Departments of Medicine, Psychiatry, Medical Microbiology & Immunology
University of Alberta, Edmonton AB

Objectives (20 III 08):

1. **Familiarity with principal immune cells in the nervous system.**
2. **Understand the major mechanisms underlying the development of HIV-associated dementia.**
3. **Familarity with HIV-related neuropathies**

Cardinal features of *inflammation* (*Celsus, 1 CE)*

Rubor **(redness)**
Dolor **(pain)**
Calor **(heat)**
Tumor **(swelling)**

Host defense versus disease process?

Neuroinflammation

- **A major pathogenic component in most neurological diseases: multiple sclerosis, Alzheimer disease, stroke, HIV dementia, brain tumors and several peripheral neuropathies**
- **Involves both the central and peripheral nervous systems; both systems are comparatively encased in a protective *barrier*.**
- **Caused by both adaptive and innate immune mechanisms although innate immunity predominates (no lymphoid structures in nervous system) .**
- **Type and severity of neuroinflammation dictated by cell type involved, immunogen and the host genetic background.**

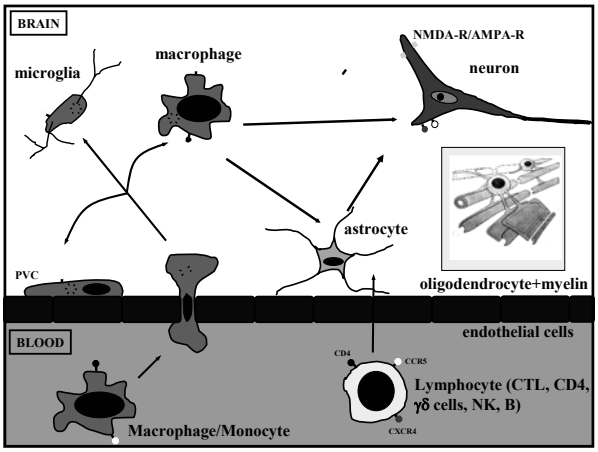
Key aspects of neuroinflammation

- Initiated from outside the CNS with subsequent leukocyte infiltration of the CNS
- Also initiated from within the CNS with ensuing leukocyte infiltration
- The CNS as an "immune privileged" organ (Medawar 1948)
- Interrelationship between neuroinflammation and neurodegeneration (neural cell injury and death)

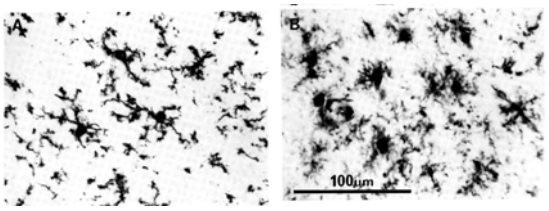
- **Inflammation in the CNS has both good and bad properties**
- **A *general* immuno-suppressant may be counter-productive in the long term**
- **An anti-inflammatory drug with *selective* sparing of the beneficial aspects of inflammation is a favourable therapeutic strategy**

Neural cells

- **Central nervous system (CNS): neurons**
- **(+ axons), astrocytes, oligodendrocytes (+myelin), endothelial cells and microglia/macrophages-protected by the blood-brain barrier.**
- **Peripheral nervous system (PNS): neurons (+ axons), Schwann cells, macrophages-protected by the blood-nerve barrier.**



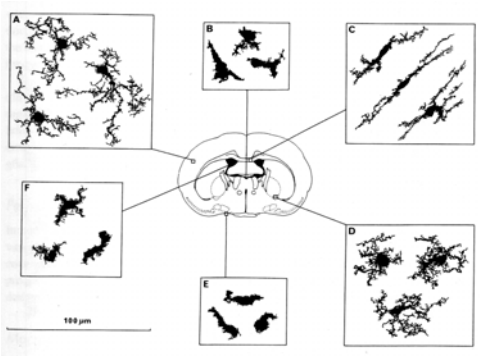
Microglia:bone marrow-derived brain cells



