# Hot Topics on CNS and HIV

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# Disclosures

**Research awards were paid to UC San Diego on behalf of Dr. Letendre:**

- National Institutes of Health

**Travel to a scientific conference for Dr. Letendre was paid by:**

- ViiV Healthcare

# Overview

## Antiretrovirals & Other Drugs

- ART Neurotoxicity
- Long-acting ART
- Broadly Neutralizing Antibodies
- Polypharmacy

## The ’Omes

- Genome
- Glycome
- Microbiome
- Virome (CMV)

## Mental Health

- Depression
- Emotional health
- Risky sexual behavior

## Addictions

- Methamphetamine
- Cannabis
- Alcohol
- Tobacco

## Comorbidities

- Aging
- Vascular Disease
- Metabolic Syndrome

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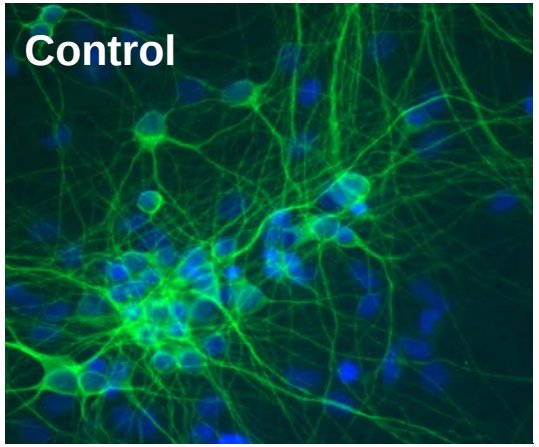
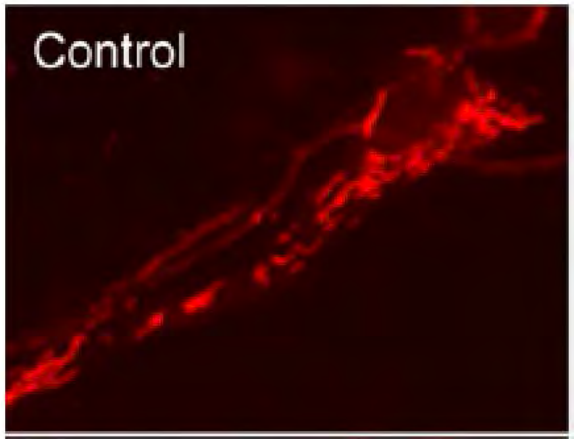
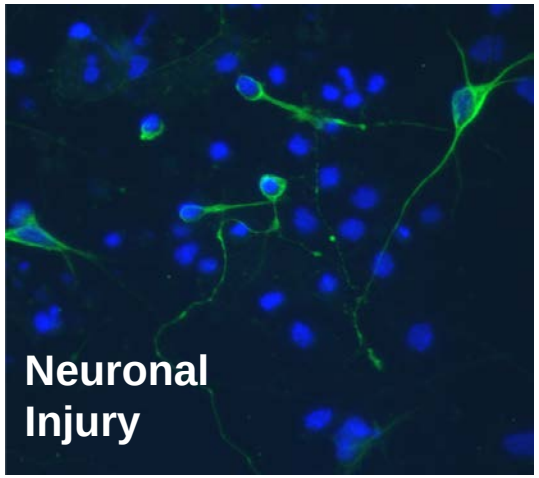
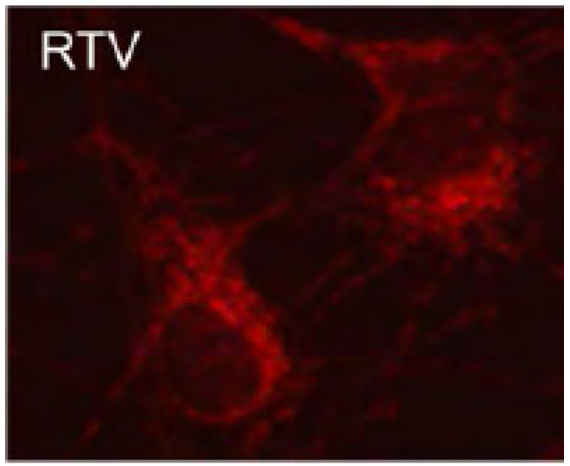
# Antiretrovirals & Other Drugs

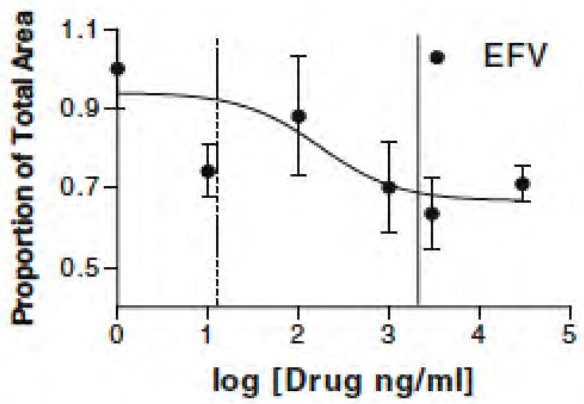
# *In Vitro* Analyses of ART Toxicity in Fetal Rat Cortical Neurons

