

Effects of HIV and Aging on the brain



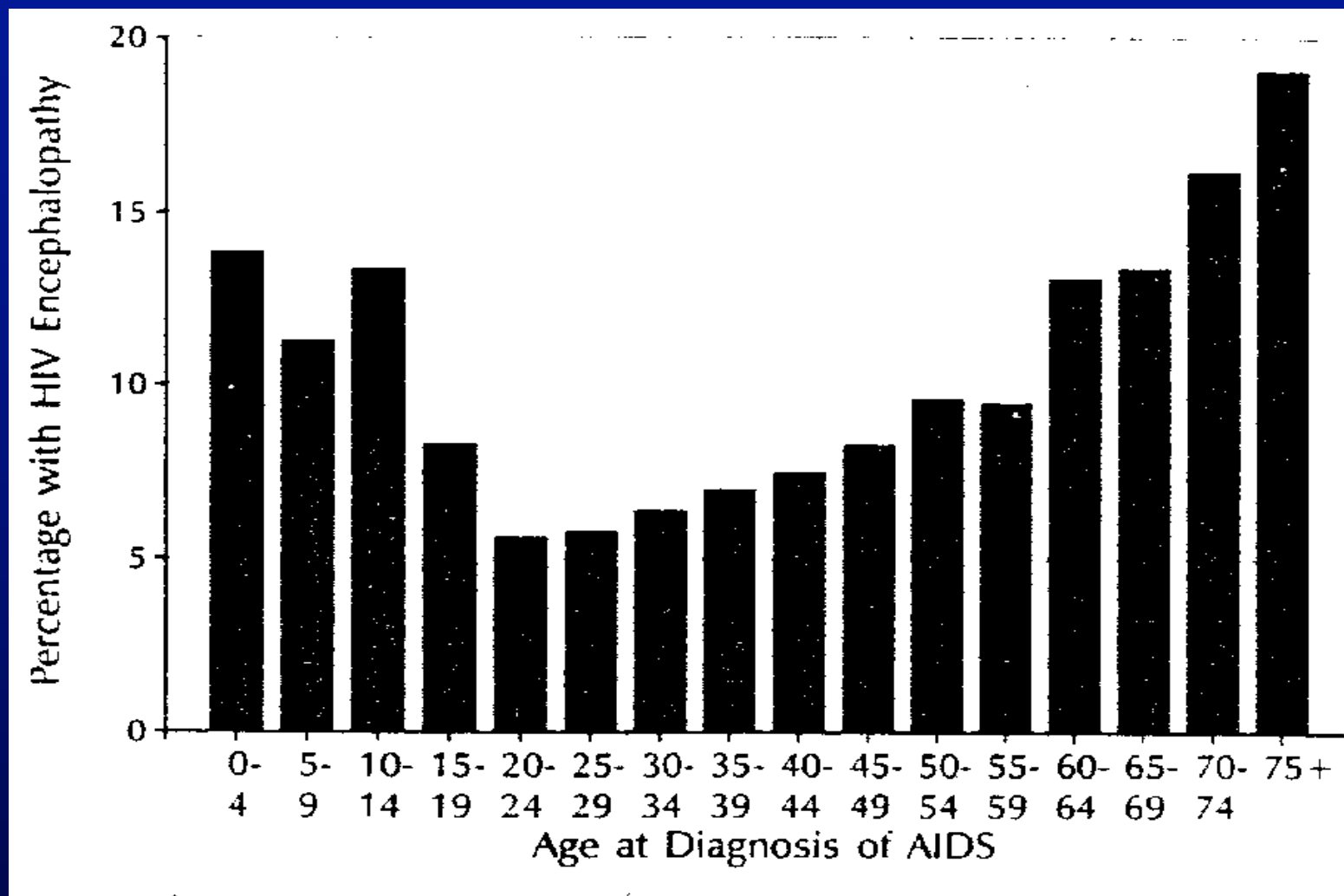
Avi Nath

Chief, Section of Infections of the Nervous System

National Institute of Neurological Diseases and Stroke, NIH

HIV dementia and aging-CDC data 1987-1991:

(Janssen, et al., Neurology 1992)



Cognitive impairment despite cART

Heaton et al., 2011

n=1555 (CHARTER cohort)

50% with mild cognitive impairments

No correlation with CSF TNF, MCP-1 or viral load

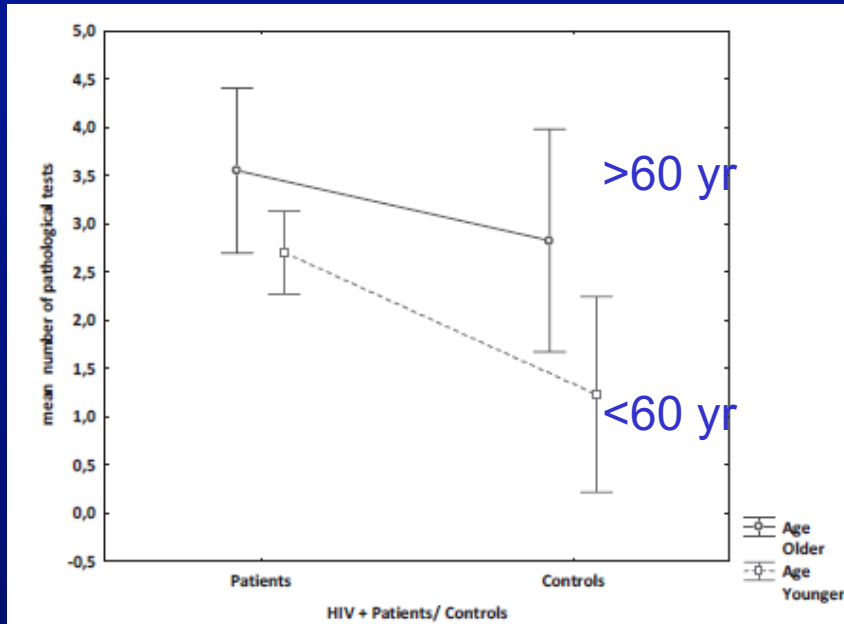
CD4 nadir	VL in plasma	HAND
>200	undetectable	30%
>200	detectable	45%
<200	all	50%

Raltegravir Treatment Intensification Does Not Alter Cerebrospinal Fluid HIV-1 Infection or Immunoactivation in Subjects on Suppressive Therapy

Viktor Dahl,¹ Evelyn Lee,² Julia Peterson,² Serena S. Spudich,^{2,a} Idris Leppla,² Elizabeth Sinclair,³ Dietmar Fuchs,⁴ Sarah Palmer,¹ and Richard W. Price²

Effect of Aging and Human Immunodeficiency Virus Infection on Cognitive Abilities

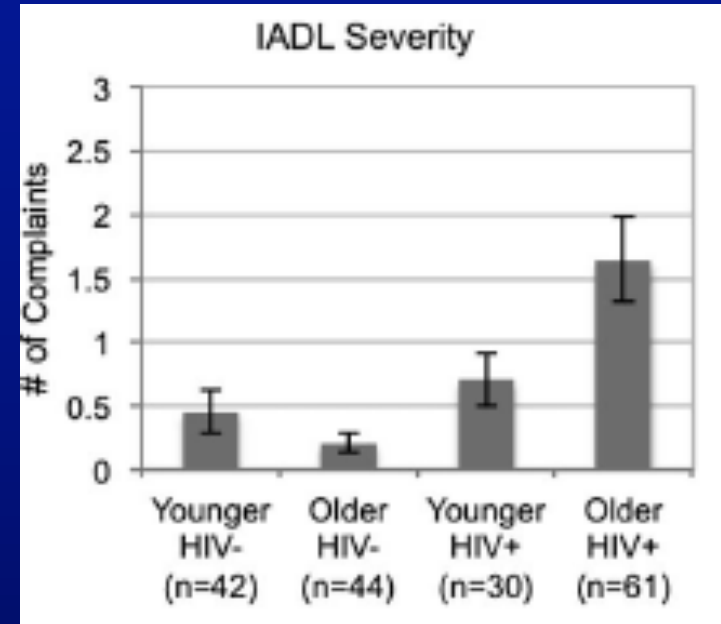
Nicoletta Ciccarelli, PsyD,^{**†} Massimiliano Fabbiani, MD,^{*} Eleonora Baldonero, PsyD,^{**†} Iuri Fanti, EngD,^{*} Roberto Cauda, MD,^{*} Simona Di Giambenedetto, MD, PhD,^{*} and Maria Caterina Silveri, MD[†]



J Am Geriatric Soc 2012

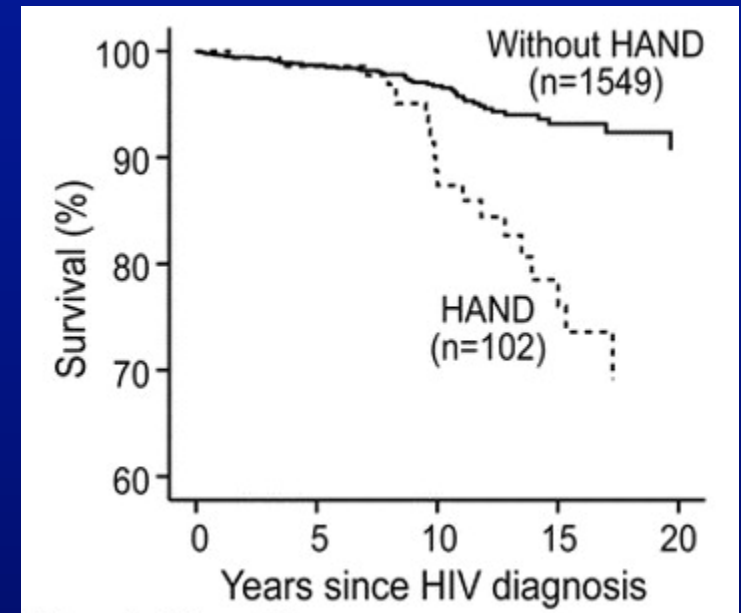
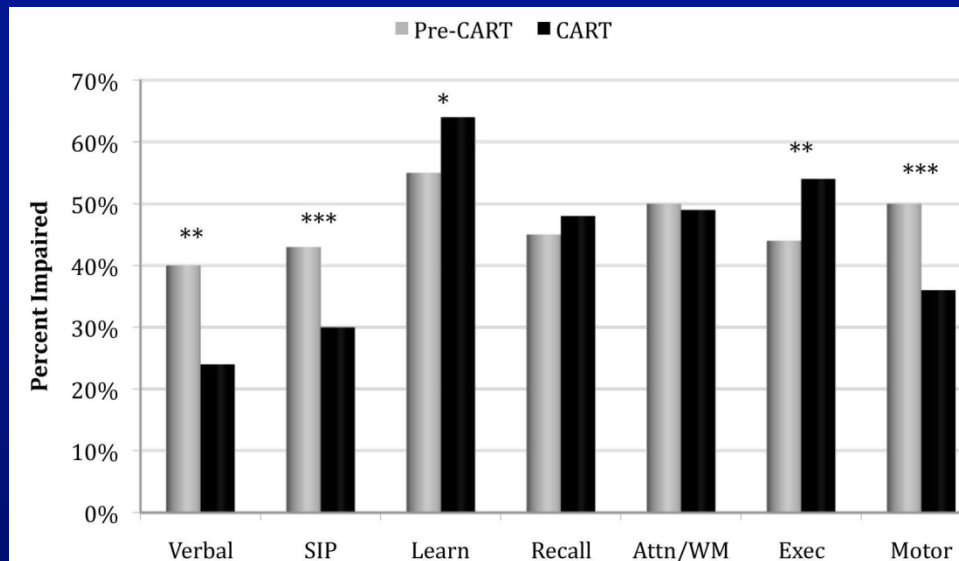
Synergistic Effects of HIV Infection and Older Age on Daily Functioning