Health-quiescent **Disease-activated**

Perry and Gordon , 1997

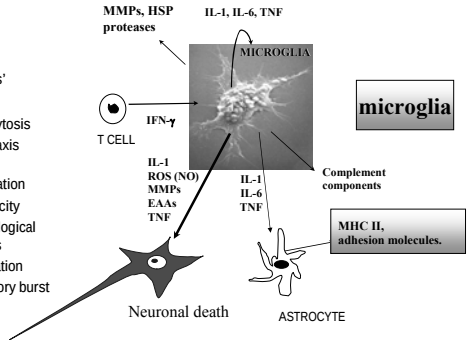
Microglia: regional differences in morphology



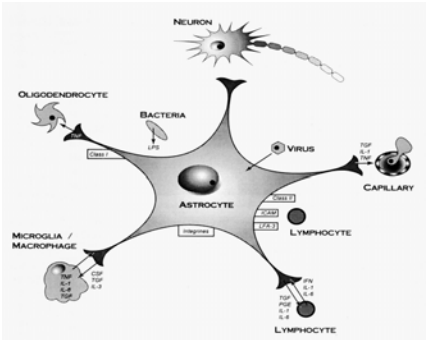
Activated microglia: key players in brain inflammation

Normal
- immune 'sensors'

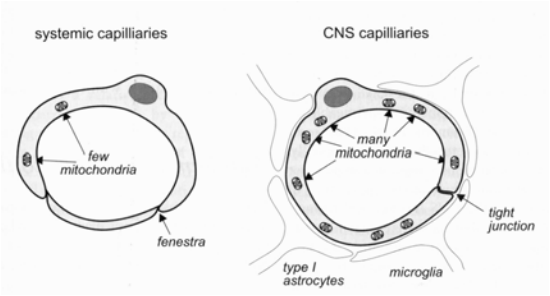
Activated
- phagocytosis
- chemotaxis
- antigen presentation
- cytotoxicity
- morphological changes
- proliferation
- respiratory burst



Astrocyte: the most abundant cell in the brain

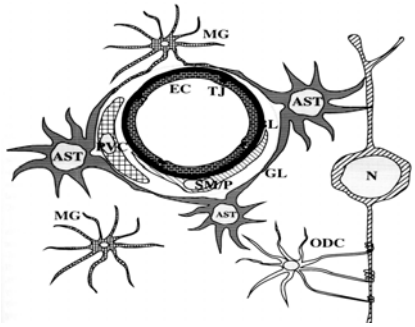


Blood-brain barrier



Ehrlich 1900

Cells contributing to the blood-brain barrier



Mechanisms of immunity within the nervous system

- **Innate immunity**

(A) Endogenous: microglia/macrophages, astrocytes

(B) Exogenous: neutrophils, mast cells, dendritic cells, NK and γδ cells

- **Adaptive immunity**

(A) CMI (CTL/CD8; DTH/CD4)

(B) ADCC

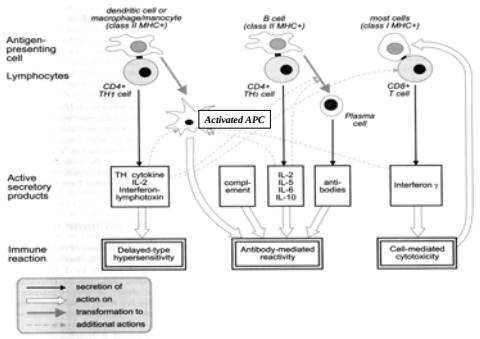
(C) molecular mimicry (B and T cells)