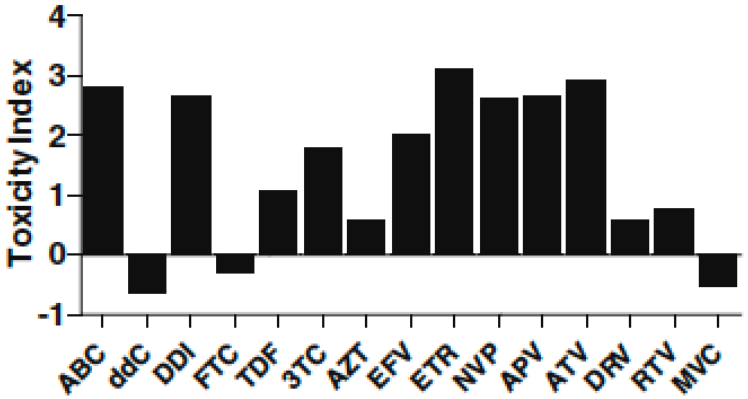


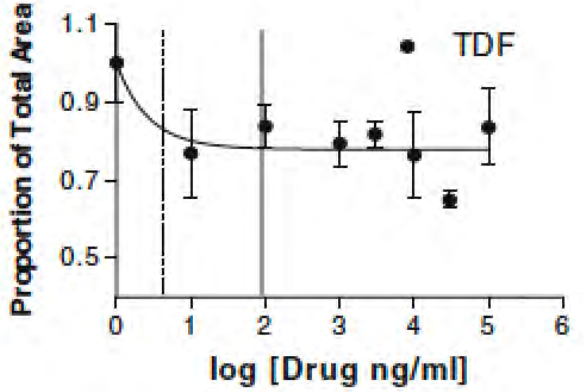



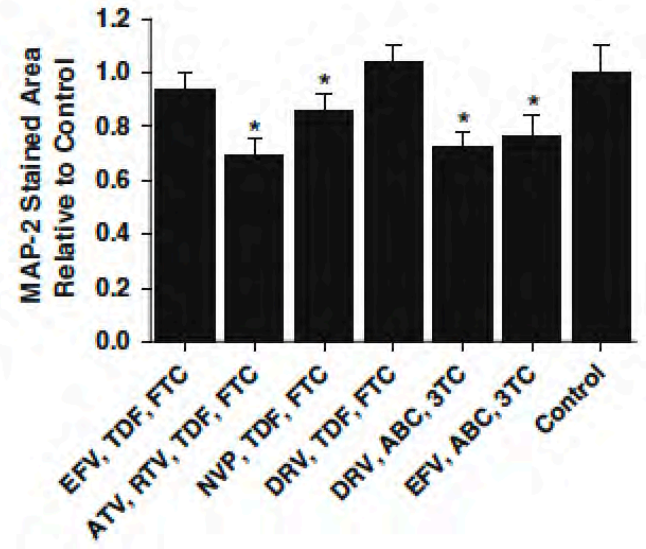



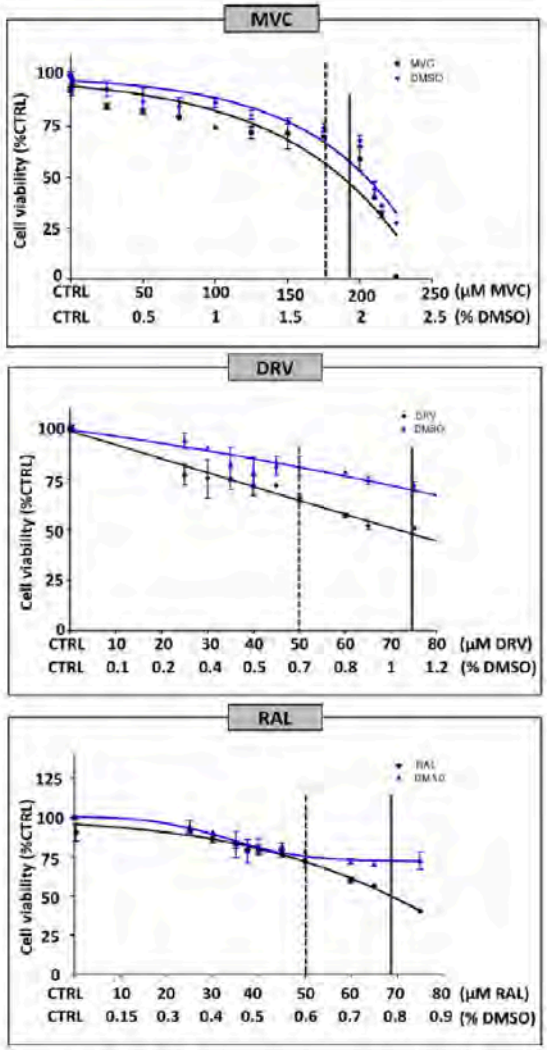




*Robertson et al, J Neurovirol 2012, 18: 388-299*