Erin E. Morgan, PhD,^{*} Jennifer E. Iudicello, PhD,^{*} Erica Weber, MS,[†] Nichole A. Duarte, PhD,^{*} P. Katie Riggs, BS,[‡] Lisa Delano-Wood, PhD,^{*§} Ronald Ellis, MD, PhD,[‡] Igor Grant, MD,^{*} and Steven P. Woods, PsyD,^{*} For The HIV Neurobehavioral Research Program (HNRP) Group



J Acquir Immune Defic Syndr 2012

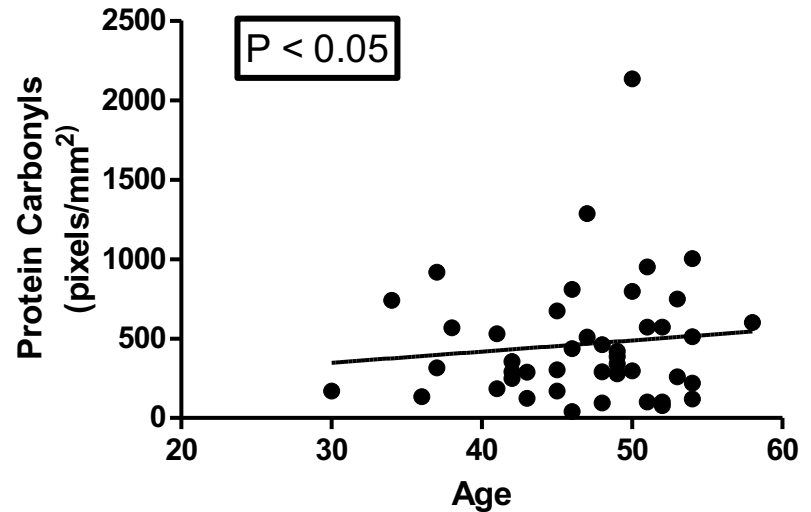
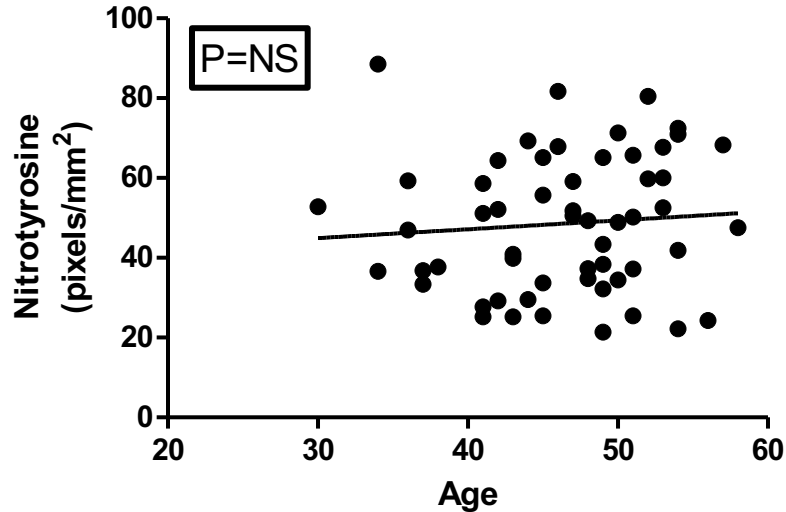
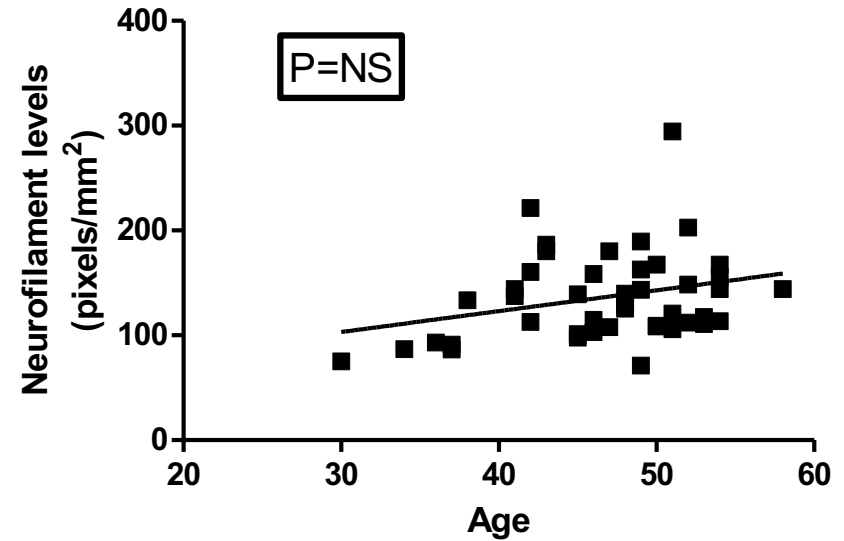
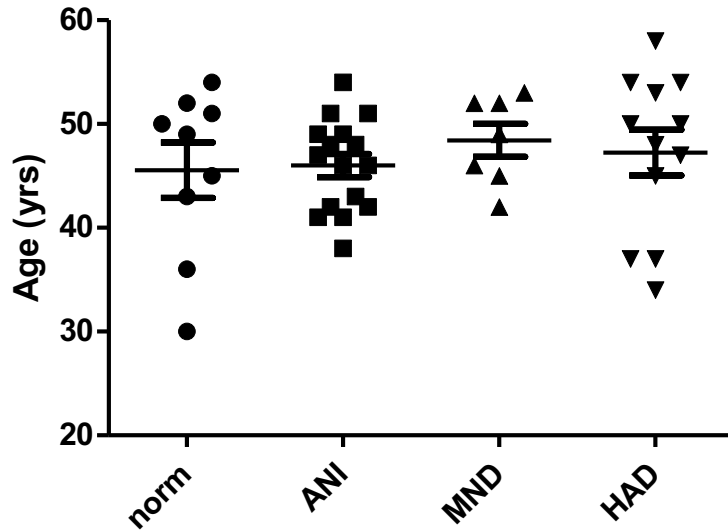
Increased cognitive impairment despite anti-retrovirals



