

HIV, Aging and the Neurologic System

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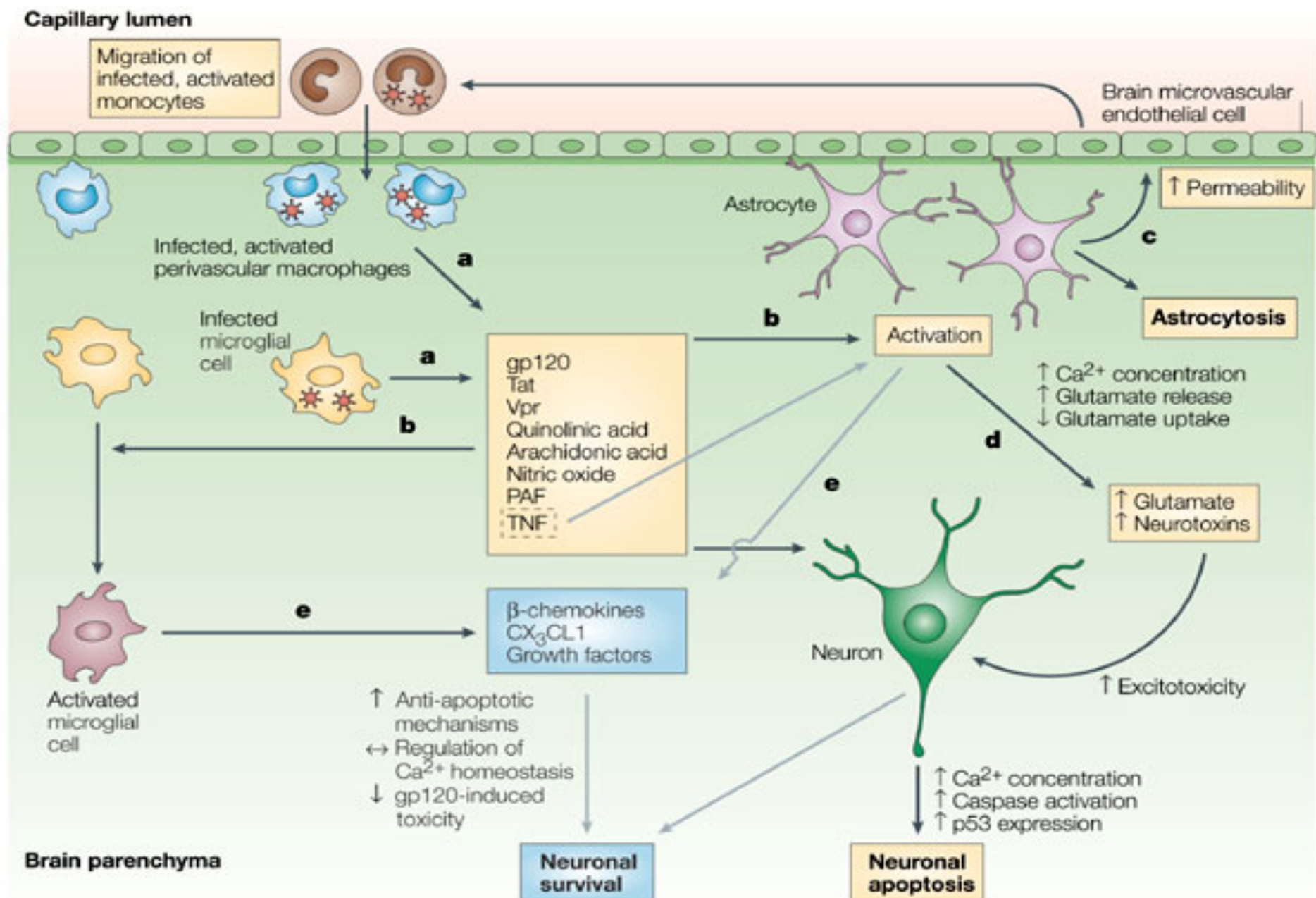
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UCSF

Overview

- Review of HIV neuropathogenesis
- Current understanding of HIV and aging
 - Synergistic and/or parallel mechanisms to increased impairment
 - New findings in the past year
- Major areas where methodology can be improved
 - Focus on etiology/pathogenesis rather than just “impairment”, what is meant by age, existing limitations in assessment of function

