

Management of common neurological diseases in HIV/AIDS

Avindra Nath

**Professor, Neurology and Neuroscience
Director, Division of Neuroimmunology and
Neurological Infections**

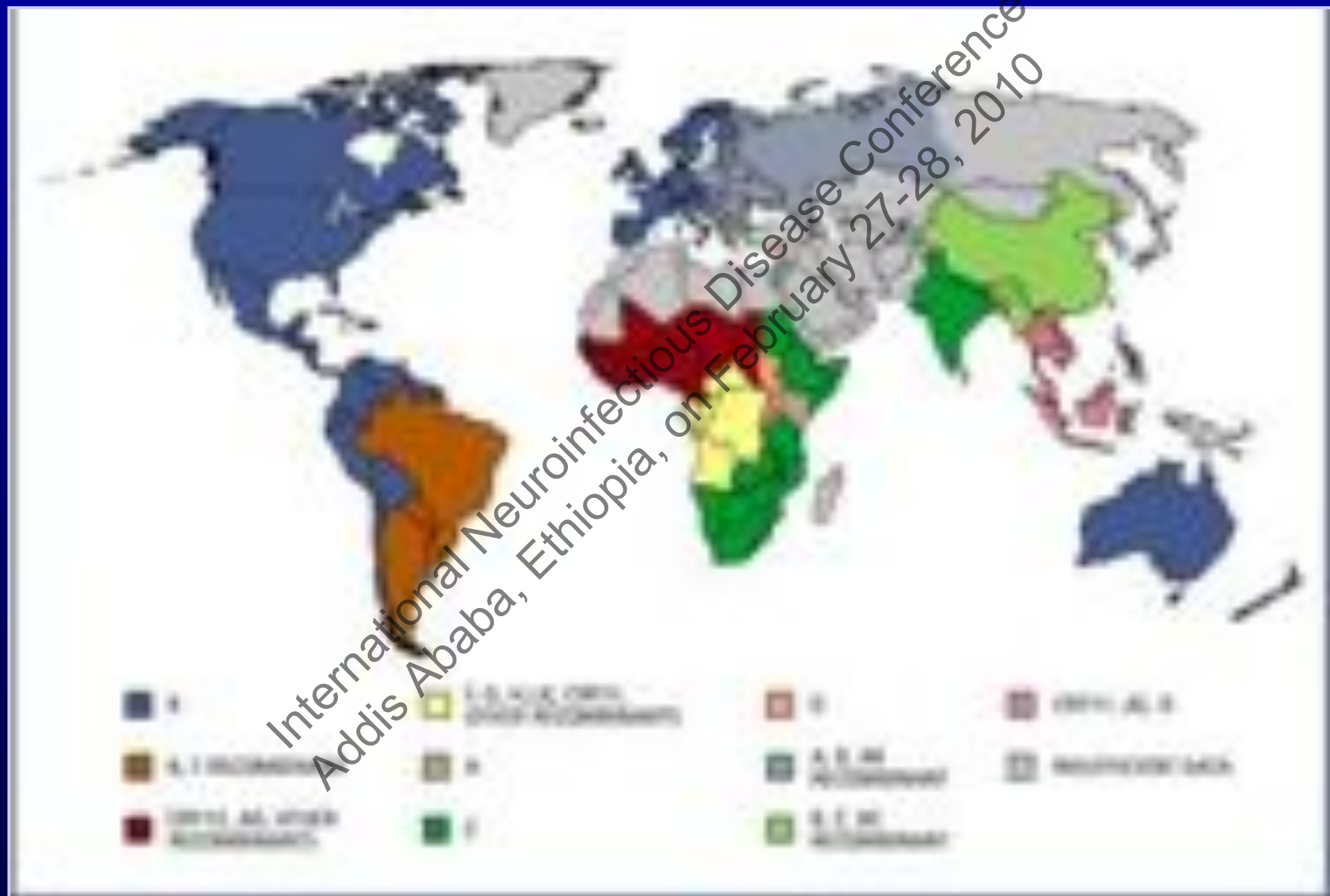
**Johns Hopkins University
Baltimore**

International Aids and Infectious Disease Conference
Addis Ababa, Ethiopia, February 27-28, 2010



International Neuroinfectious Disease Conference
Addis Ababa, Ethiopia, on February 27-28, 2010

HIV clades worldwide



Neurological Manifestations of HIV infection

Directly due to HIV

- Sensory neuropathy
- Vacuolar myelopathy
- Dementia

Unmask autoimmune diseases

polymyositis

myasthenia gravis

Acute inflammatory demyelinating neuropathy
(GBS)

Multiple sclerosis

Opportunistic infections

Complications of ART

Immune reconstitution syndrome

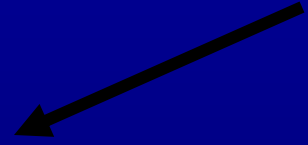
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**35 yrs with weakness in limbs and
memory dysfunction for 1-2 weeks**

**Focal/ lateralizing
signs**

**Opportunistic
infections**

CNS lymphoma



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**35 yrs with weakness in limbs and
memory dysfunction for 1-2 weeks**

Non-focal signs:

**Cognitive decline,
retropulsion, limb rigidity
and hyperreflexia**

**Meningitis or
HIV dementia**

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Differentiation of encephalopathy in AIDS

	HIV Dementia	CMV encephalitis	PML
Clinical Features	Psycho-motor slowing	Delirium, seizures, brainstem signs	Focal signs
Course	months	Days-weeks	Weeks-months
CD4 count	<500	<100	<100
MRI	Diffuse atrophy/WM hyperintensities	periventriculitis	Subcortical WM lesions
CSF	Non-specific	PCR+90%	PCR+80%

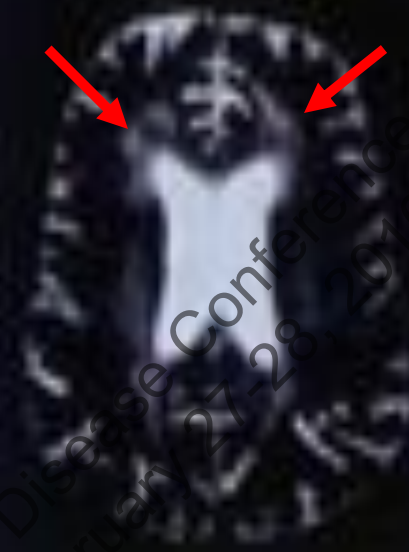
HIV Dementia:
Early

Deep white
matter
hyperintensity.
No
enhancement
with contrast



HIV Dementia:
Late

Deep white
matter
hyperintensities.
No enhancement
with contrast



CMV
Encephalitis

Periventricular
lesions



PML

Subcortical white
matter lesions. No
enhancement
with contrast



Progression of HIV dementia: clinical features

- 6 months mean progression *untreated*
- severe apathy and psychomotor slowing
- memory loss, poor insight
- gait & motor impairments, tremor, hyper-reflexia, hypertonia
- associated syndromes:
 - myelopathy
 - sensory neuropathy

Neurological Signs useful in Diagnosis of HIV-dementia

Slow rapid eye movements,

Slow limb movements

Postural instability

Hyperreflexia

Hypertonia

Frontal release signs

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HIV DEMENTIA SCALE

Johns Hopkins University Neurology Program

Patient Score	Maximal Score
11	4
11	6
11	4
11	2

Memory Registration

Give four words to recall (log, hat, green, peach) - 1 second to say each. Then ask the patient at 4 after you have said them.

Attention

Anti-saccadic eye movements: 20 trials. Record errors. ≤ 3 errors = 4; 4 errors = 3; 5 errors = 2; 6 errors = 1; ≥ 8 errors = 0

Psychomotor Speed

Ask the patient to write the alphabet in uppercase letters horizontally across the page and record the time in seconds.

≤ 21 sec = 6; 21.1 - 24 sec = 5; 24.1 - 27 sec = 4; 27.1 - 30 sec = 3; 30.1 - 33 sec = 2; 33.1 - 36 sec = 1; ≥ 36 sec = 0

Memory Recall

Ask for four words from Registration. Give 1 point for each correct word. For a correct word, prompt with a cue (see instructions).

Constructional

Ask the patient to copy a 3D cube. Record the time in seconds.

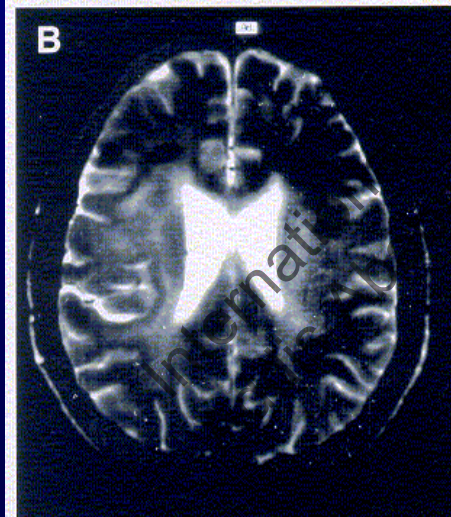
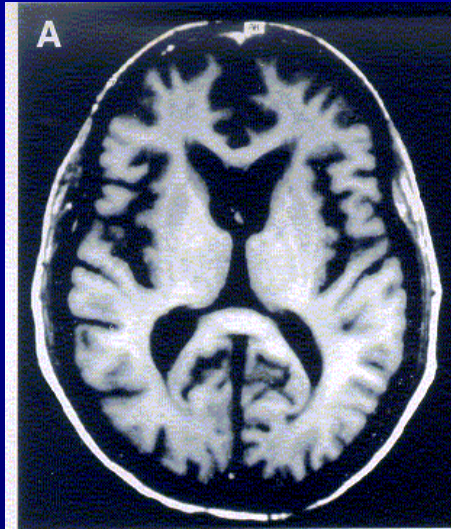
≤ 25 sec = 2; 25.1 - 30 sec = 1; ≥ 30 sec = 0



Modified HIV dementia scale:

- robust screening tool, *but not specific*
- sensitivity = 70%
- specificity = 71%

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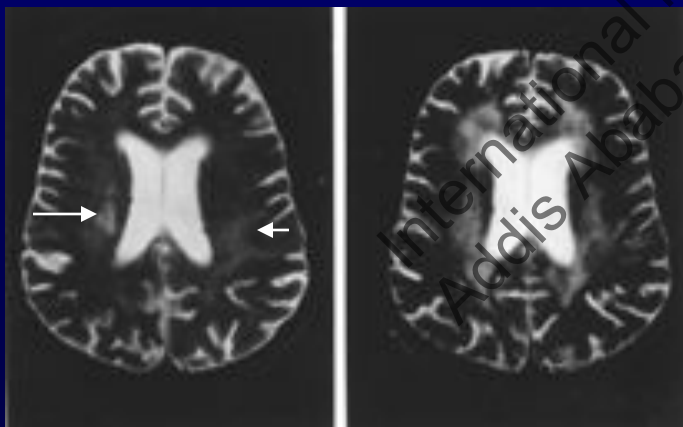
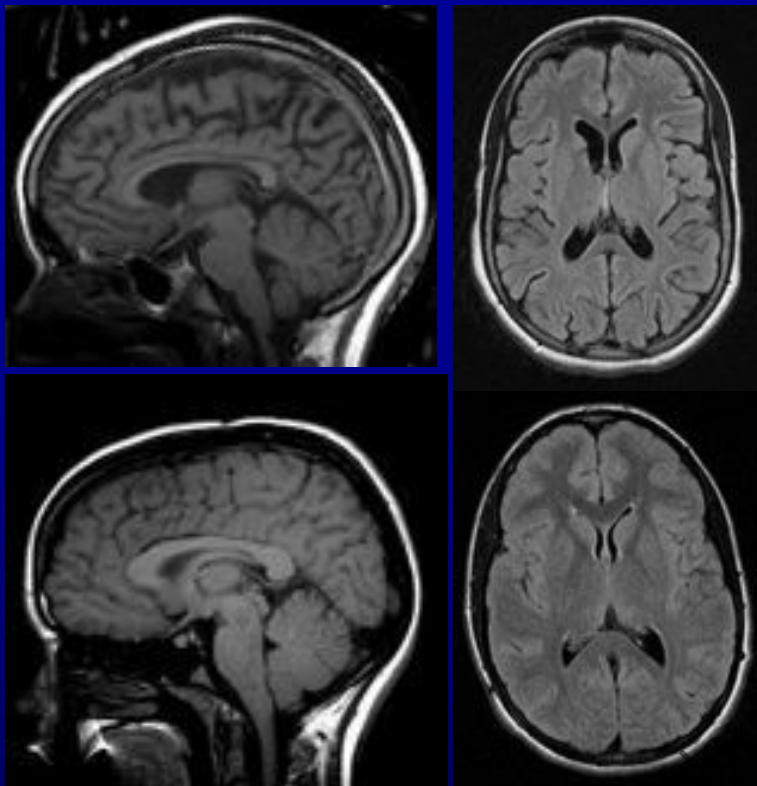