Heaton et al., 2011; CHARTER cohort; n=1555

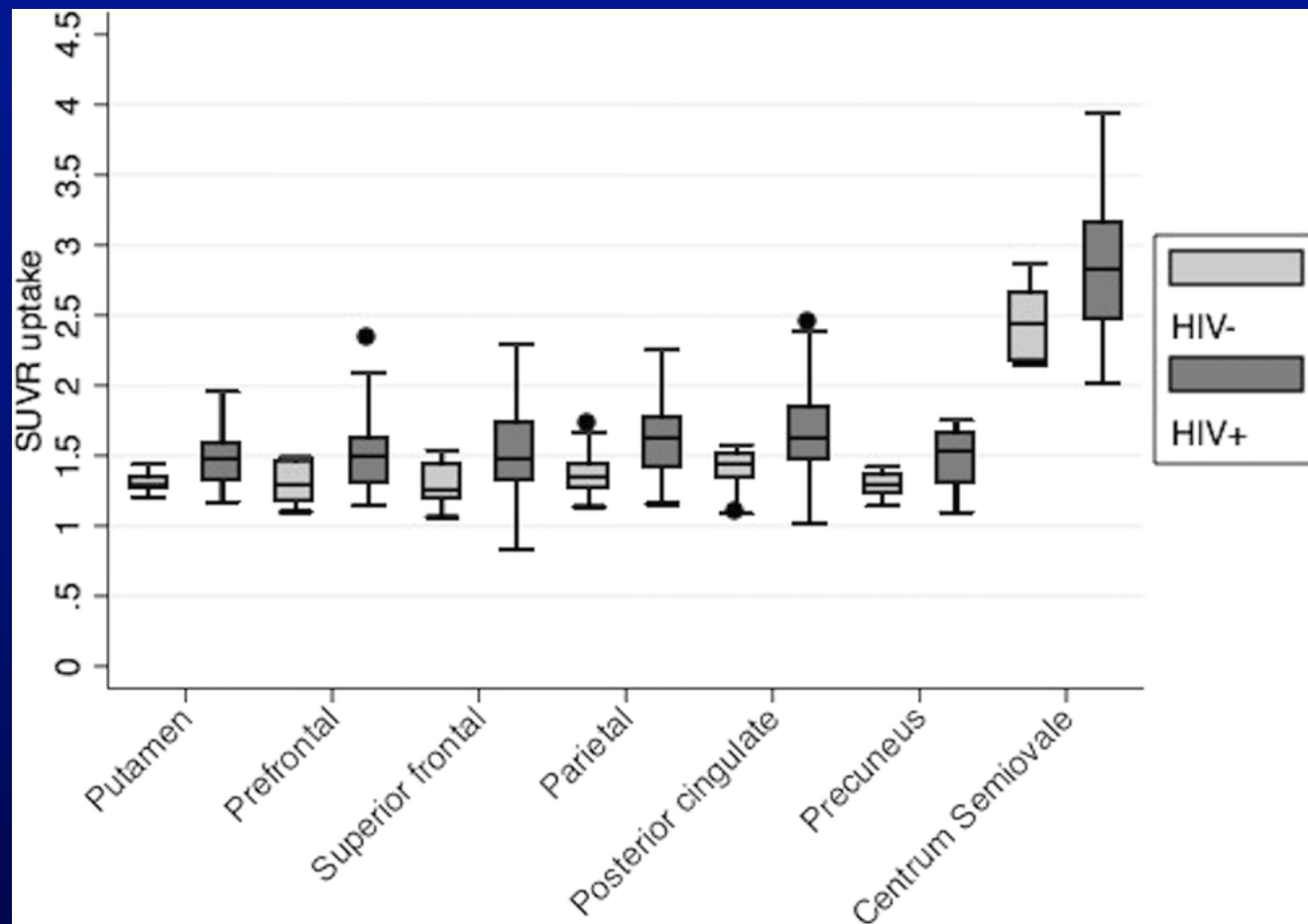
Vivithanaporn et al., 2010

Relationship of Age To Markers of Neurocognitive Decline in CSF



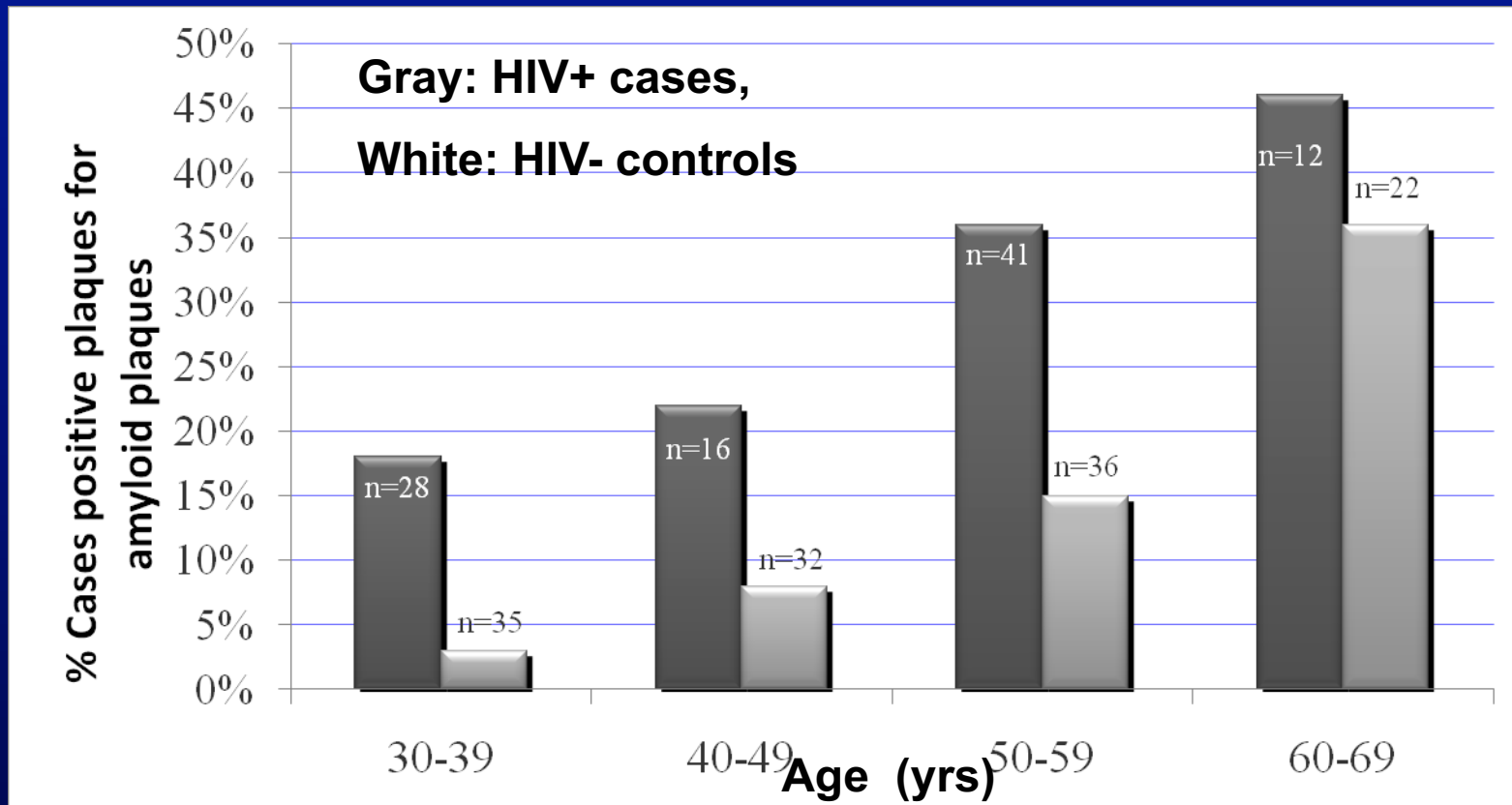
Beta-amyloid ($A\beta$) uptake by PET imaging in older HIV+ and HIV- individuals

Mona Mohamed¹ · Richard L. Skolasky^{2,3} · Yun Zhou^{1,4} · Weiguo Ye¹ · James R. Basic¹ · Amanda Brown² · Carlos A. Pardo² · Peter B. Barker^{1,5} · Dean F. Wong^{1,2,6,7,8} · Ned Sacktor²



Amyloid plaques are more frequent in HIV cases

Esiri et al, J Neurol Neurosurg Psychiatry 1998



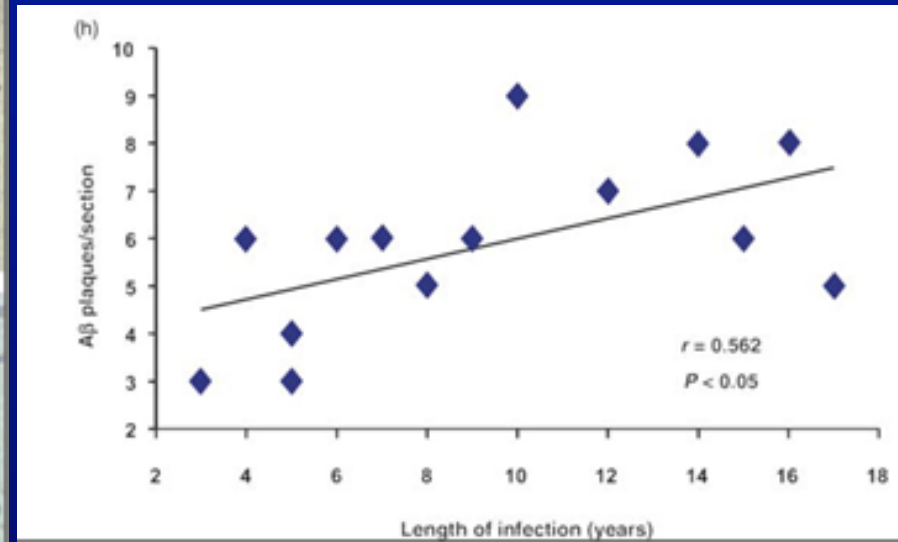
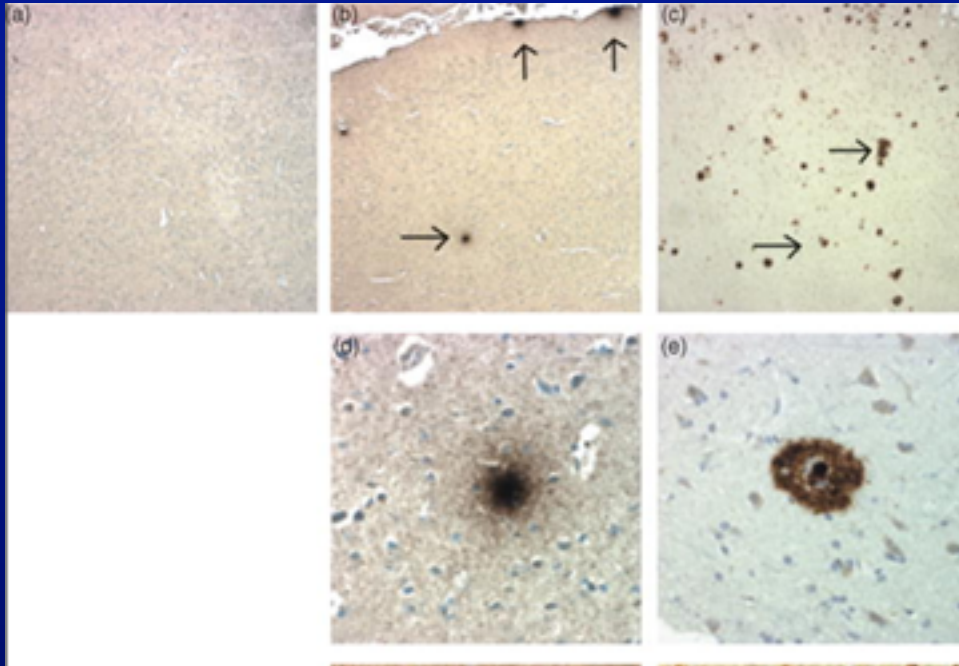
Amyloid deposition and duration of HIV infection

(Rempel and Pulliam AIDS 2005)