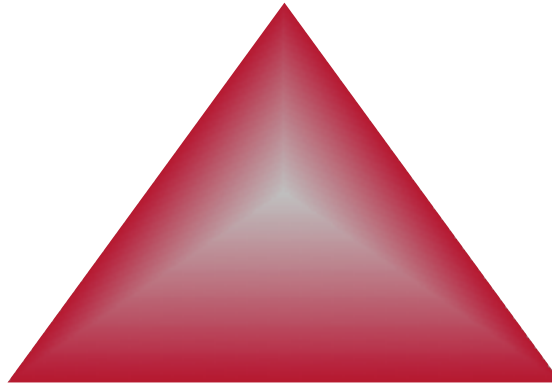


Clinical Features

reflective of anatomic pathology

Cognition

Memory loss
Concentration
Mental slowing
Comprehension



Behavior

Apathy
Depression
Agitation, mania

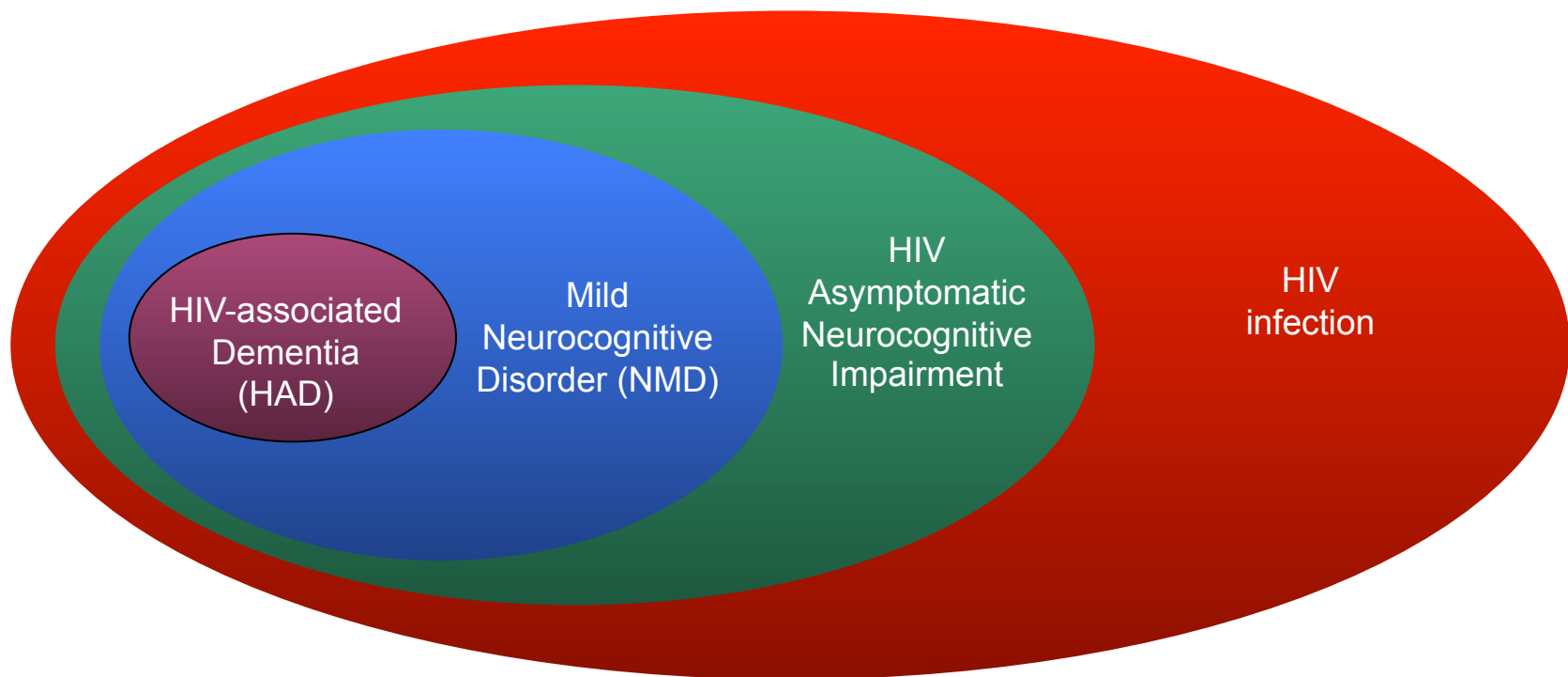
Motor

Unsteady gait
Poor coordination
Tremor

Cognitive Impairment in HIV

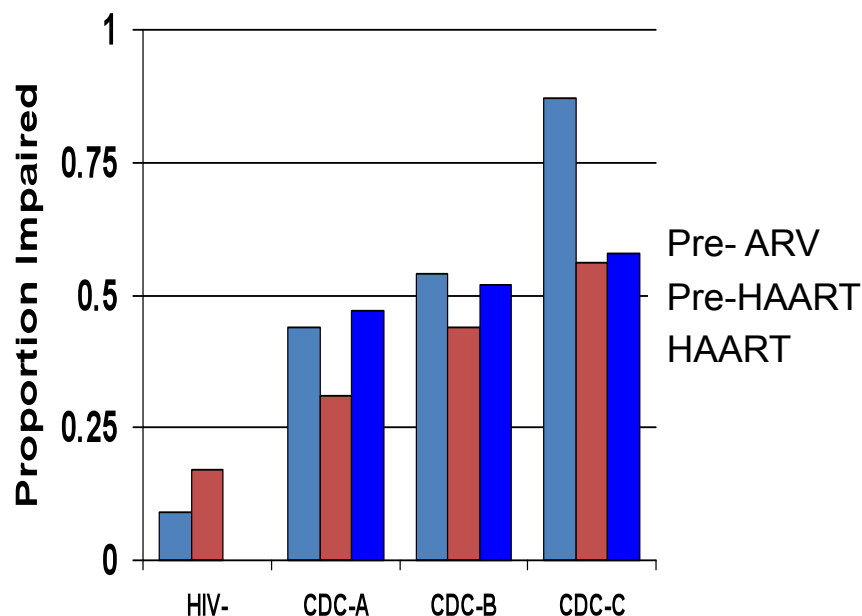
Heavily focused on neuropsychological testing impairment

- Asymptomatic disease has unclear pathological relevance, but is associated with impaired function



Neurology 2007

No change in the frequency of cognitive impairment despite HAART



Caveats

- Less than 2% with dementia
- No specificity for etiology
- No requirement for symptoms
- Rare progressive disease
- Highest risk with
 - Comorbidity
 - Viral detectability/low CD4
 - age



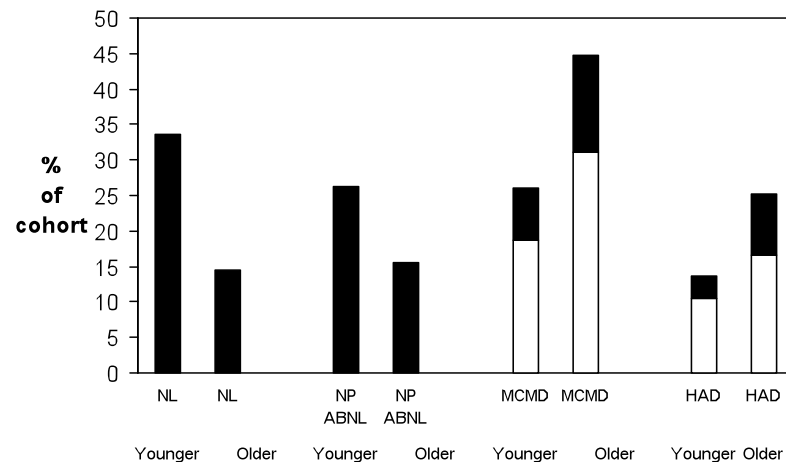
Conference on Retroviruses and
Opportunistic Infections 2009



Grant et al CROI 2009

Higher Frequency of Dementia in Older HIV Individuals.