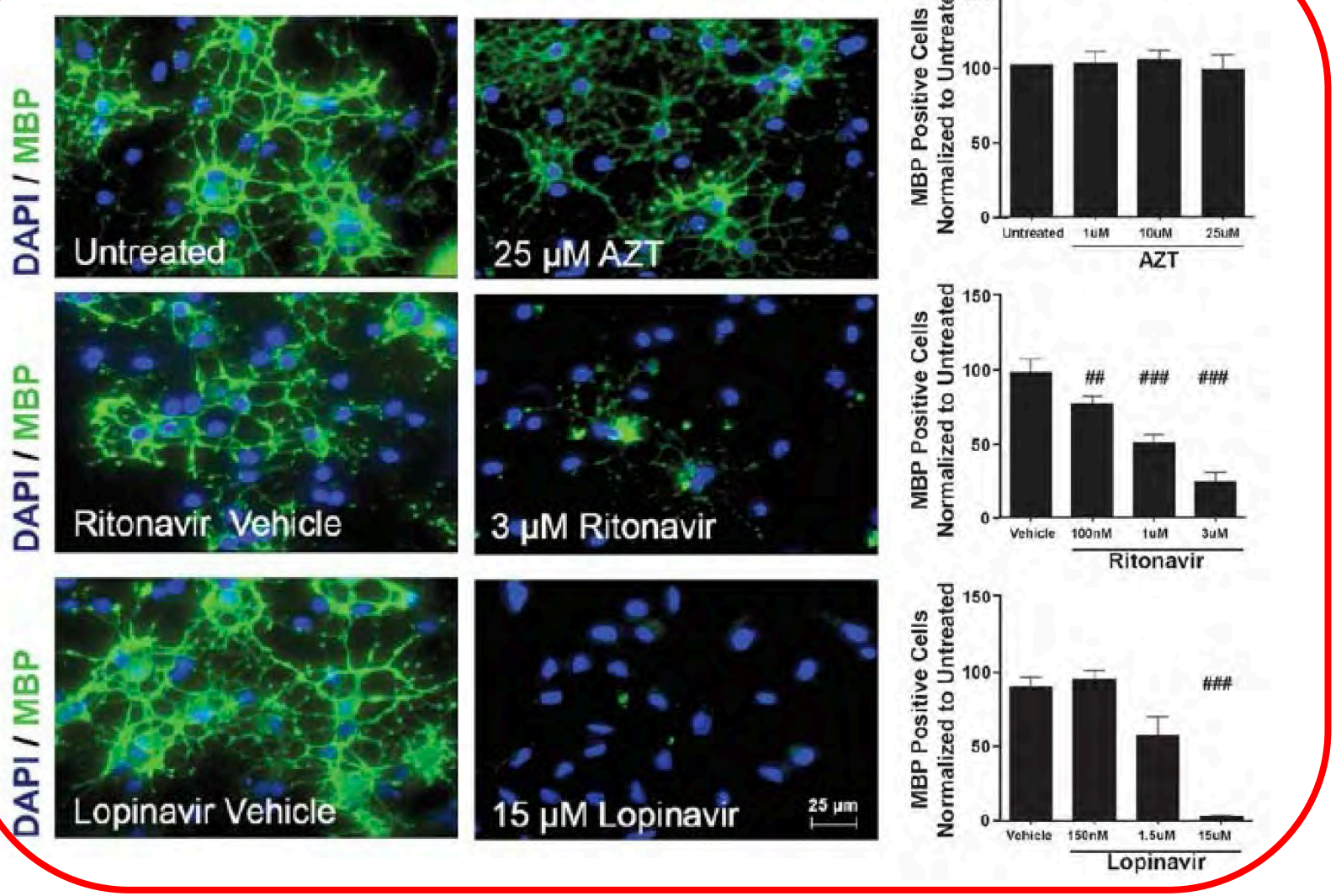
# ART Toxicity in Other Glial Cells

## Astrocytes



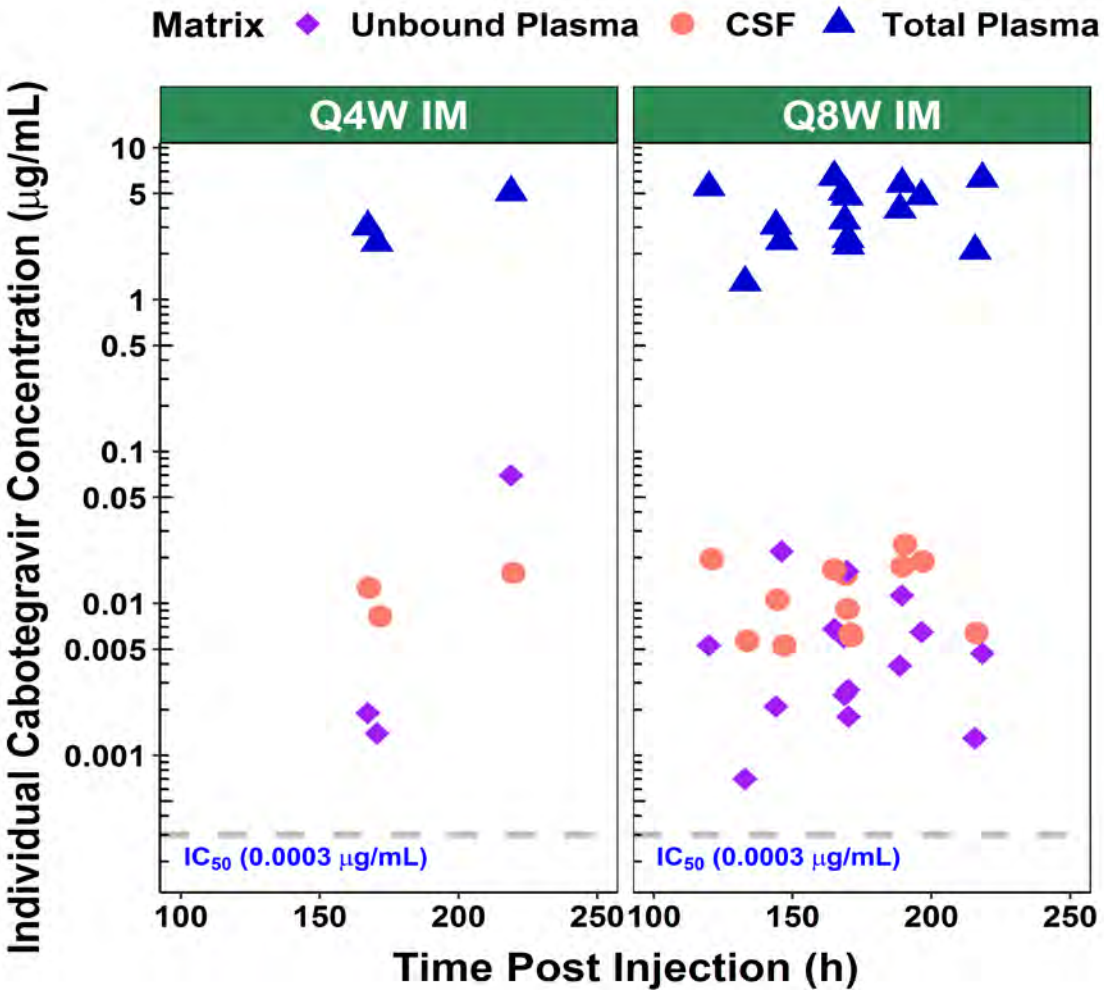

*Latronico et al, J Neurochem 2018, 144: 271-84*

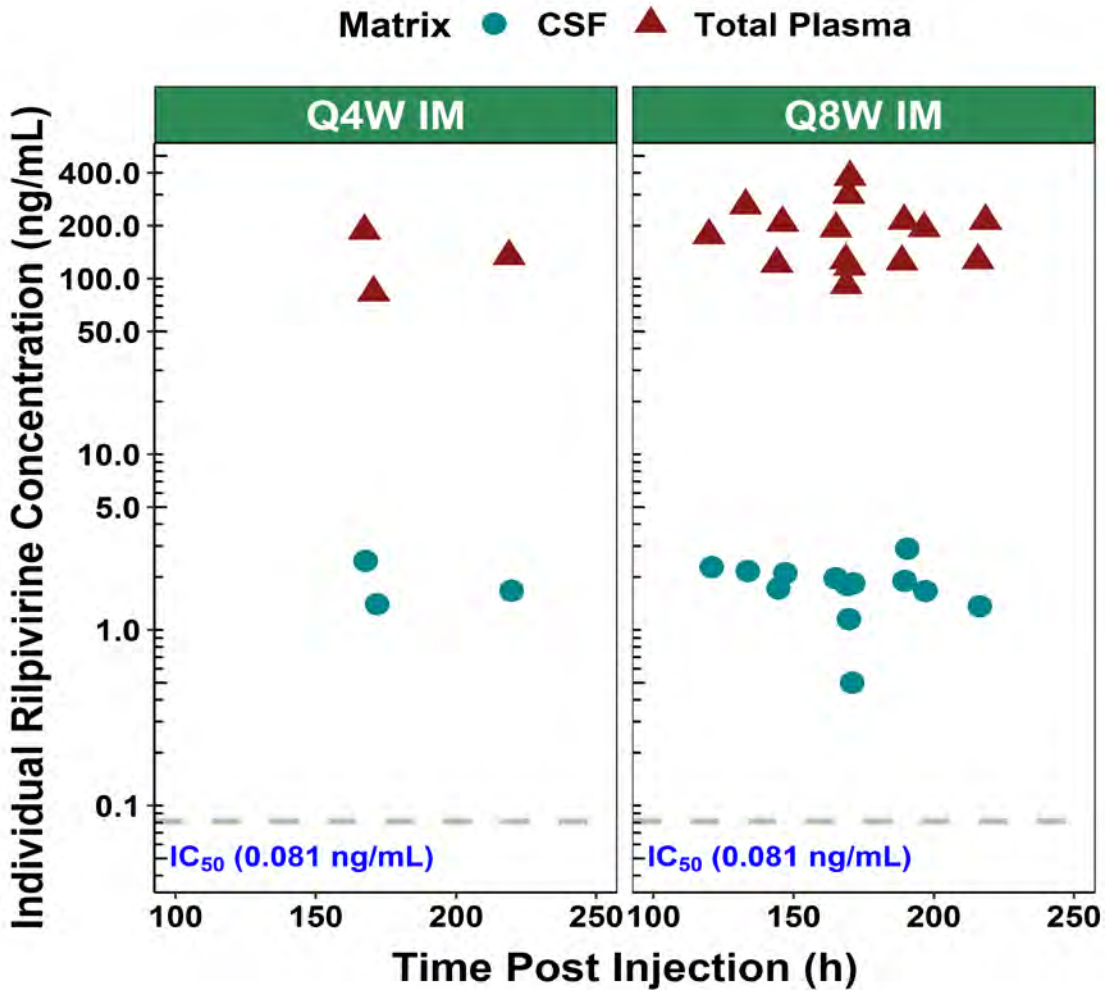
