor dysfunction, often involves limb incoordination, weakness, corticospinal tract signs (hyperreflexia)
- Significant apathy and social withdrawal is common
- Alternatively, onset of disinhibition, poor judgment, irritability, & emotional lability may occur

Impact/consequences of HAND

- Poorer survival[1,2]
- Diminished self-care ability and quality of life[3]
- Deterioration in work performance, higher unemployment rate[4]
- Suboptimal drug adherence[5,6]
- Impaired driving, increased accident risk[7]
- Significant personal, economic and societal burden

1. Sevigny JJ, et al. Arch Neurol 2007;64:97–102; 2. Vivithanaporn P, et al. Neurology 2010;75:1150–8;
3. Heaton RK, et al. J Int Neuropsychol Soc 2004;10:317–31; 4. Heaton RK, et al. Psychosom Med 1994;56:8–17;
5. Woods SP, et al. Arch Clin Neuropsychol 2008;23:257–70; 6. Hinkin CH, et al. Neurology 2002;59:1944–50;
7. Marcotte TD, et al. J Clin Exp Neuropsychol 2006;28:13–28

“Cortical” vs. “Subcortical” Brain Disorders

“Cortical” (e.g., AD)

- Aphasia
- Apraxia
- Agnosia
- Acalculia
- Executive deficits
- Memory deficits (rapid forgetting)

“Subcortical” (e.g., HIV)

- Bradyphrenia (slowing)
- Complex attentional deficits
- Retrieval problems
- Mood disturbance
- Executive deficits
- Memory deficits (learning efficiency and retrieval)

AD = Alzheimer’s disease

Subcortical pattern of NP sxs

- Neuropathology: Cerebral atrophy with prominent lesions of subcortical white matter and subcortical gray matter structures (e.g. basal ganglia and thalamus)

- Early impairments may be mild, and involve attention, EG, verbal fluency, word finding, memory, psychomotor speed (bradyphrenia) deficits

- Deficits in fine manual speed and/or dexterity are common

Subcortical pattern 2

- Deficits in VS functions develop along with worsening memory deficits.
- Memory deficits initially reflect inefficient encoding and poor retrieval (recognition cues help), but worsen as disease progresses
- Language functions remain grossly intact, although verbal fluency and word finding may be present

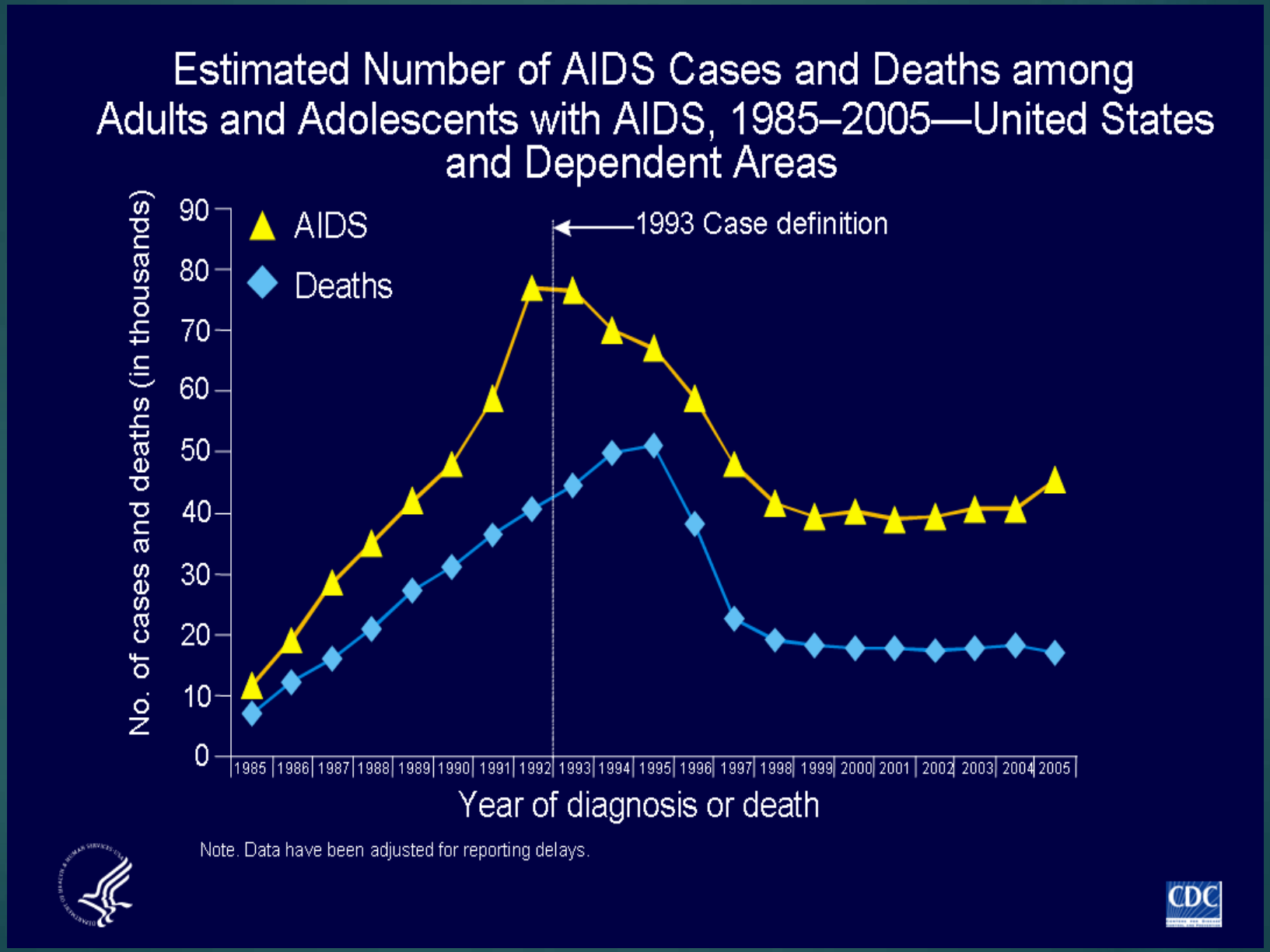
NP symptoms 2

- As Major NCD progresses, increasing global cognitive deterioration occurs.
- Onset of seizures, prominent motor deficits, mutism, incontinence and eventually coma.
- In addition to HIV cognitive disorders, often complications associated with HIV infection that lead to NP deficits: brain abscess (bacterial or fungal), cerebral toxoplasmosis, primary CNS lymphoma, progressive multifocal leukoencephalopathy, meningitis, encephalitis, meningoencephalitis, meningovasculitis, transverse myelitis, vasculitis
- 4% of HIV pts suffer strokes

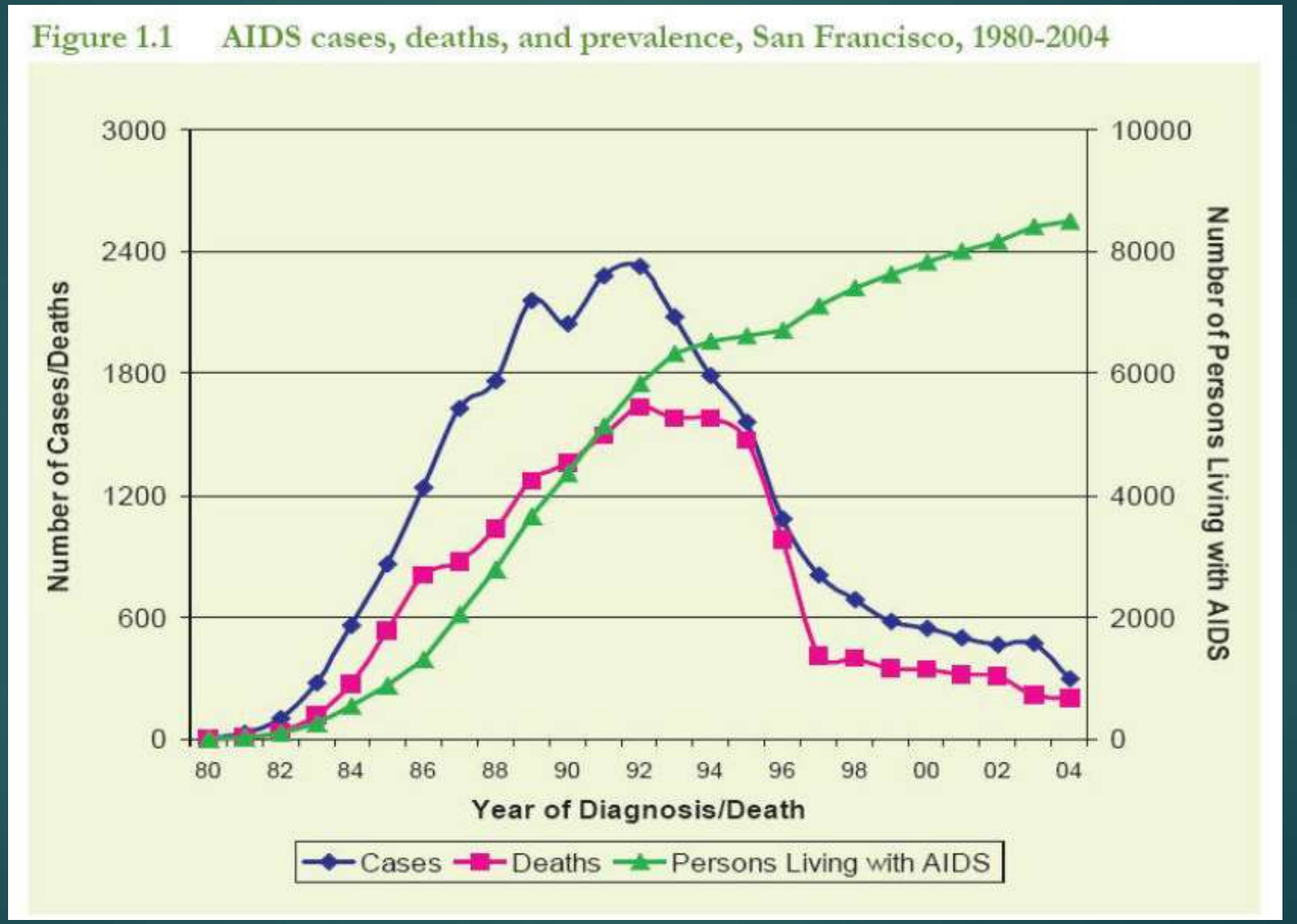
Incidence and Prevalence of NCD due to HIV (Prior to HRT (Highly Active Antiretroviral Therapies))

- After a diagnosis of AIDS, new cases of NCD occurred at a rate of 7% per year
- 15-40% of individuals developed NCD prior to death
- Median survival after NCD was 6 months

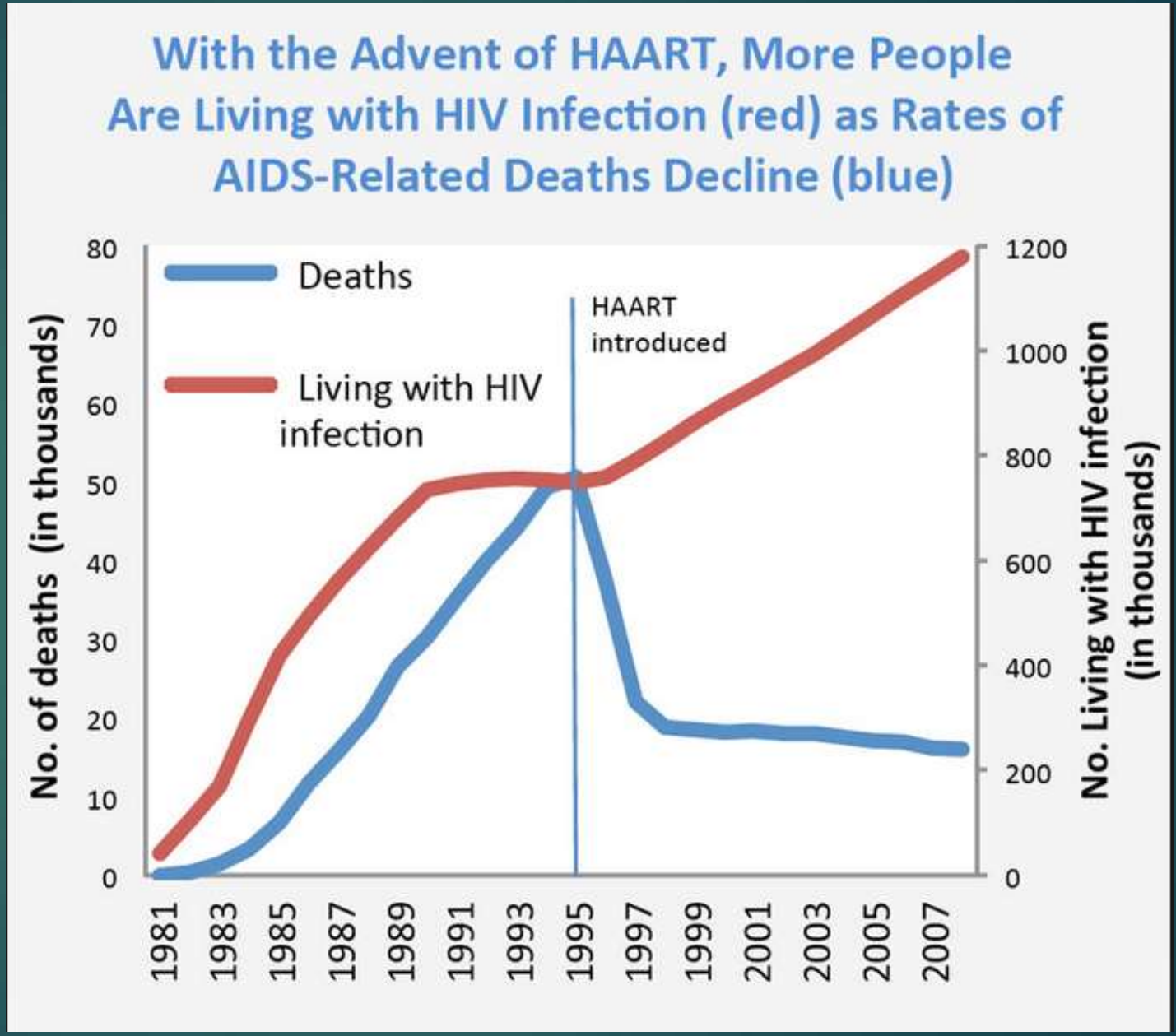
Good News: Less Early Death



Cases, Death, Survival



HRT & Deaths


With the Advent of HAART, More People Are Living with HIV Infection (red) as Rates of AIDS-Related Deaths Decline (blue)
Deaths
Living with HIV infection
HAART introduced
No. of deaths (in thousands)
No. Living with HIV infection (in thousands)
0
10
20
30
40
50
60
70
80
0
200
400
600
800
1000
1200
1981
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007

Incidence and Prevalence of HIV-Associated Neurocognitive Disorders (HAND)

Prior to HRT (before 1995)	After HRT (1996+)
New cases of Major NCD occurred at a rate of 7% per year	Incidence of all types of primary HIV neuropsychiatric disease have decreased dramatically
15-40% of individuals developed Major NCD prior to death	Incidence of cognitive impairment has been halved and Major NCD is rare
Median survival after Major NCD was 6 months	With proper treatment, HIV is considered a chronic disease

Good News and Bad News

- Steven Deeks MD IAS-USA May 2009:
- Poor life expectancy
- 10-30 years less
- "Patients receiving long term antiretroviral therapy are at increased risk of age associated non-AIDS related morbidity/mortality…"

Higher rates of non-AIDS dx

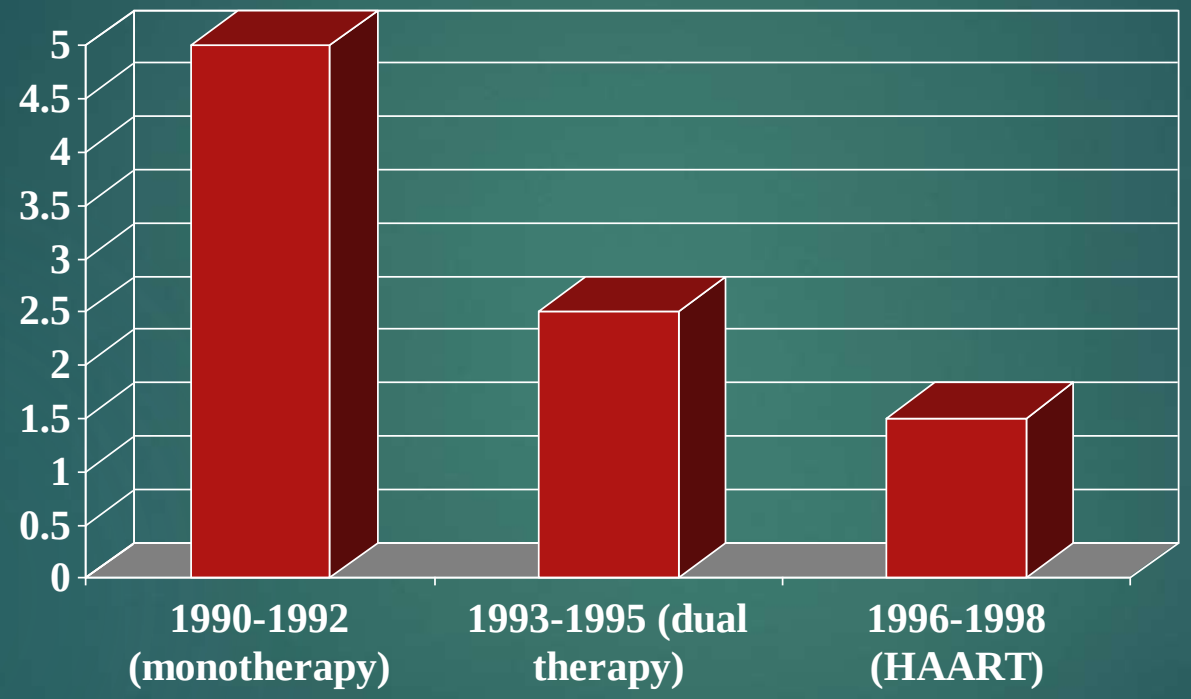
- Cardiovascular disease
- Cancers
- Osteopenia
- Left Ventricular Dysfunction
- Liver Failure
- Kidney Failure
- Cognitive Decline

- Accelerated aging/chronic inflammation

Incidence and Prevalence of NCD due to HIV (Since HRT)

- Incidence of all types of primary HIV neuropsychiatric disease have decreased dramatically.
- Incidence of NCD has been halved.
- Survival time since diagnosis of NCD has increased dramatically.