Hawaii Aging with HIV Cohort

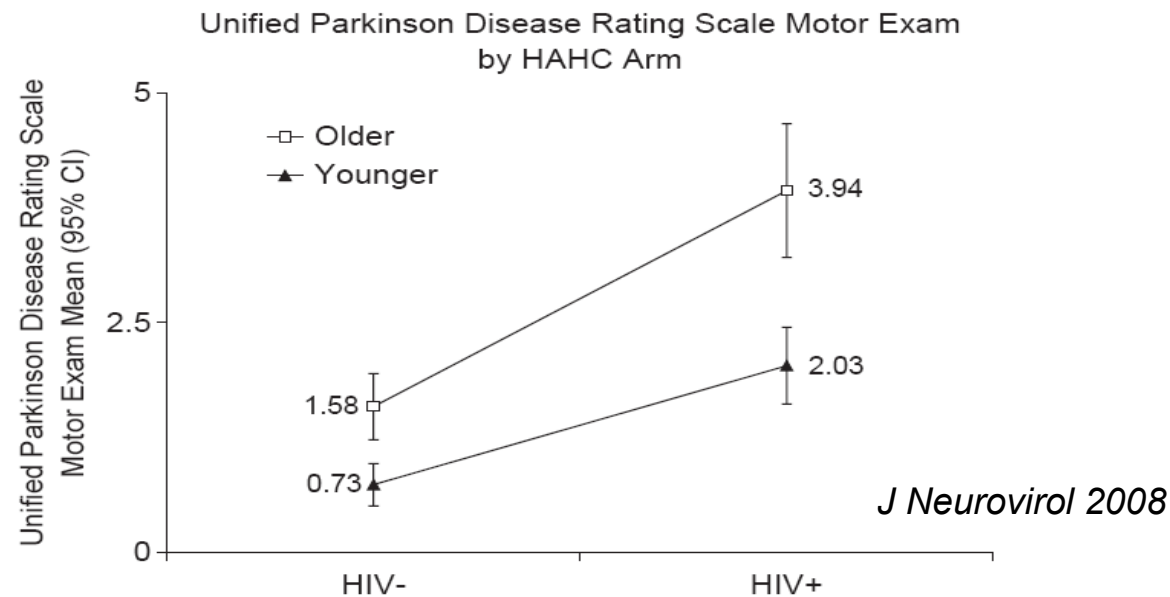


Older: 50+ Younger 20-39

- Consistently, studies identify greater rates of cognitive diagnoses with increased age
- Most impairment in this study was thought to have contributions from other disease processes (parallel mechanisms)

Neurology 2004

Age related neurological changes extend beyond cognition

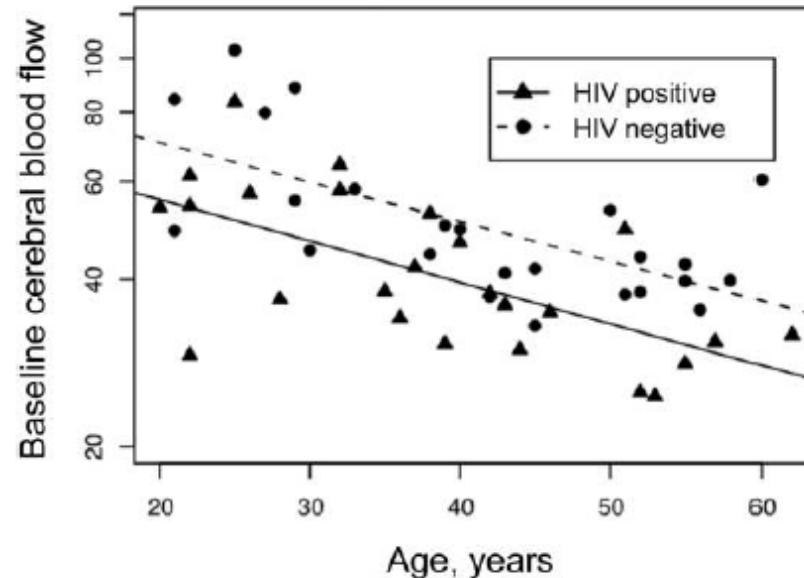


Parkinson's disease – rate increased to 4-8 times normal for 50 year old individuals (but still accounted for only 3 observed cases out of 2500) *Tisch 2009 Neurology*

Synergistic effects of age and HIV

- Exceedingly difficult to prove due to confounding and tissue access
 - ? accumulation of proteins associated with neurodegeneration
 - ? increased processing speed deficits
 - No evidence for interaction with age and HIV on testing performance (Valcour 2011 JINS and Lucette 2011 J Neuropsychiatry Clin Neurosci)