Effectors of Neuroinflammation and Neurodegeneration

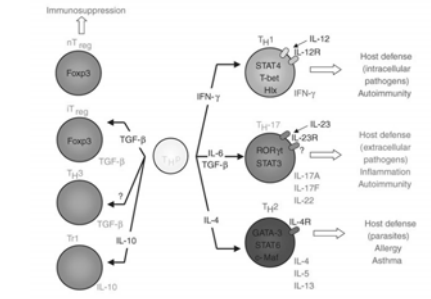
Innate immunity
Astrocytes, macrophages/microglia, Mast, dendritic, NK, γδ T cells, neutrophils
↓↓↓
cytokines, chemokines, ROS, PG/LTs, Proteases, NO

Adaptive immunity
B and T lymphocytes, APCs (DCs, Mϕ, astrocytes, Neurons, B cells)
↓↓↓
Antibodies, TCR-mediated, CTLs, Tregs

Mechanisms of neuroinflammation



T_H progenitors can be differentiated into several distinct lineages

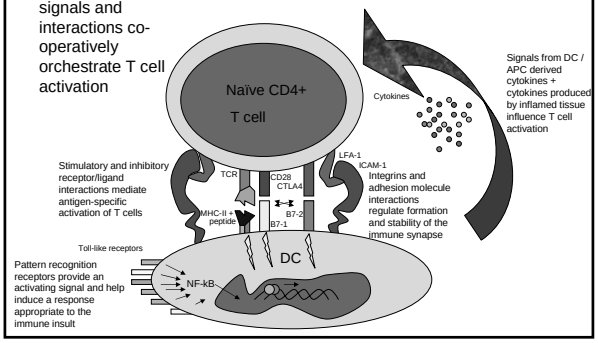


Regulatory lineages "Effector" lineages

Image adapted from: Estelle Bettelli, Mohamed Oukka & Vijay K Kuchroo. Nature Immunology 8, 345 - 350 (2007)

Activation of T cells

Key point - Many signals and interactions co-operatively orchestrate T cell activation

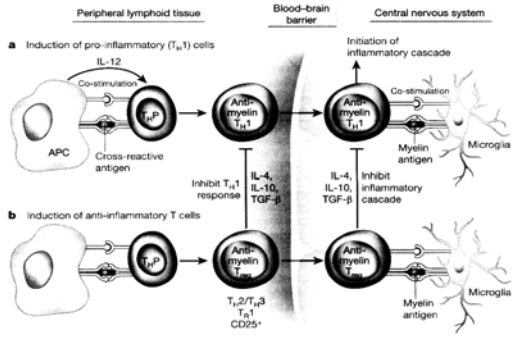


T_H1 cytokines tend to be pro-inflammatory, while T_H2 cytokines tend to be anti- inflammatory

Potential APCs in the brain

Cell Type	In vivo		In vitro	
	MHC Class I Restricted	*MHC Class II Restricted*	*MHC Class I Restricted*	*MHC Class II Restricted*
Neurons	Possibly with some viral infections, otherwise no	No	No	No
Oligodendrocytes	[a]Possible	No	Yes	No
Astrocytes	[a]Possible	[a,b]Possible	Yes	Yes
Microglia	[a]Possible	[c]Yes	Not tested	Not tested
Perivascular cells	[a]Possible	[c]Yes	Not tested	Not tested
Other CNS macrophages	[a]Possible	[c]Yes	Not tested	Not tested
Endothelial cells	[d]Yes	[e]Species dependent	Yes	[f]Yes
Smooth muscle cells/ pericytes	[a]Possible	[a]Possible	Not tested	[g]Yes

T lymphocyte actions in the nervous system



Mediators of inflammation present during neuroinflammation

Neurological infections

- ***Unique aspects of CNS infections:***

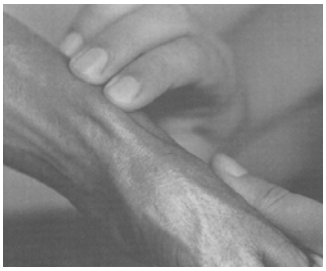
1. Localization of the infection dictates the clinical presentation (CNS vs. PNS).