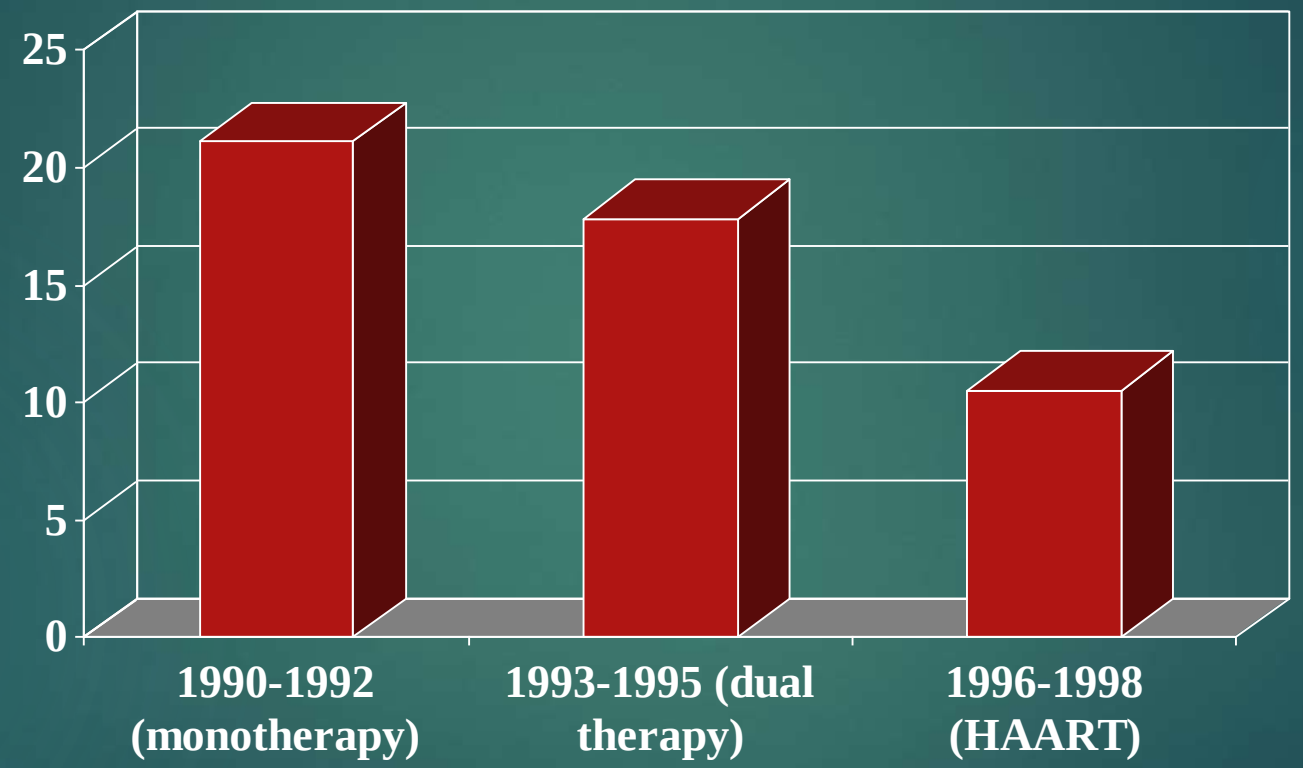
Changes in Incidence of Cryptococcal Meningitis



Incidence rates are number per 1000 person-years.

(Sacktor et al.,

Changes in Incidence of NCD due to HIV



Incidence rates are number per 1000 person-years.

(Sacktor et al., 2001)

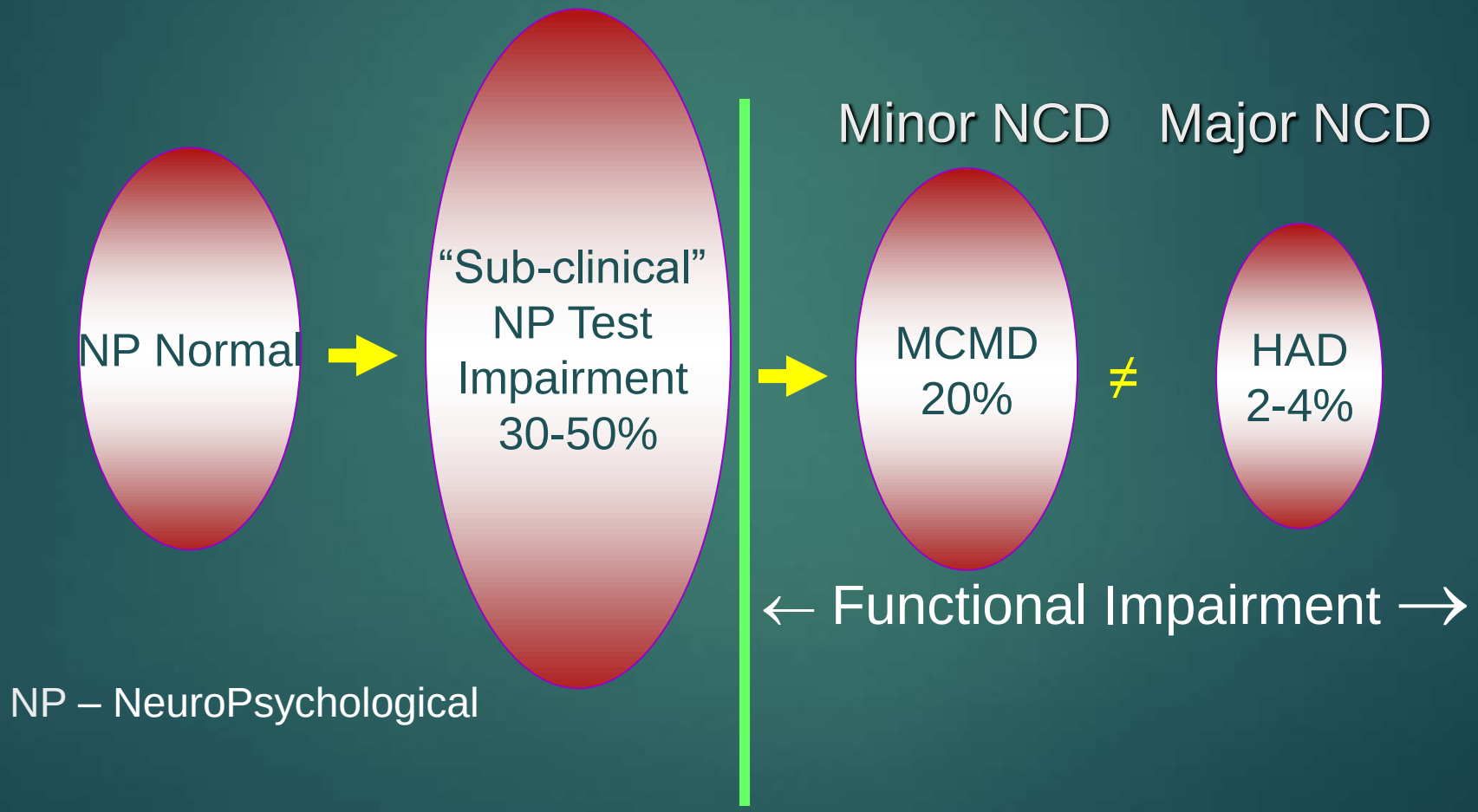
NCD due to HIV in the Era of HRT

- Although incidence of HIV-NCD has decreased, it continues to be a problem for many individuals.
- After over 25 years of research, the specific triggers for NCD due to HIV remain unknown.
- Improved survival means that more individuals with NCD must learn to cope with the effects of impaired cognition.

NCD due to HIV in the Era of HRT

- Effective treatments for NCD due to HIV are not yet available.
  - Individuals who are treated with HRT shortly after the first symptoms of NCD appear may show dramatic improvement.
  - Individuals who have shown symptoms of NCD for a while do not seem responsive to treatment.

Prevalence of HIV Associated Neurocognitive Disorders



Neuroimaging studies: AIDS & PML

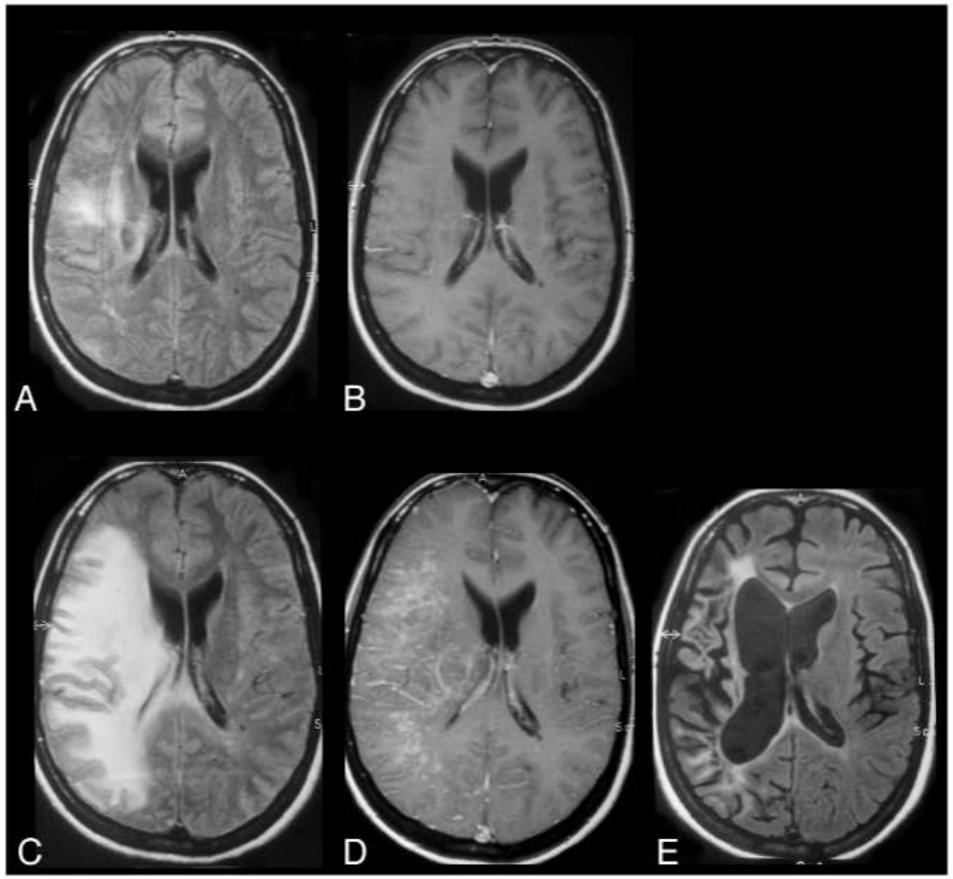


Fig 1. PML-IRIS. Patient with AIDS and PML whose initial MR imaging on axial FLAIR (*A*) and contrast T1WI (*B*) shows subcortical and deep white matter lesions due to PML, evidenced by high FLAIR signal without any enhancement. One month later, after HAART initiation, a marked increase in FLAIR high signal (*C*) compatible with interstitial edema, mass effect, and on contrast T1WI parenchymal and perivascular enhancement (*D*) develops compatible with PML-IRIS. Long-term follow-up MR imaging with axial FLAIR (*E*) shows resolution of most of the high-signal abnormalities and atrophy with cortical sulcal and ventricular dilation and no enhancement (not shown). Figures were reproduced with permission from Thurnher et al.[71]

- Pre HRT- subcortical & Periventricular White Matter Changes due to PML
- Post HRT (C,D,E)- mixed cortical and subcortical features

Stage of HIV Disease and Neuropsychological Test Performance

- Decline on neuropsychological testing is closely linked to general systemic illness.
- In general, observable cognitive changes are not seen during early, medically asymptomatic stages of HIV disease.
- Data from HIV-positive subjects with known dates of seroconversion suggest that there is no relationship between duration of HIV seropositivity and neuropsychological decline.

Prevalence of NCD due to HIV Infection

- 50% of HIV infected individuals are NP normal
- HIV neurocognitive disorders in 30-50% of persons living with HIV
- 30-50% of HIV infected individuals have at least mild NCD, but some don’t meet criteria for mild NCD; asymptomatic (no functional effects)
- 25% with HIV will have mild NCD
- 5%-10% have major NCD

Assessment of NCD due to HIV

- NCD due to HIV is generally considered a subcortical NCD.
  - NCD due to HIV symptoms are more associated with motor slowing and loss of executive control than with language and memory disturbance.
  - Later stage illness affects both cortical and subcortical regions and may affesct memory.

Typical features of HIV-associated Major NCD

Cognitive impairment	○ Mental slowness or loss of mental stamina ○ Memory problems ○ Poor concentration and comprehension
Behavioural abnormalities	○ Apathy ○ Lethargy ○ Diminished emotional response ○ Reduced gregariousness ○ Depression ○ Agitation/increased irritability
Motor dysfunction	○ Unsteady gait ○ Poor balance ○ Incoordination ○ Abnormal tone ○ Tremors

Navia BA, et al. Ann Neurol 1986;19:517–24

Mild NCD due to HIV (MND)

- Can appear any time after HIV infection (pre- or post-AIDS); Often does not present for any treatment and is not recognized nor diagnosed

- Prevalence post HRT
  - 5% in asymptomatic, 15% in early, & 25% in late stage

- Typical presentation:
  - Normal MMSE
  - Prominent psychomotor and cognitive slowing
  - Only the most demanding IADLs are impaired
  - Mild impairment in at least two areas (1 s.d.)
    - e.g., motor skills, attention, information processing speed, abstract thinking, memory, verbal fluency, working memory, response inhibition

Mild Neurocognitive Disorder (MND)

- Deficits in executive functioning can lead to deficits in prospective memory, “remembering to remember”.
- This increases the risk of nonadherence to complex antiretroviral medication regimens.
- Higher failure rates in driving simulators and on-road tests.
- Need for reminders (text messaging system, etc.)

Mild Neurocognitive Disorder (MND)

- Patient Complaints:
  - Complex task difficulty
  - Memory problems
  - Distractibility
  - Adherence problems

- Complications:
  - Occupational
  - Treatment adherence

Mild NCD due to HIV (MND)

Clinical Features

- Mild impairment in functioning
- Impaired attention or concentration
- Memory/concentration problems
- Low energy/slowed movements
- Impaired coordination
- Personality change, irritability or emotional lability

Patient Complaints/Symptoms

- Patients may not recognize the problem since their is mild functional impairment
- Has difficulty with complex tasks
- Mild memory problems
- Distractibility/confusion
- Needs to make lists
- Adherence problems
- May make excuses for forgetting

Major NCD due to HIV

- Major Neurocognitive Disorder due to HIV Definition:
  - HIV+
  - loss of intellectual abilities of sufficient severity to interfere w/ social or occupational functioning or ADL's, progressing over weeks or months
  - in the absence of concurrent illness or condition other than HIV to explain the findings (e.g., focal CNS disorders)

Major NCD due to HIV (old HAD)

- Most common after onset of AIDS, especially w/CD4 count <50
- Prior to highly active antiretroviral therapy, or HRT, 67% mortality rate in 6 months
- Now, much different, more subtle NCD that strikes 4 or more years before death
- Even w/ HRT, NCD still occurs in 5-10% of HIV+ pts and is gradually increasing due to longer survival rates
- Risk Factors: Age, low CD4 count, high viral load, low hematocrit, cocaine use, medication resistance, co-infection

Major NCD due to HIV 2

- May improve with antiretroviral therapy
- Between 5-10% of AIDS pts get Major NCD
- Often similar to subcortical NCD
- Level of cognitive impairment tends to correlate with severity of illness as measured by CD4 count
- Strong correlation between Major NCD and time to death.

Major NCD due to HIV 3

- NOTE: Major NCD is *not* invariably progressive.
  - Can remain static or fluctuate and may improve with medication.
  - May worsen abruptly in the presence of a severe metabolic disorder such as hypoxemia from pneumonia, then improve when the condition is treated.