Changes in brain oxygenation (activation) with stimulation

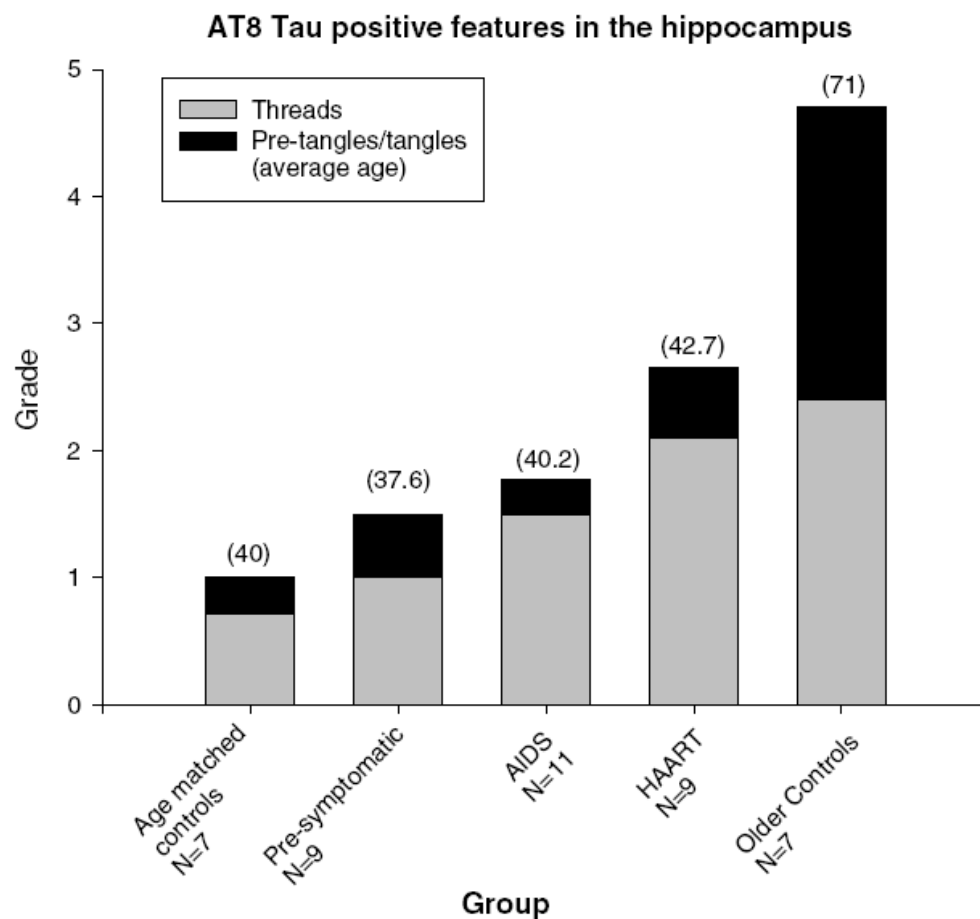


HIV and age effects noted without substantial interaction

Ances 2010 Neurology

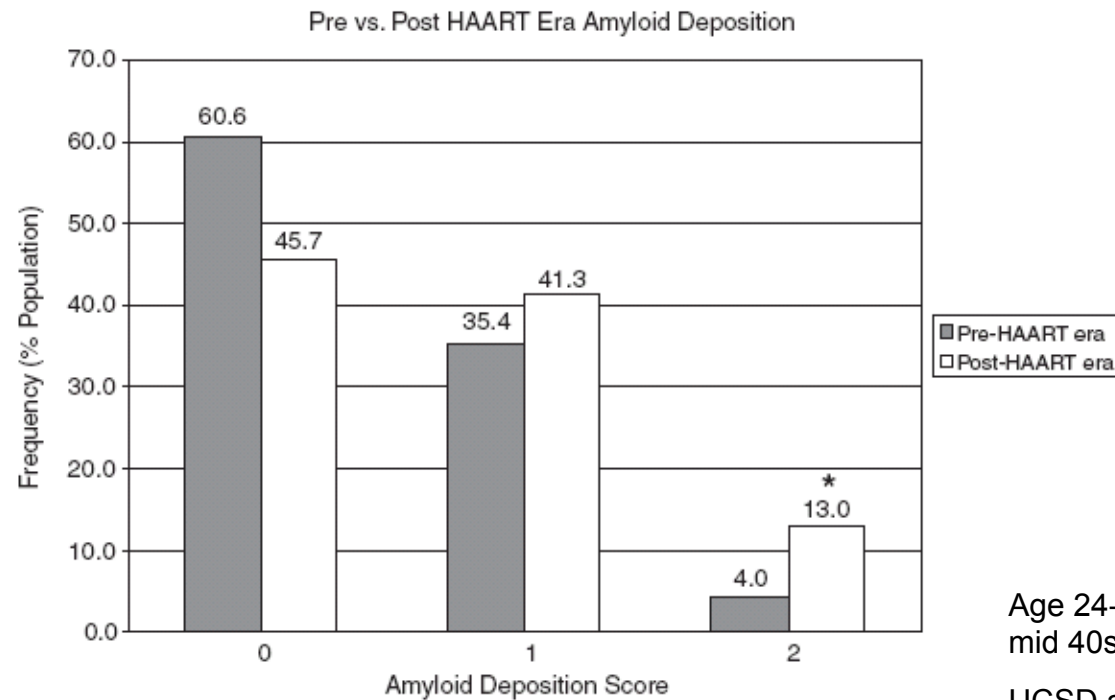
Tau expression in hippocampus

Elevated despite viral control with HAART



Anthony, Bell, et al. J Neuropath Exp Neurol 2006

What is due to HIV vs. other factors



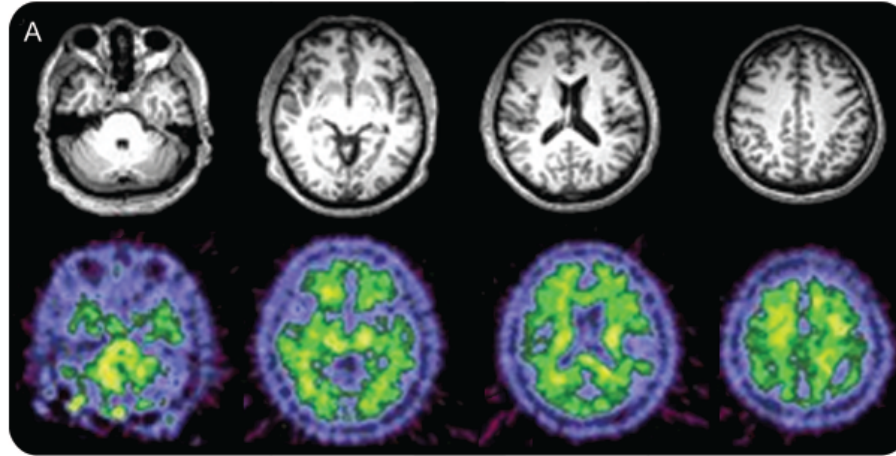
Age 24-75, mean age in mid 40s

UCSD and UCLA brain banks

Green et al AIDS 2005