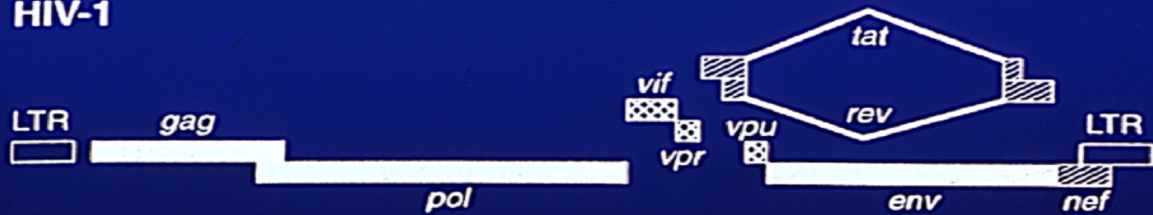
Control

HIV

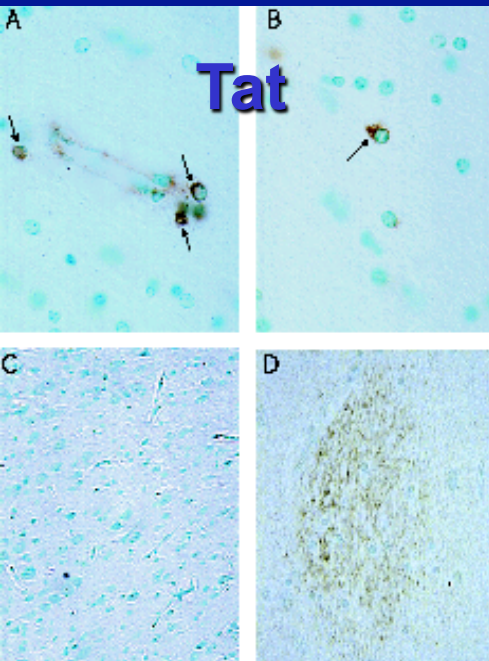
Alz Demen



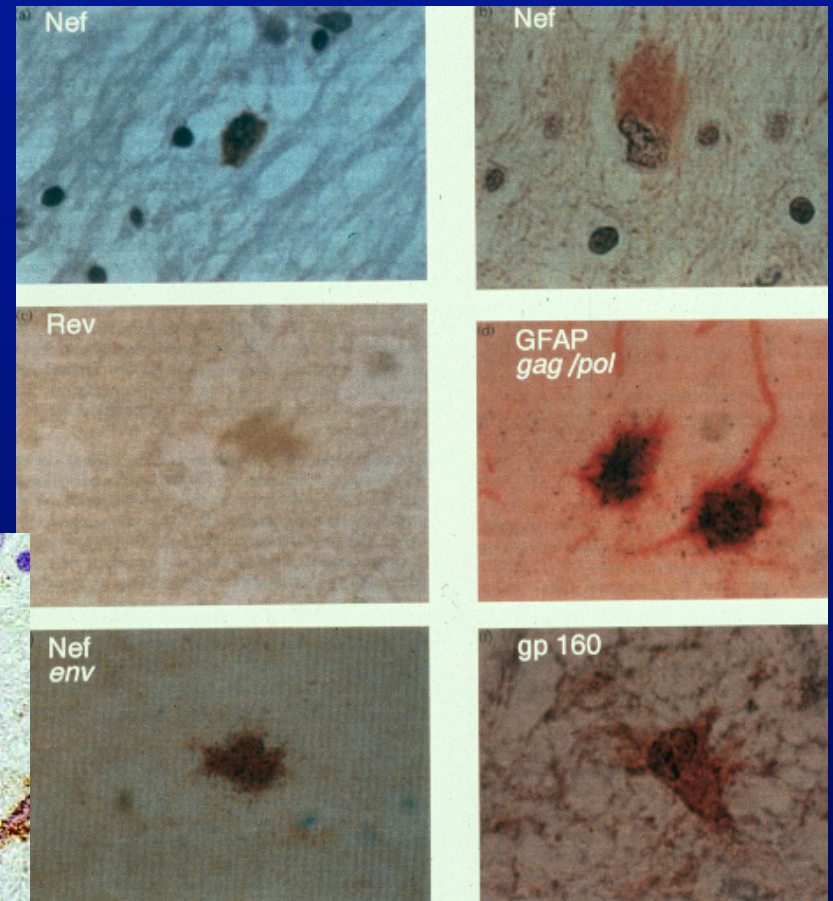
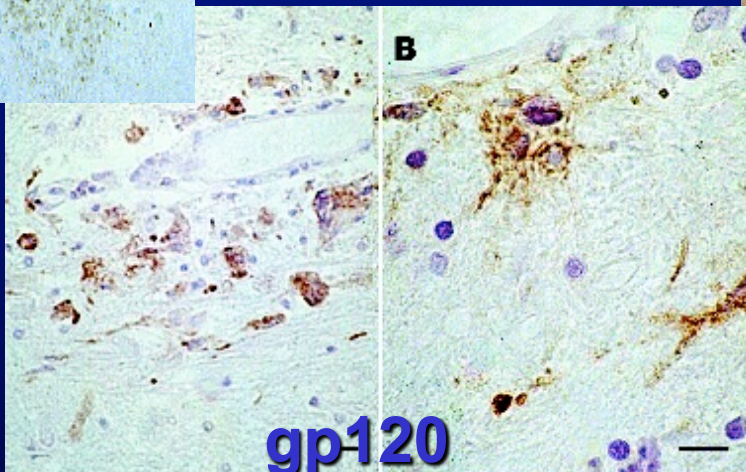
HIV-1



Latent Infection in astrocytes



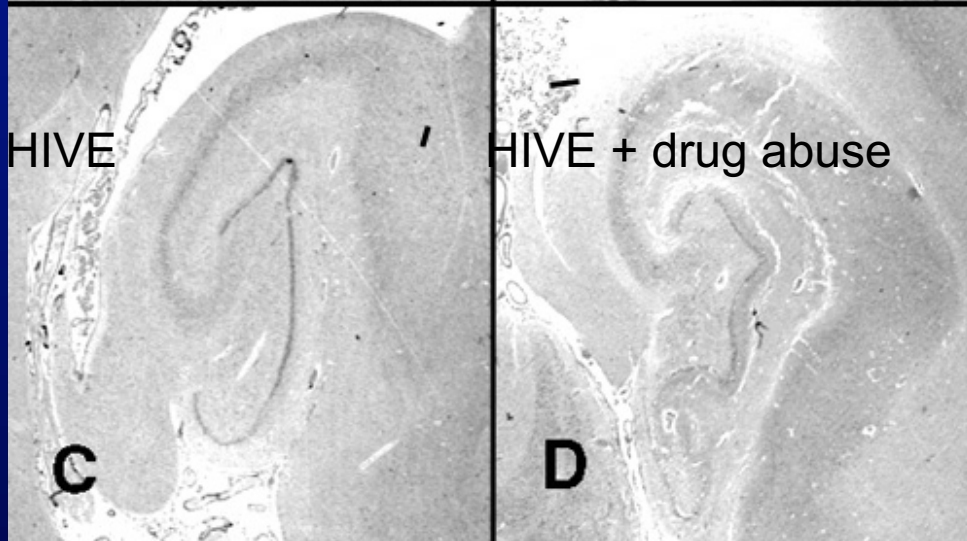
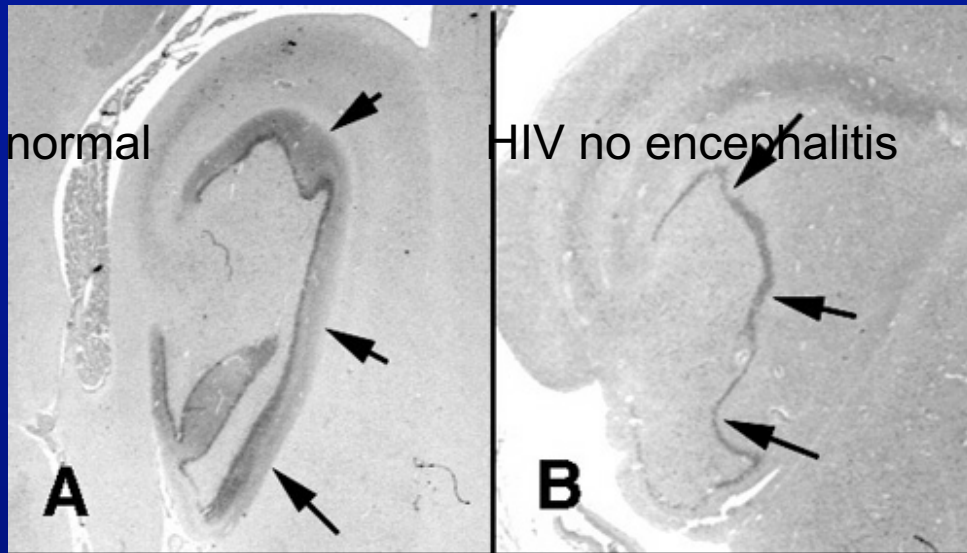
Productive Infection in perivascular macrophages