Major NCD due to HIV: Cognitive Sxs 4

- Cognitive symptoms:
  - Slowed cognitive processing and psychomotor speed
  - Learning and memory
    - Especially delayed
    - Difficult keeping discrete memories separate (intrusions)
    - Difficulty with temporal aspect of memory
    - Cueing tends to be helpful
    - When severe, may misremember or confabulate

Major NCD due to HIV: Cognitive Sxs 5

- Decreased attention and concentration
- Frontal lobe dysfunction
  - Mental flexibility
  - Abstract reasoning
  - Planning
  - Decision-making
- Verbal fluency
- Slowed speech or hypophonia
  - Aphasia is uncommon and may suggest focal dysfunction

Major NCD due to HIV: Behavioral Symptoms 6

- Apathy, lethargy, diminished emotional responsiveness
- Loss of libido
- Agitation, hallucinations
- Withdrawal from social and business contacts
- Irritability or decreased flexibility to change
- Impulsivity, disinhibition
- Organic mania occurs in a small percentage

Major NCD due to HIV: Motor Symptoms 7

- Decreased motor speed and agility
- Unsteady gait, leg weakness
- Slowed reaction time: “bradyphrenic”, like Parkinson’s patients
- Incoordination, decreased handwriting legibility
- Tremor

Major NCD due to HIV (HAD)

Clinical Features

- Cognitive, motor, and behavioral problems
- Attention/concentration problems
- Slowed decision-making
- Abstraction/reasoning problems
- Visuospatial skill problems
- Memory/learning impairment
- Speech/language problems

Patient Complaints, Symptoms

- Memory problems/“I’m very forgetful”
- Distractibility/“I lose track of conversations”
- “I can’t keep up with work”
- Anger/irritability
- Fatigued/slow
- “I am depressed”/sadness
- Complains of poor balance, clumsiness

Major NCD due to HIV (HAD)

Overview

Prevalence pre HRT (antiretroviral tx)

- Early studies estimated 15-20%
- Current studies estimate 5-10%

Prevalence post HRT

- 50% reduction; not as prominent as other CNS opportunistic infections

Possible Risk Factors

- Older age, low CD4 count, high viral load, drug interactions, co-infections, gender, previous delirium

Aging and HIV

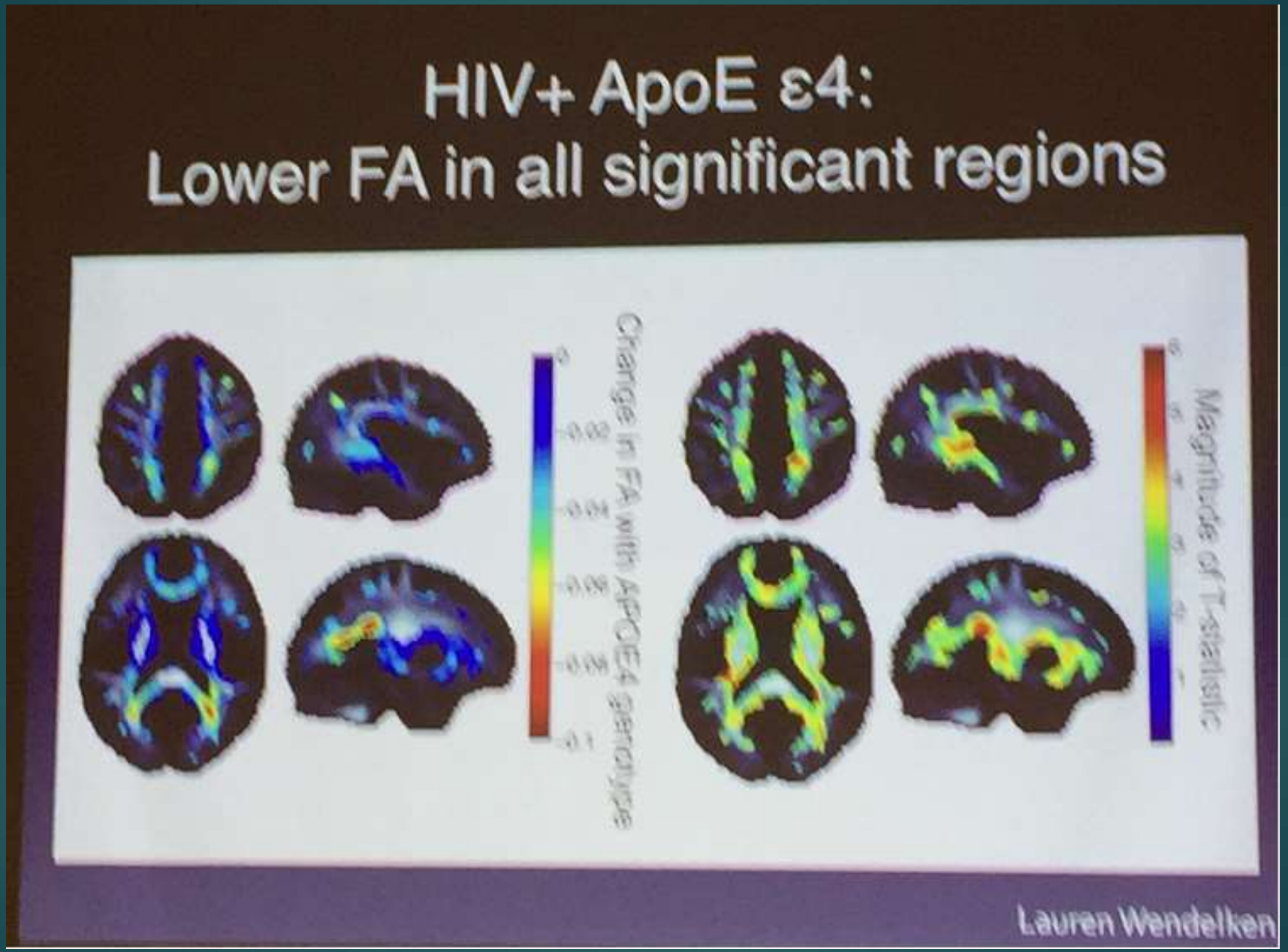
- Mortality rates in HIV have decreased dramatically with HRT; increased prevalence of older HIV pts.
- > age 50 have 3 x higher rates of NCD
- Higher rates of medial temporal pathology
- APOe4 associated with 3x risk for Major NCD in older pts.

ApoE4 and HIV

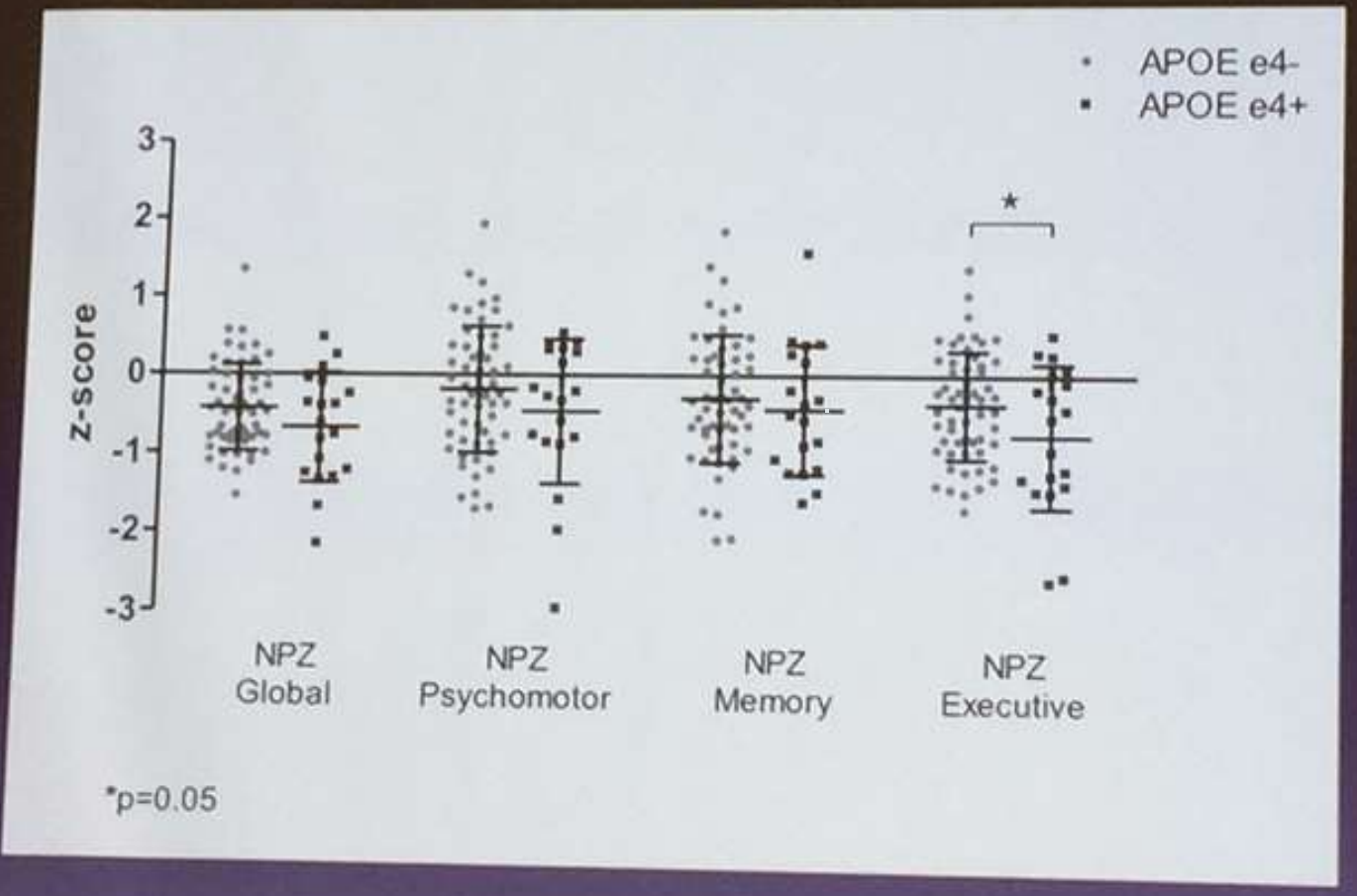
- Concurrent neurodegenerative diseases; evidence of posterior ventricular expansion
- BG atrophy, atrophy in CC, thalamus, brainstem
- ApoE4 acceleration of other intracellular viral infections

- More diffusion & FA decrease in HIV + ApoE4, especially EF decline
- ApoE4 effect may be due to CV effects

HIV+ ApoE ε4:
Lower FA in all significant regions



HIV+ ApoE ε4: Decreased cognitive performance



Lauren Wendelken

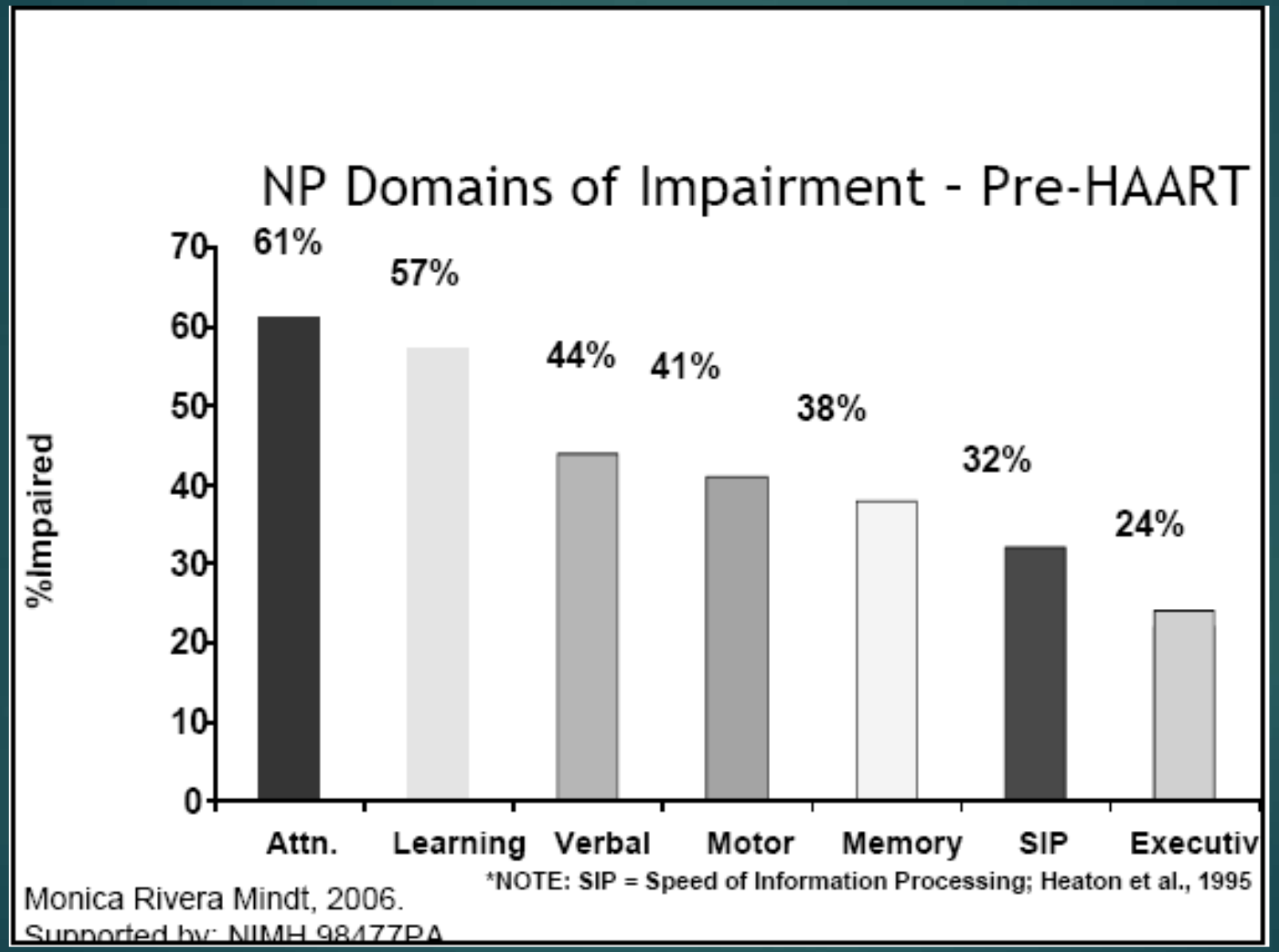
NCD due to HIV Diagnosis

- Diagnosis made by ruling out alternative diagnoses.
- Requires neurological examination, brain scans (MRI or CT Scan), and lumbar puncture to evaluate cerebrospinal fluid.
- No single test available to confirm the diagnosis, but history, lab findings and examination can reliably establish diagnosis.
- The amount of virus in the brain does not correlate well with the degree of Major NCD, suggesting that secondary mechanisms are also important in manifestation of ADC.
- http://en.wikipedia.org/wiki/HIV-associated_neurocognitive_disorder

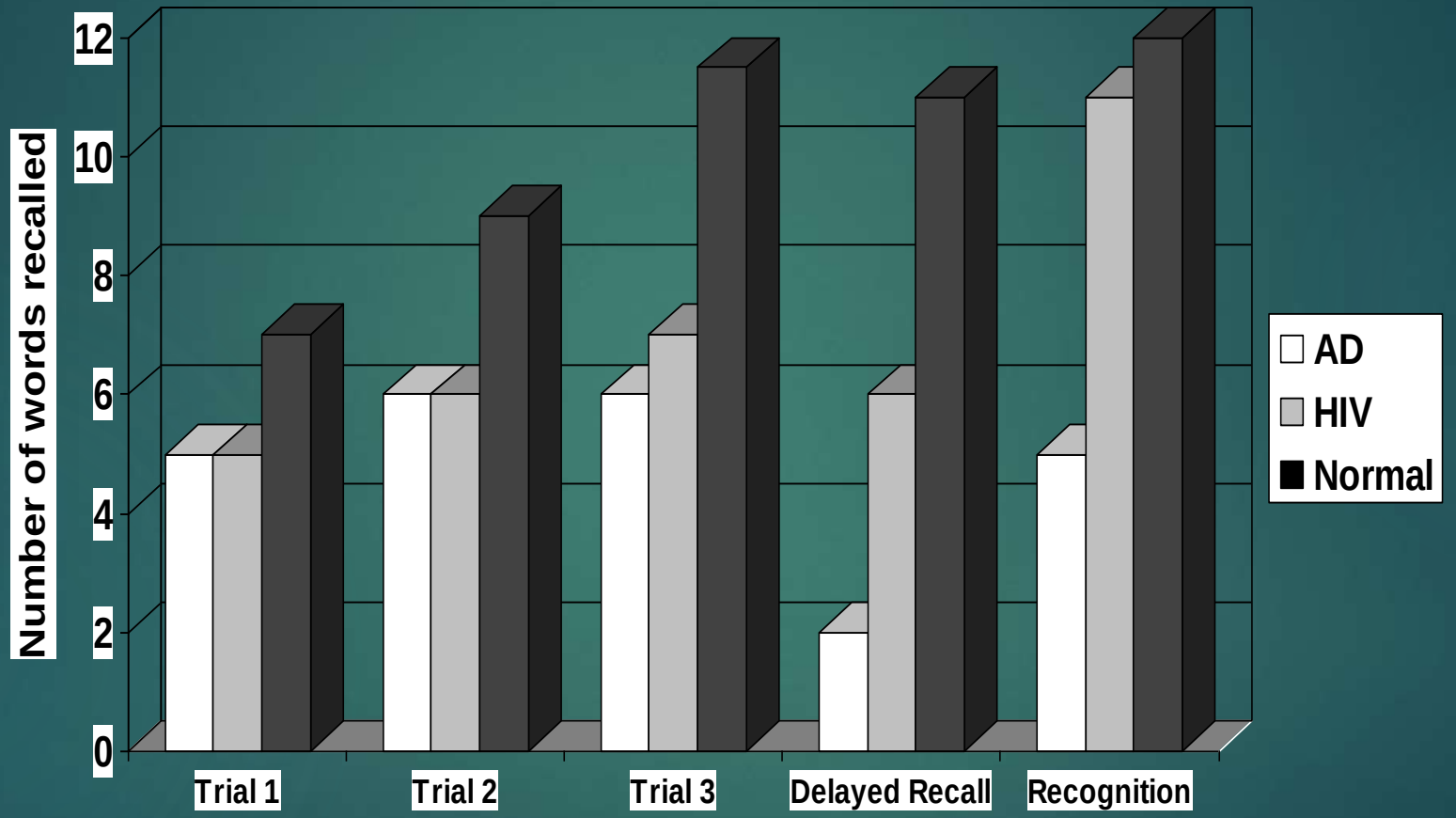
Diagnosing patients with neurocognitive impairment

- Neurological examination for focal signs
- Referral for full neuropsychological assessment (IHDS or MoCA as alternative to facilitate diagnosis)
- Evaluation for confounding factors
- Investigation for other treatable causes
- Neuroimaging
- CSF examination: opportunistic infection; CSF HIV RNA level

NP Domains of Impairment: Pre-HRT



Verbal Memory in AD & HIV: Number of Words recalled



AD = Alzheimer's disease (example of "cortical" memory profile)
HIV (characteristic of "subcortical" memory profile)

Neuropsychological Impairment

- The greater the degree of immunological compromise, the greater the NP impairment
- There is inconsistency regarding cognitive dysfunction in individuals in early & asymptomatic stages of the illness.
- There is conclusive evidence for later stages.
- Initial symptoms are neuropsychological in 10-30% of cases

Asymptomatic Stage

- • Rates on NP below are 3x higher than for HIV+ seronegative individuals
  - Naming
  - Speeded psychomotor tasks (Bornstein et al., 1993; Heaton et al., 1995)
  - New Learning

Symptomatic stage

- Motor functioning !!
- Problem-solving
- Executive functioning
- Information processing
- Speed
- Language skills

AIDS – (Subcortical NCD)

- Significant Impairments:
  - Motor functioning (greatest effects)
  - Attention and Concentration
  - Executive functioning
  - Information processing speed
  - Immediate visual memory
- Moderate Impairments:
  - Language
  - Visual construction

Greatest Decline from early to late HIV

- HIV is a white matter disease initially, then a gray matter disease
- Information processing speed
- Motor Functioning
  - Reaction time tests
  - Motor measures
- Executive Skills
  - Trail Making test
  - Stroop Color Interference
- Memory (usual in later stages)

Cognitive evaluation in African American & Hispanic HIV pts

- First, a cautionary note:
  - 2005 study: 50% of African-American and Hispanic HIV+ pts. Major NCD
  - reading level more than 2 years below years of education.
  - Reading/education discrepancies accounted for lower performance in all neuropsych domains, whereas racial/ethnic minority status did not.