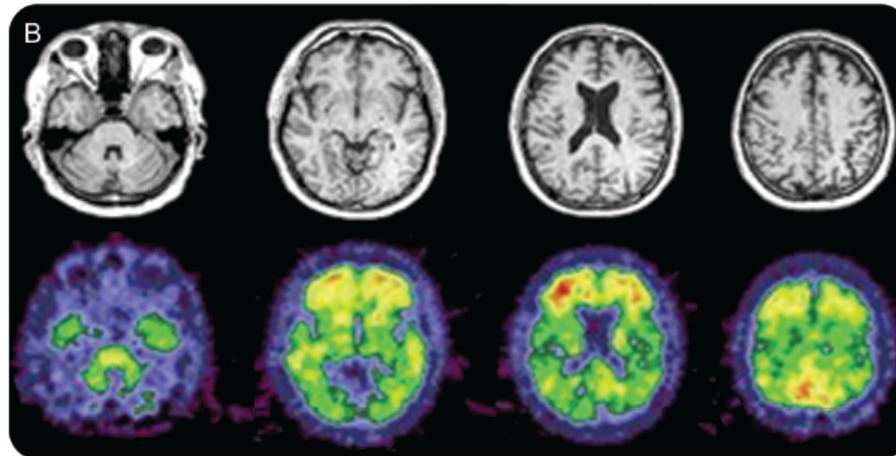
^{11}C -PiB binding

Cognitively
normal HIV
negative subject
with low CSF
 β_{1-42} amyloid



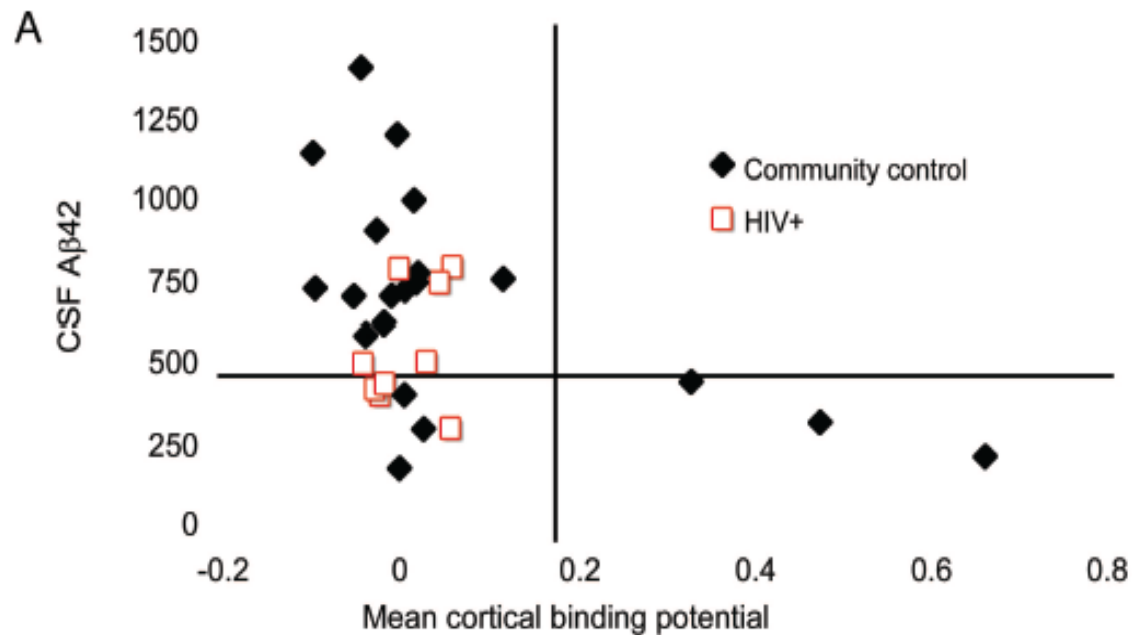
Ances 2010
Neurology

Cognitively
normal HIV+
subject with low
CSF β_{1-42} amyloid



Caveats: PiB binds only to neuritic plaques, thought to be a final stage in AD amyloidosis; age around 50 for both groups; no cognitive impairment

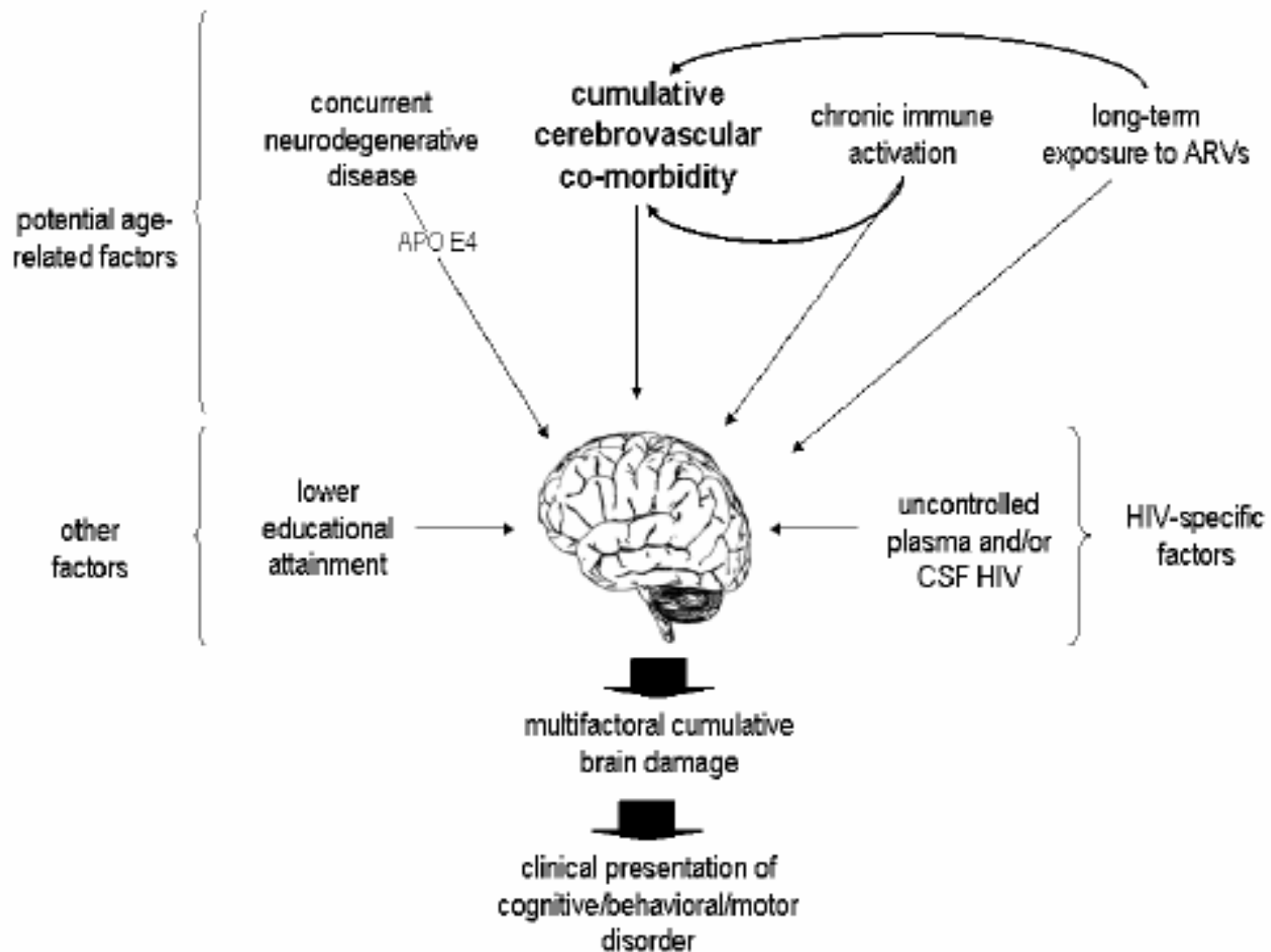
Complete disconnect between CSF amyloid and PiB