2. Brain is an immune privileged organ

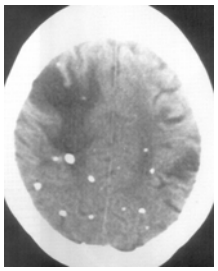
⇒Blood-brain barrier protection

⇒ *innate* (macrophages, neutrophils) vs. *adaptive* (CTL and Abs) *immunity*.

Mycobacterial neurological infections



Lepromatous leprosy

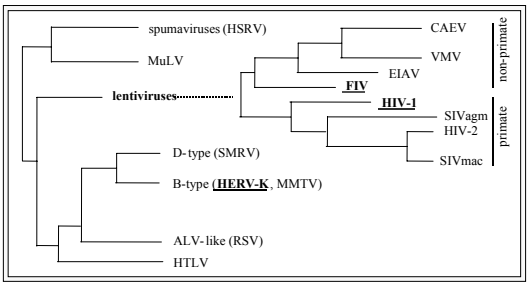


CNS tuberculomas

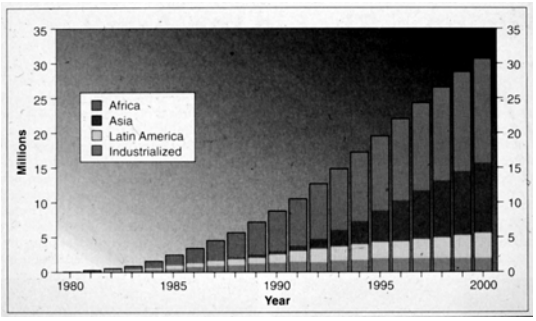
EMERGING NEUROLOGICAL INFECTIONS

- Variant CJD
- Nipah virus encephalitis
- West Nile virus encephalitis
- Enterovirus 71 encephalitis
- Usually xenotropic and usually RNA viruses

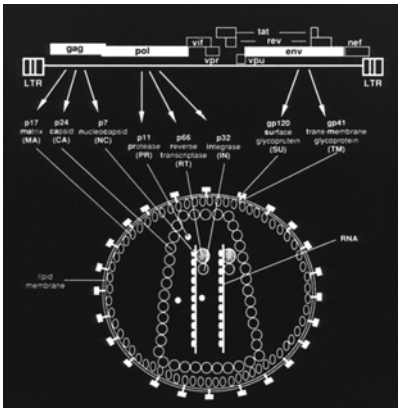
Neurotropic retroviruses



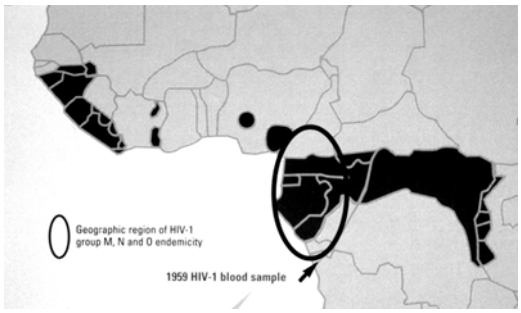
GLOBAL PROJECTIONS FOR HIV-1 INFECTION

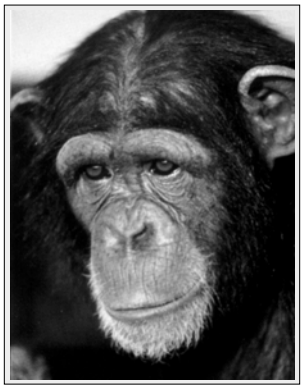


HIV-1



Sources of HIV-1 and HIV-2



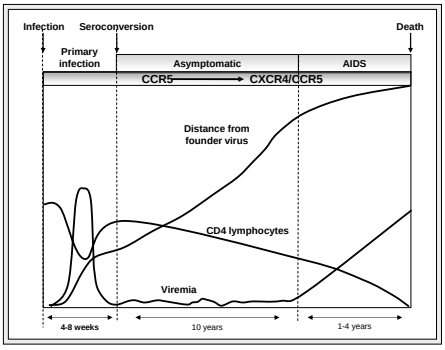


Chimpanzee (*Pan troglodytes*)