CSF

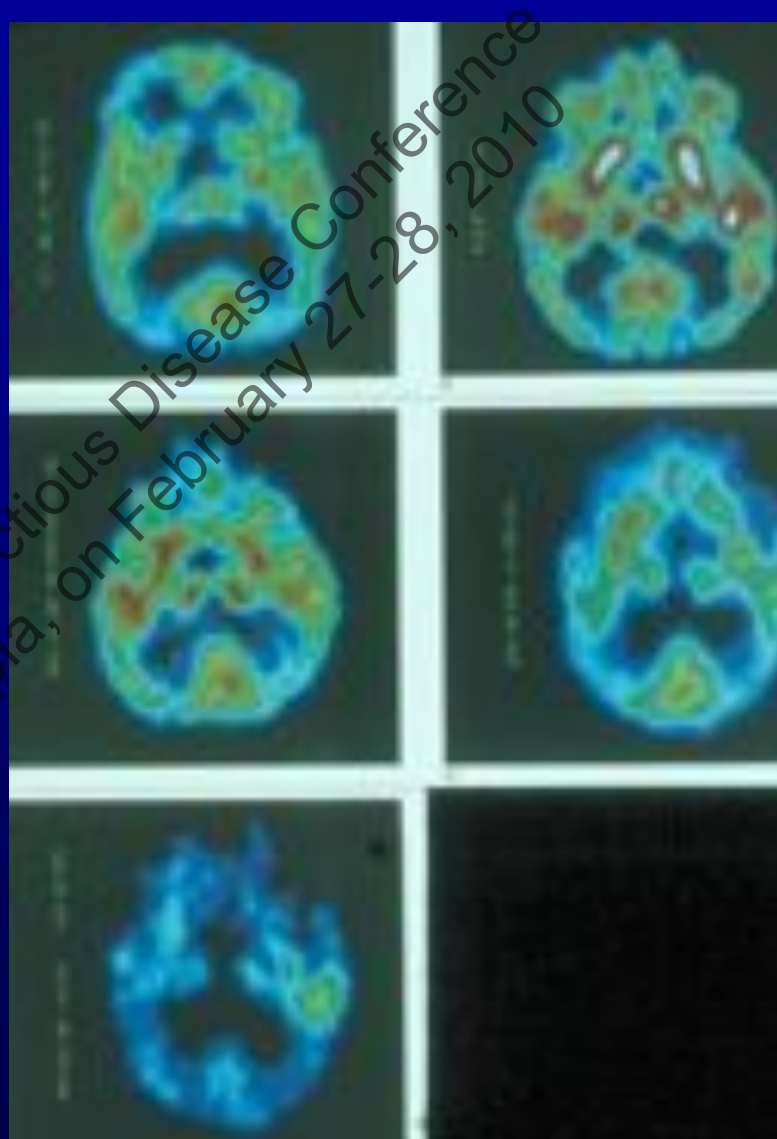
Normal or slight increase
in cells or protein

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MRI scan (Age:15ys)



PET scan



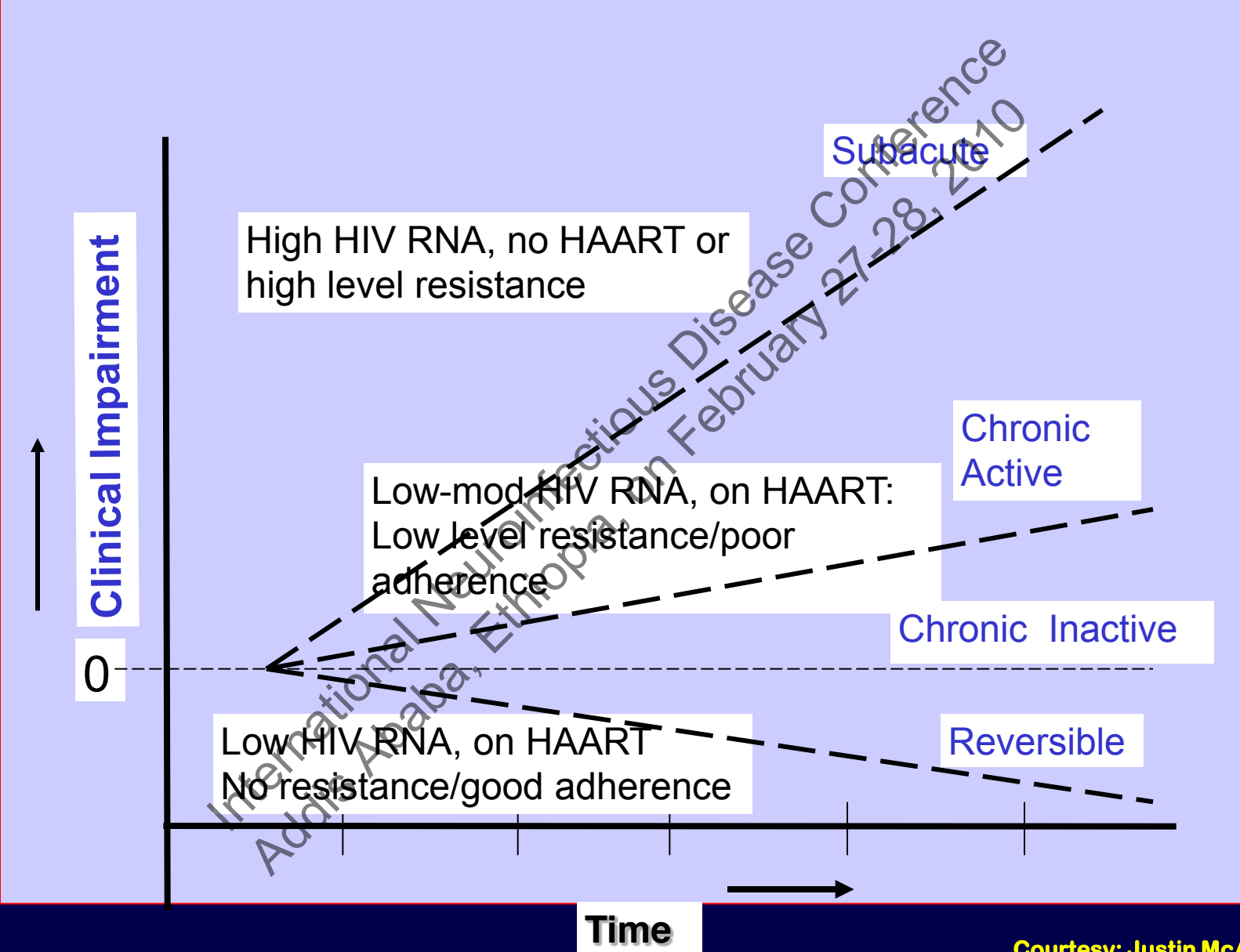
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HIV associated Neurocognitive Disorders (HAND)

- Asymptomatic
- Mild
- Dementia

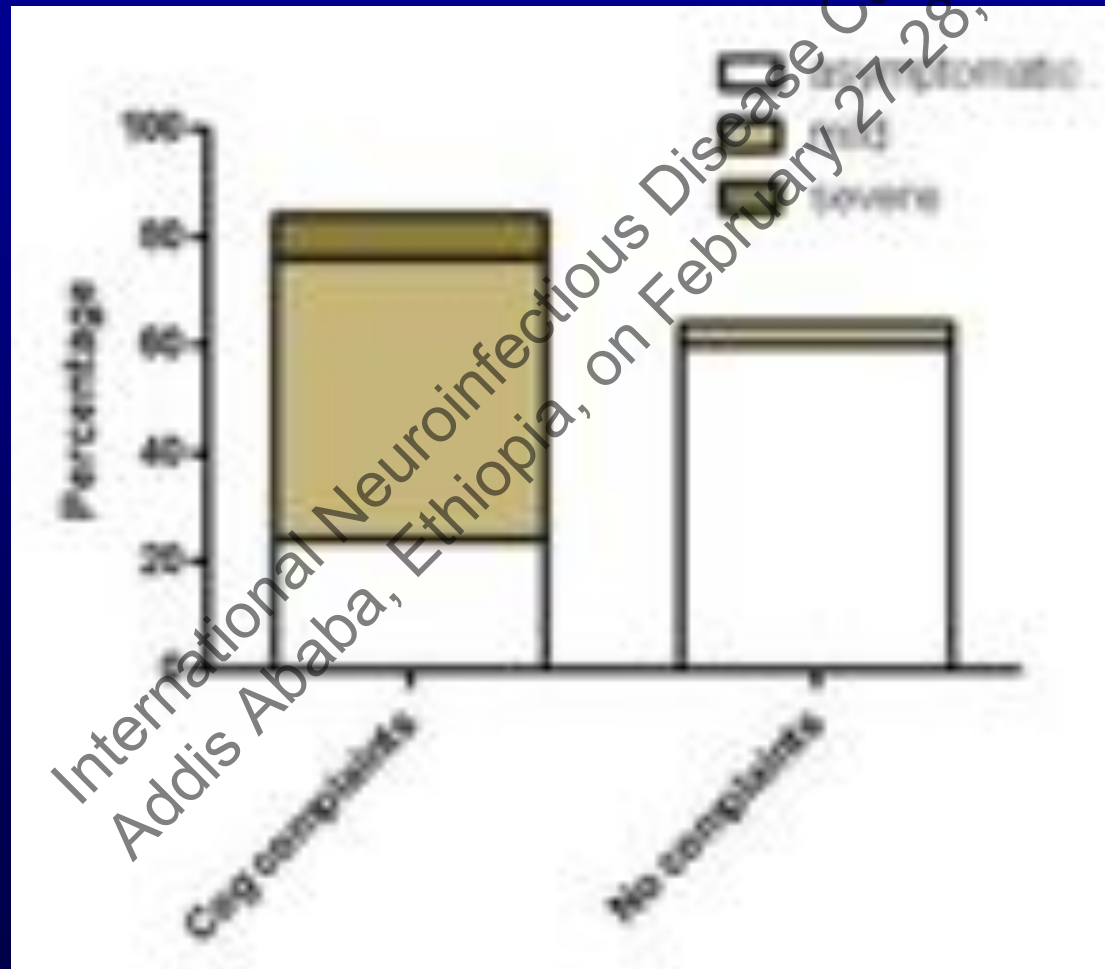
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Course of HAND in the Era of HAART

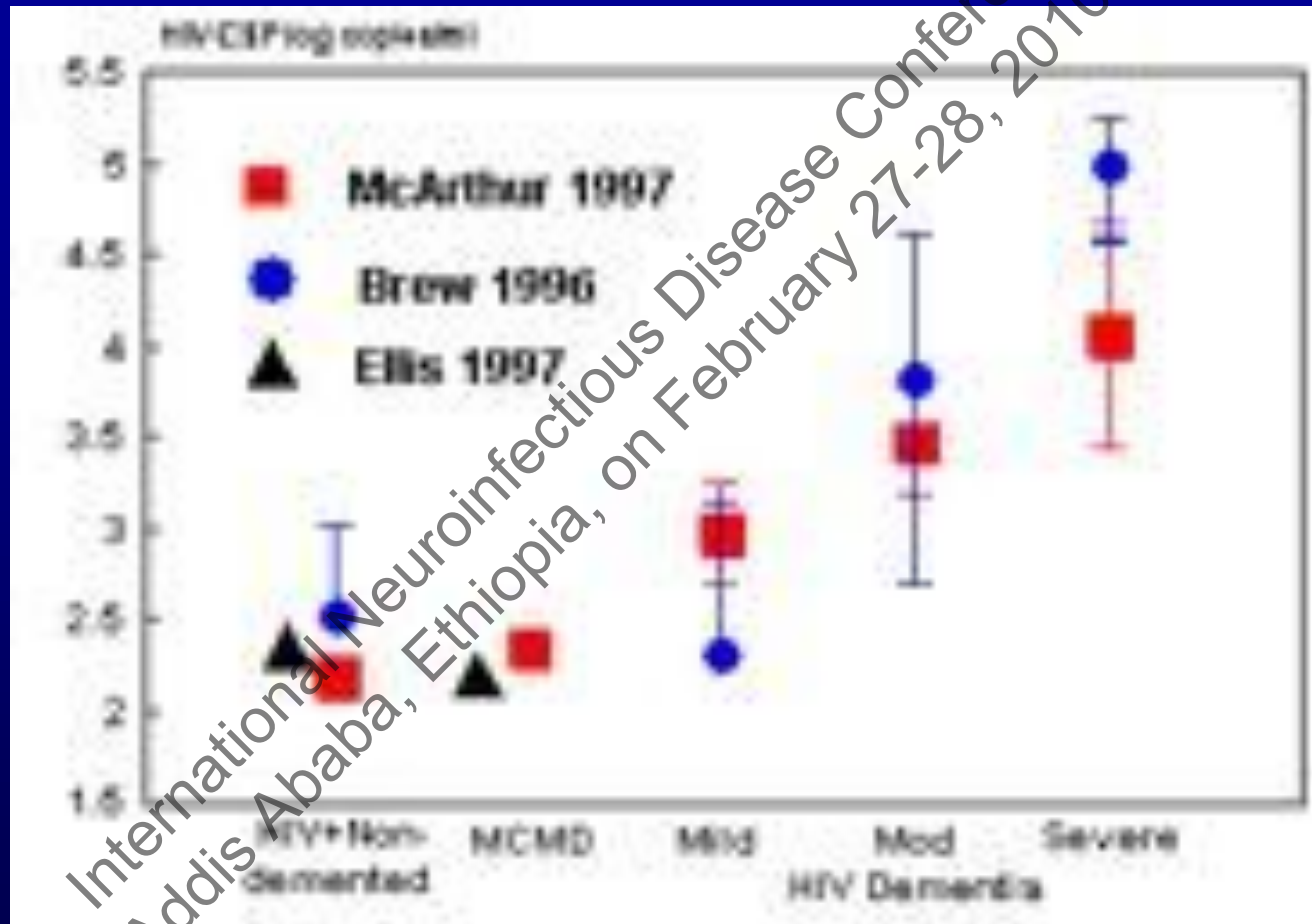


Courtesy; Justin McArthur

Prevalence of HAND in aviremic patients (Simioni et al. 2009)