Raises important questions related to amyloid processing in HIV

Ances 2010 Neurology

Parallel mechanisms: HIV and aging



Parallel mechanisms

- Cerebrovascular disease
 - carotid IMT and glomerular filtration rate were significantly associated with psychomotor speed, whereas IMT was associated with memory test performance (Becker 2009 Neurology)
 - Insulin resistance and diabetes associated with impairment (Valcour 2005 JAIDS)

79-year old male – impaired

(yet, asymptomatic)



3T Image

Summary

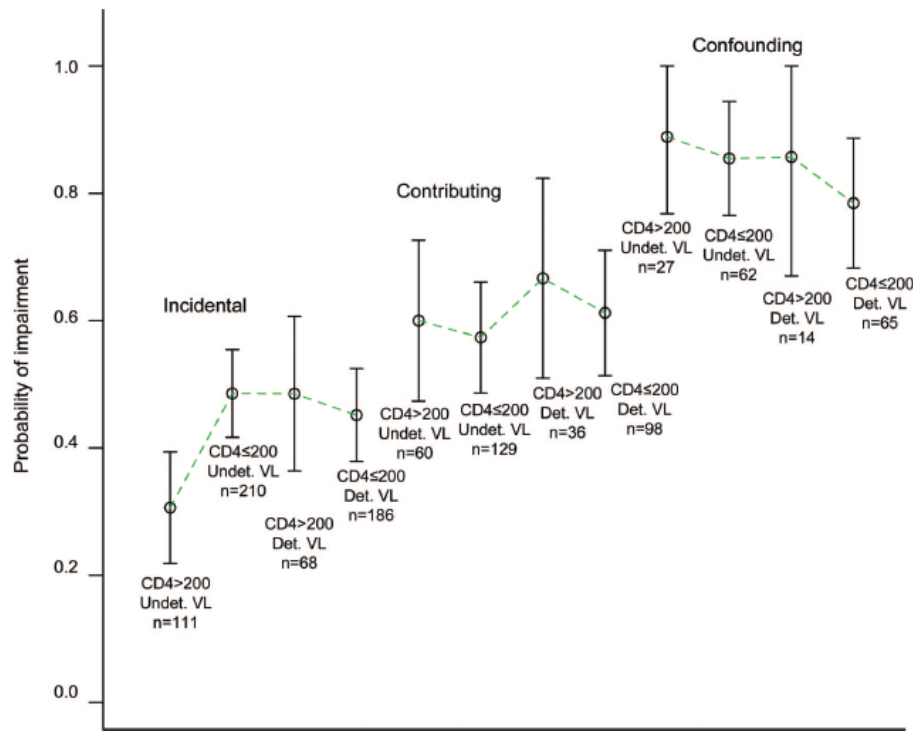
- Neuropsychological testing impairment rates are unchanged in the setting where HAART is available
 - Not specific to pathogenesis
 - Strongest predictors are non-adherence, resistance, comorbidities
 - Most impairment is “asymptomatic”
- Age is consistently a risk for medical diagnosis for impairment (although not necessarily for NP impairment with matched controls)
 - is at least theoretical risk for both synergistic and parallel mechanisms for increased risk for impairment

How can we improve?

Improved Disease Specificity

- Specificity for disease rather than “impairment” alone
 - Unique methodology employed for HIV will not due for understanding neurodegeneration
- It will be impossible to define pathogenesis without clear clinical characterization
 - Terms like Asymptomatic Neurocognitive Impairment are not sufficient

Risk for NP impairment in HIV



Heaton 2010 Neurology

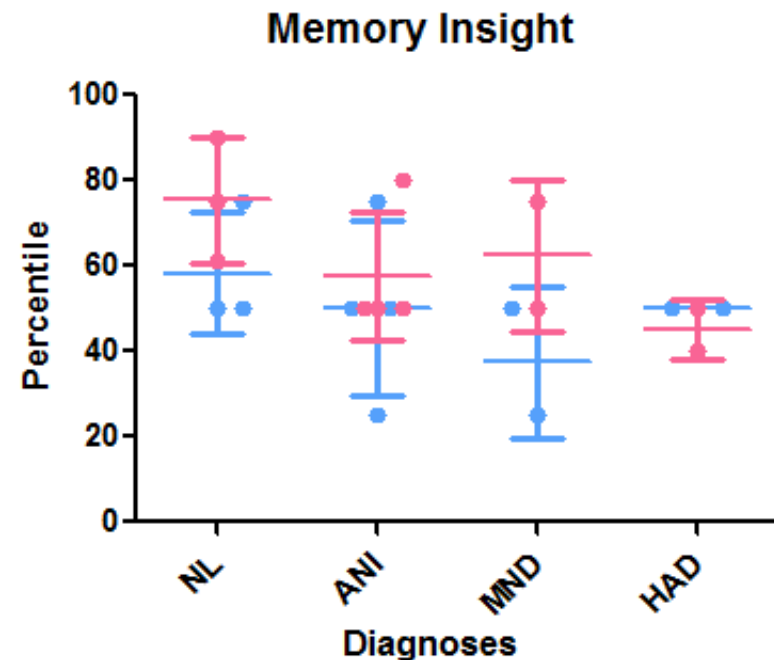
- Risk factors
 - Age
 - Low CD4
 - Detectable VL
 - Comorbidity
- Does not help us understand risk in people with long-term control
- Does not speak to mechanisms