- SO, norms based on education may inflate impairment rates among this population. Their grade levels may not match cognitive ability

  - Give PIAT or WRAT-4 to help identify appropriate normative standards.

Problem with recognition of HAND

- Vast majority of patients with HAND have mild or no symptoms
- Patients may not volunteer symptoms from lack of awareness or insight
- ID physicians caring for HIV/AIDS patients may not have relevant training for diagnosis and management of HAND
- Practical difficulties with routine screening for HAND in busy clinic settings
- Limited access to formal neuropsychological testing

Screening questions for evaluation

Patients:

- Are you slower in your thinking than you used to be?
- Are you more forgetful than you used to be?
- Is it harder to organise things?
- Are you less able to find pleasure in the thing that you used to enjoy? (to exclude depression)

Significant others:

- Is the patient more forgetful?
- Has the patient’s personality changed?
- Is the patient finding it harder to organise his life?

Observed clues

- Decreased precision and clarity of history
- Circumstantiality
- Perseveration
- Word finding difficulty, paraphrasia
- Paucity of details and absence of imagery
- Emotional lability
- Decreased concern about limitations
- Decreased drug adherence

Assessment of functional impairment

- Self-report or by informant
- Cognitively related instrumental ADLs
- Shopping, food preparation, laundry, housekeeping, transport, use of telephone
- Medication management, financial management, work performance or efficiency
- Increased need for assistance

EACS (European AIDS Clinical Society) guidelines: Diagnosis of HAND

- Patients **with** cognitive symptoms, evaluate with
  - Neurological examination
  - Neuropsychological testing
  - CSF examination
  - Brain MRI

- Patients **without** symptoms, screen with 3 questions and IADL questionnaire:
  - Frequent memory loss
  - Slower reasoning, planning, problem solving
  - Difficulty with attention
  - Exclude confounding conditions (psychiatric condition, psychotropic drugs, alcohol abuse, other CNS disease)

EACS Guidelines Nov 2012
[www.europeanaidsclinicalsociety.org]

3 Questions

- 1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
- 2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
- 3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?

Neuropsychological Testing:
When to Refer (or Administer Tests)

- Patient reports cognitive complaints and it is not clear whether these are related to mood, medical complications, alcohol or drug use, or HIV-related brain changes
- Partners, caregivers or significant others notice functional cognitive changes
- To establish a baseline for later comparison
- To monitor progress with antiretroviral treatment
- Functional or everyday activities are at issue

Screening instruments for HAND

- Mini-Mental State Examination (MMSE)
- HIV Dementia Scale (HDS)
- International HIV Dementia Scale (IHDS)
- Montreal Cognitive Assessment (MoCA)
- Medical Outcomes Study HIV Health Survey (MOS-HIV)
- Other screening protocols

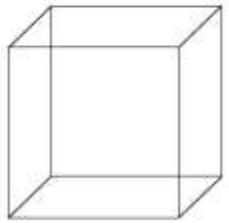
- None measure motor speed decline

HDS: HIV Dementia Scale

HIV DEMENTIA SCALE

DEPARTMENT OF NEUROLOGY, JOHNS HOPKINS UNIVERSITY

Maximum Score	Score	
		MEMORY - REGISTRATION Give four words to recall (dog, hat, green, peach) – 1 second to say each. Then ask the patient all 4 after you have said them.
4	( )	**ATTENTION** Anti-saccadic eye movements: 20 commands _____errors of 20 trials ≤3 errors = 4; 4 errors = 3; 5 errors = 2; 6 errors = 1; >6 errors = 0
6	( )	**PSYCHOMOTOR SPEED** Ask patient to write the alphabet in upper case letters horizontally across the page and record time. _____ in seconds. <21 sec = 6; 21.1 to 24 sec = 5; 24.1 to 27 sec = 4; 27.1 to 30 sec = 3; 30.1 to 33 sec = 2; 33.1 to 36 sec = 1; >36 sec = 0
4	( )	**MEMORY/RECALL** Ask for 4 words from Registration above. Give 1 point for each correct. For words not recalled, prompt with a "semantic" clue, as follows: animal (dog); piece of clothing (hat), color (green), fruit (peach). Give 1/2 point for each correct word after prompting.
2	( )	**CONSTRUCTION** Copy the cube below; record time: _____ seconds <25 sec = 2; 25 to 35 sec = 1; >35 sec = 0



TOTAL SCORE: _____ /16

IHDS

International HIV Dementia Scale (IHDS)

Memory-Registration – Give four words to recall (dog, hat, bean, red) – 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

1. Motor Speed: Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.

    4 = 15 in 5 seconds
    3 = 11-14 in 5 seconds
    2 = 7-10 in 5 seconds
    1 = 3-6 in 5 seconds
    0 = 0-2 in 5 seconds

    ____

2. Psychomotor Speed: Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5thdigit. Demonstrate and have patient perform twice for practice.

    4 = 4 sequences in 10 seconds
    3 = 3 sequences in 10 seconds
    2 = 2 sequences in 10 seconds
    1 = 1 sequence in 10 seconds
    0 = unable to perform

    ____

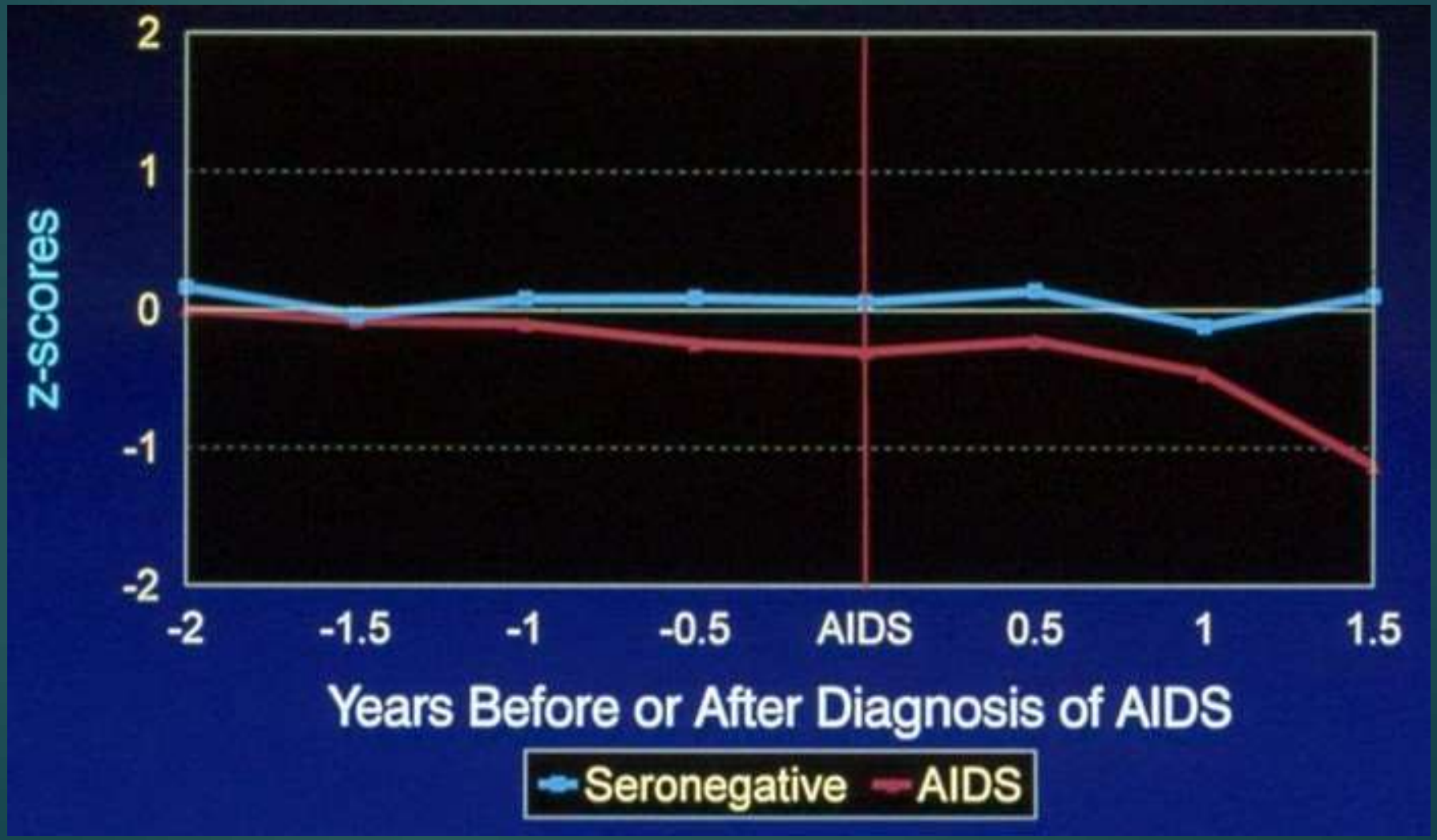
3. Memory-Recall: Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).

    Give 1 point for each word spontaneously recalled.
    Give 0.5 points for each correct answer after prompting
    Maximum – 4 points.

    ____

Total International HIV Dementia Scale Score: This is the sum of the scores on items 1-3. The maximum possible score is 12 points. A patient with a score of ≤10 should be evaluated further for possible dementia.

Changes in Performance on Trails B Before and After Diagnosis of AIDS



Grooved Pegboard (GP)

- Requires minimal operator training
- Measures
  - Manipulative dexterity
  - Visual-motor coordination
  - Performance and speed in fine motor tasks
- Administered to dominant and non-dominant hands
- Trial time allowed: 5 minutes
- Several scores may be recorded:
  - (1) Time (in seconds) to perform each trial from start to end
  - (2) No. of unintentional “drops” of peg from time of pick-up to correct placement in hole during each trial
  - (3) No. of pegs correctly placed in the holes in each trial

Klove H. Med Clin N America 1963;47:1647–58
Lafayette Instrument Grooved Pegboard Test User’s Manual; Lafayette, USA

Motor & Psychomotor Abilities

- Gross motor ok
- Bradykinesia (slowed movement) hallmark (gait speed, fine motor speed & dexterity ↓)
- Bradyphrenia (cognitive processing speed ↓, reaction time ↓)

- Need to factor these out in NP testing, i.e. WAIS PIQ

Neuropsychological Test Batteries for HIV Assessment

Domain	Tests
Attention /Speed of Processing	TMT-A WAIS D-S
Executive f(n)	TMT-B PASAT WCST
Working Memory	WAIS-IV L-N
Language	COWAT Action fluency Animal naming

Tests commonly used in HIV assessment from Tate et al

Neuropsychological Test Batteries for HIV Assessment

Domain	Tests
Motor	GPB
Visuospatial Processing	WAIS Symbol Search
Learning and Memory	HVLT-R Brief visuospatial memory test- R Story memory test Figure memory test
Academic	WRAT Reading subtest

Tests commonly used in HIV assessment from Tate et al

Neuropsychological Test Batteries for HIV Assessment

Domain	Tests
Behavioral	FrsBe (Frontal systems behavioral scale)
Activities of daily living	Questionnaires
Mood	CES depression scale BDI-II

Tests commonly used in HIV assessment from Tate et al

Steven Paul Woods Battery, UCSD

- CVLT-II (or HVLT-R)
  BVMT-R (Brief VS Memory Test)
  Trails A/B
  WAIS-III PSI
  Action fluency
- DKEFS category switching
  Pegs
  WCST-64
  PASAT-50
  Digit Span

  That would basically give you 2 tests per cognitive domain (per the Antinori diagnostic recommendations) in ~1hr. In addition, I would throw in the modified Lawton & Brody ADL questionnaire and the POMS (Profile of Mood States).

Lawton IADL

The Lawton Instrumental Activities of Daily Living Scale

A. Ability to Use Telephone

1. Operates telephone on own initiative; looks up and dials numbers 1
2. Dials a few well-known numbers 1
3. Answers telephone, but does not dial 1
4. Does not use telephone at all 0

B. Shopping

1. Takes care of all shopping needs independently 1
2. Shops independently for small purchases 0
3. Needs to be accompanied on any shopping trip 0
4. Completely unable to shop 0

C. Food Preparation

1. Plans, prepares, and serves adequate meals independently 1
2. Prepares adequate meals if supplied with ingredients 0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet 0
4. Needs to have meals prepared and served 0

D. Housekeeping

1. Maintains house alone with occasion assistance (heavy work) 1
2. Performs light daily tasks such as dishwashing, bed making 1
3. Performs light daily tasks, but cannot maintain acceptable level of cleanliness 1
4. Needs help with all home maintenance tasks 1
5. Does not participate in any housekeeping tasks 0

E. Laundry

1. Does personal laundry completely 1
2. Launders small items, rinses socks, stockings, etc 1
3. All laundry must be done by others 0

F. Mode of Transportation

1. Travels independently on public transportation or drives own car 1
2. Arranges own travel via taxi, but does not otherwise use public transportation 1
3. Travels on public transportation when assisted or accompanied by another 1
4. Travel limited to taxi or automobile with assistance of another 0
5. Does not travel at all 0

G. Responsibility for Own Medications

1. Is responsible for taking medication in correct dosages at correct time 1
2. Takes responsibility if medication is prepared in advance in separate dosages 0
3. Is not capable of dispensing own medication 0

H. Ability to Handle Finances

1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income 1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc 1
3. Incapable of handling money 0

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

Suggested Battery in detecting NCI in context of HIV (Gold Standard)

- Motor-
  - Grooved Pegboard
- Processing speed-
  - Trails part A,
  - WAIS-III Digit Symbol Coding,
  - WAIS-III Symbol Search
- Executive Functioning-
  - Trails B,
  - WCST (perseverative responses)

Suggested Battery in detecting NCI (2)

- Learning-
  - Brief Visual Memory Test (Delayed Recall),
  - Hopkins Verbal Learning Test (Total Recall)
  - CVLT
- Memory-
  - Brief Visual Memory Test (Delayed Recall),
  - Hopkins Verbal Learning Test (Delayed Recall)
- Working Memory-
  - WAIS III Letter Number Sequencing

Suggested Battery in detecting NCI (3)

- Verbal Fluency-
  - COWAT
- Reading Level –
  - WRAT-Reading 3rd Edition

Carey CL, Woods SP, Rippeth JD, et al. Initial validation of a screening battery for the detection of HIV-associated cognitive impairment. *The Clinical neuropsychologist*. 2004;**18**(2):234–48

Gold Standard NP Tests **

Neuropsychological Domain/Test	Normative Data Source
Motor	
Grooved Pegboard – DH	Heaton, Miller, Taylor & Grant[39] [1,2,3,4]
Grooved Pegboard – NDH	Heaton, Miller, Taylor & Grant[39] [1,2,3,4]
Processing Speed	
Trail Making Test, Part A	Heaton, Miller, Taylor & Grant[39] [1,2,3,4]
WAIS-III Digit Symbol Coding	Heaton, Taylor & Manly[40] [1,2,3,4]
WAIS-III Symbol Search	Heaton, Taylor & Manly[40] [1,2,3,4]
Executive Functioning	
Trail Making Test, Part B	Heaton, Miller, Taylor & Grant[39] [1,2,3,4]
Wisconsin Card Sorting Test – Perseverative Responses	Kongs et al.[41] [1,2]
Learning	
Brief Visual Memory Test – Total Recall	Benedict[42] [1]
Hopkins Verbal Learning Test – Total Recall	Benedict et al.[43] [1]
Memory	
Brief Visual Memory Test – Delayed Recall	Benedict[42] [1]
Hopkins Verbal Learning Test – Delayed Recall	Benedict et al. [43] [1]
Working Memory	
WAIS-III Letter Number Sequencing	Wechsler[44] [1,2,3,4]
Verbal Fluency	
Controlled Oral Word Association Test	Gladsjo et al. (1999) [1,2,4]
Reading Level	
Wide Range Achievement Test – Reading 3rd Edition	Wilkinson[45] [1]

Note. Wechsler Adult Intelligence Scale (WAIS). Normative data provides adjustments for the following demographic characteristics, as indicated: [1] Age; [2] Education; [3] Gender; [4] Ethnicity

Table 1: Gold-Standard Neuropsychological Test Battery

Kaiser San Francisco NP Battery

- Our protocol:
  - WAIS-IV
  - CVLT-2
  - WMS-III with Spatial Span (or NAB memory tests)
  - Trail Making
  - Action Fluency
  - COWAT/Animal Naming
  - CVLT-II
  - Finger Tapping
  - Grooved Pegboard
  - WCST or Booklet Category Test
  - PHQ9
  - Executive Function Questionnaire
  - May need PIAT/WRAT

Attention, WM, Executive Function

- Attention deficits (selective, divided, sustained ↓)
- WM ↓ - multimodal (WAIS Letter-Number Sequencing**)
- Executive Dysfunction (Category, WCST **, Stroop, Iowa Gambling ↓)

NP Profile for HIV+

- HIV- associated neurocognitive disorders in 30-50% of individuals living with HIV.
  - Of these, 1/2 – 2/3 are ‘asymptomatic’ (independent in IADLs)

Cognitive “profile” of HIV infection

- Pre-HAART: Dementia frequent and motor deficits were hallmark
- Post-HAART: milder forms of cognitive impairment particularly focusing on executive function, attention, and learning.