CSF viral load correlates with severity of Dementia (Pre-HAART era)



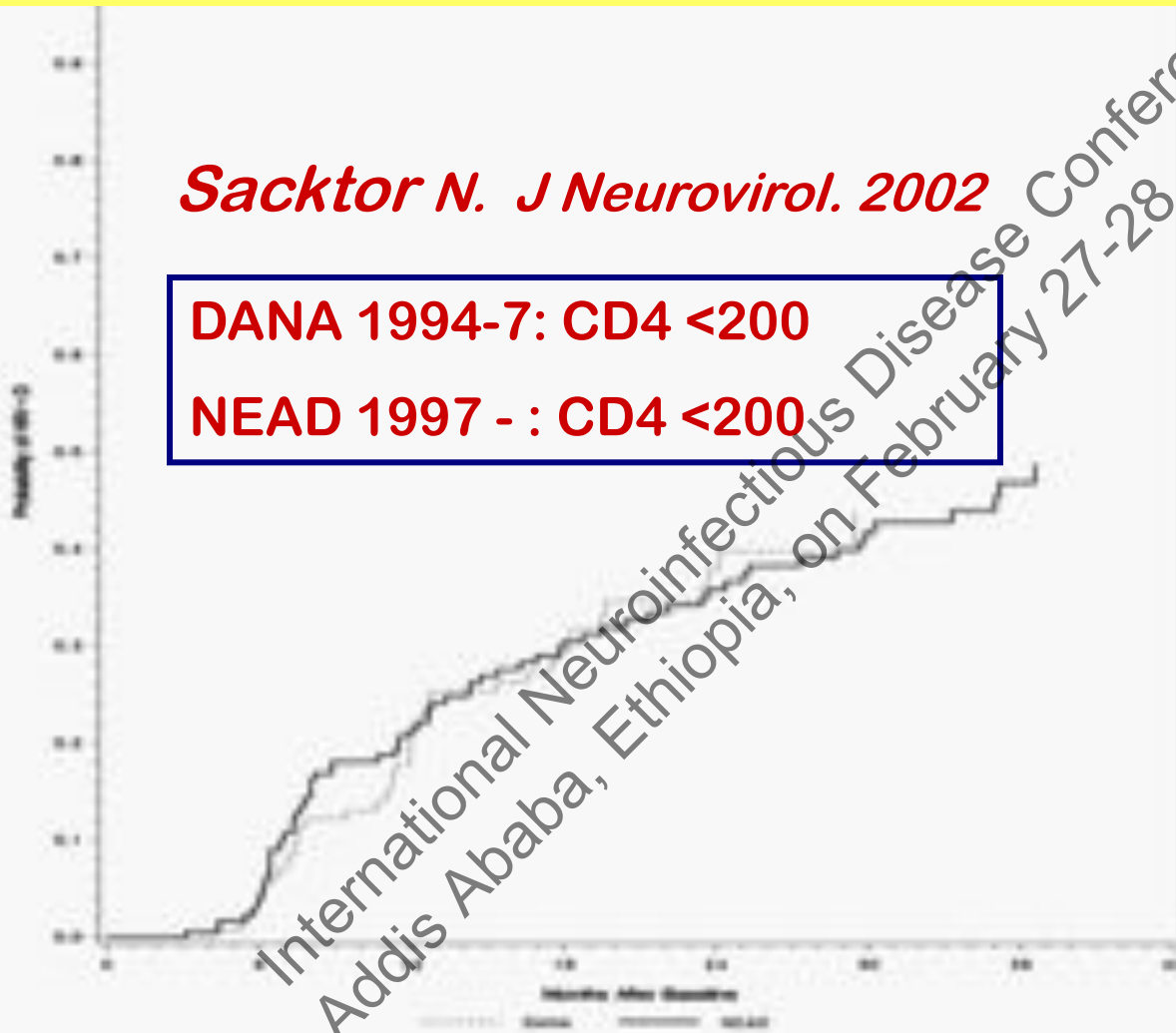
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Cumulative Incidence of HIV-Dementia DANA vs. NEAD cohorts

Sacktor N. J Neurovirol. 2002

DANA 1994-7: CD4 <200

NEAD 1997 - : CD4 <200



Risk Factors for HIV associated Neurocognitive Disorders (HAND)