Ranki et al., 1995

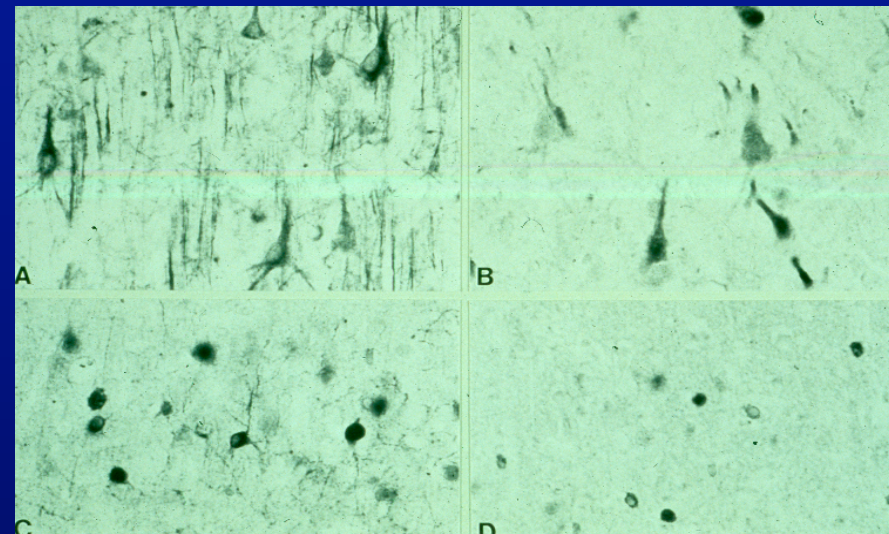
Jones et al., 2000; Kruman et al., 1998

Dentate Gyrus



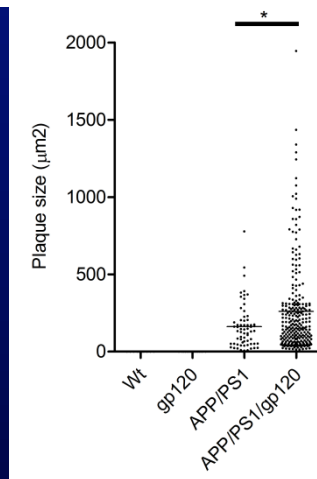
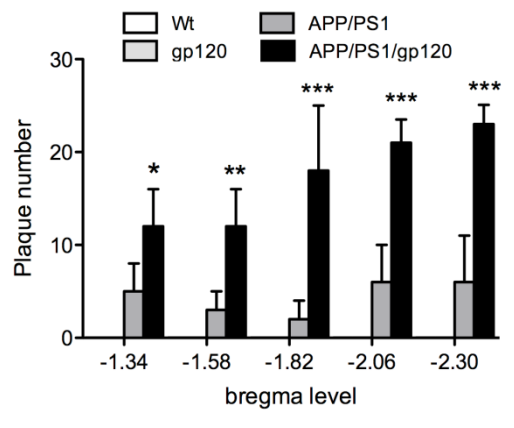
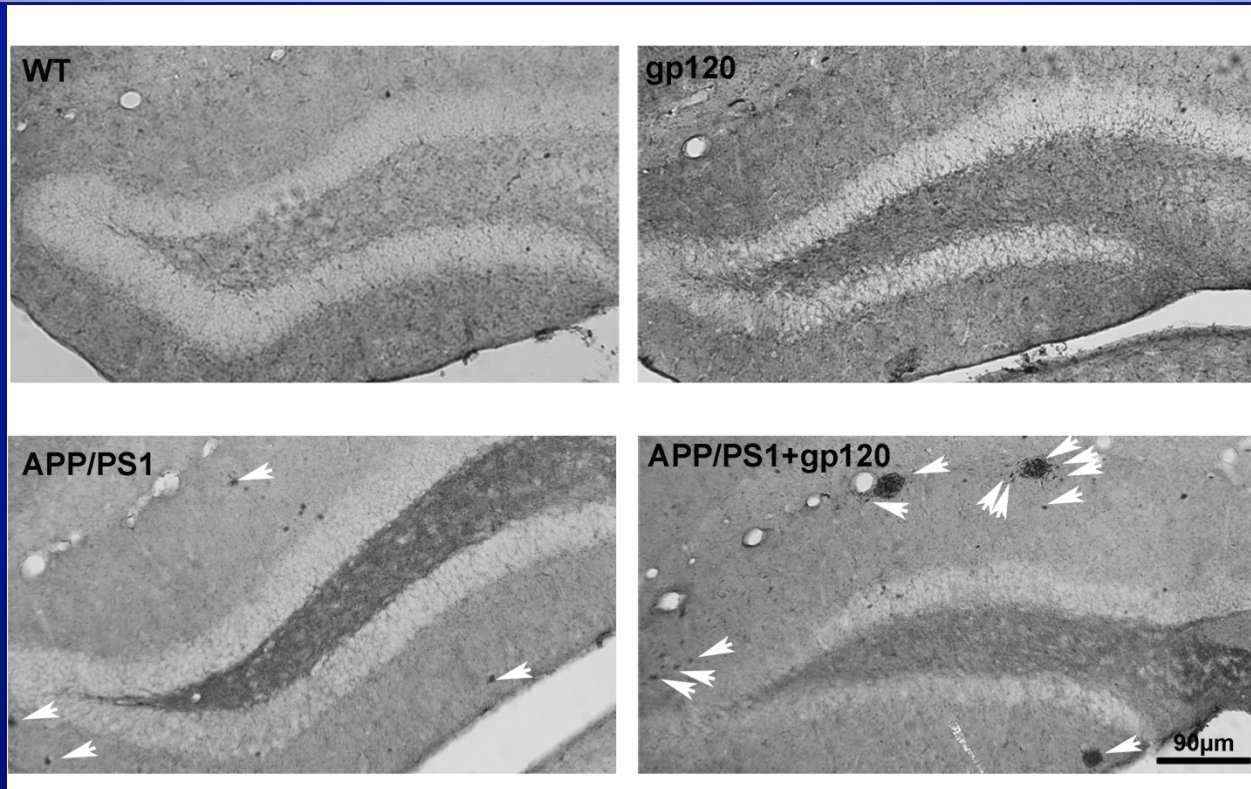
Normal

HIVD

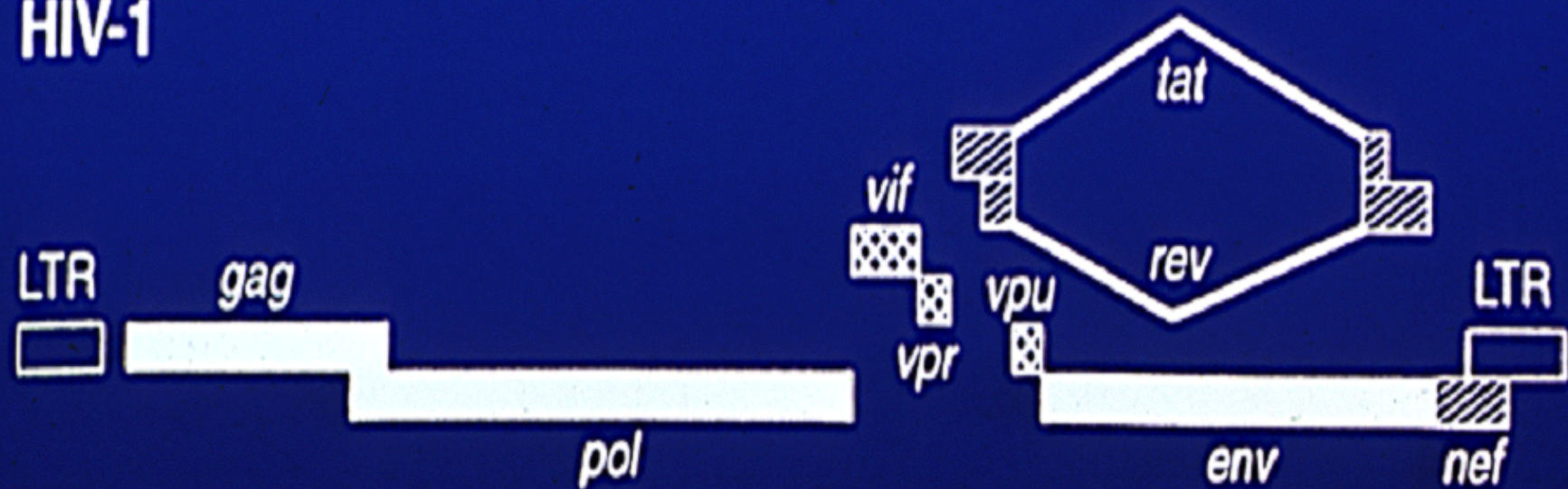


Courtesy: Chris Power, U. Alberta

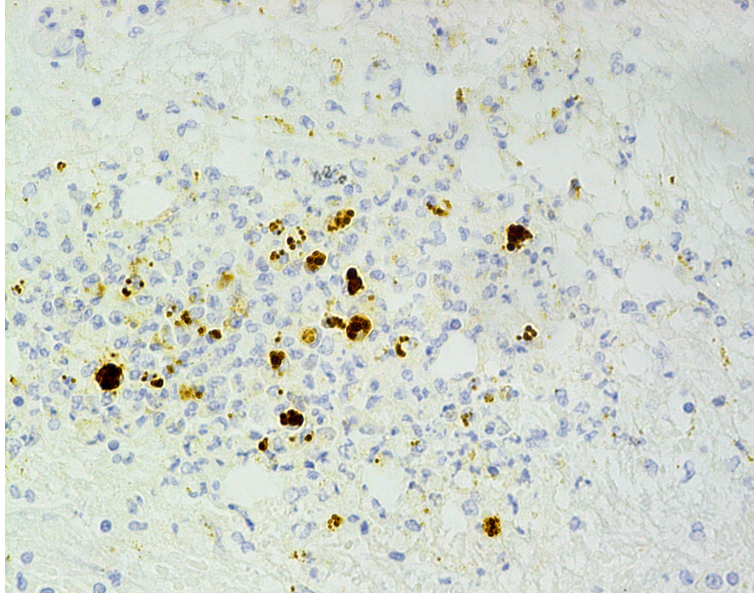
Accelerated A β deposition in APP/PS1/gp120 mice



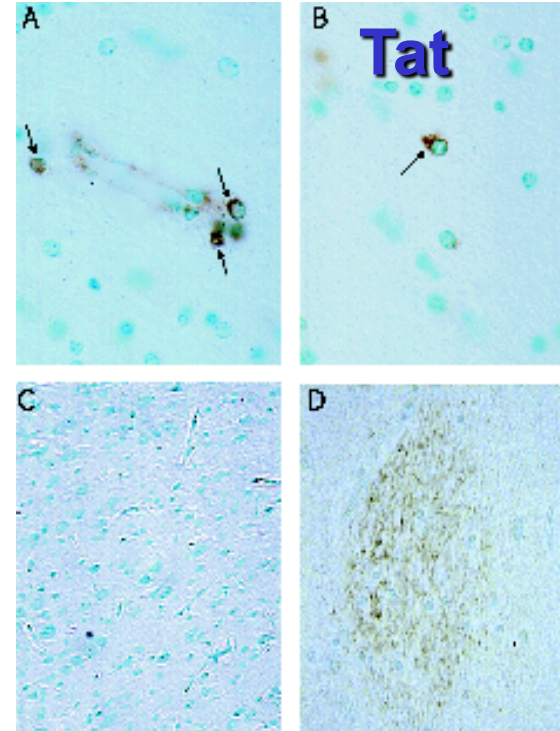
HIV-1



Tat in macrophages in HIVE and SHIVE

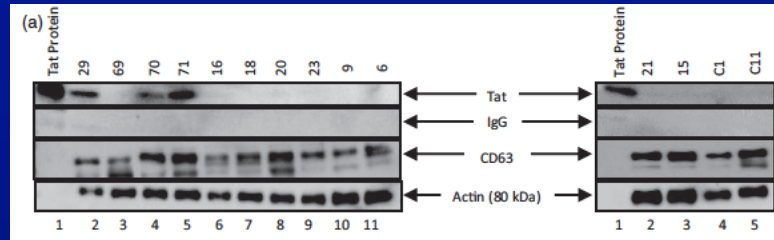
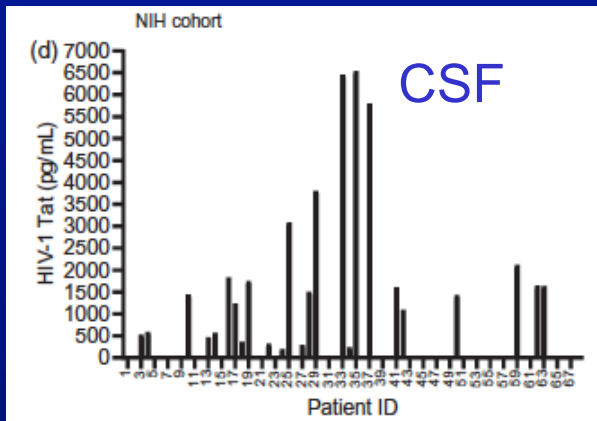