Nomenclatures: CDC based on CD4 cell count

CD4 cells/ µL	CDC A	CDC B	CDC C
Category 1 ≥ 500	Asymptomatic, acute HIV or persistent generalized lymphadenopathy	Symptomatic conditions and not A or C – common conditions include bacillary angiomatosis, oral candidiasis, pelvic inflammatory disease, fever, diarrhea lasting >1 month, peripheral neuropathy, herpes zoster ≥ 2 episodes	AIDS- conditions including bacterial pneumonia, lung candidiasis, cervical carcinoma, cryptococcosis, cytomegalovirus, encephalopathy, herpes simplex, Kaposi's sarcoma, lymphoma, TB, PML, and toxoplasmosis
Category 2 200-499			
Category 3 <200			

AIDS Dementia Complex (ADC) staging

Stage	Description
Stage 0 Normal	Normal mental and motor f(n)
Stage .5 subclinical	Minimal cog &motor symptoms; Mild neurological sxs, Gait & strength WNL, IADLs OK
Stage 1 Mild	Cognitive & motor sxs, can walk w/ assistance, mild difficulties w/IADLs
Stage 2 Moderate	Cognitive & motor sxs, ambulatory w/ help, cannot work, IADLs impaired, ADLs OK
Stage 3 Severe	Significant cognitive impairment, Significant motor impairment – cannot walk unassisted, impaired ADLs
Stage 4 end stage	Nearly vegetative, mute. Intellectual impairment, double incontinence, paraparetic/paraplegic

Staging by American Academy of Neurology

AAN	Cog/Behave	Motor	IADLs
Asymptomatic	Not sig	Not sig	Not sig
Mild cognitive motor disorder (MCMD)	Hx of impaired cog or behavioral f(n)	Hx of motor dysfunction	Minimal
HIV-associated dementia (HAD)	Abnl 2+ cog domains; Abnl neuropsychiatric /psychosocial (e.g. motivation, emotional control, social behavior)	Abnl motor	Impaired IADLs

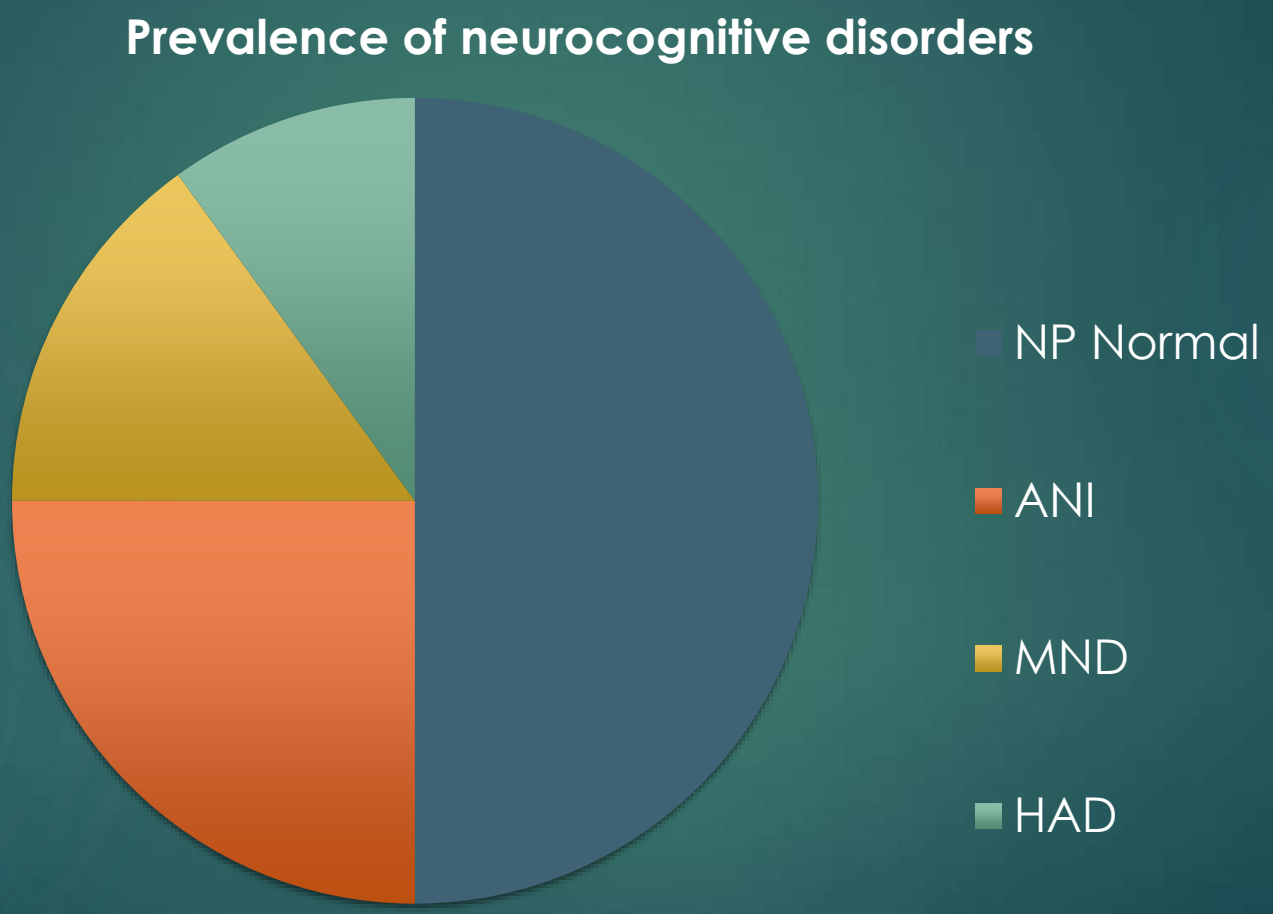
NIMH HIV-associated neurocognitive disorder (HAND)

HAND stage	Cog	IADLs/ ADLs
Asymptomatic Neurocognitive Impairment (ANI)	2+ domains > 1 SD	No change in IADLs/ ADLs
Minor Neurocognitive Disorder (MND)	2+ domains > 1 SD	Mild
HIV- Associated Dementia (HAD)	2+ domains > 1 SD	Marked

HIV-related cognitive impairment nomenclatures

- HAND: HIV-Associated Neurocognitive Disorders
- HAD: HIV-Associated Dementia
- ANI: Asymptomatic Neurocognitive Impairment (≥ 1 SD below mean on 2+ cognitive domains not due to premorbid factors)
- MND: Mild Neurocognitive Disorder

Prevalence: Mild Neurocognitive Disorder and HAD



Motor and Psychomotor Abilities

- **Bradykinesia earliest identified and most striking feature**
  - **E.g. gait velocity, fine motor dexterity (GPB)**
- Bradyphrenia: slowness of thought
  - Common in more severe stages
- Gross motor abnormalities (e.g. parkinsonism, chorea, myoclonus, dystonia) infrequent
  - May be present with advanced HIV disease

Attention

- Attention problems common, and worsen as disease advances
- Simple attention relatively spared in asymptomatic and symptomatic patients
- Complex attention impaired even in asymptomatic and in era of HAART
- One of most consistent findings

Attention and Working Memory

- Difficulties most noted in:
  - Selective attention
  - Complex visual search and discrimination
  - Divided attention
  - PASAT
  - Digit Symbol Test
  - Impaired performance on sustained attention tasks may be secondary to psychomotor slowing

- Working memory
  - Impairment across modalities
  - Related to the involvement of frontostriatal dysfunction in HIV

Executive Functioning:

- Dysfunction noted even in early stages of HIV disease
  - Increase in severity and prevalence in AIDS
  - Observed on Category Test, WCST (perseveration), Stroop (interference), TMTB
  - Research on decision making and Iowa Gambling Task suggest greater risk taking and possibly impulsivity.
- Post-HAART, continue to highlight deficits in executive f(n)

Prospective Memory (ProM)

- Mild to Moderate deficits on both time and event-based tasks.
- Biomarkers of HIV disease severity such as macrophage activation (e.g. moocyte chemoattractant protein 1 (MCP-1) and neuronal injury (e.g. tau) are associated with ProM
- Associated with IADLs decline and antiretroviral medication non-adherence.

Declarative Memory

- Aprox 50% HIV+ have deficits in both verbal and visual memory*
  - Associated with **frontostriatal circuit** dysfunction… i.e. deficits in executive functioning with respect to encoding and retrieval
  - ↓ free recall
  - ↑ repetitions
  - ↓ organizational encoding strategies

- Memory consolidation impairment is rare prior to HAD

- With HAD, rapid forgetting due to shallow encoding?
  - Evidenced from increased Recency Effect

*Heaton et al 1995 in Woods et al, 2009

Language

- Fluency deficits common in HIV, but not generally severe and more likely in advanced stages (Tate et al, 2010)

- Gross aphasia is rare in non HAD population
  - Receptive language well preserved
  - Expressive:
    - ? Motor problems? Ataxic dysarthria?
    - Phonemic & Semantic fluency (modest)
      - Impaired strategic search and retrieval & less switching
      - **Frontostriatal circuit pathology???**
    - Action Fluency sensitive to HIV-neurocognitive d/o with #words < Animal Naming

(Woods et al, 2009)

Sensory-Perception

- Spatial ability is generally well preserved in HIV disease

- Sensory-Perception: may be present and impact daily functioning and neuorpsych test results
- ¼ w/ HIV-associated NP impairment also have sensory-perceptual deficits on Reitan-Kløve Sensory-Perceptual exam, esp bilateral tactile form recognition
- Distal sensory polyneuropathy (DSPN) up to 50% of AIDS patients
  - Distal degeneration of long axons
  - painful dysesthesias, paresthesias, numbness- most common **in lower extremities**
  - Ask about neuropathy – impact TPT, GPB?

Sensory Continued:

DSPN	Vision	Otologic/Audiologic	Olfactory
• Older age • Lower CD4 • Other medical conditions (e.g. Hep C) • Neurotoxic antiretroviral drugs	• In advanced HIV – retinopathies common	• Ear infections • Advanced HIV – sensorineural hearing loss common	• Deficits in odor detection and identification

Daily Functioning

- Employment:
  - Neurocognitive decline impacts employability which can have profound impact on self-esteem and financial security
- Driving:
  - Processing speed, selective and sustained attention, motor sequencing, judgment, planning….
- Medication Adherence
  - Optimal adherence associated with less morbidity and mortality
  - Nonadherence → drug-resistance
  - HIV meds: many medication and complicated cARTs regiments
  - ProM, episodic memory, executive dysfunction

Neuropsychological Battery: Which Tests to Use

Attention and Concentration

- Digit Span* (look at forward vs. backwards)
- Spatial Span* (WMS-R)
- Letter-Number Sequencing (WAIS-III) **
- Digit Vigilance (time and errors)
- Simple, choice, and sequential reaction time

Asterisk refers to tests recommended by NIMH HIV working group (Butters et al., 1990); ** by Woods

Neuropsychological Battery: Which Tests to Use

Executive Processing Skills

- Trail Making Test: Part B* **
- Working memory tasks*
- Category Test*
- Wisconsin Card Sorting Test**
- Stroop

Memory

- Verbal & visual episodic memory ↓ in 50%: lower free recall, increased repitition, low semantic clustering, recognition ok
- Prospective memory deficit (predicts neuronal loss, IADL ↓ , medication nonadherence)
- Nondeclarative memory deficits (motor skills learning ↓, semantic priming ↓)
- Normal memory correlated with ability to return to work

Neuropsychological Battery: Which Tests to Use

Verbal and Visual Learning and Memory

- California Verbal Learning Test*
- Rey Auditory Verbal Learning Test
- Hopkins Verbal Learning Test **
- Story Learning and Memory
- Figure Learning and Memory*
- Rey Osterrieth Complex Figure Test
- Brief Visual Memory Test **

Language

- Normal receptive language
- Mild to moderate expressive deficits (ataxic dysarthria, letter & category fluency, category switching, esp. action fluency)
- Action fluency ↓ predicts IADL ↓

General Cognitive Functioning

- 50% rate of delirium in hospitalized HIV pts (with higher mortality rates)
- Fluid IQ measures lower due to processing speed issues

Neuropsychological Battery: Which Tests to Use

Language and Premorbid IQ Estimation

- WAIS-R Vocabulary* & Information

- ANART*
- Boston Naming Test*
- Phonemic (FAS) and category fluency*
- Thurstone Written Fluency
- WRAT-4**
- COWAT**

Neuropsychological Battery: Which Tests to Use

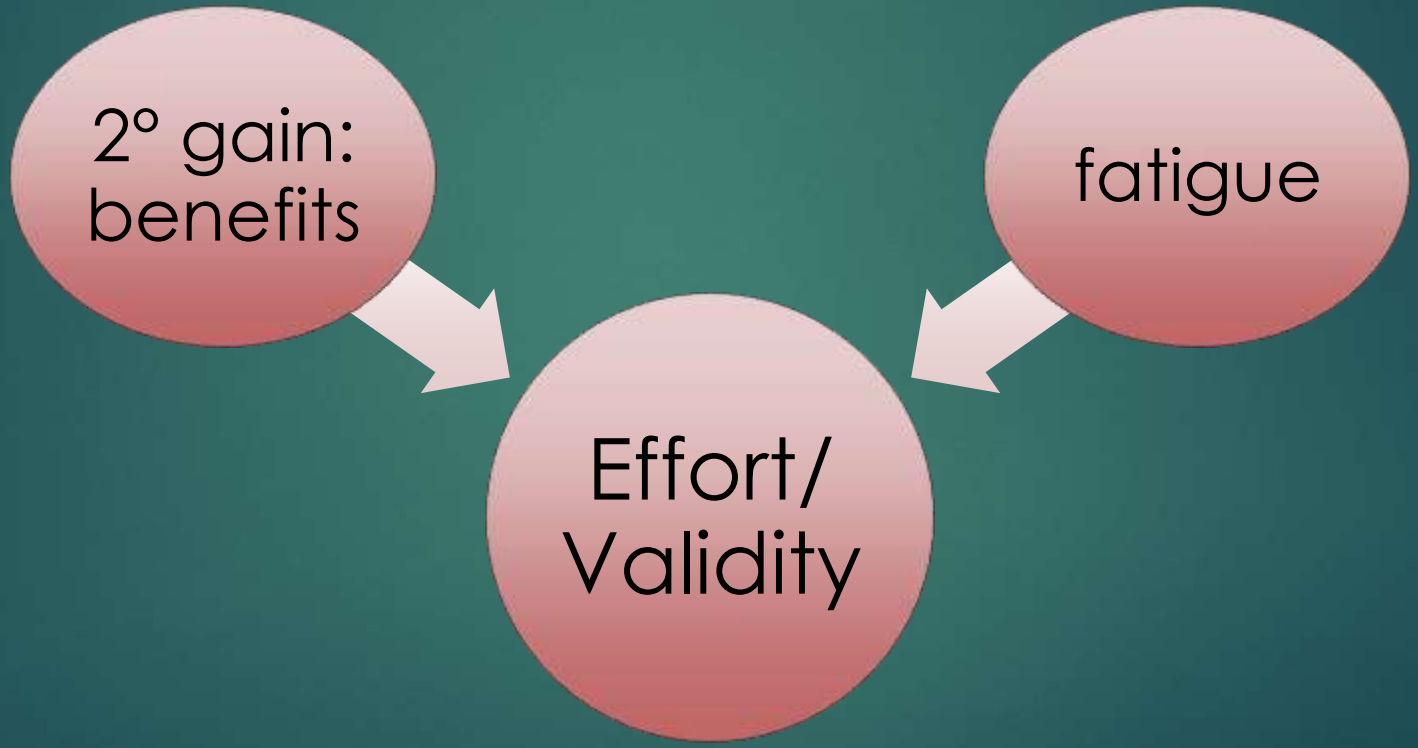
Speed of Processing and Psychomotor Skills

- WAIS-R Digit Symbol* **
- Symbol Digit Modalities Test
- Trail Making Test: Parts A and B* **
- Reaction time (simple and complex)*
- Rey Osterrieth Complex Figure Test
- Sternberg Search Task*
- Grooved Pegboard* **

Sensory-Perception

- 28% show bilateral tactile form recognition ↓ on Reitan-Klove
- Peripheral neuropathy affects 50% of AIDS pts (dysesthesias, paresthesias, numbness) – reduce IADLs and QAL.
- 33% have ear disease

Suboptimal Effort



Effort and Symptom Validity

- 20 % of HIV pts on SSD benefits
- Slick: 7-18% false positive
- Few studies
- Use effort measures!!