Unsuppressed plasma or CSF HIV RNA

CD4 <200

Extremes of age

History of drug abuse

Anemia

Low body weight

Genetic factors

ApoE4

MCP-1, CCR-2

TNF receptor polymorphisms

Differential Diagnosis of HAND

Anxiety

Depression

Alcohol

Recreational drugs

Medication side effects

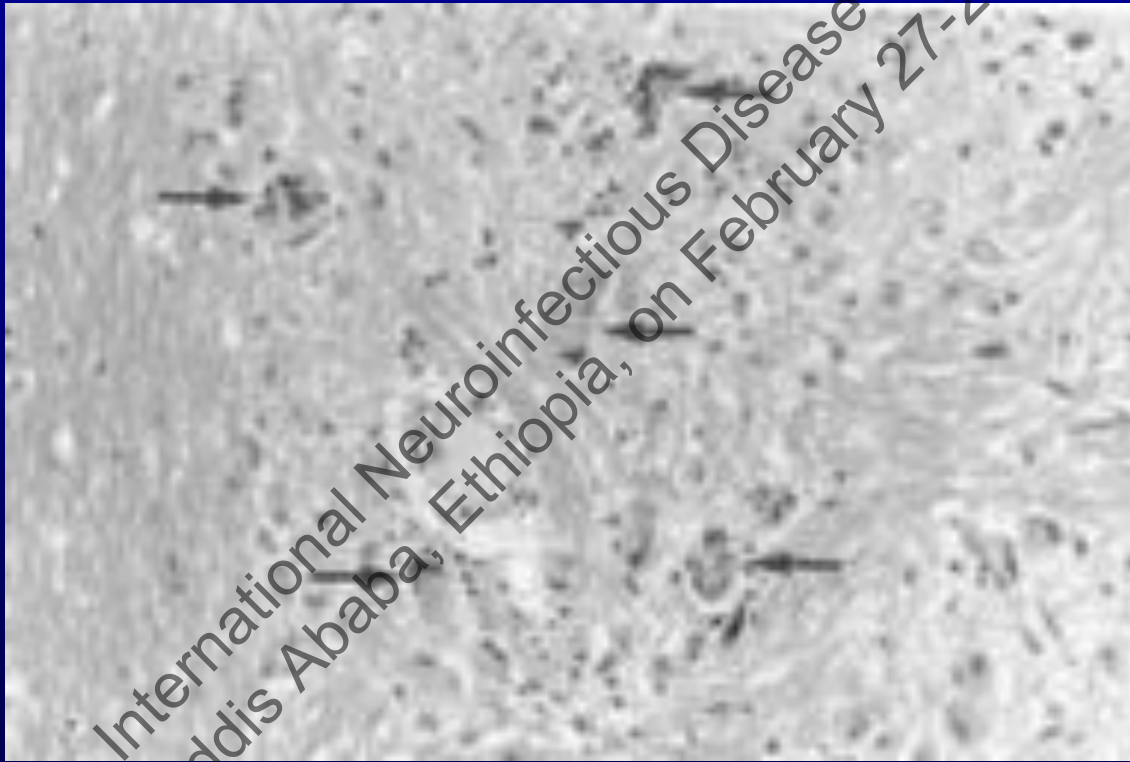
Metabolic encephalopathy

Hypothyroidism

Vitamin B₁₂ deficiency

Drug interactions with protease inhibitors

Pathology of HAND

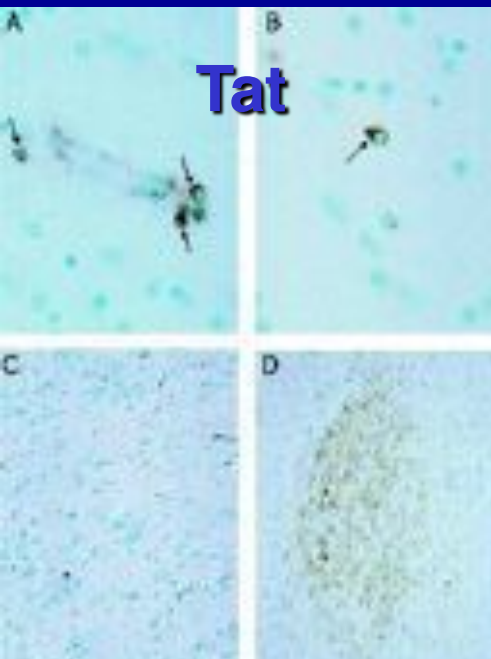


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HIV-1

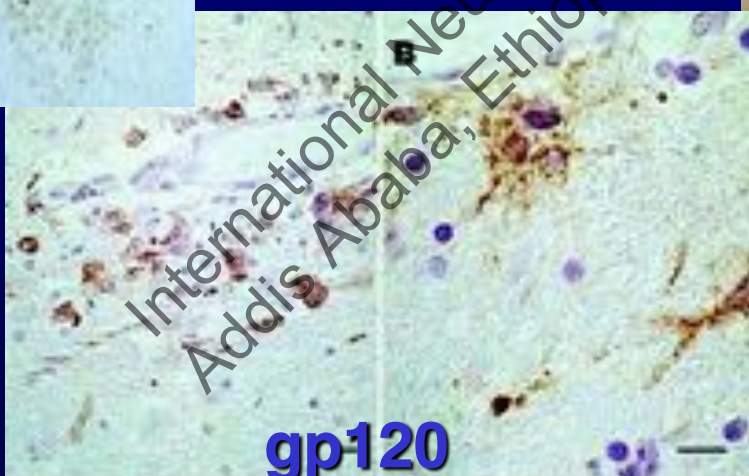


Latent Infection in astrocytes

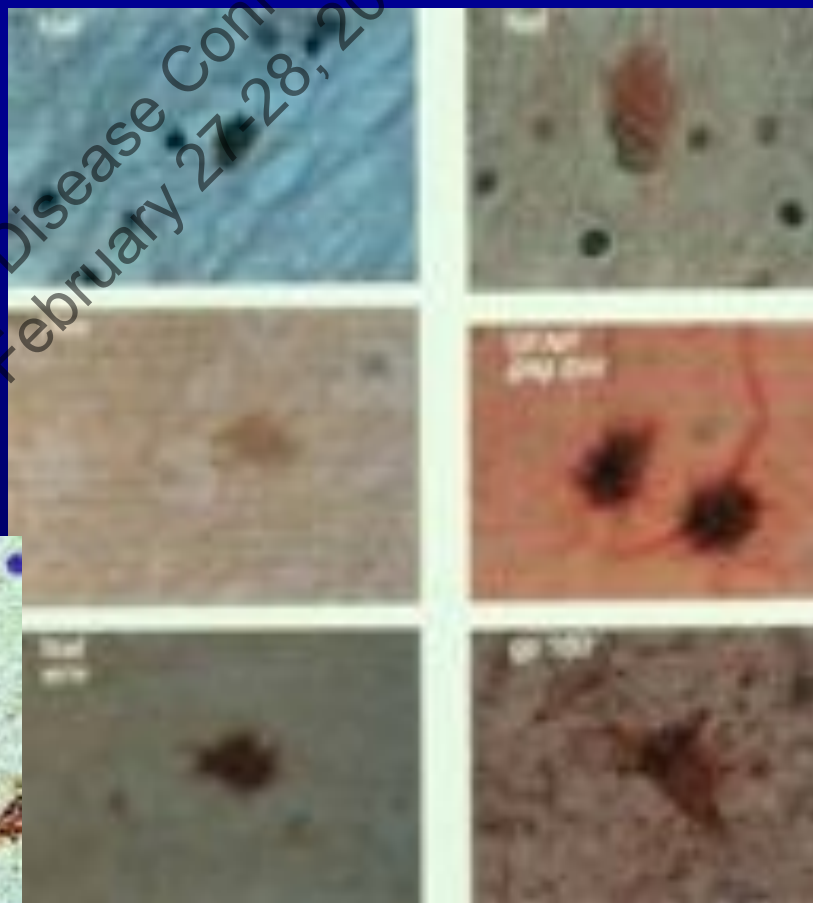


Tat

**Productive
Infection in
perivascular
macrophages**

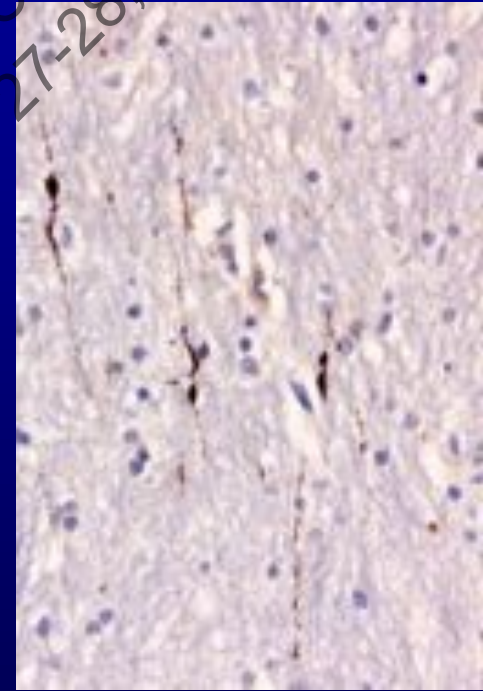
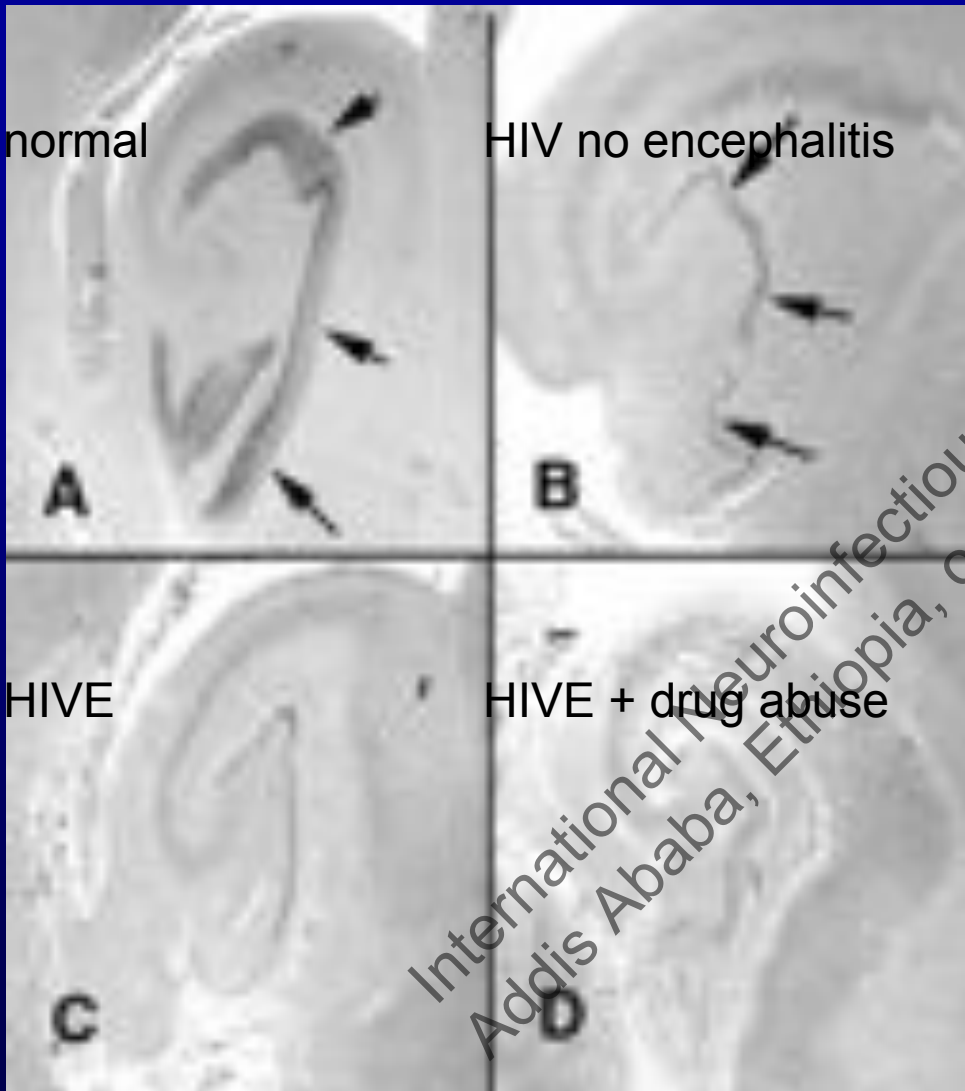


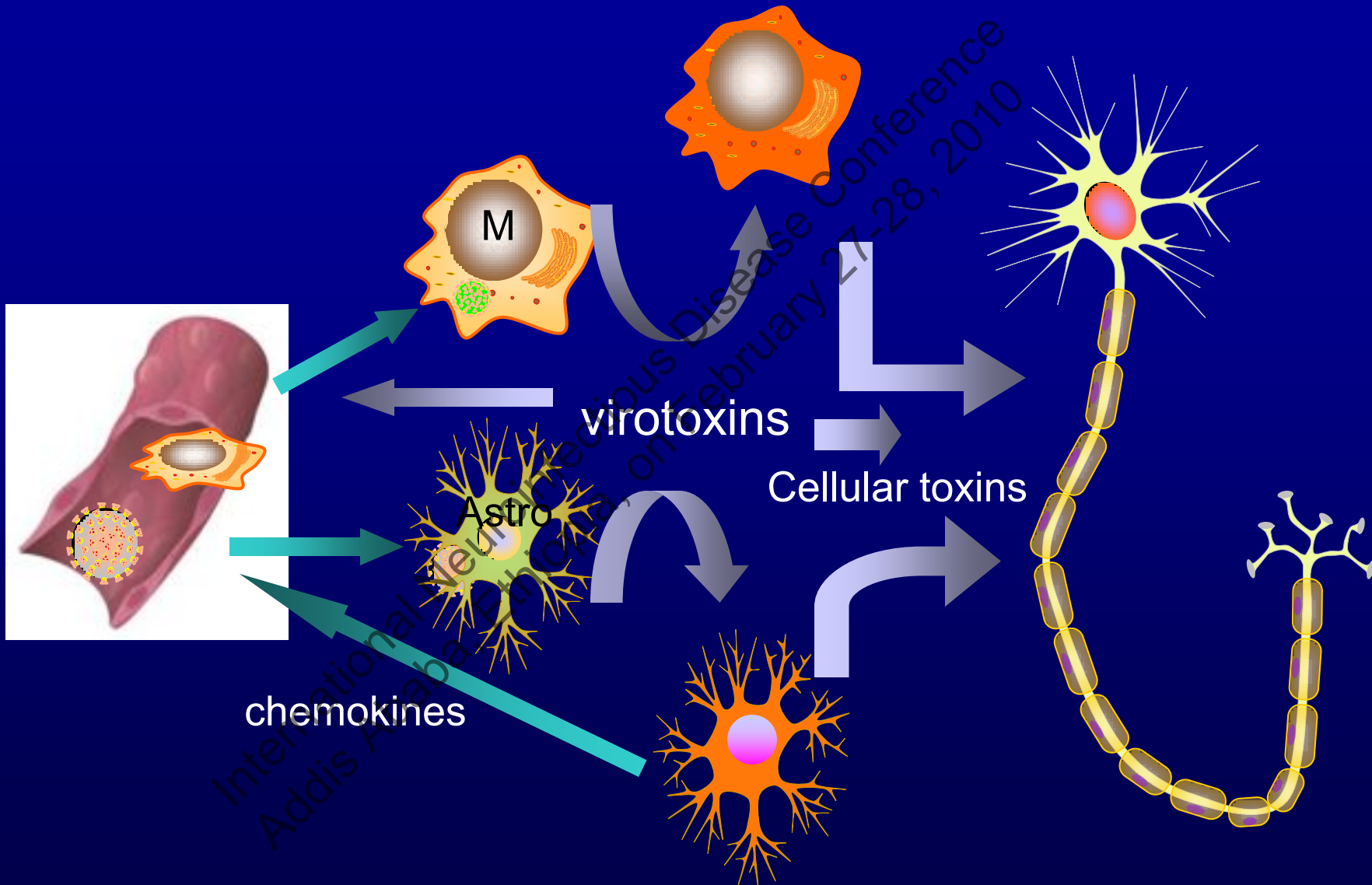
gp120



Ranki et al., 1995

Dentate Gyrus





Principles of Therapy for HIV CNS infection

- **Maximize antiretrovirals to suppress CSF HIV RNA**
- **Preferably use CNS-“penetrant” agents**
- **Construct simplified regime - BD or QD**
- **Supervised therapy:**

CSF penetrating ARTs

Definition: CSF level exceeds the level needed to inhibit replication of HIV

NRTI

stavudine (D4T)

zidovudine (ZDV)

abacavir (ABV)

NNRTI

efavirenz (EFV)

nevirapine (NVP)

Protease Inhibitors

indinavir (IDV)

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Problems with current ART

Poor penetration across BBB

P-glycoprotein

organic transporters

Drug resistance

No effect post viral integration

viral reservoirs spared

early viral proteins still produced

Symptomatic Therapy

Neuroleptics: Atypical antipsychotics

Antidepressants: Low dose fluoxetine (Prozac)

Anticonvulsants: valproate, levetiracetam, gabapentin or topiramate.

Headaches: Triptans interact with Protease inhibitors

Parkinsonism: poor response to dopamine agonists

Sleep disturbance: Sleep apnea-protease inhibitors; Insomnia-efaverinz

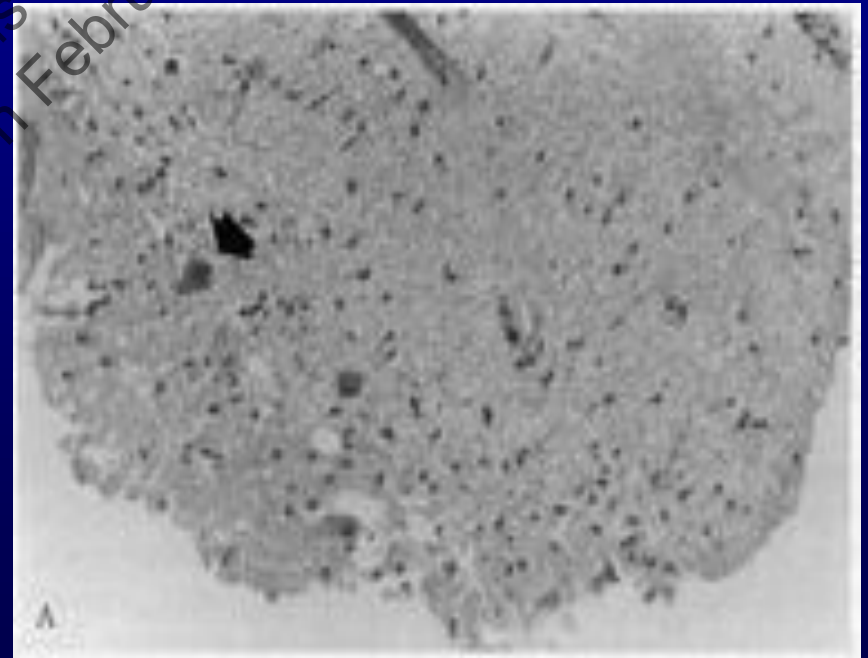
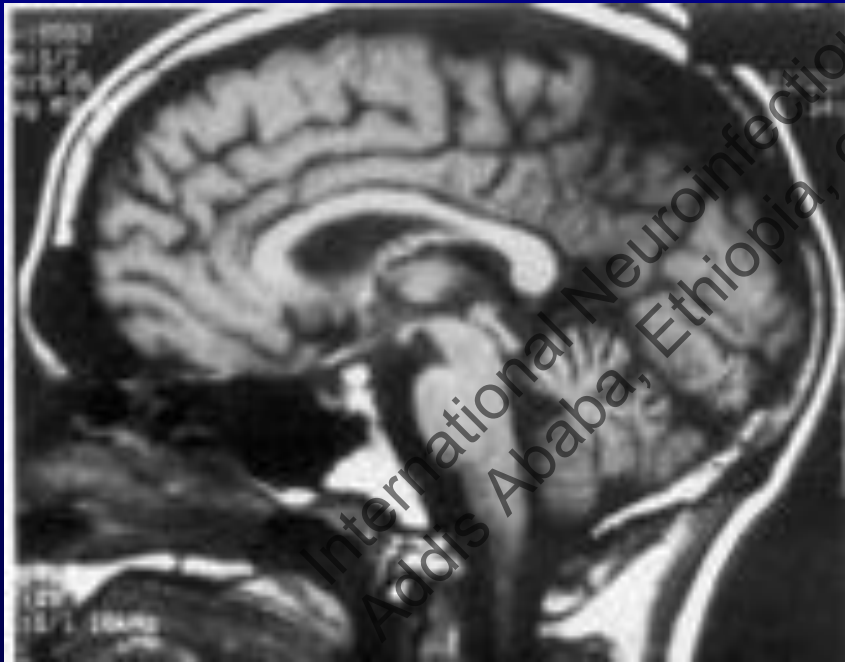
Unusual Manifestations