Texas A03



Presence of Tat and transactivation response element in spinal fluid despite antiretroviral therapy

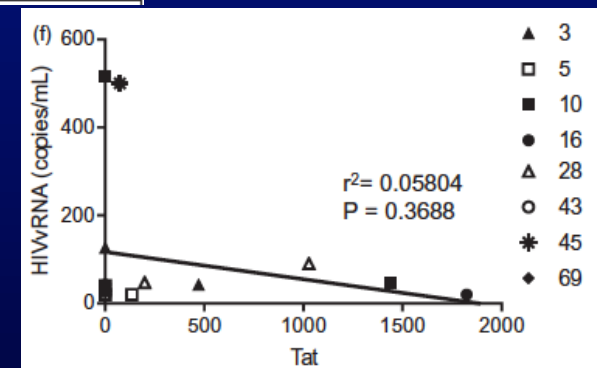
Lisa J. Henderson^a, Tory P. Johnson^b, Bryan R. Smith^a,
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 Catherine Demarino^d, Robert A. Barclay^d, Joseph Snow^e,
 Ned Sacktor^b, Justin McArthur^b, Scott Letendre^f,
 Joseph Steiner^c, Fatah Kashanchi^d and Avindra Nath^a



Exosomes

II. Clinical Variables	Tat Undetectable (N=43)	Tat Detectable (N=25)	P-value
Average T-score, mean (SD)	50.4 (5.3)	48.6 (7.5)	0.24
HAND diagnosis, n (%)	10 (23.3%)	7 (28%)	0.88
Attention/Working Memory Domain, mean (SD)	47.9 (7.1)	48.3 (7.4)	0.82
Executive Functioning Domain, mean (SD)	46.8 (6.4)	48.5 (7.4)	0.32
Information Processing Domain, mean (SD)	54.4 (8.4)	49.2 (12)	0.02
Verbal Fluency Domain, mean (SD)	52.4 (7.6)	52.3 (9.5)	0.97
Learning Domain, mean (SD)	49.4 (9.4)	47.3 (10.0)	0.37
Psychomotor Domain, mean (SD)	45.8 (8.5)	41.7 (8.4)	0.04
Memory Domain, mean (SD)	47.9 (8.9)	47.0 (9.6)	0.68

I. Demographics and Virologic Characteristics	Tat Undetectable (N=43)	Tat Detectable (N=25)	P-value
Age, mean (SD) years	52.8 (6.8)	53.3 (7.2)	0.77
Female sex, n (%)	9 (21%)	11 (44%)	0.08
African-American race, n (%)	24 (56%)	12 (48%)	0.71
Hispanic ethnicity, n (%)	2 (5%)	0 (0%)	0.73
Time since HIV diagnosis, years, mean (SD) years	18.8 (10)	19.1 (9)	0.89
Time on antiretroviral therapy, mean (SD) years	15.4 (19)	13.2 (8)	0.60
Time from HIV diagnosis to antiretroviral therapy, mean (SD) years	3.3 (16)	5.7 (7)	0.49
Nadir CD4 under 200 cells/mm ³ , n (%)	26 (65%)	16 (70%)	0.93
Current CD4, mean (SD) cells/ul	593.4 (251)	740.3 (324)	0.04



What drives T cell activation in patients on HAART?

Other Infections: E.coli – LPS; CMV

Abnormal Innate and cellular immune responses

HIV

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Human Immunodeficiency Virus Type 1 Tat Upregulates Interleukin-2 Secretion in Activated T Cells

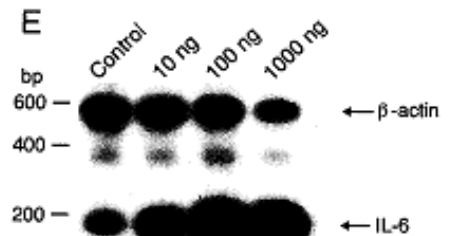
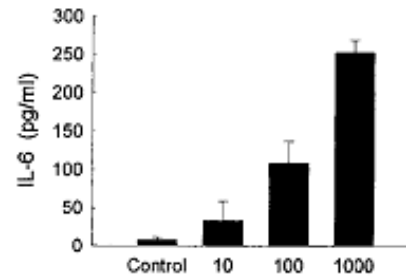
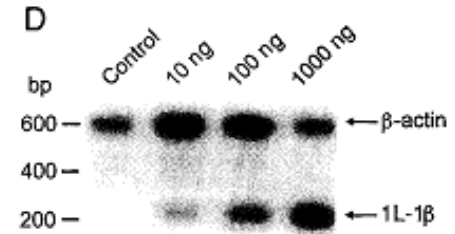
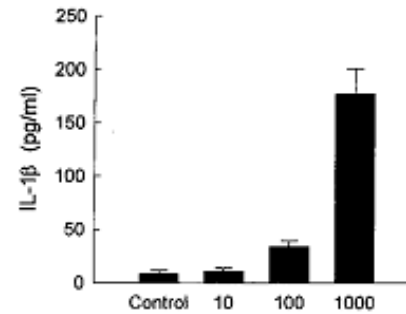
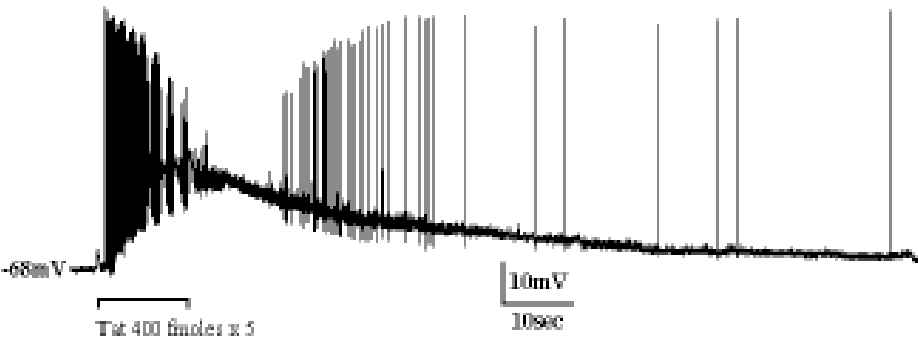
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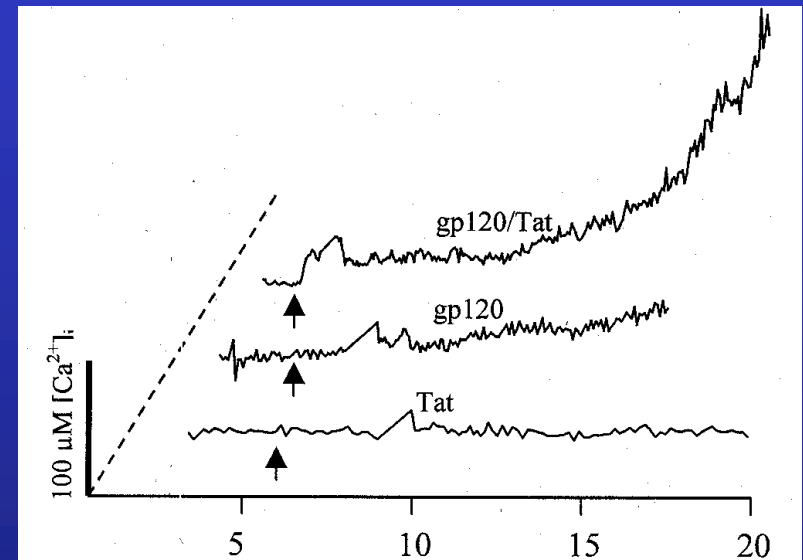
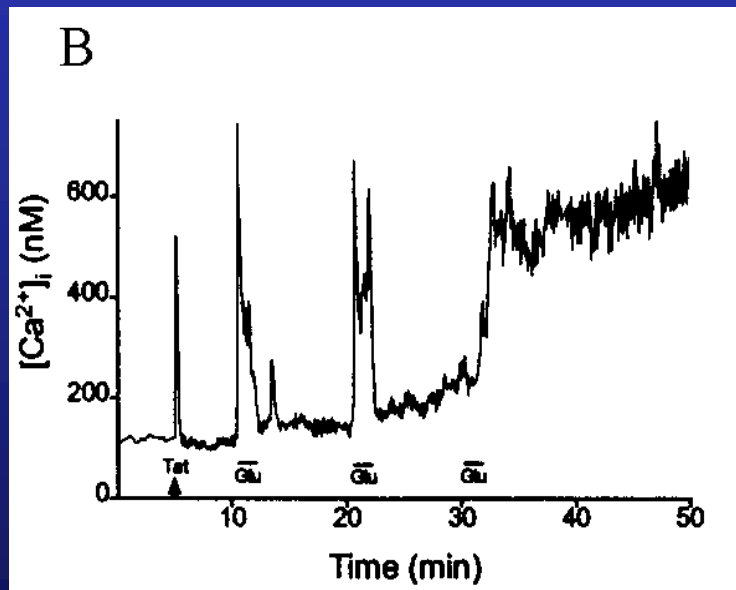
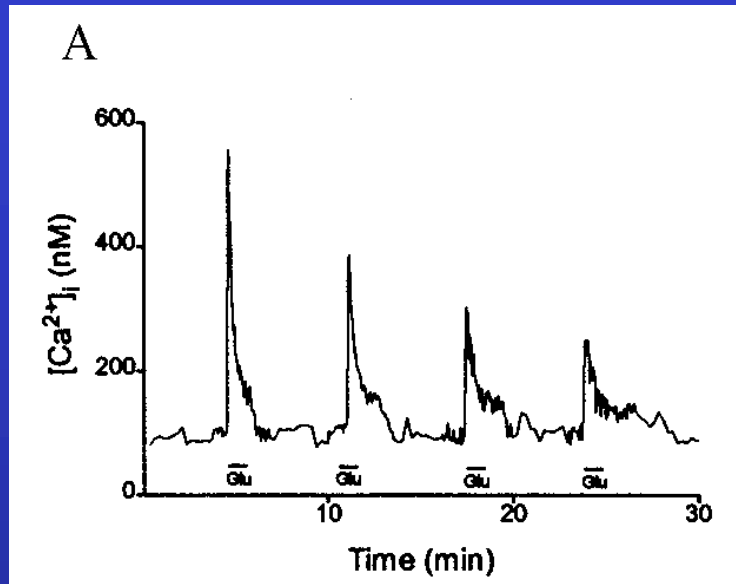
Tat causes neuronal injury and glial cell activation