Overview of Psychiatric issues

- Psychiatric disorders are common with Individual living with HIV/AIDS (Bing 2001, Mellins 2002, McKinnon 2008)
  - 50% Mood and Anxiety disorder
  - 25% current Substance abuse or dependence
  - 26% Personality Disorder
- Psychiatric dx are linked to slower rates of virologic suppression and treatment (Pence et al 2007)
- Treatment of Psychiatric disorders is associated
  - Slower disease progression and mortality (Belanoff 2005)
  - Improved treatment adherence (Wyatt 2004)
  - Decrease in HIV transmission risk behavior (Sikkema 2008, Wyatt 2004)
  - Improved quality of life (Sikkema 2005)

Medication Adherence

- Adherence to HRT associated with dramatic reductions in morbidity & mortality.
- Nonadherence related to development of drug resistance.
- HIV cognitive deficits associated with medication nonadherence, esp. due to memory and executive deficits.
- More complex the med regime, greater the nonadherence.
- Prospective memory deficit especially correlated to nonadherence.

Psychiatric Comorbidities

- MDD most common comorbidity, up to 50%; poorer TX outcomes, reduced med adherence; no additive effect on cognition
- Anxiety: up to 38%
- Bipolar: comorbid Bipolar has additive cognitive decline

Vulnerability to NeuroAIDS

- Risk for neuropsychological impairment differs
  - Genetic factors
    - APOE ε-4

Comorbidities

- Psychiatric and Substance Abuse Disorders are risk factors for medication non compliance.
- Bipolar D/O and ETOH/Substance abuse are risk factors for risk taking behaviors

(Woods et al, 2009)

Comorbidities

- Depression: up to 50%
- Anxiety: up to 38%
- Depression and anxiety: no clear evidence that HIV is biologically (as opposed to psychologically) causal in cognitive decline
- Bipolar Disorder: may be primary or secondary to HIV infection.
  - Additive risk of cognitive decline
  - HIV+ and BPD alone less impairment than if comorbid.

(Woods et al, 2009)

ETOH

- HIV+ is risk factor for etoh abuse
- ETOH abuse is risk factor for acquiring HIV
  - risk taking
- ETOH impacts immune response and reduce effectiveness of cART
- Worsen white matter damage
- ETOH increase cognitive deficits in HIV+ individuals

(Woods et al, 2009)

Marijuana

- Widely used
- Regular MJ use associated with decline in memory (likely reversible)
- MJ suppresses immune function
- MJ may be neuroprotective in HIV
- MJ may have benefits on chronic neuropathic pain

(Woods et al, 2009)

Methamphetamines

- Meth dependence common in HIV population and meth abuse is risk factor for contracting the virus
- Both independently associated with cognitive dysfunction and impact fronto-striatal circuits
  - HIV: volume atrophy in frontal cortex and caudate nucleus
  - Meth – cortical (parietal) and basal ganglia volume increase
- Individuals with both methamphetamine abuse and HIV are susceptible to greater cognitive deficits.

(Woods et al, 2009)

Differential Diagnosis

- Bipolar disorder versus Organic mania:
  - History of previous manic episodes? Episodes of depression?
  - Family history of Bipolar disorder?
  - Slowed manual dexterity? (in real mania, it's fast)

Differential Diagnosis of Bipolar 2

Memory testing

- Bipolars retain 60-70% over 30-minute delay (like normals).
- Major NCD pts: immed verbal mem mild imp, delayed mod to sev impaired
- Delayed visual memory very poor after 30- minute delay
- Perseverations, simplifications, intermingling of different test stimuli

Differential Diagnosis #3

Major NCD versus Alcohol-Related Deficits

- If CD4 is high, probably not Major NCD
-
- If pt no longer drinking and mem problems developed suddenly, probably is Major NCD
- Alcohol will lead to cerebellar problems such as wide-based gait
- Major NCD: look for cognitive and motor slowing
- Memory problems similar in both

HIV and substance abuse

- Up to 75% of HIV+ have history of past or current substance abuse
- H/o drug abuse associated with amount of cognitive impairment
- Injection drug use accounts for >1/3 of all HIV/AIDS cases in US
- Either directly or because drug use, HIV associated with increased risky sexual behaviors and reduced medication adherence.

Substance Abuse #2

- Opiates and other IV drug use seem to increase vulnerability to effects of virus on CNS (Vazquez/Justo 2003)
- HIV + substance abuse can lead to greater impulsivity even when CD4 count WNL, leading to impulsive decisions/behaviors
- Greater than additive effects seen in HIV+ pts who drink heavily on measures of visual attention, motor dexterity, and speed (TMT-A, Grooved Pegboard)
- Suspected synergistic adverse effects on motor and visuomotor functioning
- Drinking severity, WCST failures to maintain set, and higher Beck Depression scores assoc w/ more frequent medication non-compliance (they forget to take them!)

Substance Abuse #3

- Recent heavy alcohol use may represent a potential risk factor for more rapid or pronounced cognitive decline. This may be even more pronounced w/ comorbid substance abuse.

- Decrements more pronounced in domains preferentially affected by both HIV and ETOH:
  - Psychomotor/motor speed
  - Reaction time

HIV caused Neurological Disorders

- People living with HIV are at high risk for brain-related problems because immune system is so depleted, it can no longer fight off the virus or other threatening infections. These include:
  - HAD (HIV associated Major NCD)
  - Progressive multifocal leukoencephalopathy (PML)
  - Toxoplasmosis
  - Cryptococcal meningitis

http://www.aidsmeds.com/articles/NeurocognitiveDisorder_20399.shtml

CNS Disorders in HIV pts

- Two **key** things to ALWAYS remember in the management of HIV infected patients
  - HIV infection does not prevent the development of a non-HIV related problem
  - Opportunistic problems are related to the CD4 (+) cell count.
    - If the count is > 200-300, the problem is probably not related to the HIV infection.

Secondary Neurologic Syndromes in Chronic HIV Infections

- The following CNS disorders were very common pre-HRT, less common now
- Especially present in immunosuppressed individuals (CDR4 <200)

Most common CNS Neurological Disorders in immune suppressed HIV pts

- Space Occupying Lesions
  - **Toxoplasmosis**
  - **Lymphoma**
  - **PML**
  - **Tuberculoma**
  - Cryptococcoma
  - Pyogenic abscess
  - Nocardia
  - CNS Syphilis (gumma)
- Diffuse Disease
  - **Cryptococcal Meningitis**
  - **Acute Infection**
  - **HIV Major NCD**
  - Tuberculous Meningitis
  - CNS Syphilis
  - Toxoplasma encephalitis
  - Cytomegalovirus encephalitis

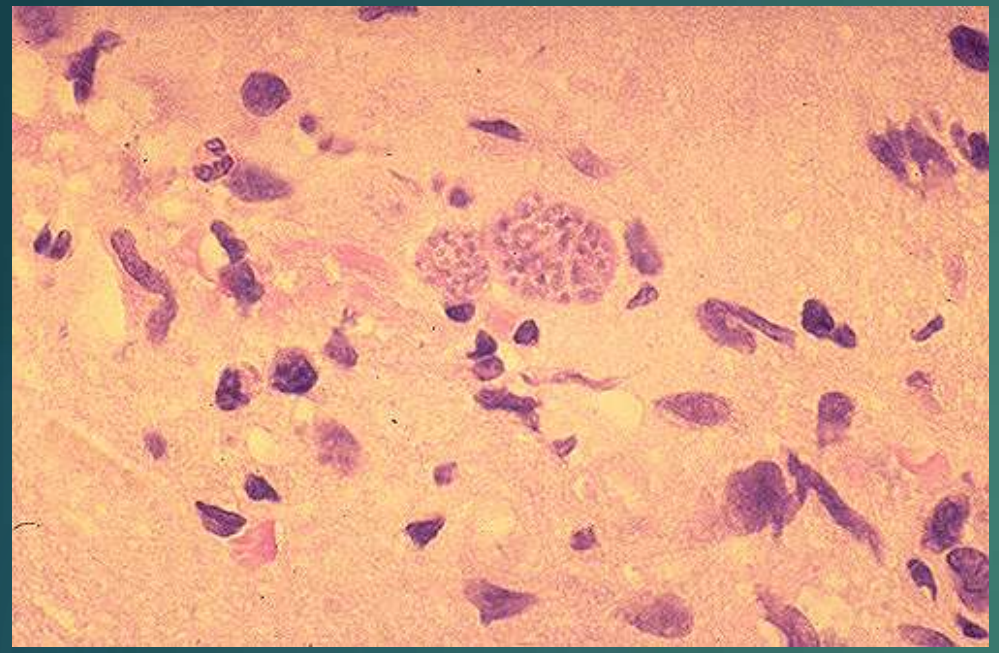
Toxoplasmosis

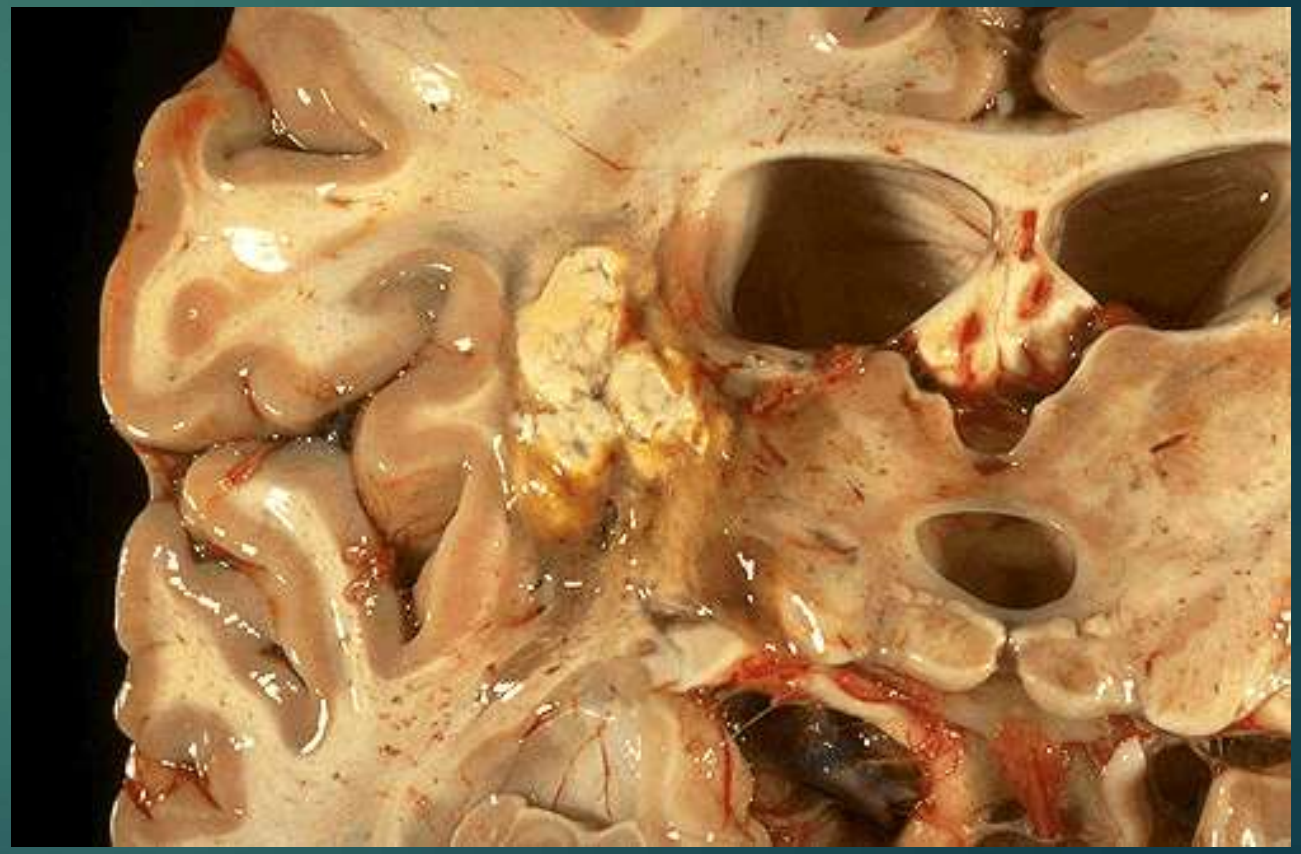
- The most common in the West of the CNS space occupying lesions in a person with a CD4 count <200 (**usually < 100**)
  - Prevalence of toxoplasma CNS disease is unknown in many countries
  - Seroprevalence is low
- Reactivation disease
  - Cat feces
  - Meat
- Presentation is typically sub acute and focal: confusion
  - May be seizures

Clinical manifestations of CNS toxoplasmosis in 166 AIDS pts

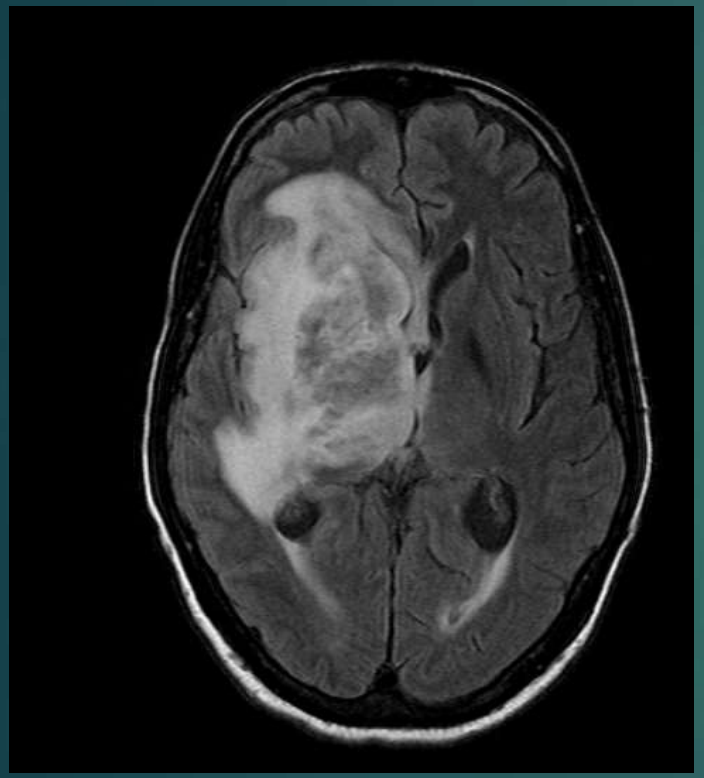
Clinical manifestation	%
Headache	96
Fever	84
Stiff neck	48
Hemiparesis	45
Conscious change	
Drowsy	43
Stupor	4
Cranial nerve palsy	42
Seizure	39

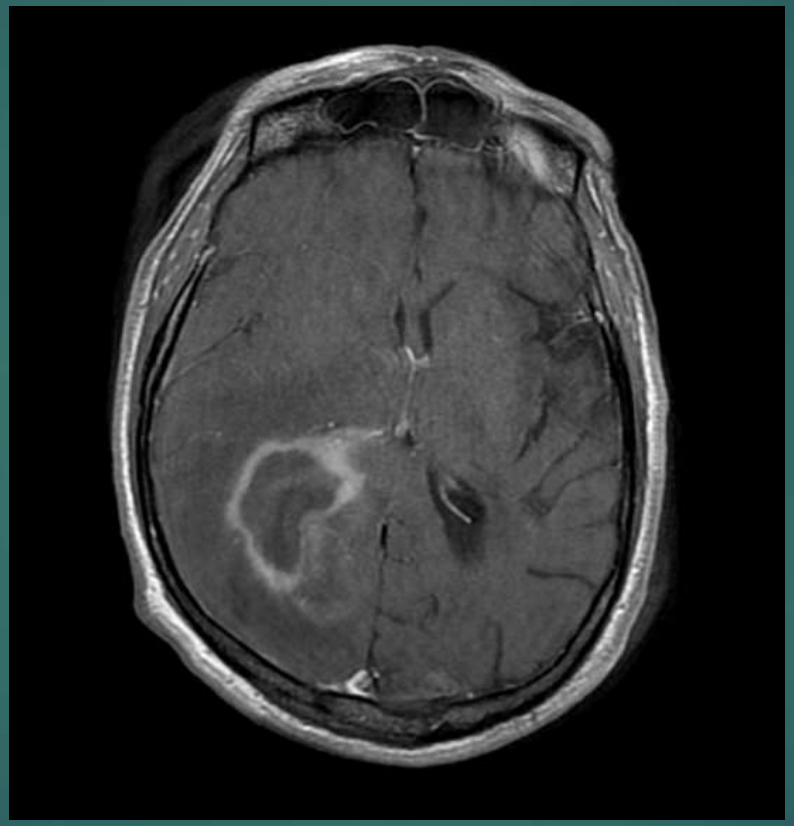
Toxoplasmosis

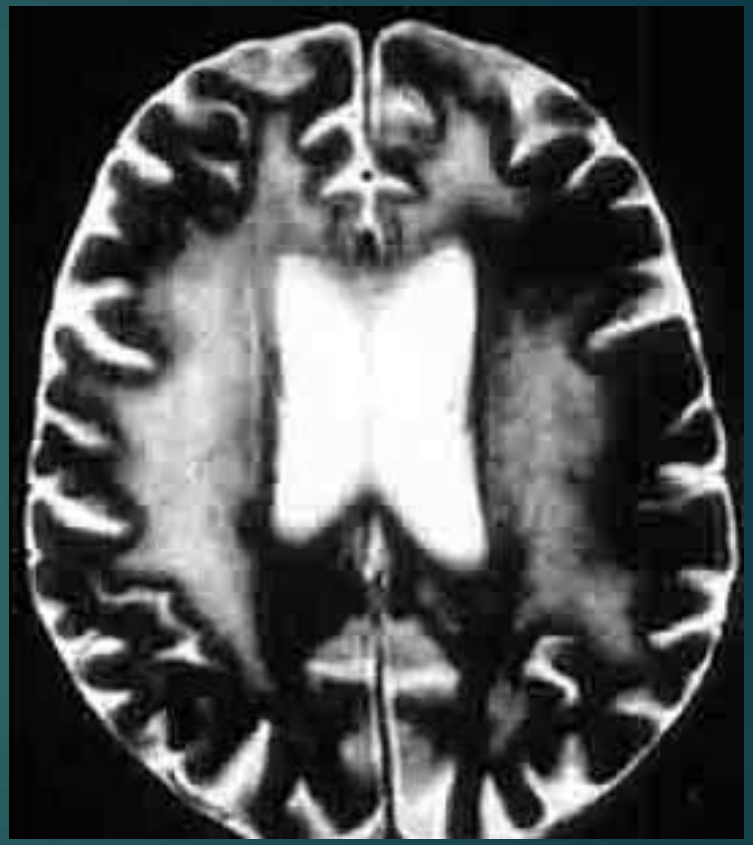




MRI of Toxoplasmosis







Primary CNS Lymphoma

- Most common neoplasm of the brain in AIDS
- Etiology is thought to be Epstein Barre virus (which causes mononucleosis)
- Presentation: focal abnormalities, but subtle initially
- 70% mortality rate in 6 months; with or without Tx