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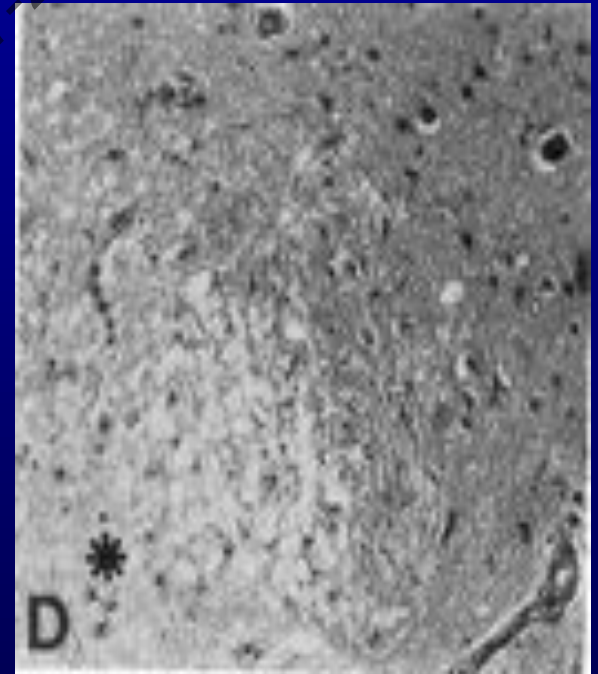
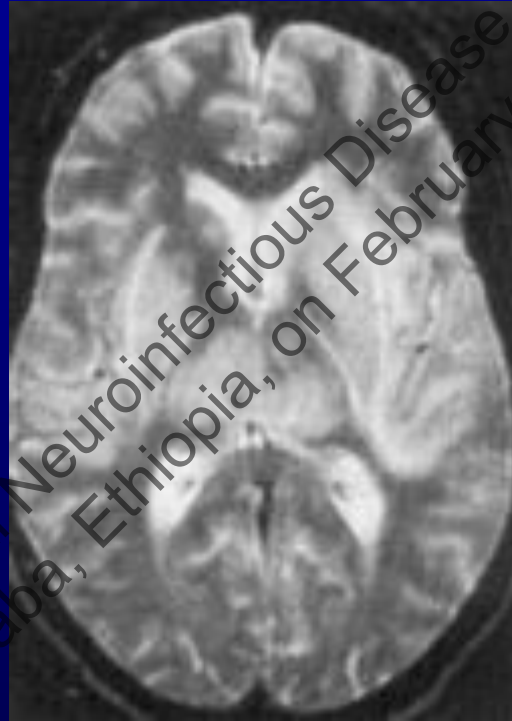
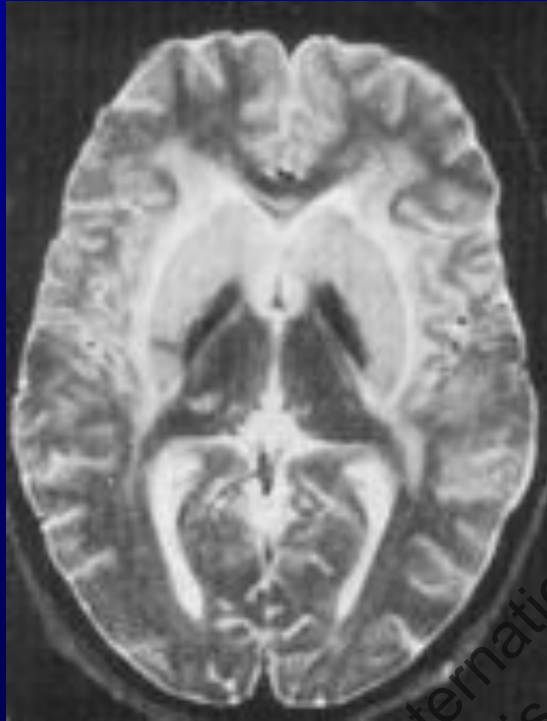
HIV infection and Cerebellar degeneration

(Tagliati et al., Neurology 1998;50:244-51)



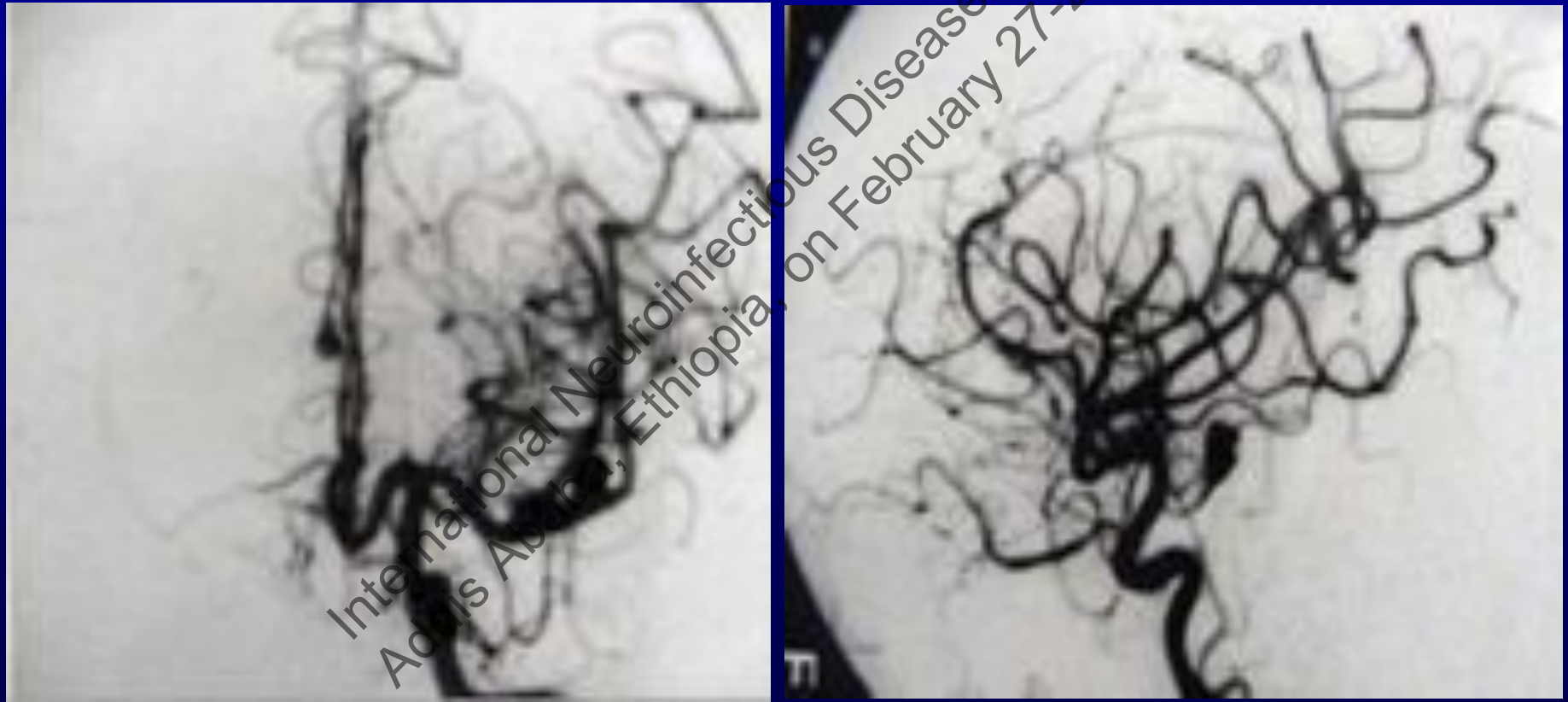
HIV+ Cocaine

(Meltzer et al., AJNR 1998;19:83-9)



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8yr old with congenital HIV infection with microcephaly and developmental delay developed sudden onset of hemiparesis. CT showed subarachnoid hemorrhage



56 yrs old woman started on ART 4 month ago

Generalized seizure 2 wks ago

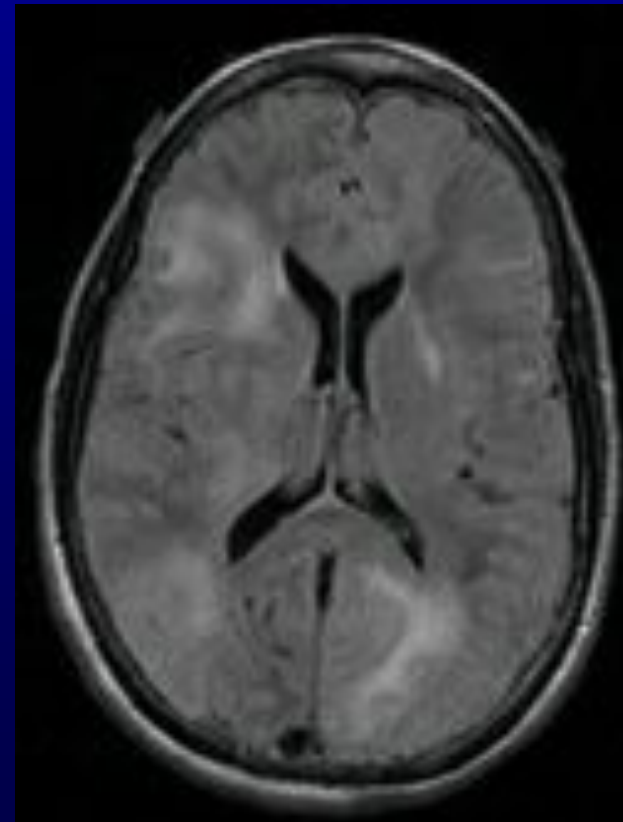
Progressive decrease in consciousness x 2
days

CSF: 4 WBC; Protein 78;

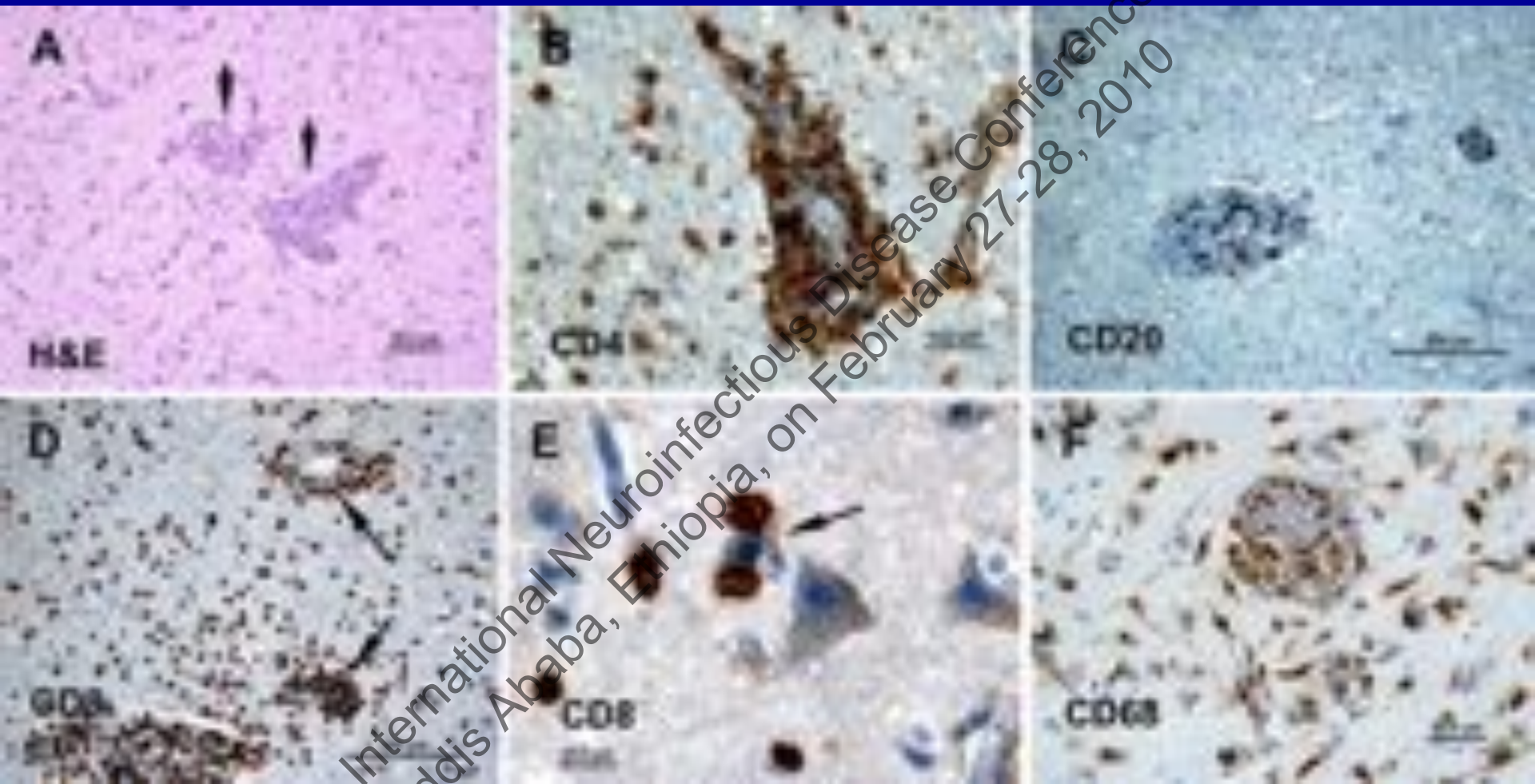
HIV viral load 9,024

CD4 count 319;

Plasma viral load 3,782



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methylprednisone 1g/day x 5 days

Dramatic improvement in mental status

Discharged on prednisone 60mg/day

tenofovir, lopinavir/ritonavir, zidovudine

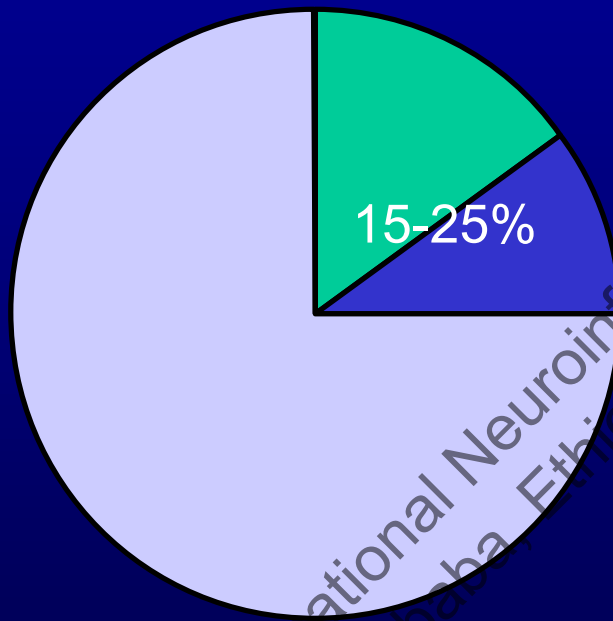
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Immune Reconstitution Inflammatory Syndrome