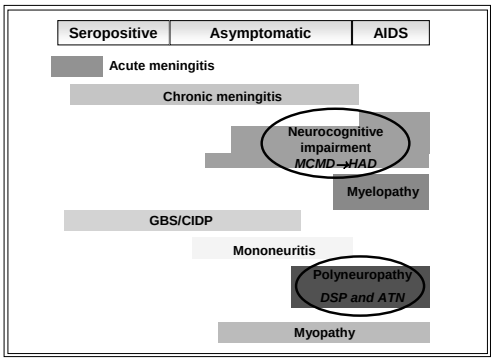
- **presumed source of HIV-1**

- **42 million HIV positive today**
- **5 million new infections/yr worldwide**
- **4000 new infections/ year in Canada**

HIV systemic disease course



Primary HIV-induced neurological syndromes



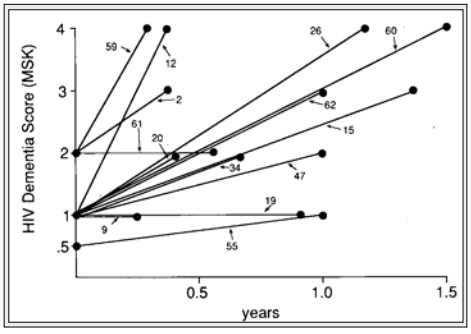
HIV-associated dementia (HAD)

- Affects 10-20 % of patients with HIV infection, usually after the development of AIDS and heralds a poorer survival prognosis.
- Usually preceded by Minor Cognitive-Motor Disorder (MCMD).
- Risk factors: extremes of age; CCR5 δ32; APOE ε4; polymorphisms in promoters of TNF-α and MCP-1.
- Synonymous terms: AIDS dementia complex (ADC), HIV dementia (HIVD), AIDS encephalopathy.

HIV-associated Dementia: Early Symptoms

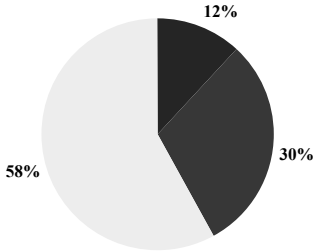
Behavior	apathy depression agitation
Cognition	memory loss concentration mental slowing
Motor function	unsteady gait leg weakness poor coordination tremor

HIV-associated dementia progression

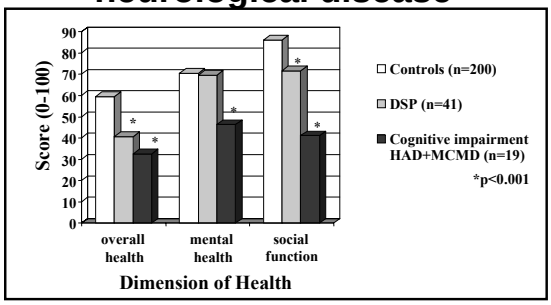


Power et al, *J Virol* (1994)

Prevalence of neurocognitive impairment in the Southern Alberta Clinic



Quality of life among HIV+ patients with and without neurological disease



Pandya et al, 2004

HIV Dementia Scale: comparison with Grooved Pegboard and MMSE

Max 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 (twenty) 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 (use back of this form) and record time: _____ 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
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 after prompting.
2	( )	**CONSTRUCTION** Copy the cube below; record time: ____ seconds. <25 sec = 2; 25 - 35 sec = 1; >35 sec = 0
		TOTAL SCORE: _____/16

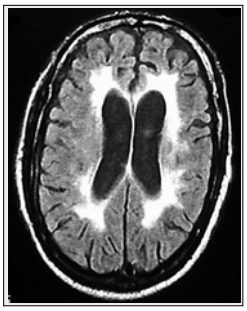
TABLE 2. *Comparison of instrument performance for the entire study population (percentage values)*

Instrument (cut-off values)[a]	Sensitivity	Specificity	PPV[b]	Efficiency
HDS (≤10)	80	91	78	84
PB (≥90 s)	91	82	72	86
MMSE (≤28)	50	88	62	72

[a] Derived from the ROC.
[b] Positive predictive value.