## Oligodendrocytes




*Jensen et al, J Neuropathol Exp Neurol 2015, 74(11): 1093-1118*

# Relationship Between CAB and RPV Concentration in Plasma and CSF

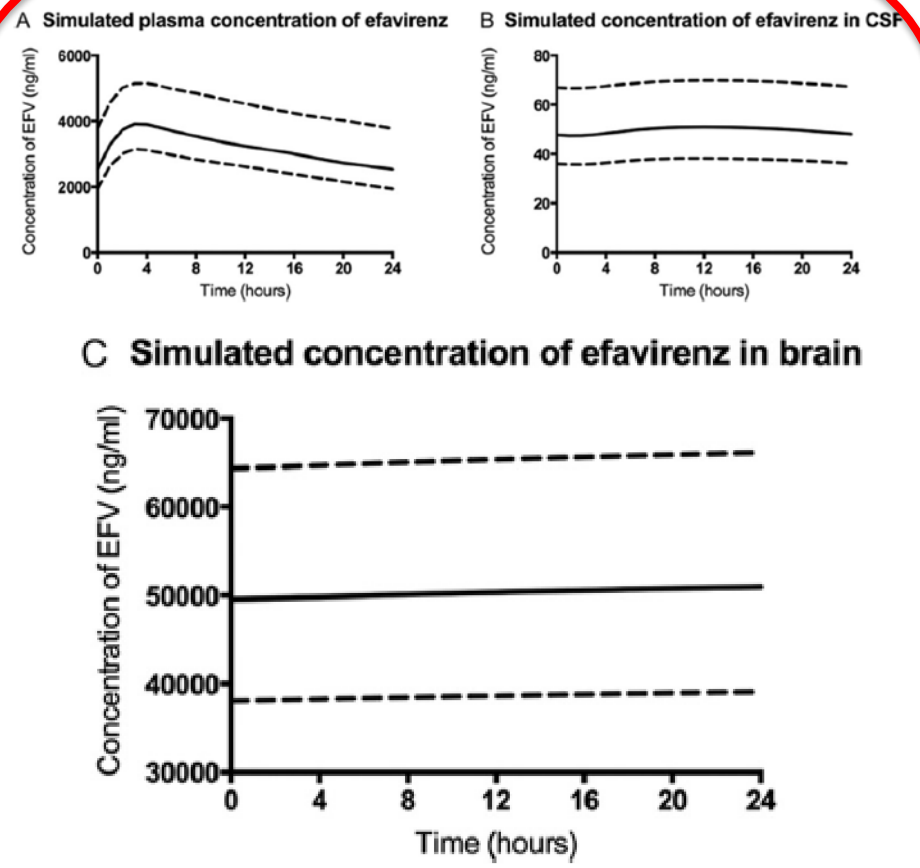