Primary CNS Lymphoma

- MRI of brain +/- gadolinium: single or multiple enhancing lesions that may have similar appearance to toxoplasmosis

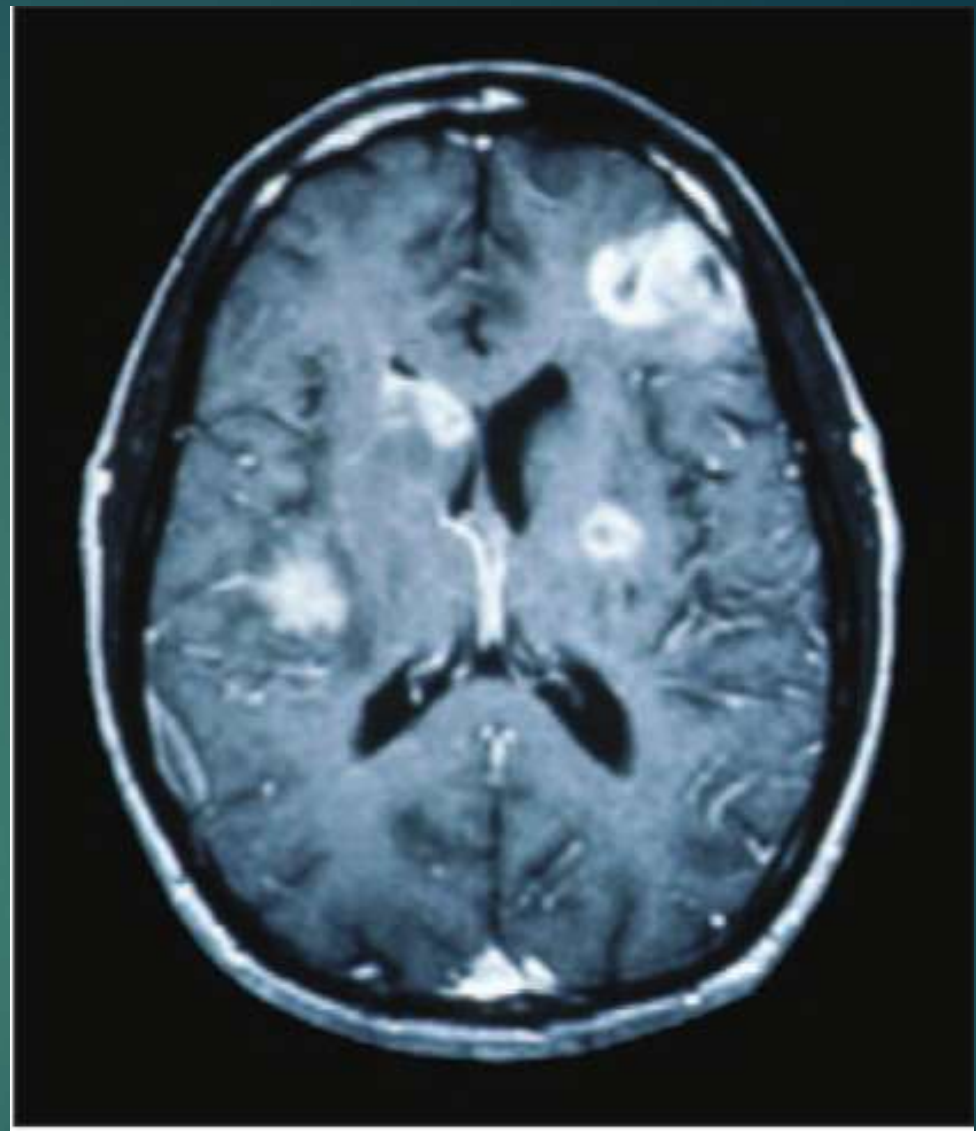
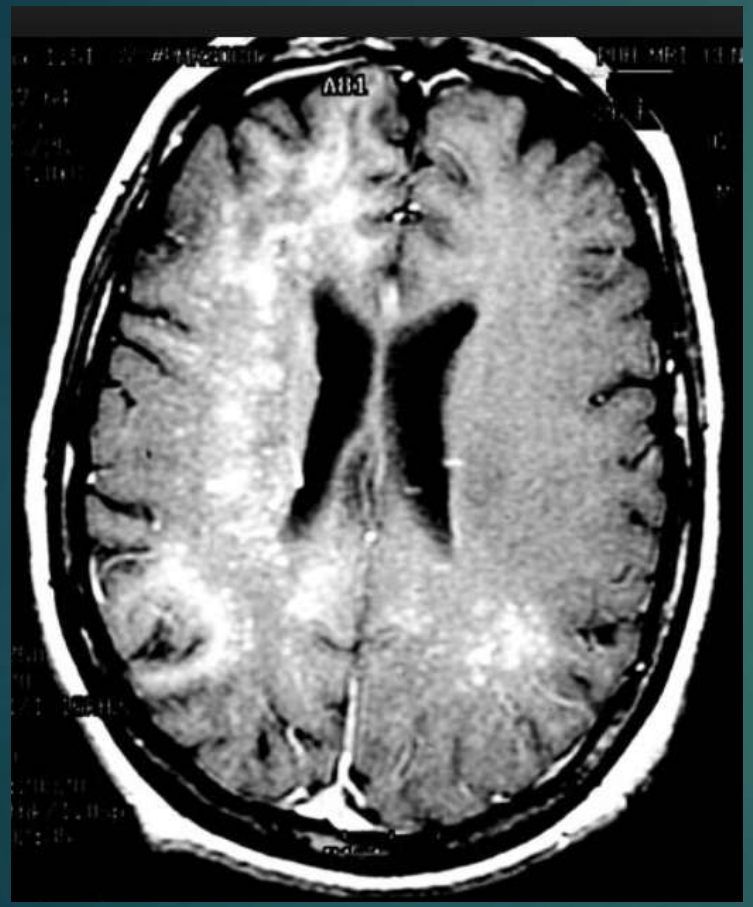


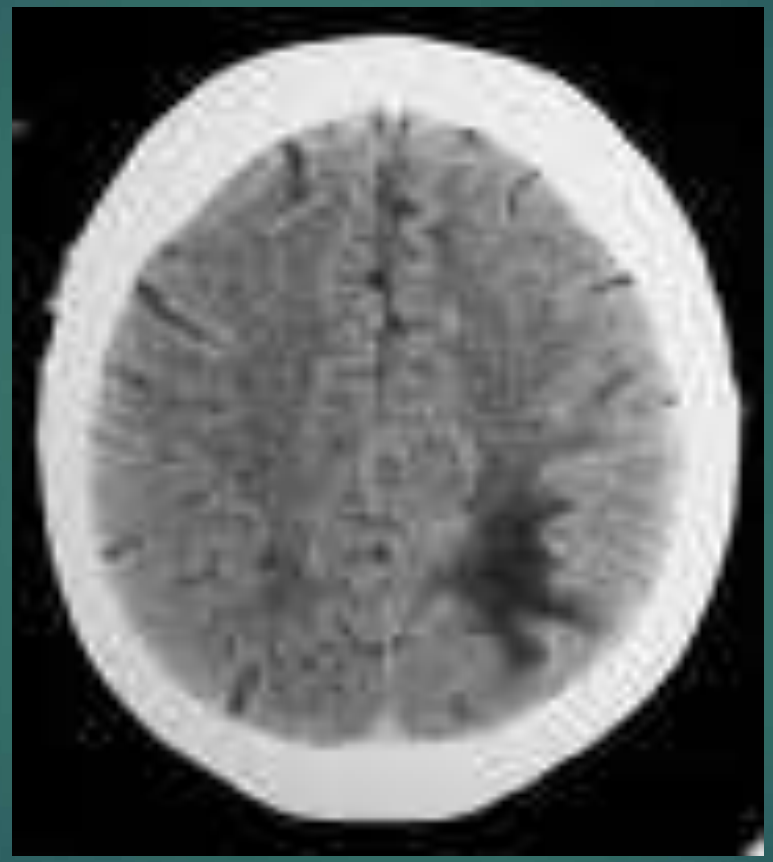
FIGURE 2. Primary Central Nervous System Lymphoma

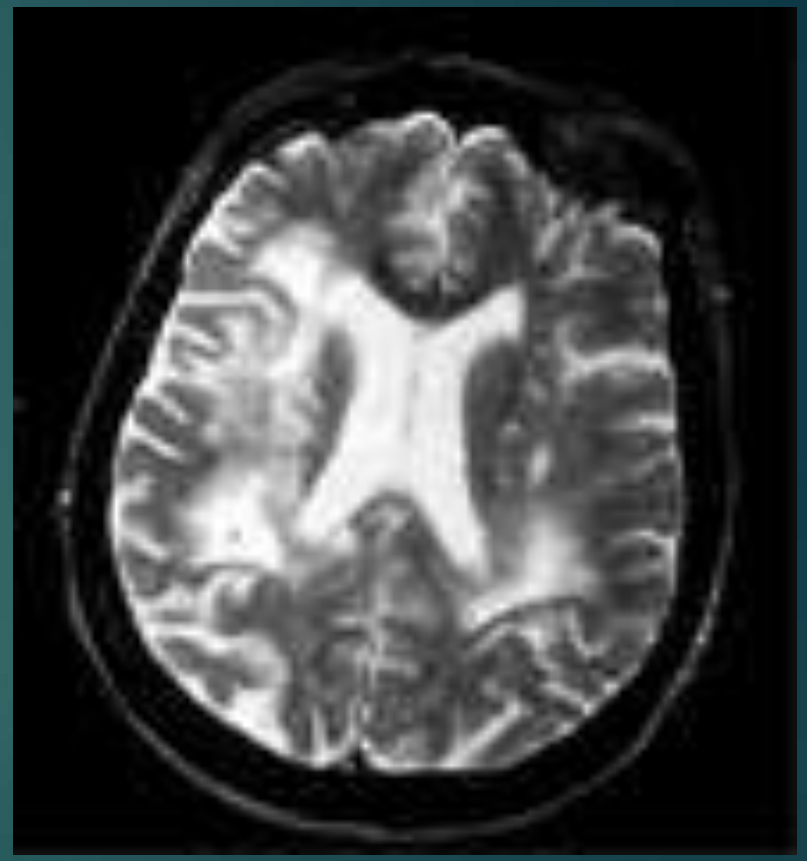
Progressive Multifocal Leukoencephalopathy (PML)

- Caused by JC virus (JC is 1st person in which virus was isolated)
- 85% of normals have this infection. In none-immune compromised normals, it is benign
- Demyelinating disease
- 85% mortality rate in 6 months

MRIs in Progressive Multifocal Leukoencephalopathy (PML)







Pharmacotherapy

- Mainstay of Tx for HIV, AIDS, and NCD is HRT

- HRT regimens, these drug combinations consist of a minimum of two active drugs from two classes, and usually contain three or more different drugs.

- The 3 major classes of medications commonly prescribed: (all of which interfere with different stages of the HIV infection and replication process):
  - Nucleoside reverse transcriptase inhibitors (NRTIs)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  - Protease inhibitors (PIs), or integrase inhibitors

NP Improvement with HRT

- Greater numbers of CSF-penetrating drugs showed greater reduction in CSF viral load.
- CSF virological suppression demonstrated greater global deficit score (GDS) improvement
- NP improvement was greater in HRT-naive versus treatment-experienced subjects.

Letendre et al., Ann Neurol 2004

Antiretroviral Treatments - cART

- Cysique et al (2009) study found that patients with HAND had improved cognitive functioning after initiating cART, peaking between 24-36 weeks later.
- Predictors of improvement included worse baseline NP and higher cART CNS penetration level.
- Highlight importance of checking the CNS penetration of the cART drugs chosen.

Non-Antiretroviral Tx

Initial findings:

- Methylphenidate helps with psychomotor slowing
- Lithium as neuroprotective and improved NP f(n)
- Citalopram (Celexa) associated with better NP performance
- Not associated with decreased depression sxs

cART

- Heaton et al published 2011 large study: **HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors**
- Combination Antiretroviral Therapy (CART) reduce medical morbidity and mortality but HAND persists
- compared pre-CART (1988-1995) with CART era (2000-2007)
- Impairment increases as CD4 decreases in both groups and nadir CD4 predictive in both
- Pattern of impairment:
  - PreCART: motor, processing speed, verbal fluency
  - CART: learning, executive functioning

Heaton et al. Conclusions:

- Consistent association of NCI with nadir CD4 (pre and post CART) suggests focus on prevention of severe immunosuppression may decrease/prevent HAND
- Current CD4 & viral loads no longer significant risk factors for NCI.
- Severe immunosuppression may initiate irreversible changes in the CNS

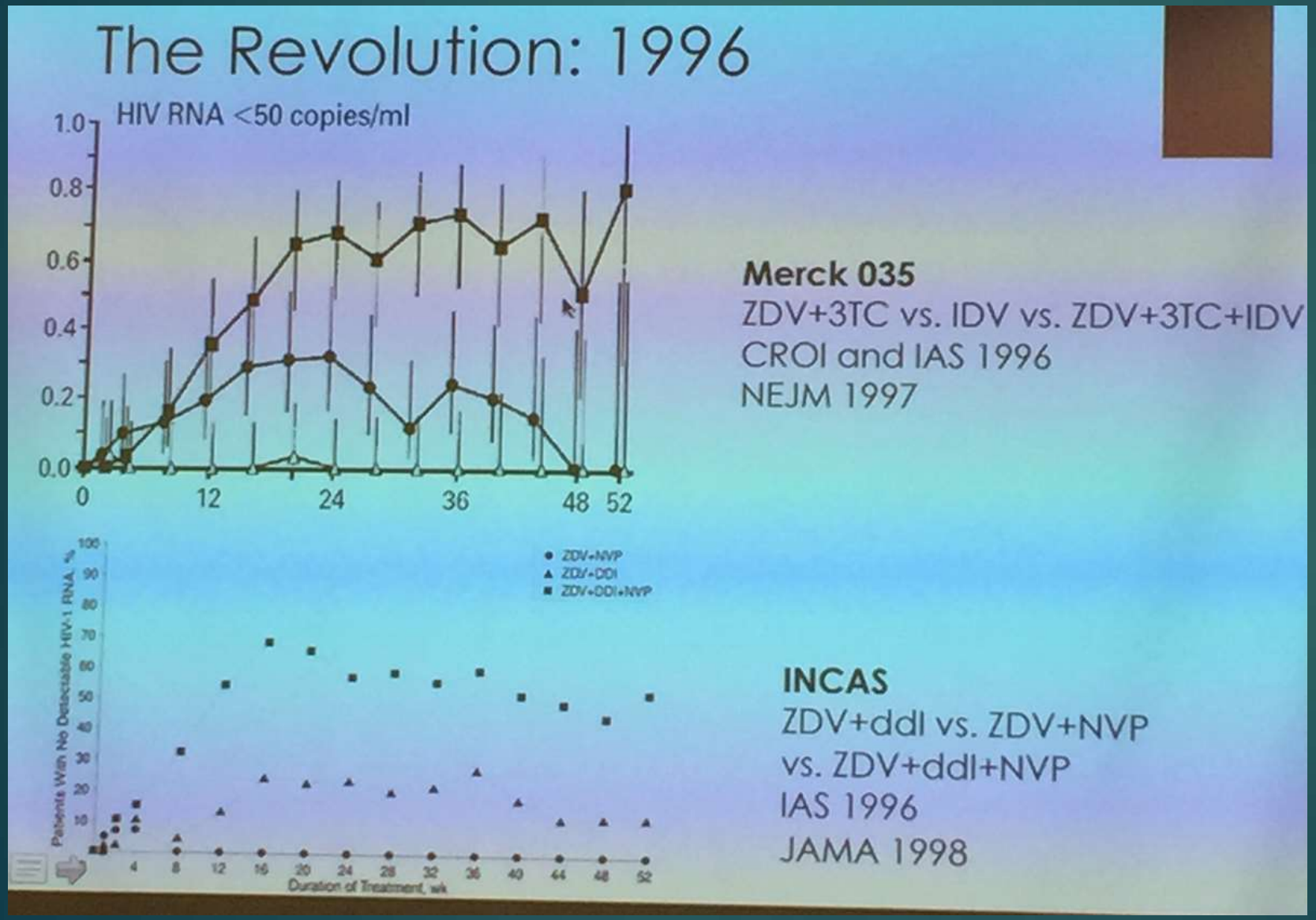
(Heaton et al, 2011)

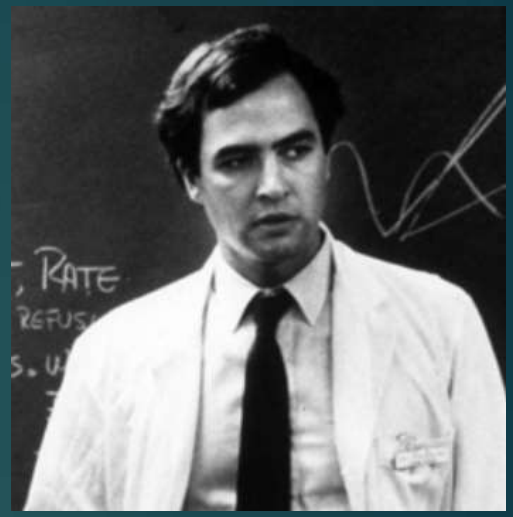
CNS Treatment Strategies

- At this time, the selection of antiretroviral regimens are based on
  - sensitivity/resistance patterns
  - Adherence issues
  - quality of life considerations