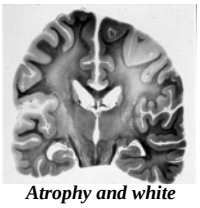
Power et al, *J AIDS and Hum. Retrovir* (1995)

Neuroimaging and Clinical Case

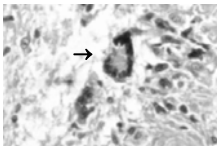


- 38 y.o. bisexual HIV+ white male with 3-6 mo. history of:
  - ➢increasing forgetfulness
  - ➢slowed cognition and motor activity with poor concentration
  - ➢irritability, apathy
  - ➢HDS score=6
  - ➢gait ataxia, tremor, hyperreflexia, parkinsonian
  - ➢CD4=100, VL=10^6
- Responded to HAART, returned to work 1 yr later

Neuropathological features of HIV infection



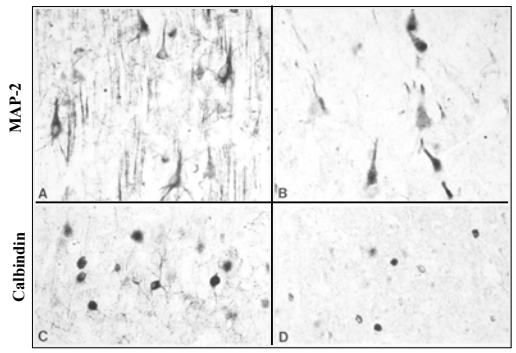
Atrophy and white matter pallor



Multinucleated giant cells

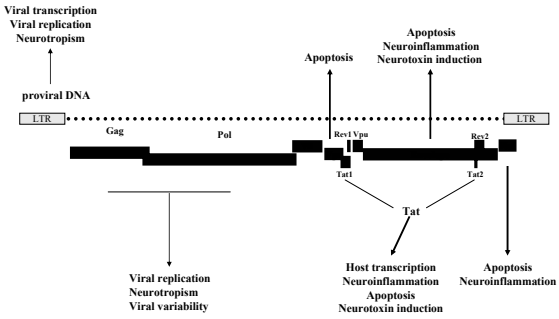
Perivascular cuffing

HIV antigen detection



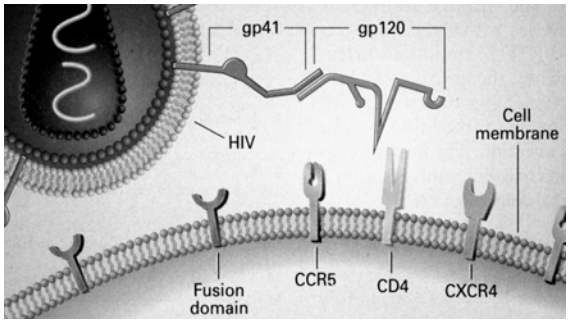
Power and Johnson, *Adv. Virus Res* (2001)