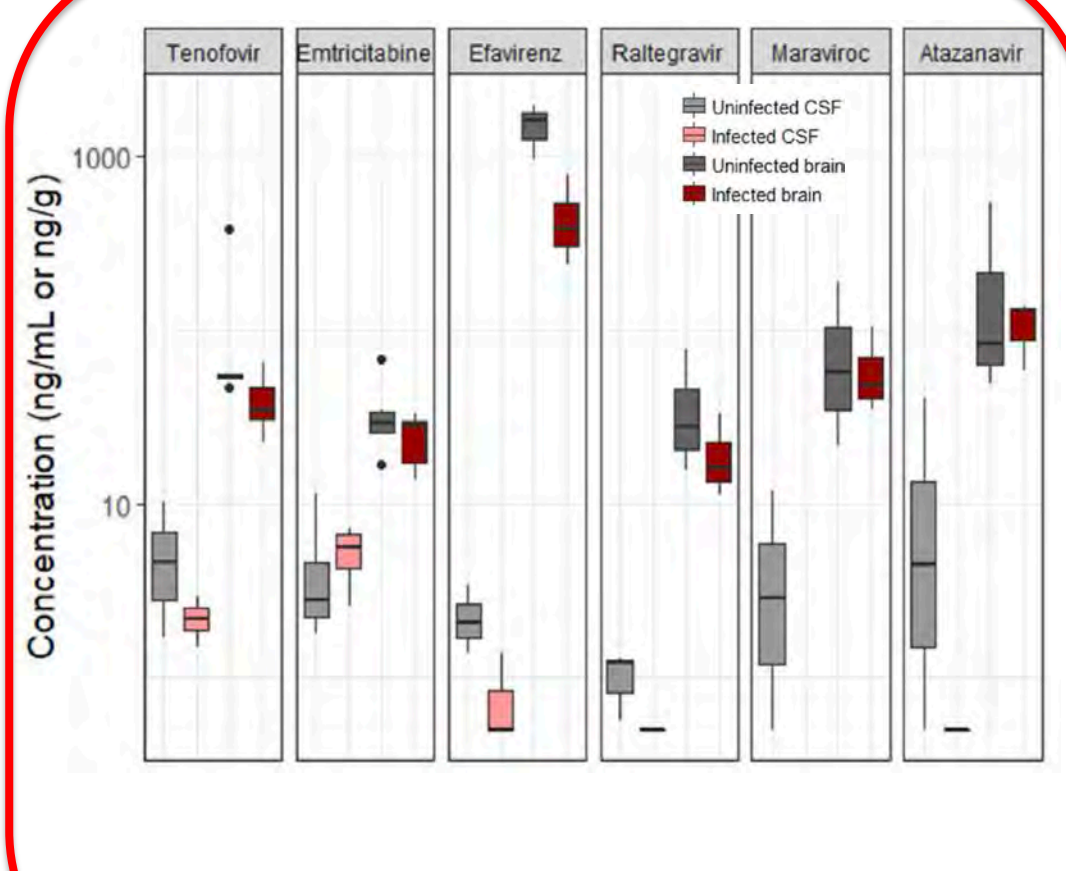

Individual unbound plasma cabotegravir concentrations are represented as mean of the 4 replicates.
CSF, cerebrospinal fluid; IM, intramuscularly; Q4W, every 4 wk; Q8W, every 8 wk.