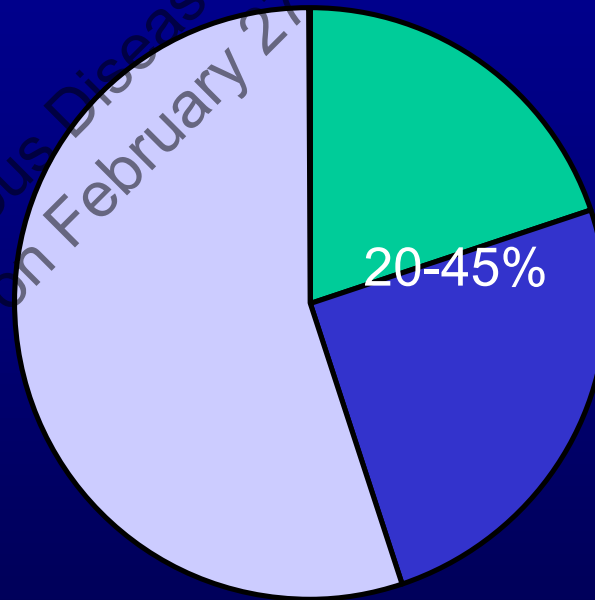
“IRIS is a *worsening* of a patient’s *clinical* condition that is *paradoxically* attributable to the recovery of the immune system after *initiation of ART*”

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EPIDEMIOLOGY of IRIS

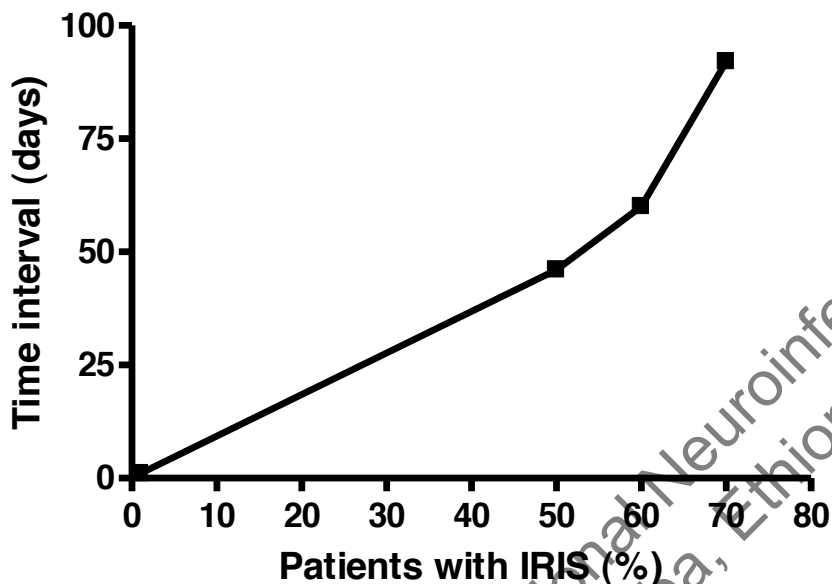


Patients on HAART

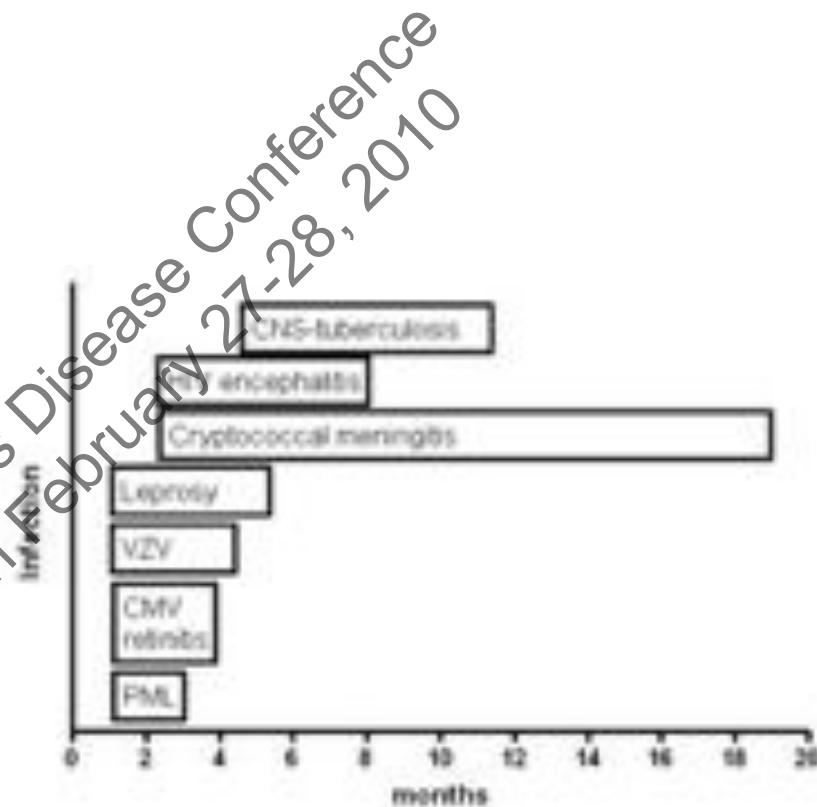


Patients with OI on HAART

Time between of Initiation of HAART and IRIS



Shelburne et al., AIDS, 2005



Johnson and Nath NYAS 2010

Treatment options for IRIS are not ideal

Steroids:

Risks from immune suppression

Interruption of HAART/immune restorative therapy:

Risk for resistance to therapy

Re-emergence of IRIS upon restarting HAART/ immune restorative therapy

Recommendation for use of steroids in IRIS

Catastrophic IRIS: high dose steroids taper with oral steroids x 1 month (with OI prophylaxis)

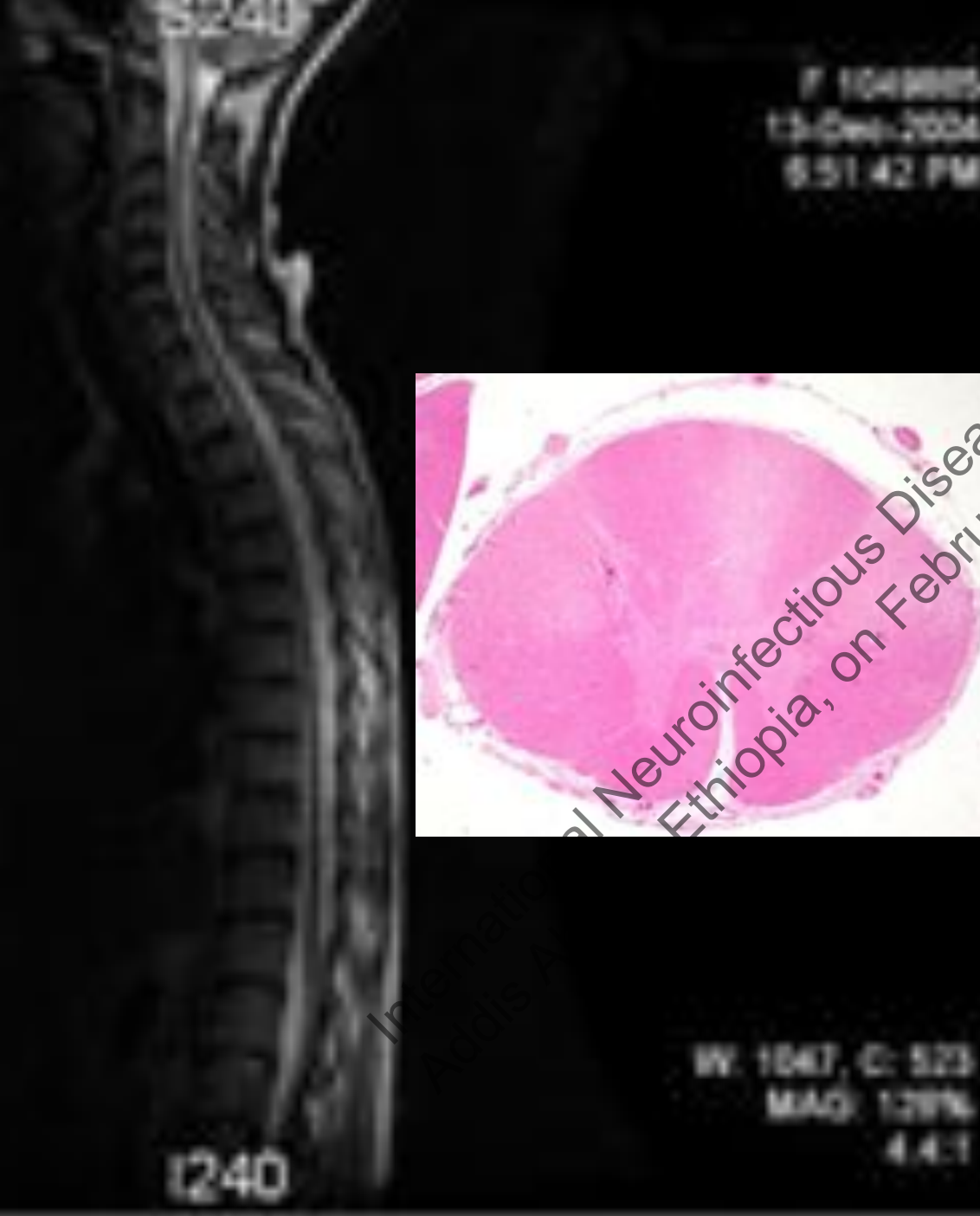
Symptomatic IRIS: high dose steroids taper with oral steroids (debatable)

Asymptomatic IRIS: wait and see (debatable)

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HIV Myelopathy

Spasticity

Sensory ataxia

**Urinary
symptoms**

Peripheral Nervous System with HIV

- Radiculopathy
- GBS
- Mononeuritis multiplex
- Sensory motor neuropathy

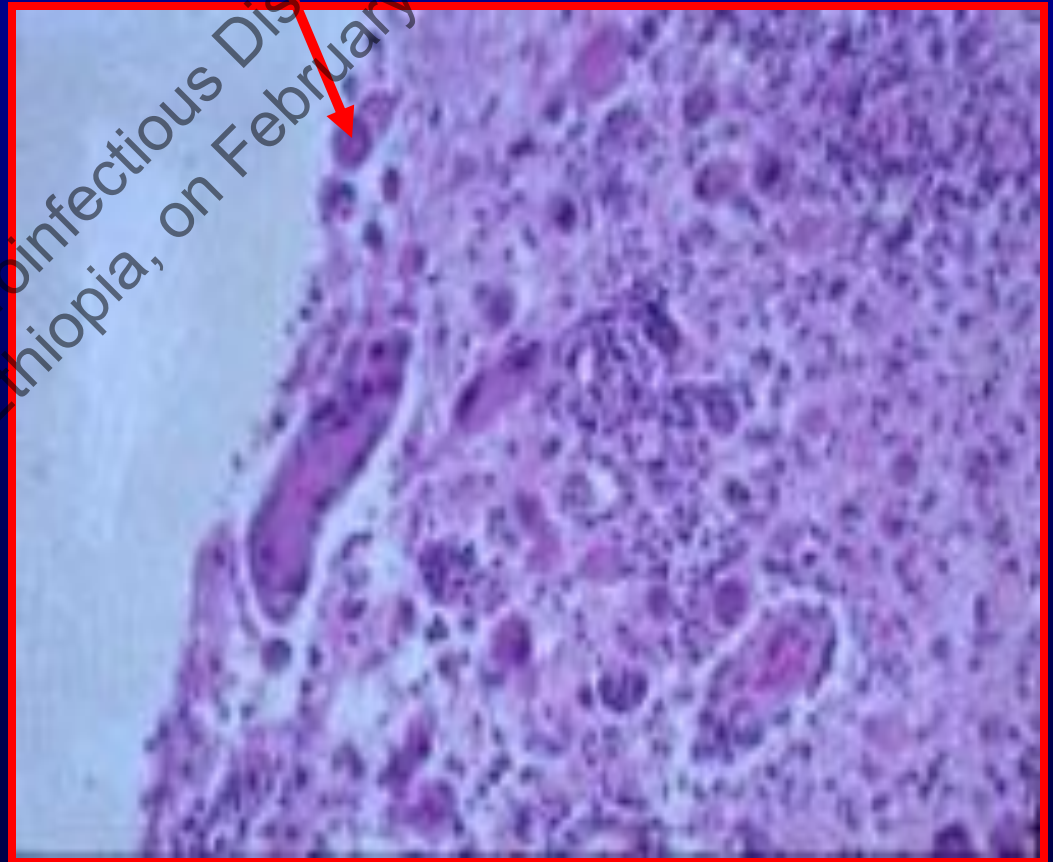
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CMV Polyradiculitis

- Occurs late in HIV infection; CD4 usually < 100 ; concurrent CMV infection in $>60\%$
- **Cauda equina** syndrome: asymmetric motor, perineal sensory, back pain, sphincter
- CSF: poly pleocytosis, \uparrow protein, \downarrow glucose, + CMV PCR+ in 95%
- Rx: *Induction*: ganciclovir [+ foscarnet]
 - *Maintenance*: valganciclovir