New focus

- Focus on patients with impairment despite “successful” treatment. Potential etiologies include:
 - Unmanaged comorbidities
 - Parallel diseases – Alzheimer’s disease
- Such work could define how current treatment approaches are insufficient
 - Reservoirs - CNS, monocytes

Address the issue of asymptomatic impairment

- Is this disease – probably
- ? Insight
- Poor proxy informants
- We will not be able to move forward with understanding dementia syndromes without clear data of functional consequences



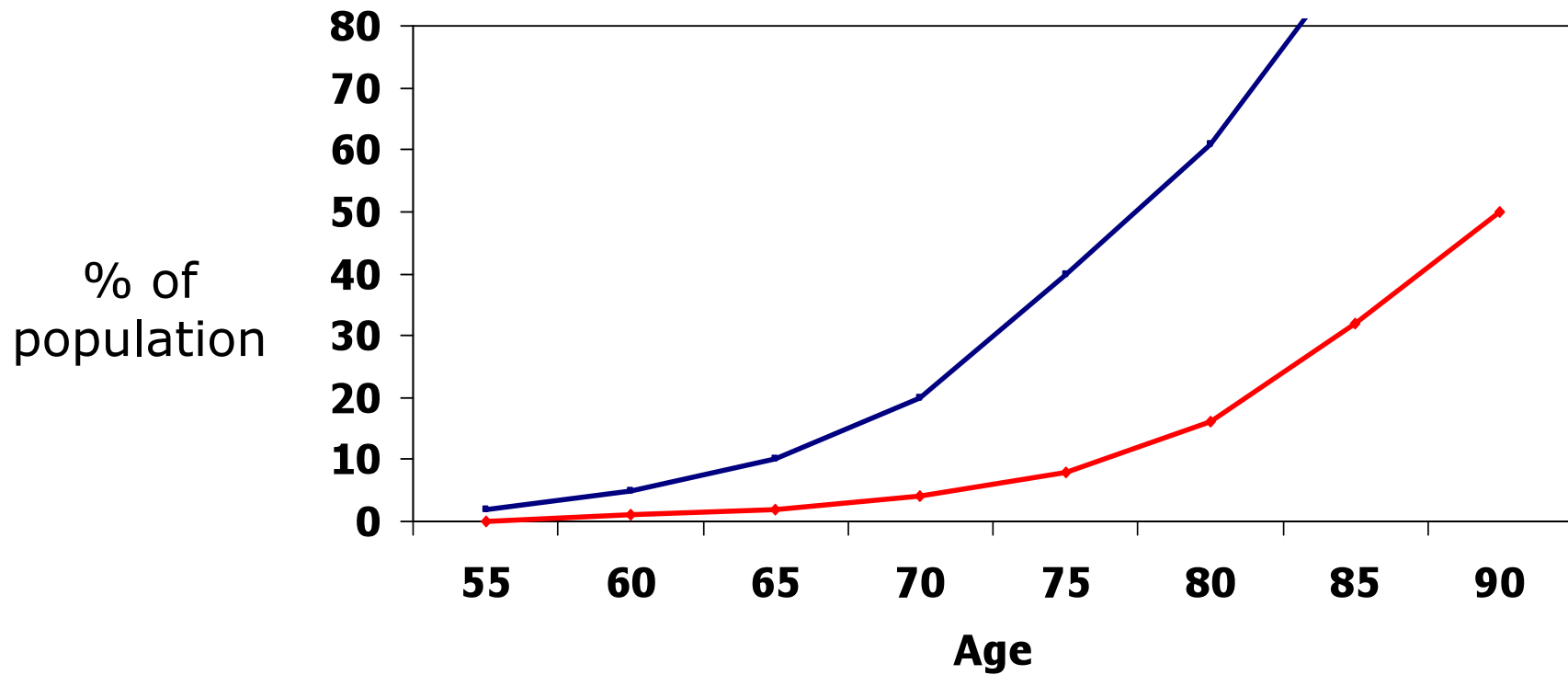
How does one define old?



“Forty is the old age of youth; fifty the youth of old age.”