*Letendre et al. HIV Glasgow; Glasgow, UK. Oral O346.*

# Animal Models Support That ART Concentrations in Brain Are Much Higher Than in CSF

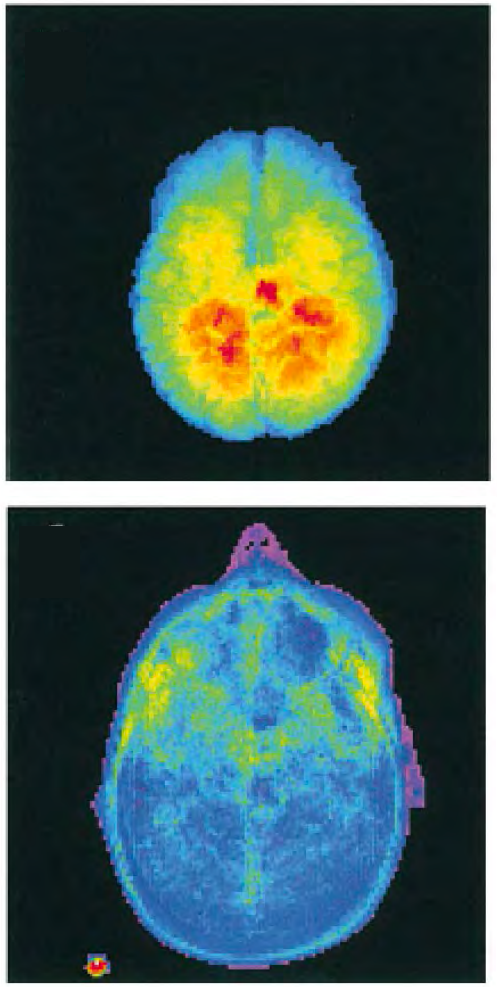


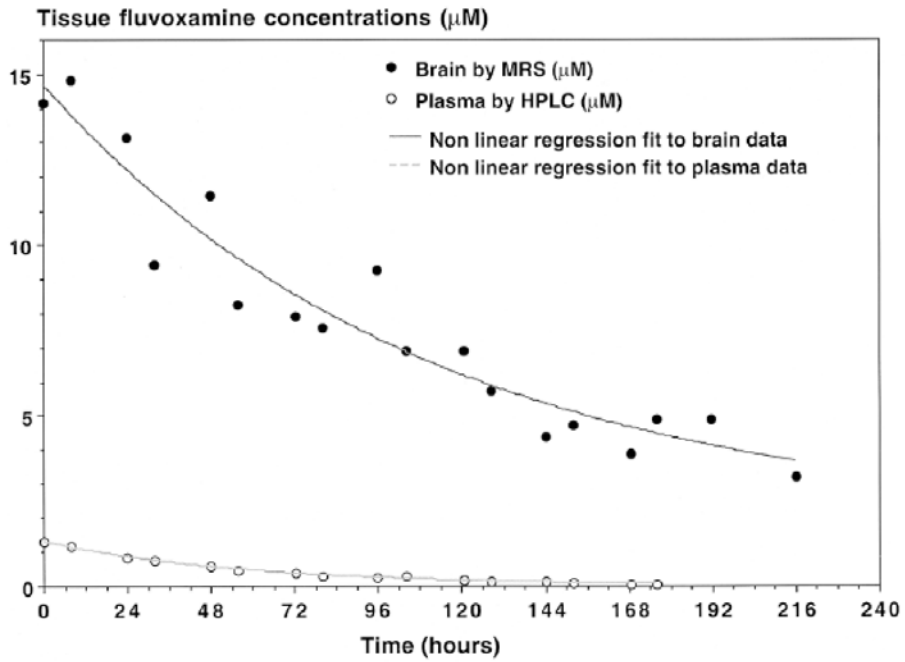

*Curley et al, AAC 2017, 61(1): e01841-16*



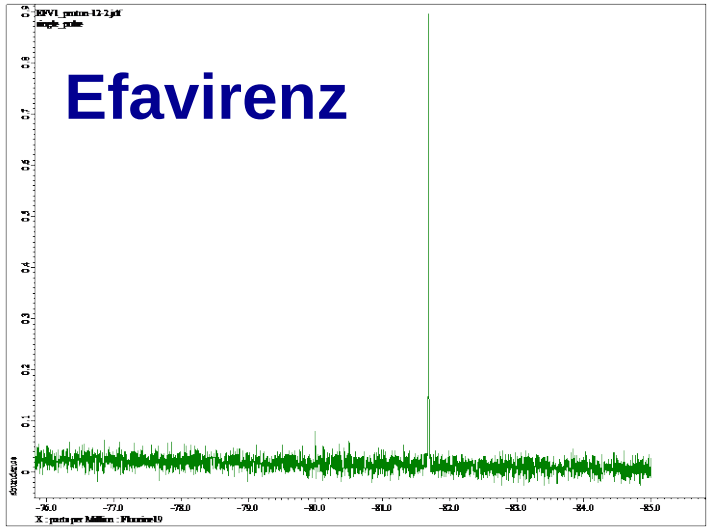

*Srinivas et al, IAS 2017, Abstract WEAB0105*
*Srinivas et al, Xenobiotica 2018, 17:1-10*

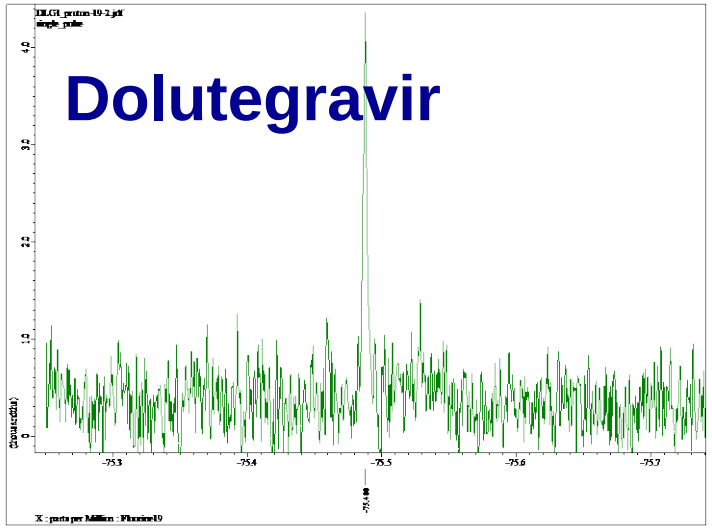
# In Vivo Measurement of Fluorinated Drugs with $^{19}$F-MRS