Magnuson et al., Ann Neurol 1995

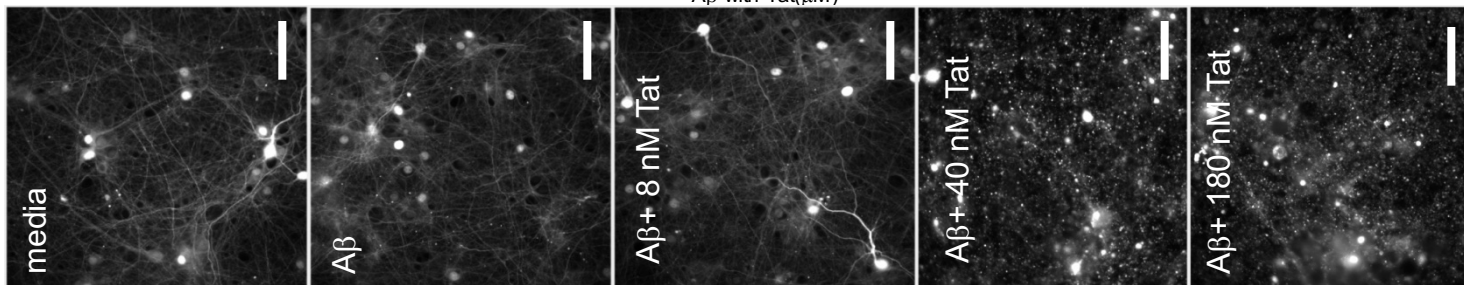
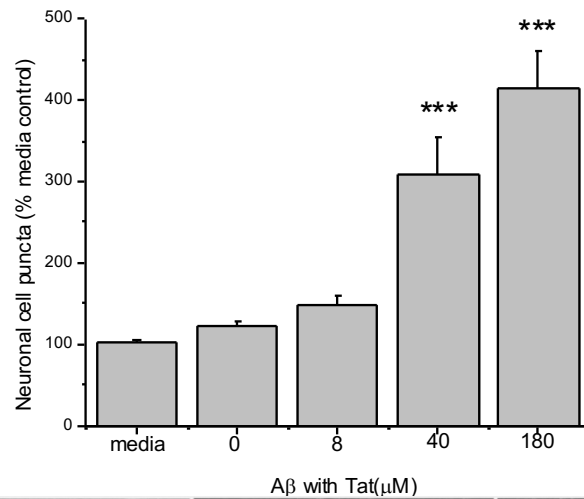
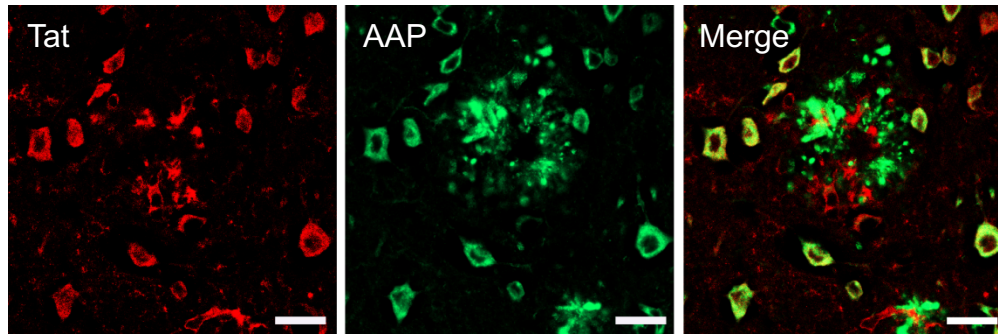


Nath et al., JBC 1999

Synergistic neurotoxicity of Tat with gp120 or glutamate (Nath et al., 2000)

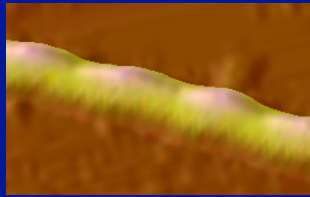


Tat and amyloid beta peptide form plaques that are neurotoxic





A β



Tat: A β ; 1 : 2600

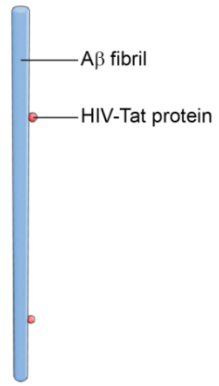


1 : 500



1 : 110

a



b

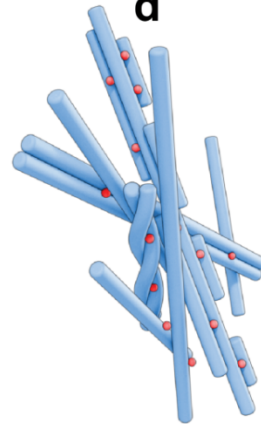


c



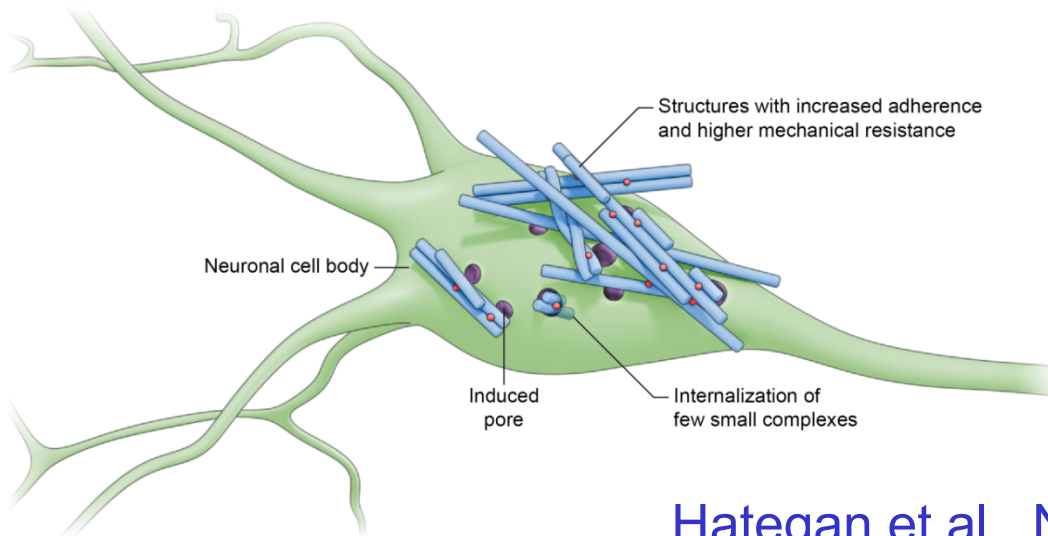
Thick irregular fibrils

d



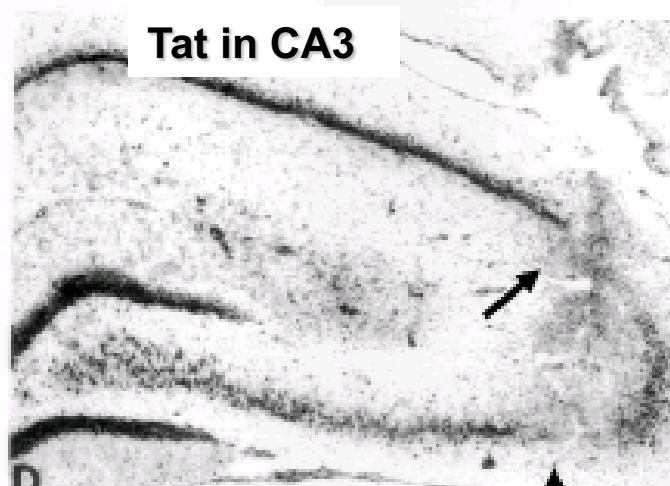
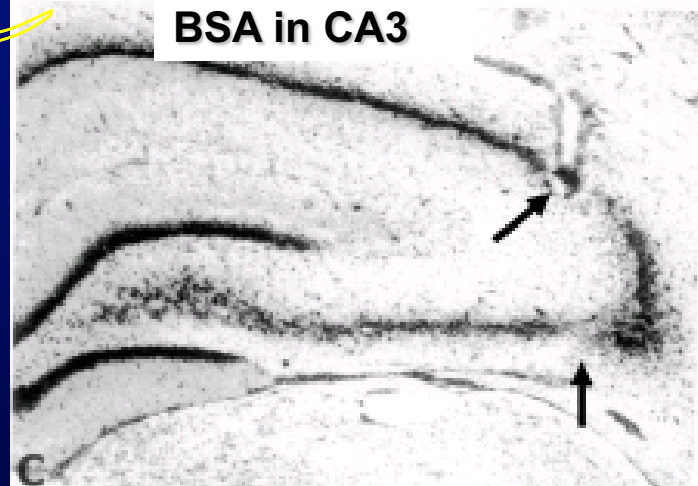
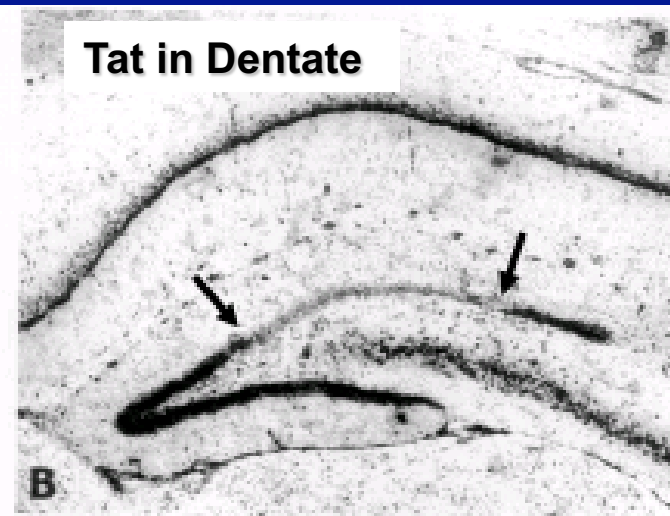
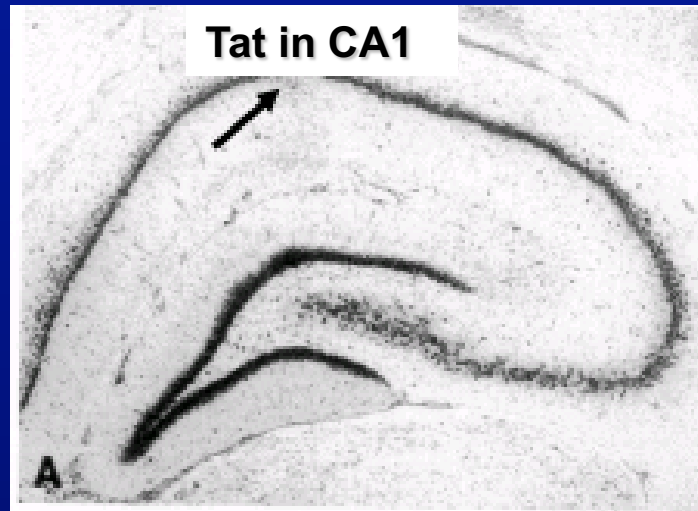
Patches