CMV polyradiculitis

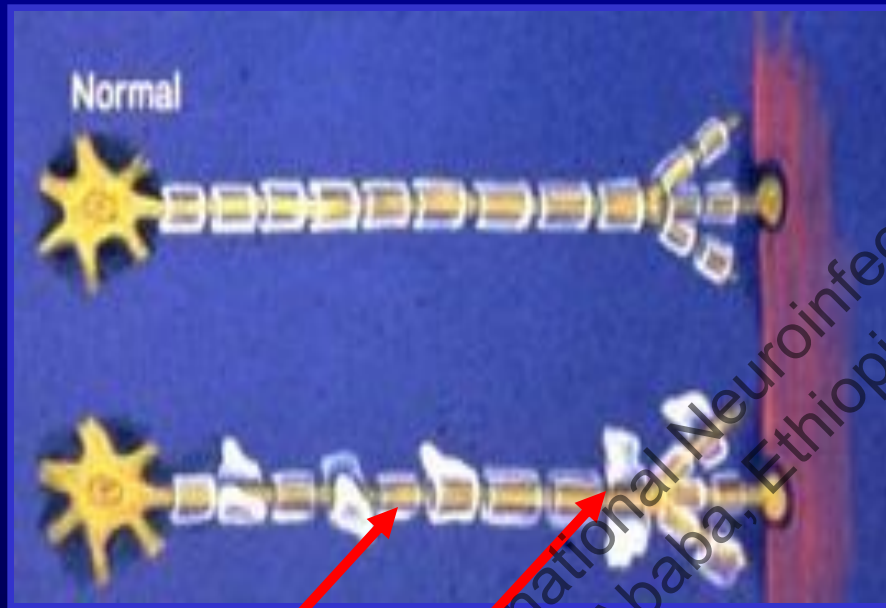
- enhancing nerve roots
- necrotic roots
- CMV inclusions
- spinal cord involvement





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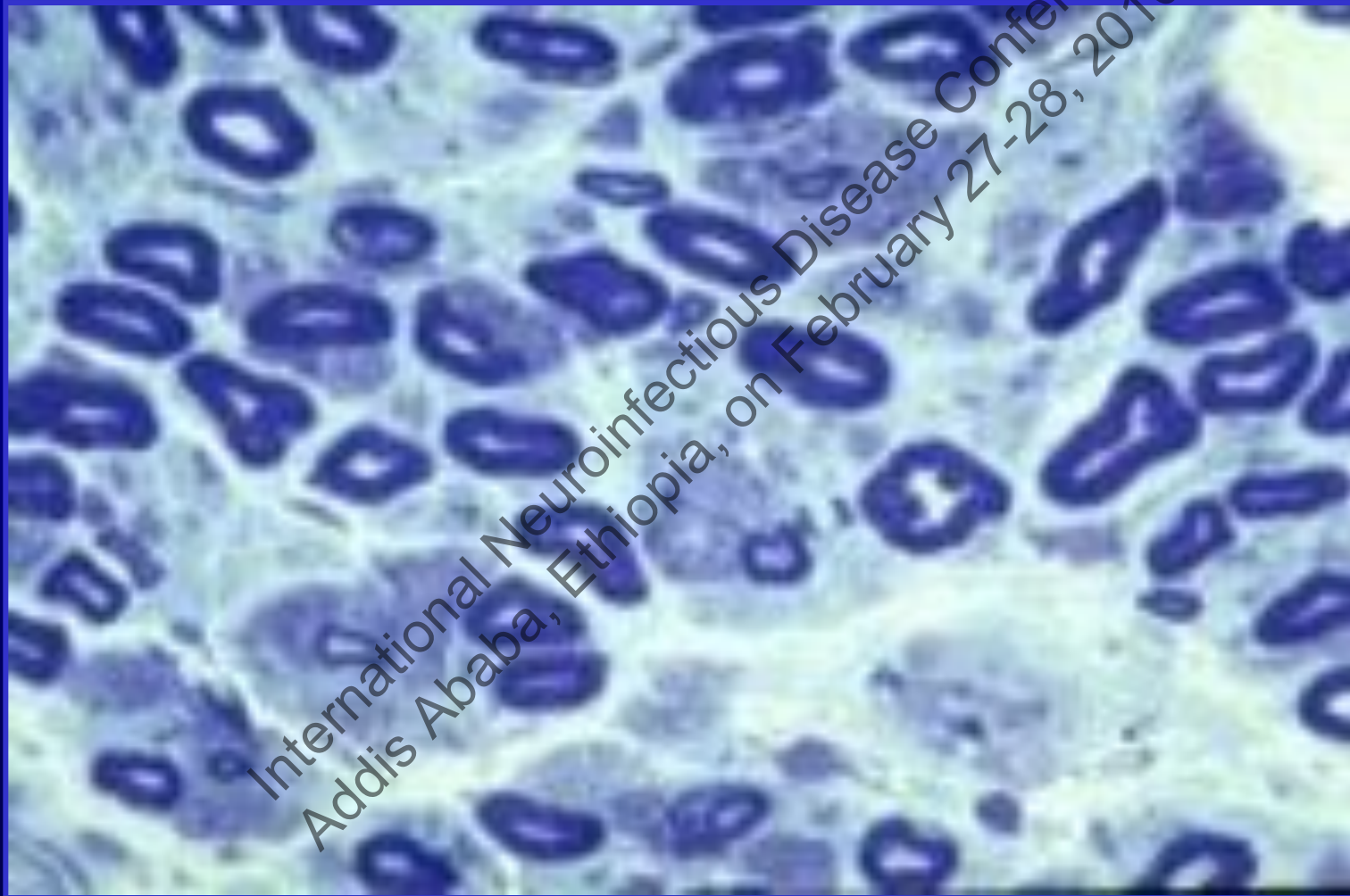
HIV-associated GBS



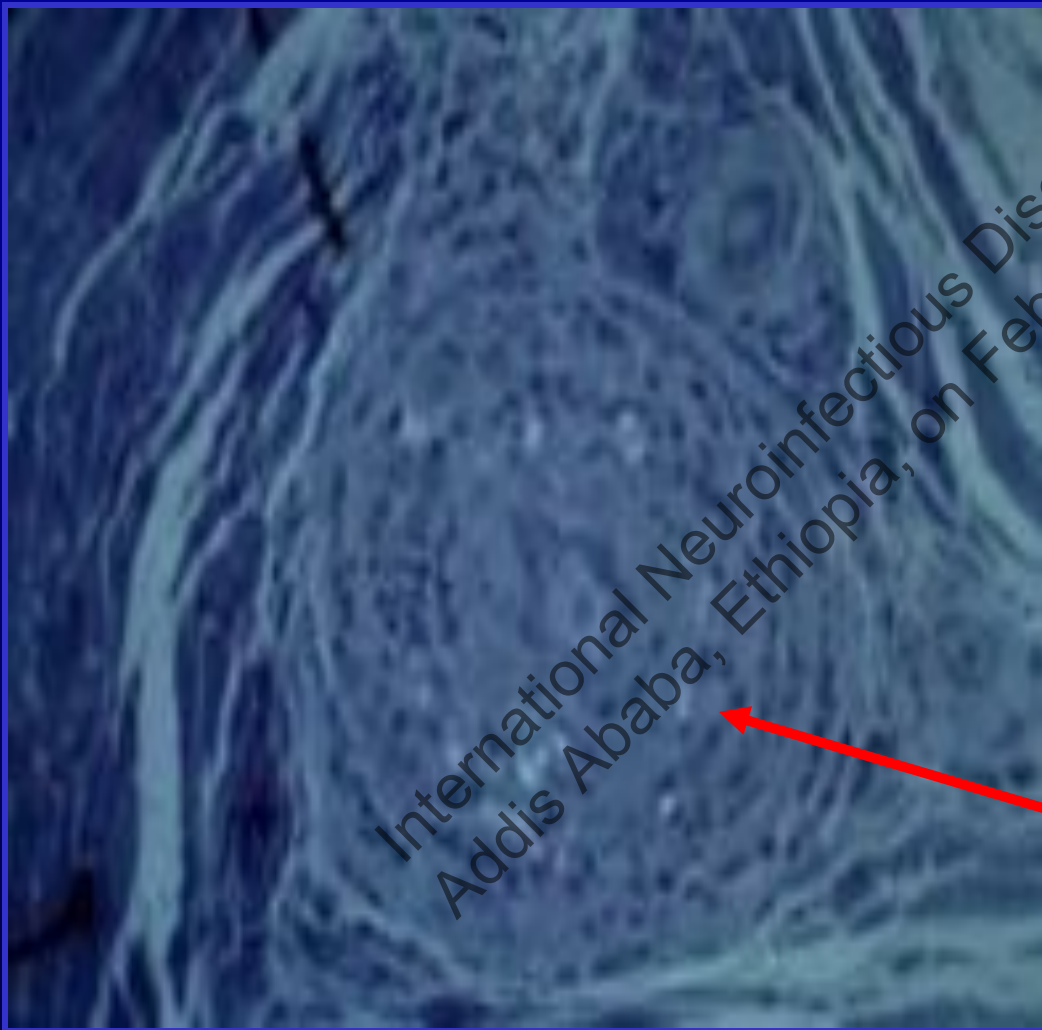
Demyelinated nerve segments

- Increased frequency of GBS relative to general population
- Similar presentation to HIV neg, except that CSF usually cellular
- Usually presents early in HIV infection
- Presumably an immune-mediated phenomenon
- Dx: NCV's/nerve bx.
- Responds to plasmapheresis or IVIG

Nerve biopsy shows macrophage mediated demyelination in HIV-associated GBS



Mononeuritis multiplex in HIV infection



- **abrupt onset**
- **severe pain**
- **Hepatitis B & C**
- **requires nerve Bx**
- **Rx: steroids**

**Vessel occlusion and
inflammation in wall**

Incidence of neuropathy

Lichenstein CID 2004

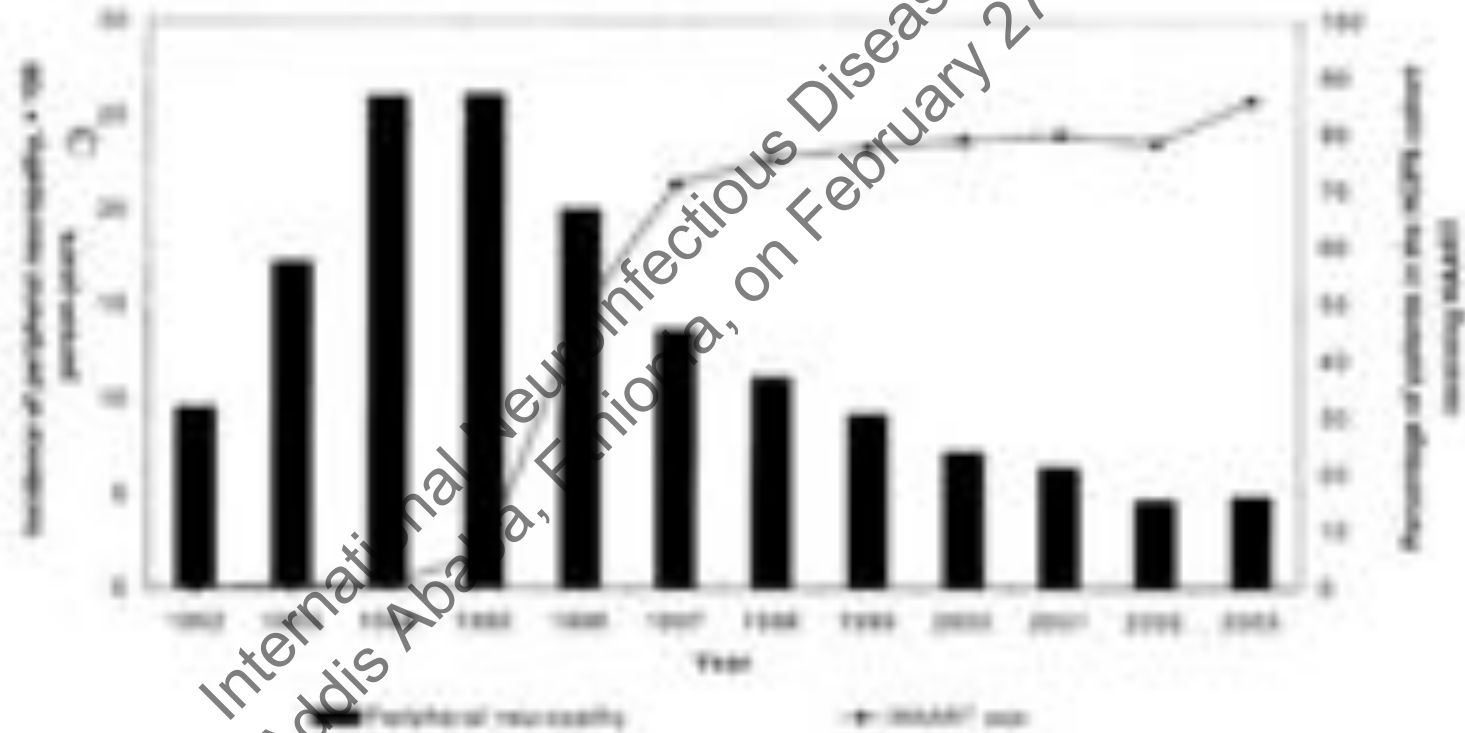


Figure 1. Incidence of peripheral neuropathy and rate of HAART use among 750 patients in the HIV Seroconversion Study (HIVS) cohort.