*Bolo et al, Neuropsychopharmacology 23:428–438, 2000*

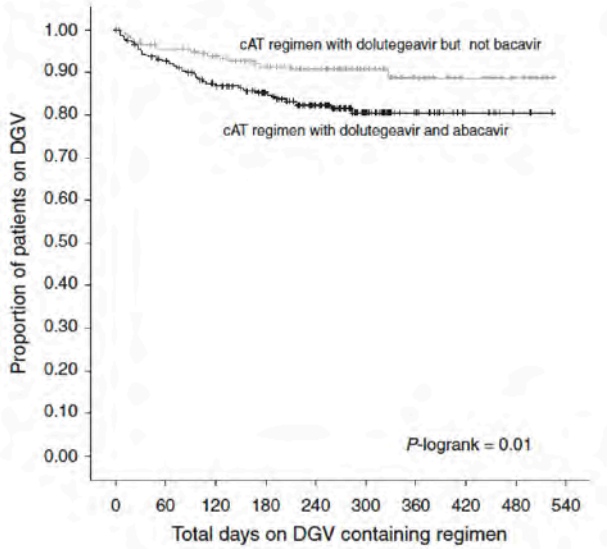



*Bussell, Brown, & Letendre, Unpublished Data*

# Dolutegravir, NP AEs, & Discontinuation

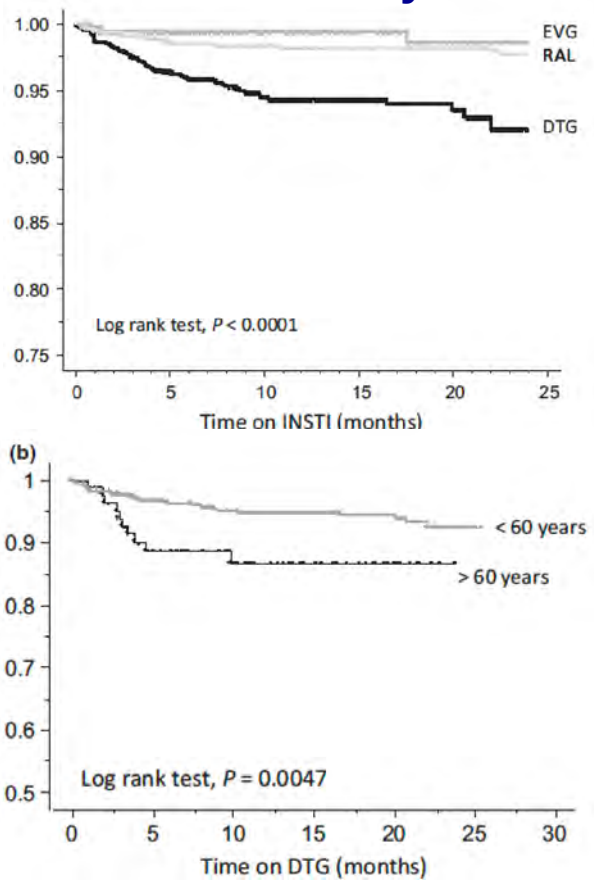
## N=565 DTG Only




| Adverse drug reaction | *n* (%) |
|---|---|
| Sleep disturbance, insomnia | 31 (5.6) |
| Gastrointestinal complaints | 21 (3.8) |
| Joint, tendon and/or muscle pain | 11 (2.0) |
| Psychological/psychiatric symptoms[b] | 14 (2.5) |
| Neurologic symptoms | 10 (1.8) |
| General malaise (headache and severe fatigue) | 24 (4.3) |
| Respiratory tract complaints | 5 (0.9) |
| Other | 9 (1.6) |

*de Boer et al, AIDS 2016, 30:2831–2834*

## N=1,950 InSTIs Only




*Hoffmann et al, HIV Medicine 2017, 18, 56--63*

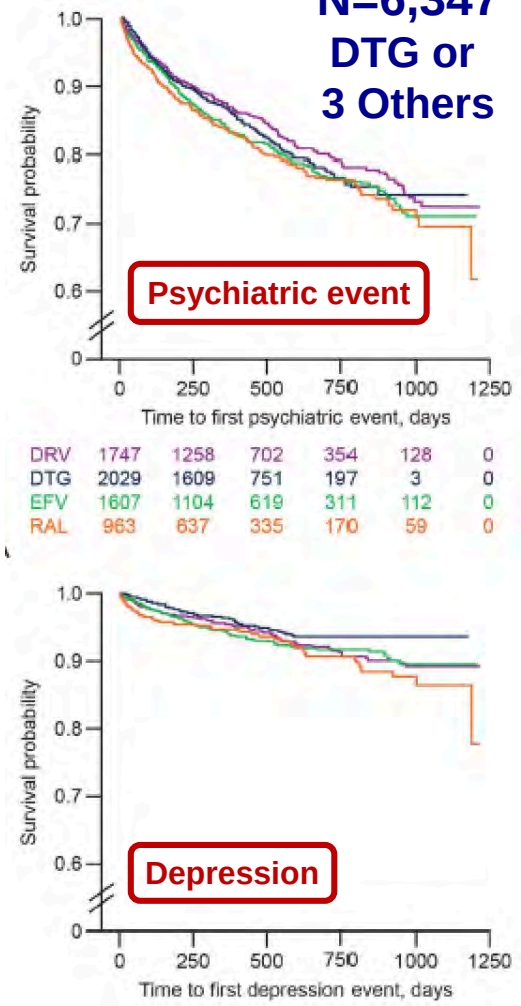
## N=4,041 DTG vs. RAL

| Variable | HR[a] | *P* value |
|---|---|---|
| Female | 1.98 | <0.001 |
| Age, per 10 years older | 0.93 | 0.319 |
| Nonwhite ethnicity | 0.75 | 0.172 |
| Prior AIDS-defining condition | 0.89 | 0.513 |
| HCV-coinfection | 0.80 | 0.221 |
| $CD4^+$ cells per μl | | |
| <350 | | |
| 350–500 | 0.98 | 0.880 |
| >500 | 1.07 | 0.735 |
| HIV RNA >100 000 copies per ml | 1.53 | 0.149 |
| Treatment naive | 1.05 | 0.858 |
| Backbone | | |
| Abacavir–lamivudine | | |
| Tenofovir–emtricitabine | 0.91 | 0.626 |
| Other | 0.97 | 0.902 |
| Raltegravir versus dolutegravir | 1.30 | 0.140 |

**Toxicity:**
**RAL 4.3%**
**DTG 3.6%**

*Elzi et al, AIDS 2017, 31:1853–1858*

## N=6,347 DTG or 3 Others




*Fettiplace et al, J AIDS 2017;74:423–431*

# Mixed Results from CROI 2019

| First author | Abstract | Sample Size | Drugs | Design | Neurobehavioral Findings | Neuroimaging Findings |
|---|---|---|---|---|---|---|
| **Vera** | 122 | 12 | Raltegravir Dolutegravir | Switch 120 Days | Global NP: No difference<br>PRO: No difference | fMRI: No difference<br>FC: Increase in 3 resting-state networks |
| **Mora-Peris** | 443 | 20 | Raltegravir Dolutegravir | Switch 120 Days | Global NP: No difference<br>PRO: No difference | $^{1}$H-MRS: Higher NAA/Cr with DTG (p=0.07) |
| **Prats** | 439 | 42 | InSTIs | Early vs. Chronic HIV 48 Weeks | NPZ12: No differences<br>Depressive, Anxiety, and Stress: Worse at Baseline in Early HIV | sMRI: Decrease in medial orbital frontal cortex in Chronic HIV |
| **O'Halloran** | 442 | 202 | InSTIs vs. Non-InSTIs | Clinical cohort | Global & Learning/Memory: InSTIs worse | sMRI: Lower total and subcortical GM with InSTIs |
| **Chan** | 440 | 254 | Dolutegravir | Switch 48 Weeks | NPZ4: Improved<br>PHQ-9 Somatic: Worsened | None reported |