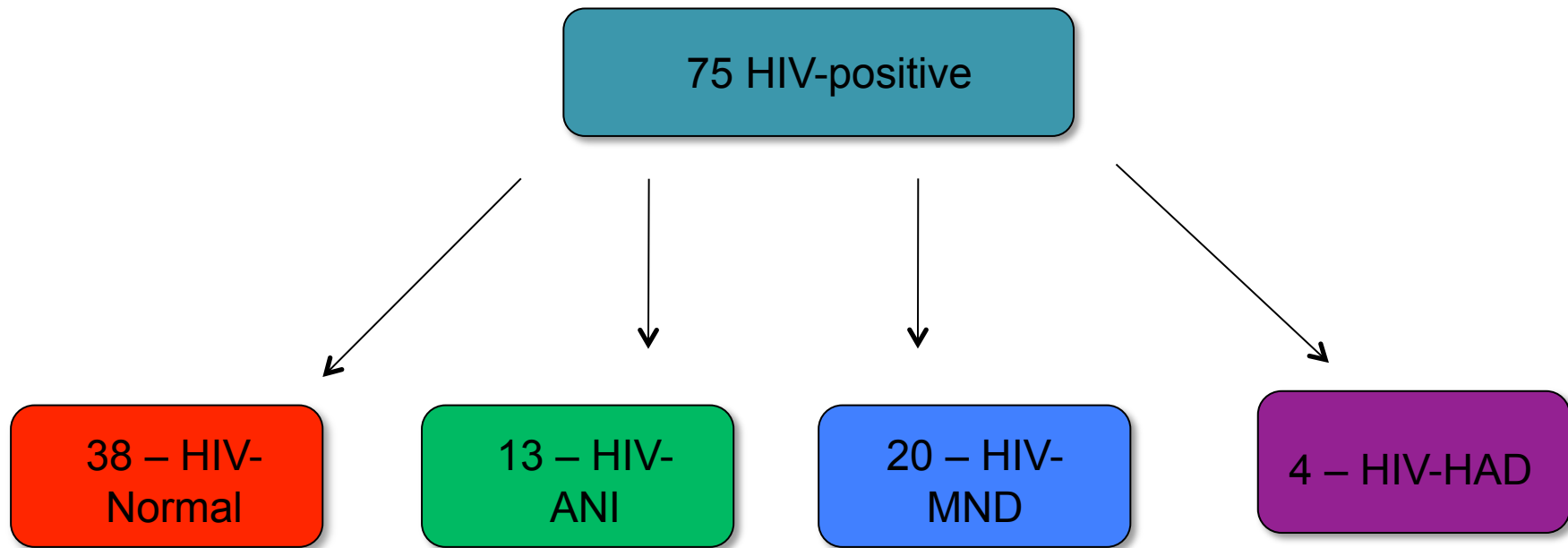
- Victor Hugo

Prevalence of Dementia



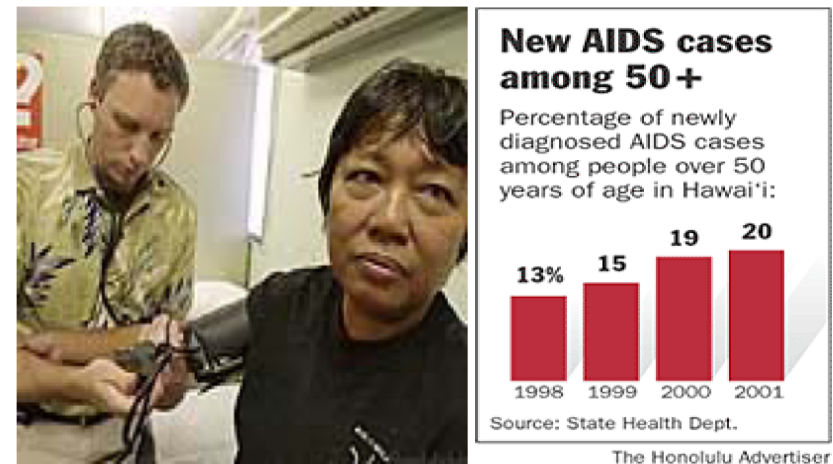
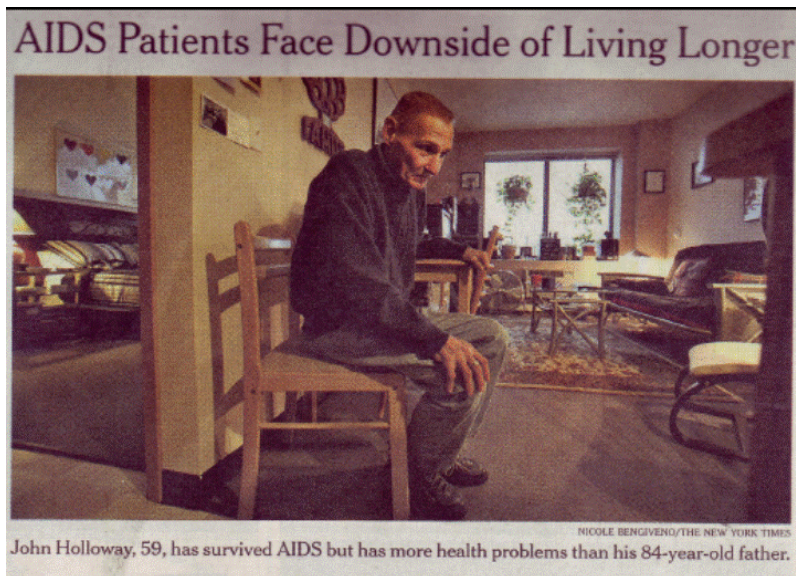
What would doubling the risk for Alzheimer's disease look like at age = 55?

UCSF 60+ HIV Cohort



Only one case of presumed AD – diagnoses completed by consensus panel using Alzheimer's Disease Research Center (ADRC/INA?NIH) methodology

Is a focus on chronological age sufficient (appropriate)?



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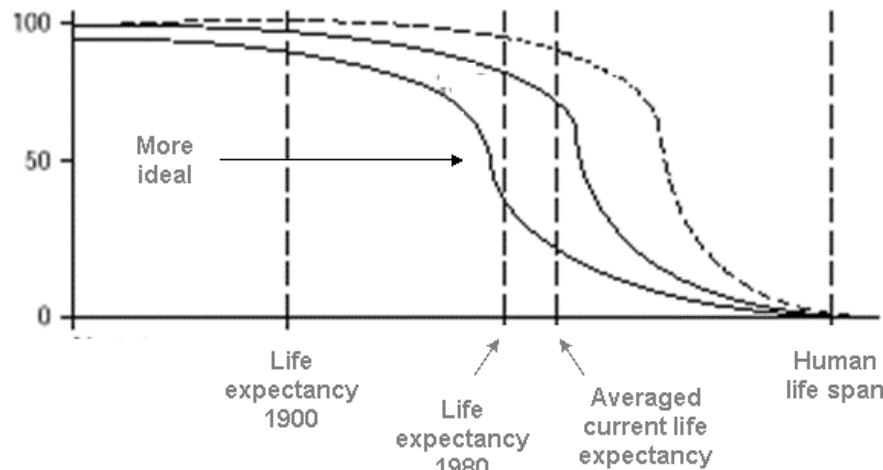
Posted on: Wednesday, June 26, 2002

Gray wave of AIDS puzzles Hawai'i

These patients are both 65 years old – are they equivalent?

- Survival factors, severity of past disease, exposure to medications, etc
 - Quantifying factors that may be associated with age (Cohort effects)
- needs to be independent of simply relating everything to “age”

Clarification of the Question at hand



J. Fries NEJM 1980

- “Accelerated” aging from a tissue stand-point? – probably difficult to prove
- Multifactorial etiology to impairment – probably important
- Risk for neurodegenerative disorders – probably necessary, but will require a truly old cohort
- Functional life expectancy?