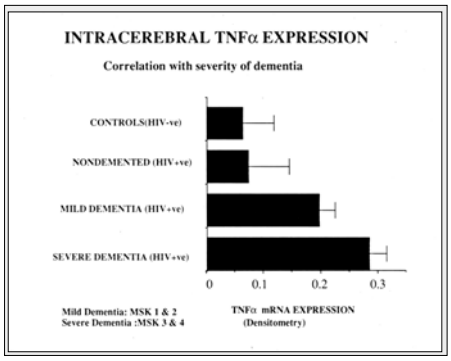
Determinants of Neurovirulence



van Marle and Power 2005

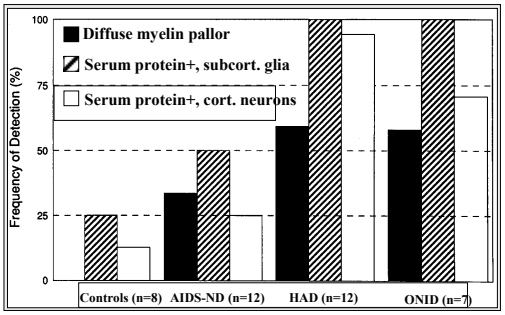
HIV interaction with its receptors





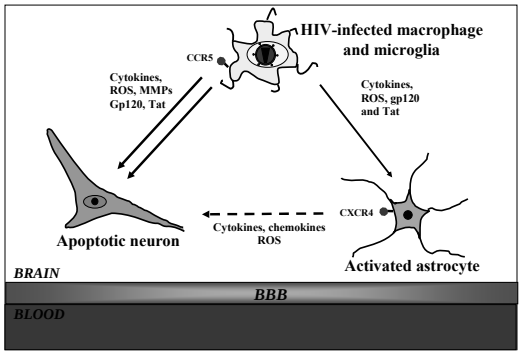
Wesselingh et al, *Ann Neurol* (1993)

Blood-brain barrier perturbation in HIV infection



Power et al, *Ann Neurol* (1994)

Cellular components in HIV neuropathogenesis



Treatment for HIV-related neurocognitive disorders

HAART: recovery is dependent on dementia severity and prior ART exposure (MSK scale)

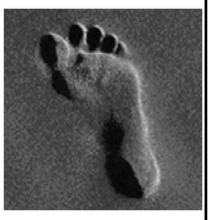
Neuroprotective drugs: NMDA receptor antagonists (memantine/amantidine), minocycline, PAF/TNF inhibitors, Valproate, growth hormone, SSRIs

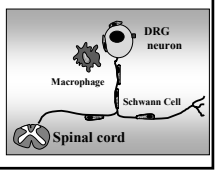
Symptomatic: quetiapine, olanzapine

HIV sensory neuropathies (HIV-SN)

***Distal Sensory Polyneuropathy* (DSP) and *Antiretroviral Toxic Neuropathy* (ATN)**

- ≈35% of HIV(+) patients
- Symmetric bilateral "burning" (neuropathic) pain, feet>>hands
- +/- bowel/bladder and gait effects
- Small diameter axonal loss, "dying back"/degeneration
- Inflammation (Mϕ and T cell) within the nerve or dorsal root ganglion (DRG)

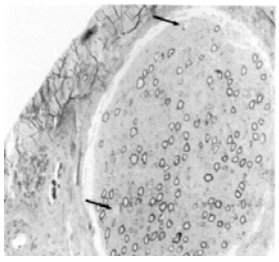




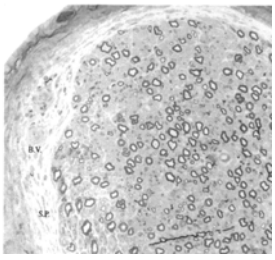
HIV distal sensory polyneuropathy (DSP) and antiretrovial toxic neuropathy (ATN)

- **DSP is common, affecting > 30% of patients with AIDS.**
- **ATN also common with select antiretrovirals: ddI, ddC and d4T (>50%).**
- **Symptoms: painful (neuropathic) feet, numbness and ataxia.**
- **Signs: diminished pinprick and temperature together with absent ankle reflexes.**