- Antiretroviral medications with higher CPE (brain penetration)
  - stavudine (D4T)
  - zidovudine (ZDV/AZT)
  - abacavir (ABV)
  - efavirenz (EFV)
  - nevirapine (NVP)
  - indinavir (IDV)
  - lamivudine (3TC)

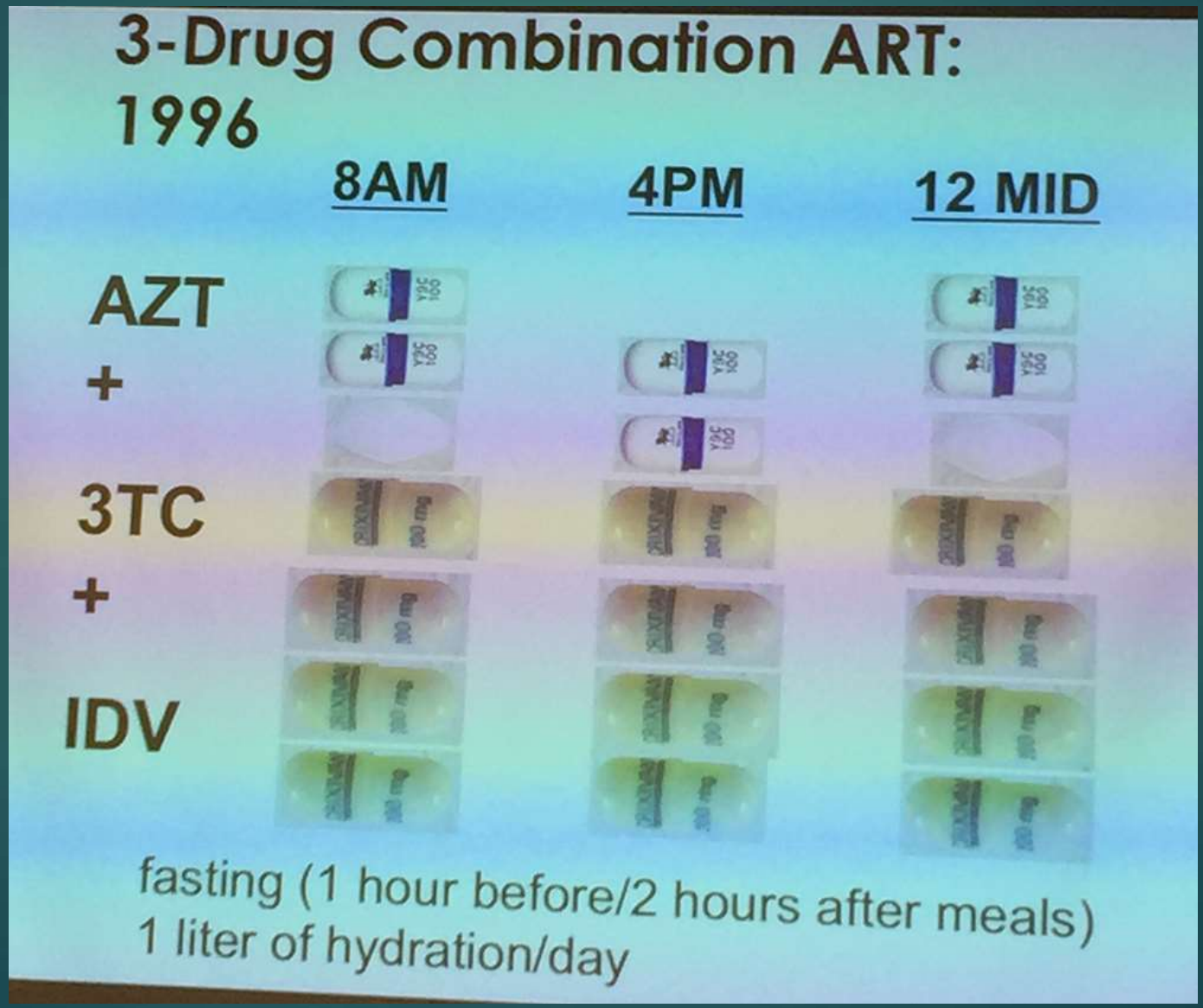
1996: 3-drug combination ART Treatment revolution





Paul Volberding

Needed good EF to do 1996 3 drug regime



COMMUNITY RESEARCH INITIATIVE
of New England

617.502.1700 www.crine.org

HIV Medications

Integrase Inhibitors

Isentress (raltegravir or RAL) | Tivicay (dolutegravir or DTG) | Vitekta (elvitegravir or EVG)

Pharmacokinetic Enhancers

Norvir (ritonavir or RTV) | Tybost (cobicistat)

Nucleoside/Nucleotide Analogs (NRTIs)

Combivir (zidovudine/ lamivudine) | Emtriva (emtricitabine or FTC) | Epivir (lamivudine or 3TC) | Epzicom (abacavir/ lamivudine) | Retrovir (zidovudine ZDV or AZT) | Trizivir (abacavir/ lamivudine/ zidovudine) | Truvada (emtricitabine/ tenofovir DF) | Videx, Videx EC (didanosine or ddI) | Viread (tenofovir DF or TDF) | Zerit (stavudine or d4T) | Ziagen (abacavir or ABC)

Multi-Class Drug Combinations

Atripla (efavirenz/ emtricitabine/ tenofovir DF) | Complera (rilpivirine/ emtricitabine/ tenofovir DF) | Genvoya (elvitegravir/cobicistat/ emtricitabine/ tenofovir alafenamide) | Stribild (elvitegravir/cobicistat/ emtricitabine/ tenofovir DF) | Triumeq (dolutegravir/ abacavir/ lamivudine)

Non-Nucleosides (NNRTIs)

Edurant (rilpivirine or RPV) | Intelence (etravirine or ETV) | Rescriptor (delavirdine or DLV) | Sustiva (efavirenz or EFV) | Viramune (nevirapine or NVP)

Entry Inhibitors

Fuzeon (enfuvirtide or ENF) | Selzentry (maraviroc or MVC)

Protease Inhibitors (PIs)

Aptivus (tipranavir or TPV) | Crixivan (indinavir or IDV) | Evotaz (atazanavir/ cobicistat) | Invirase (saquinavir or SQV) | Kaletra (lopinavir/ ritonavir) | Lexiva (fosamprenavir or FPV) | Norvir (ritonavir or RTV) | Prezcobix (darunavir/cobicistat) | Prezista (darunavir or DRV) | Reyataz (atazanavir or ATV) | Viracept (nelfinavir or NFV)

1 days HIV medication in Thailand

A Pill a Day to Keep HIV Away:
From many to 1 pill a day

Although the C.D.C. recommends immediate treatment, in 2015, only 37 percent of infected Americans had prescriptions for the drugs

‘Potentially CNS-active drugs’

- Agents with demonstrated clear CSF penetration
  - NRTIs: ZDV, ABC
  - NNRTIs: EFV, NVP
  - Boosted PIs: IND/r, LPV/r, DRV/r
  - Other classes: MAR

- Drugs with proven “efficacy”
  - NRTIs: ZDV, d4T, ABC
  - Boosted PIs: LPV/r

EACS Guidelines Nov 2012
[www.europeanaidsclinicalsociety.org]

Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons

- HIV+ patients categorized as earlier (<6 years of HIV, no AIDS-defining conditions, and CD4 nadir >200) or later stage patients (n = 100 in each group); both groups diagnosed early with access to care
- 50 matched HIV-ve control
- Neurocognitive impairment was diagnosed among 19% HIV+ patients: similar prevalence among earlier and later stage patients (18% vs. 20%, p = 0.72); similar to HIV- patients

Crum-Cianflone NF, et al. Neurology 2013;80:371–9

Pharmacotherapy Issues

- Sustiva: May cause serious psychiatric symptoms including sleep disorder, lucid/vivid dreaming, confusion, severe depression, suicidal thoughts, aggression, extreme fear, hallucinations, or unusual behavior.

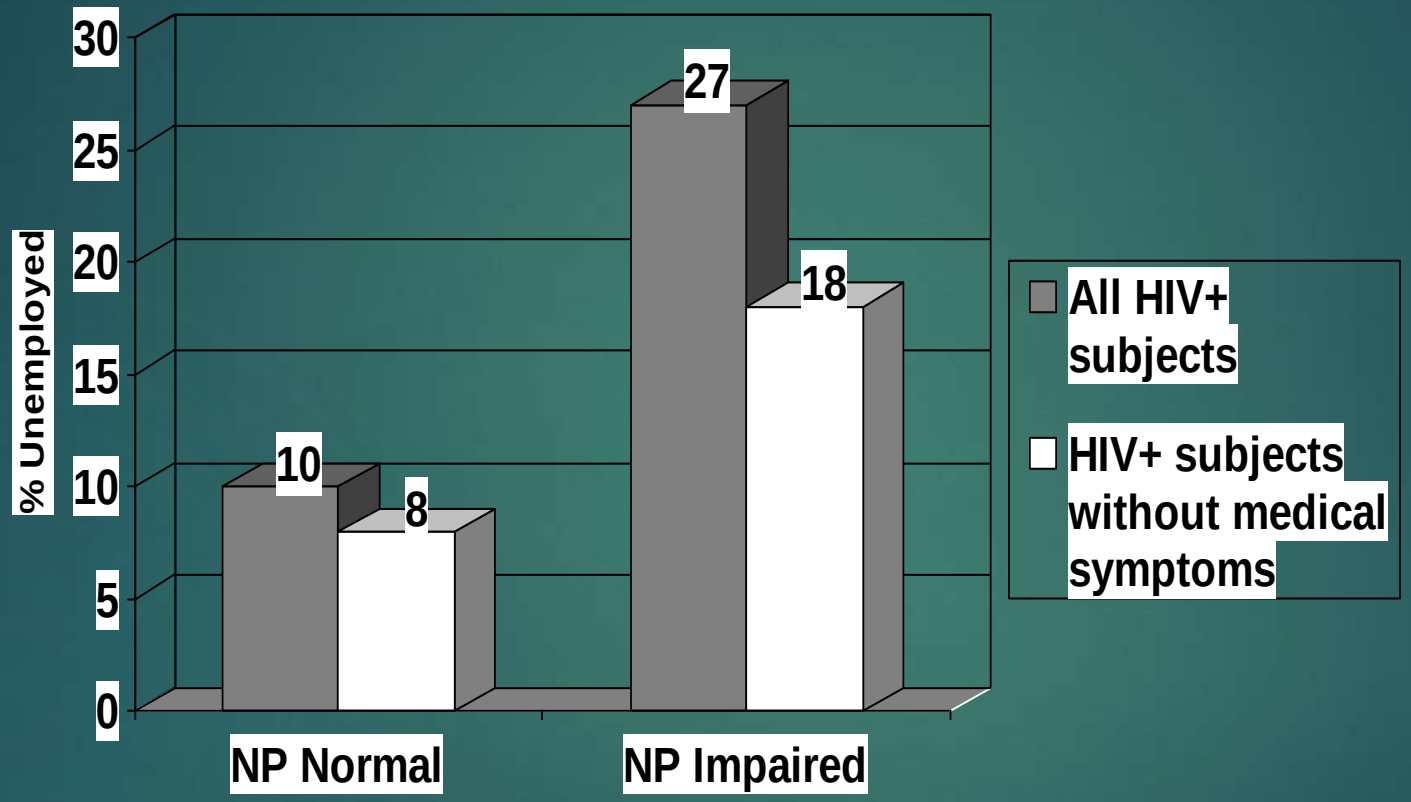
- WARNING:

  If a patient takes medications inconsistently, the virus can develop resistance, leading to drug-resistant strains in the general HIV population

Issues

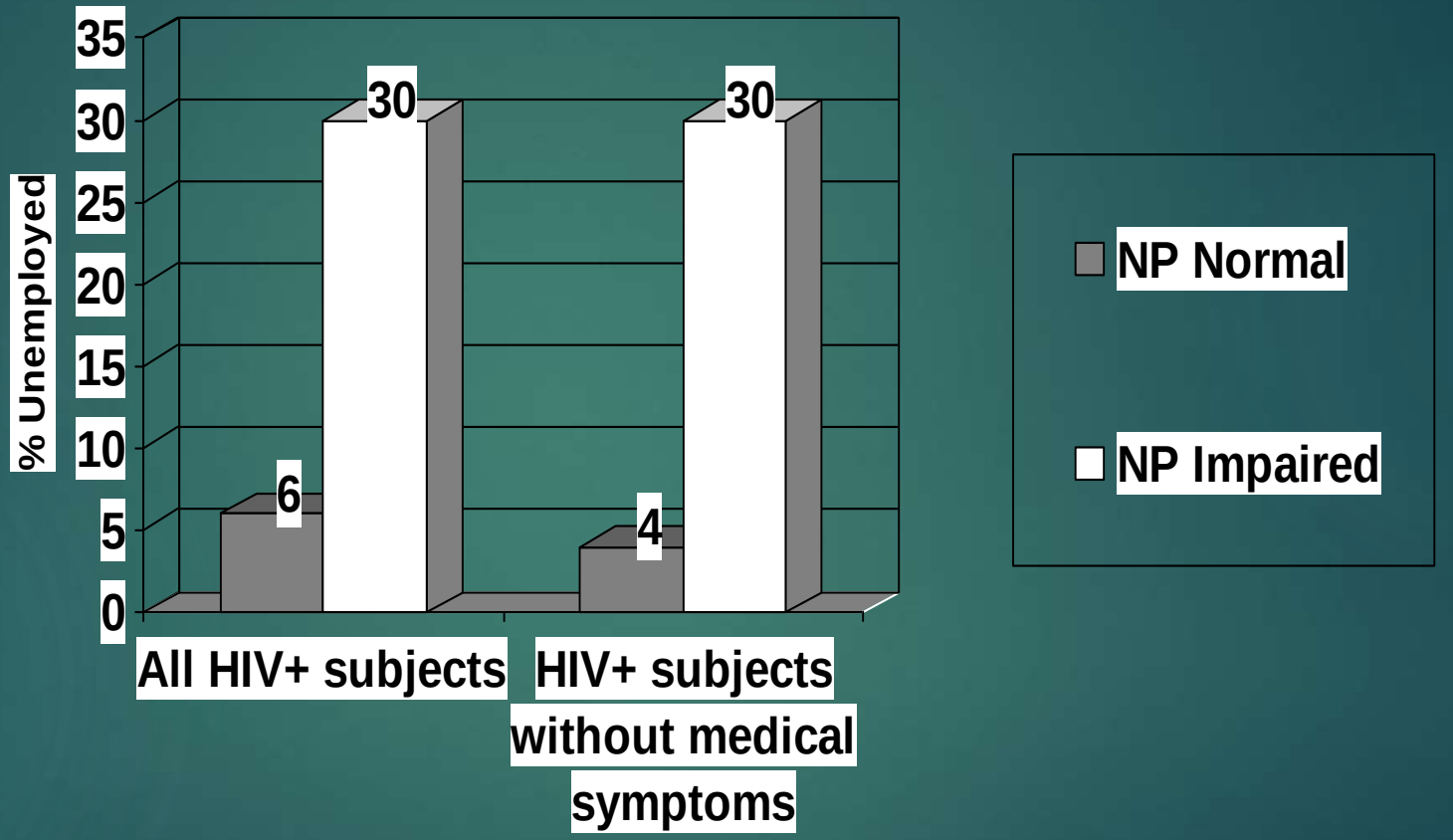
- No clear current differences between standard HRT and CPE agents in effecting NCD

Effects of “Mild” NP Impairment on Job Functioning



(Heaton et al., 1994; “non-demented” sample (N= 289); NP = neuropsychologically)

Percentage of HIV+ Subjects (Still Working) Reporting a Decrease in Job Functioning



There is a five-fold increase in complaints of difficulty at work in those who are neuropsychologically impaired and still working.

(Heaton et al., 1994; "non-demented" sample (N= 289); NP = neuropsychologically)

Controlling or preventing NCD due to HIV 2

- Treat other causes of neurological problems, as some diseases and conditions worsen brain function and increase the risk of harm from HIV related inflammation.
- High blood pressure, high cholesterol and triglyceride levels and gut fat accumulation can stress the brain, such as cardiovascular disease (CVD) limiting the amount of oxygen that reaches the brain.
- All forms of CVD causes immune cells to become inflamed throughout the body. Keep CV medical numbers normal.

Controlling or preventing NCD due to HIV 3

- Hepatitis C and B leads to greater inflammation in the brain, as can chronic kidney disease and liver disease.
- Some researchers believe chronic depression, anxiety and other mood disorders are tied to greater inflammation in the brain. Addressing each of these can sometimes ease neurocognitive symptoms.
- Increase physical exercise
- Stay socially engaged
- Stimulate your mind
- Seek out cognitive rehabilitative therapy.

- http://www.aidsmeds.com/articles/NeurocognitiveDisorder_20404.shtml

Internet Resources

- http://www.ama-assn.org/(J of American Med. Assoc. HIV/AIDS Info Centre)
- http://www.smartlink.net/~martinjh/#top
  (extensive collection of AIDS information and links)
- http://www.teleport.com/~celinec/aids.shtml
  (AIDS Resource List with links to AIDS-related resources)
- http://medstat.med.utah.edu/WebPath/TUTORIAL/AIDS/
  (Internet Pathology Laboratory from Univ. of Utah)

CDC National AIDS Hotline

- 1-800-342-AIDS (342-2437)
- 1-800-344-7432 Spanish: option 2
- 1-800-243-7889 (TTY services)