e



Selective Neuronal Vulnerability with Tat

(Maragos et al., Neurosci 2003)



Therapeutic Strategies against HIV-Tat protein

- Block effect of Tat on LTR to prevent HIV replication (LOCK and BLOCK)
- Block neurotoxic effects of Tat

Didehydro-Cortistatin A Inhibits HIV-1 by Specifically Binding to the Unstructured Basic Region of Tat


Sonia Mediouni,^a Krishna Chinthalapudi,^c Mary K. Ekka,^b Ippei Usui,^d Joseph A. Jablonski,^a Mark A. Clementz,^a Guillaume Mousseau,^a Jason Nowak,^c Venkat R. Macherla,^d Jacob N. Beverage,^d Eduardo Esquenazi,^d Phil Baran,^a Ian Mitchell S. de Vera,^{c,g} Douglas Kojetin,^c Erwann P. Loret,^f Kendall Nettles,^c Souvik Maiti,^b Tina Izard,^{a,c} Susana T. Valente^a

RESEARCH


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Tat inhibition by didehydro-Cortistatin A promotes heterochromatin formation at the HIV-1 long terminal repeat

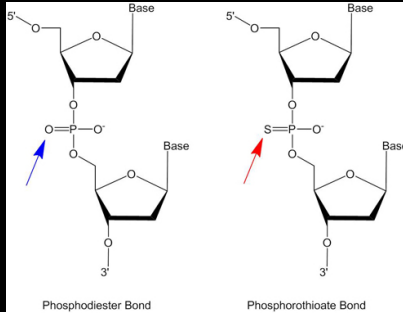
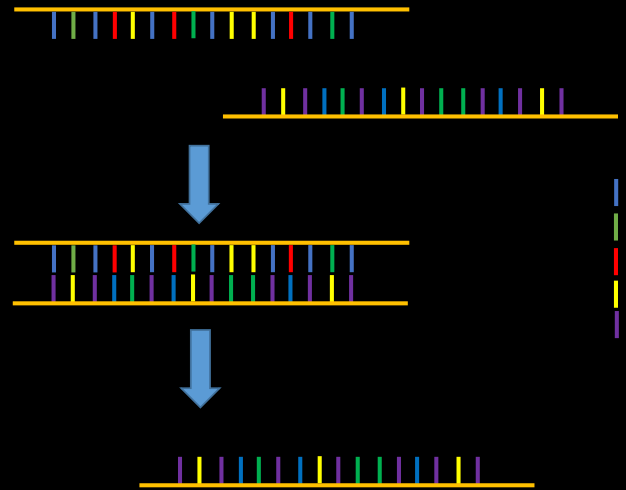
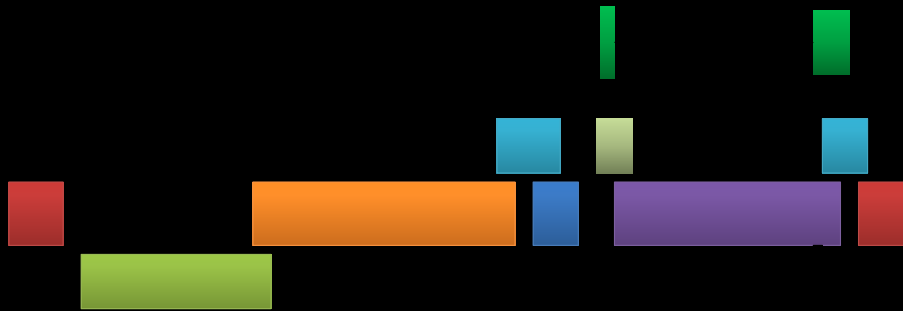


Chuan Li, Guillaume Mousseau and Susana T. Valente^{*} 

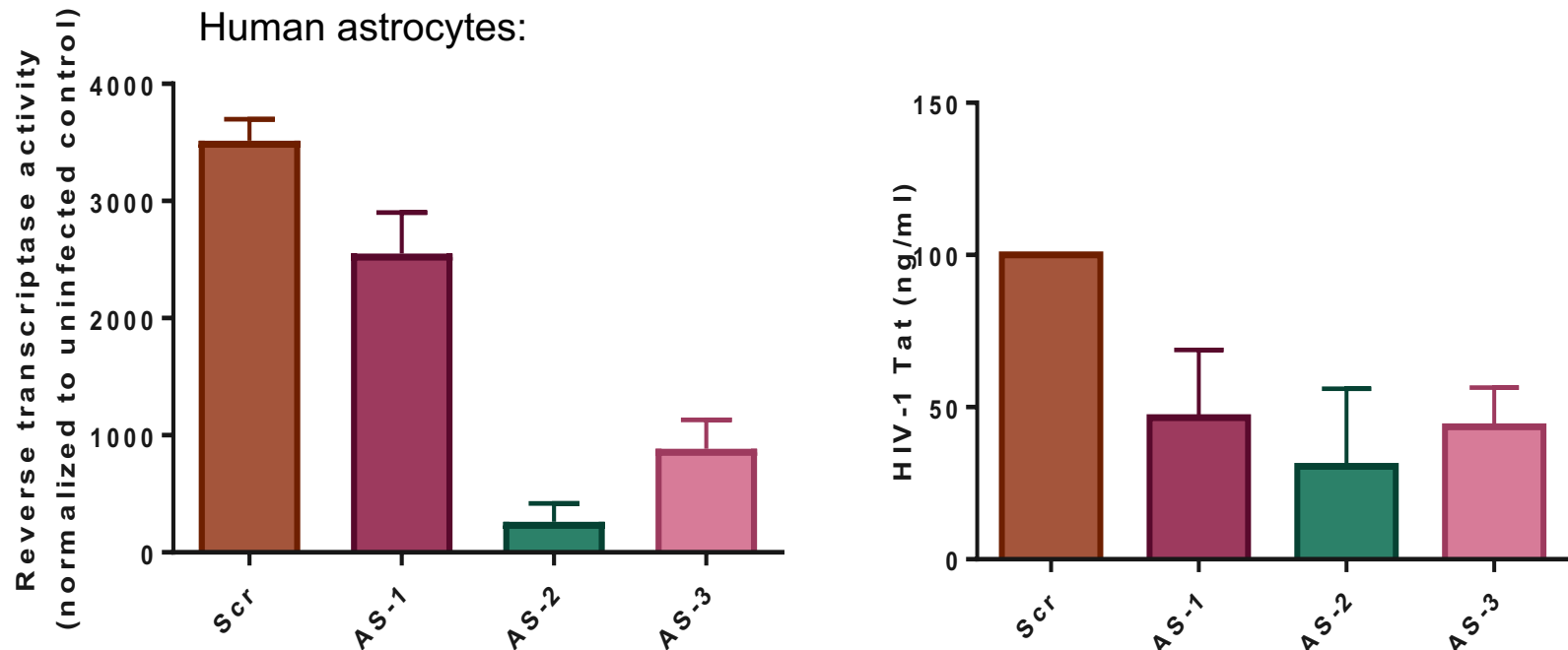
Resistance to the Tat Inhibitor Didehydro-Cortistatin A Is Mediated by Heightened Basal HIV-1 Transcription

Guillaume Mousseau,^{a*} Rachna Aneja,^a Mark A. Clementz,^{a*} Sonia Mediouni,^a Noemia S. Lima,^{b,c} Alexander Haregot,^{b,c} Cari F. Kessing,^{a*} Joseph A. Jablonski,^a Suzie Thenin-Houssier,^{a*} Nisha Nagarsheth,^{a*}  Lydie Trautmann,^{b,c} Susana T. Valente^a

TAT ANTISENSE OLIGONUCLEOTIDES



ASO directed against Tat mRNA diminish Tat production



* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ relative to scrambled ASO (N=3) as determined by Student's T-test

Summary

- There is acceleration of neurocognitive deficits with aging
- There is uncontrolled Tat production and deposition of amyloid in brain despite ART
- A LOCK and BLOCK strategy with Tat antagonists can potentially provide a functional cure and stop the age-related progression.

Acknowledgements

Tat assay

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Joseph Steiner

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