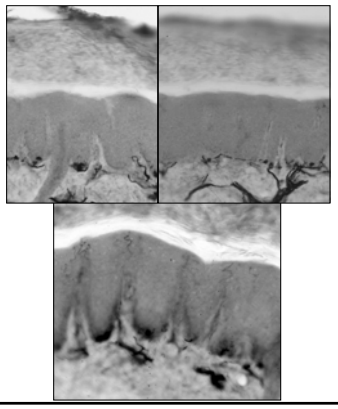
Guillain-Barre Syndrome



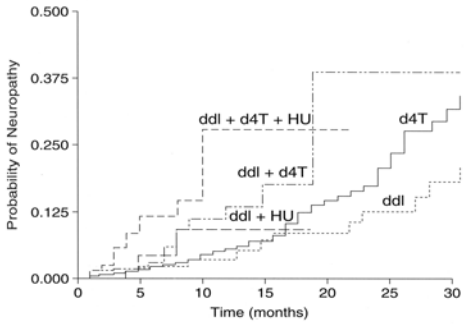
Distal Sensory Polyneuropathy



Epidermal Nerve Fibers



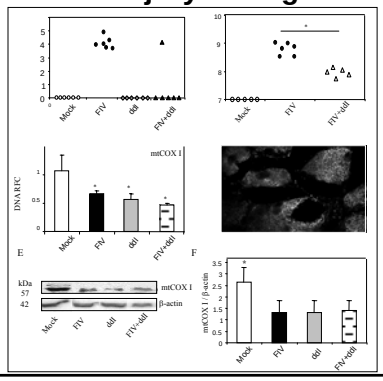
Likelihood of developing ATN with different ARTs



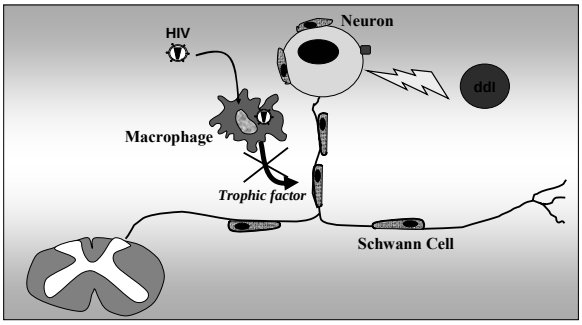
Medication-related neuropathies in HIV infection

MEDICATION	CONDITION FOR WHICH IT IS USED	NATURE OF NEUROPATHY	OTHER FEATURES THAT MAY SERVE AS CLUES TO THE DIAGNOSIS
Vincristine	Kaposi's sarcoma and lymphoma	Distal symmetric sensory with later motor involvement	Weakness preferentially involves finger and wrist extensors and distal leg muscles
Taxol	Kaposi's sarcoma	Distal symmetric sensory	—
Isoniazid	Tuberculosis (TB)	Distal symmetric sensory	—
Ethambutol	TB or *Mycobacterium avium-intracellulare* infection	Distal symmetric sensory	—
Thalidomide	Mouth and esophageal ulcers; sometimes refractory diarrhea	Distal symmetric sensory	Brittle nails and palmar erythema
HMG-CoA reductase inhibitors	Hyperlipidemia	Distal symmetric sensory	Myopathy

ddI exacerbates DRG neuronal mitochondrial injury during FIV infection



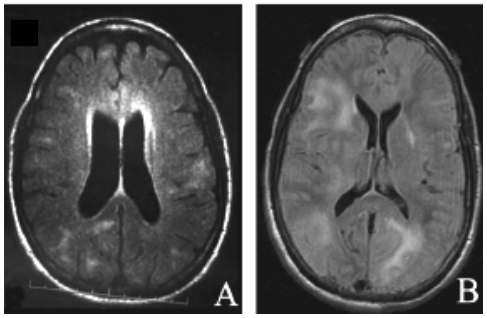
ART-mediated effects on HIV-SN



Treatment for HIV neuropathy

- Analgesics: gabapentin, pregabalin, amitriptyline, lidocaine, capsaicin, opiates
- Growth factors: nerve growth factor
- Avoid neurotoxic drugs-some antiretrovirals (ddI, ddC, d4T) and antibiotics

Immune reconstitution inflammatory syndrome (IRIS) in the Central Nervous System (NeuroIRIS)



Venkataramana *et al*. 2006. Neurology 67: 383-388

Neuropathology of IRIS