Clinical features of HIV sensory neuropathies

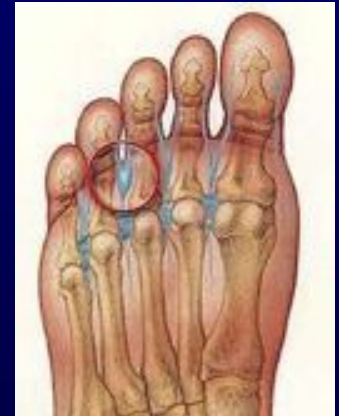
.... "springtime in nerverland"

- | | |
|-----------------------|-----|
| □ sens. thresholds | 65% |
| • Absent/reduced AJ's | 96% |
| • Distal weakness | 33% |
| • Atrophy or wasting | 30% |
| • Fasciculations | 0% |
- Features of HIV distal sensory polyneuropathy and antiretroviral toxic neuropathy are identical. Neuropathic sx. are correlated with plasma HIV RNA



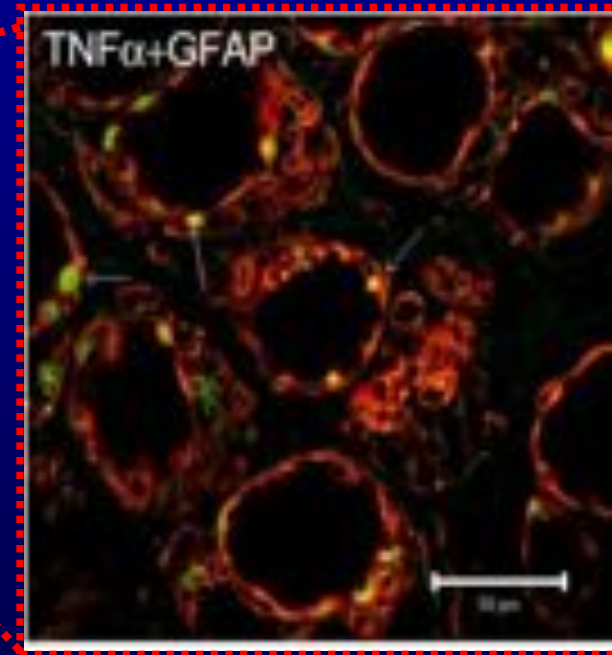
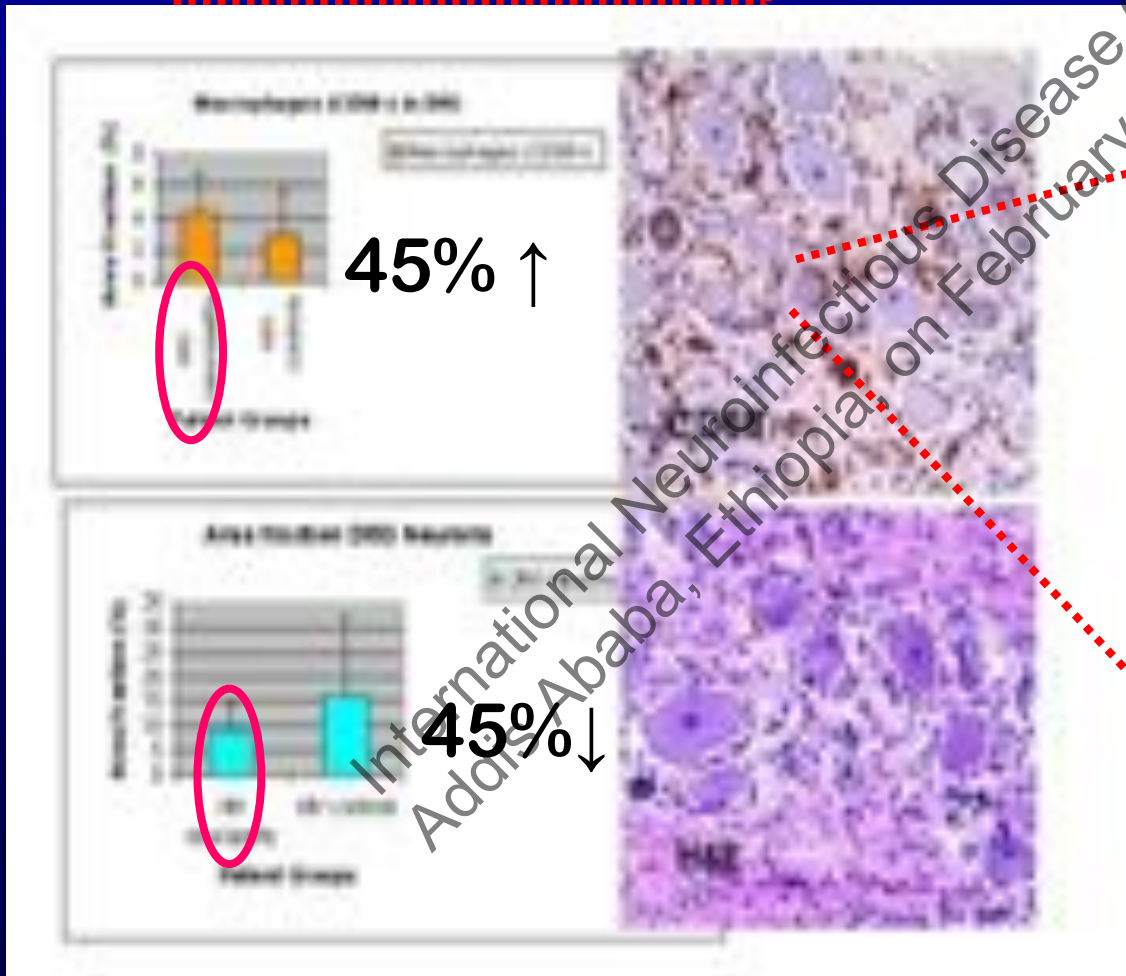
Confounding illnesses in the assessment of HIV sensory neuropathies

- Antiretroviral exposure: d4T 8-fold, ddI 4-fold
- Diabetes in 11% of HAART recipients; IGT in ~ 20%
- Alcohol abuse; hepatitis C
- Entrapment neuropathies
- Vitamin deficiencies or overuse
- Morton's neuroma



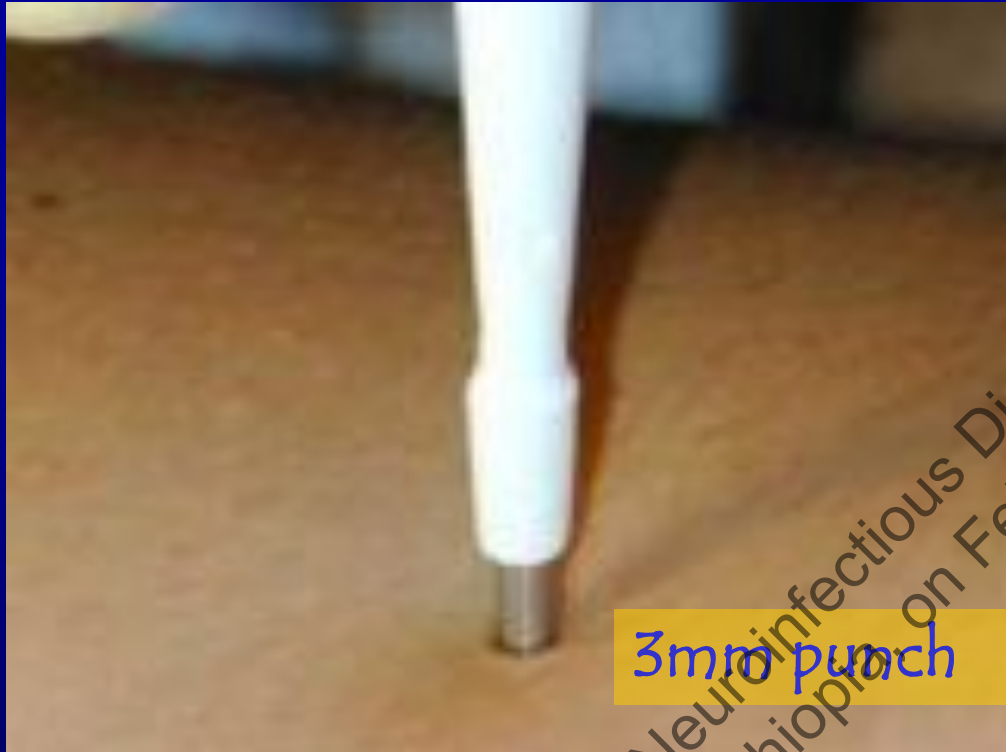
Courtesy: Justin McArthur

Macrophage activation and neuronal reduction in DRG correlates with HIV-SN (Pardo C, 2003)



Courtesy: Justin McArthur

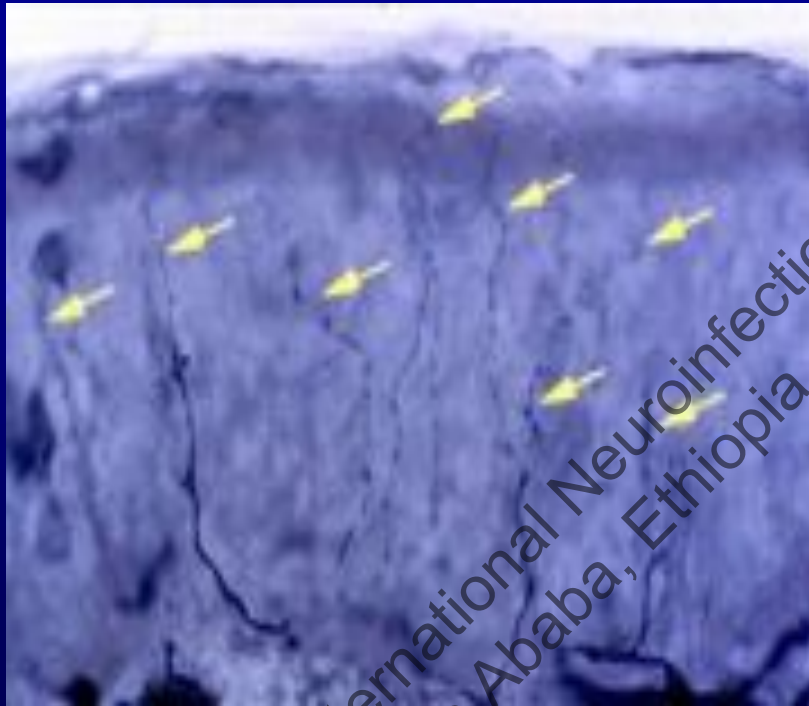
Skin biopsy technique



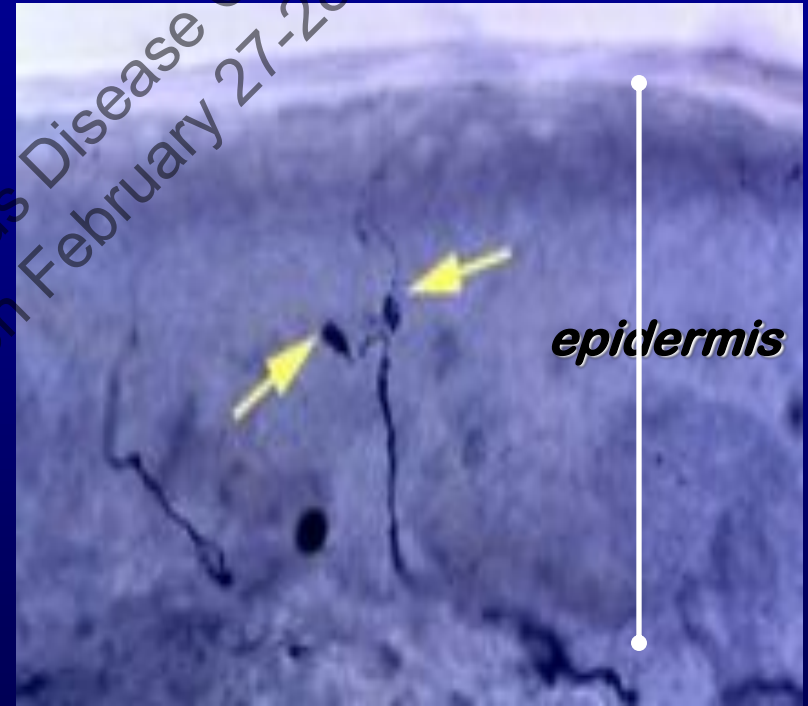
Courtesy: Justin McArthur

HIV sensory neuropathies

Skin biopsy assesses unmyelinated nerve fibers



Thigh: normal density



Distal leg: reduced density and nerve fiber swellings

(unlicensed) treatments for HIV sensory neuropathies

Lamotrigine: Na channel

Glucuronidation, rash

Topiramate: Glutamate

Renal excretion, wt loss, kidney stones

Gabapentin/pregabalin: A2delta calcium

Renal excretion, edema, sedation

Duloxetine: serotonin/norepinephrine RRI

Nausea, hepatotoxicity

Combination therapies: eg NEJM study of gabapentin

+ morphine



Courtesy: Justin McArthur

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Acknowledgements



The End



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