CROI
Conference on Retroviruses and Opportunistic Infections

*PRO=Patient-Related Outcome*
*FC=Functional Connectivity*
*InSTI=Integrase Strand Transfer Inhibitors*
*PHQ=Patient Health Questionnaire*

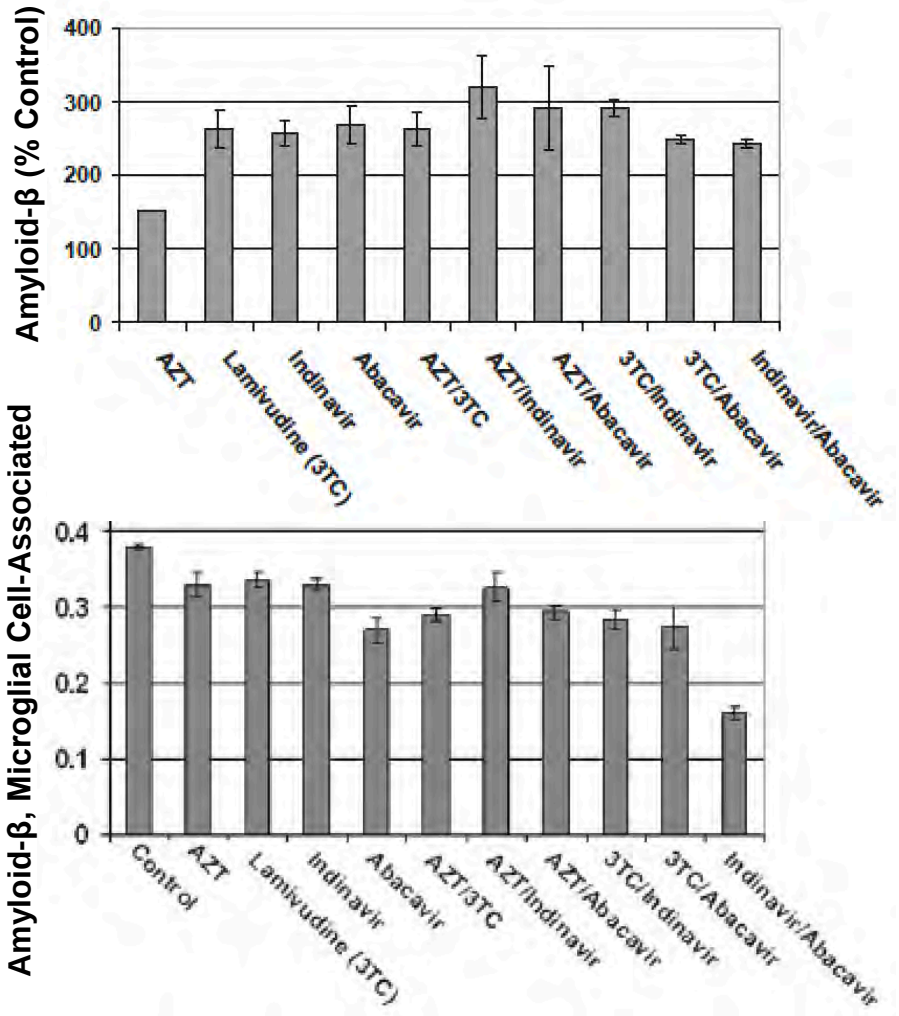
# Summary of *in vitro* Evidence of Mechanisms of Neurotoxicity

| Drug | Effect |
|---|---|
| **Maraviroc** | ↑ Microglial activation |
| **Raltegravir** | ↑ IL-8 in brain macrophages |
| **Efavirenz** | ↑ TNF-α and IL-1β |
| | Dendritic spine injury |
| | Mitochondrial alterations |
| | ↑ Autophagy |
| | ↑ β-Secretase expression, ↑ amyloid-β, ↑ ROS |
| | ↑ Endoplasmic reticulum stress |
| | ↓ ATP stores; ↓ neural stem cell proliferation |
| **Etravirine** | ↓ MAP-2 density in rat neurons |

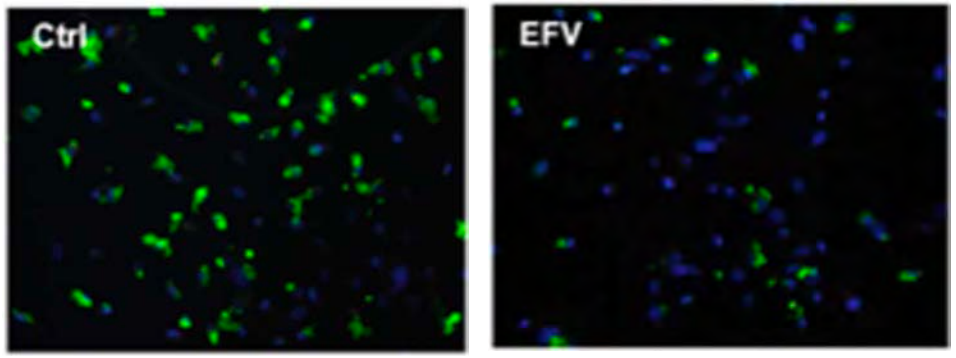
| Drug | Effect |
|---|---|
| **Zidovudine** | ↓ Mitochondrial DNA in cortical neurons |
| | ↑ Amyloid-β production |
| **Lamivudine** | ↓ Mitochondrial DNA in cortical neurons |
| | ↑ Amyloid-β production |
| **Abacavir** | ↑ Amyloid-β production |
| **Indinavir** | ↑ Amyloid-β production |
| **Lopinavir** | ↓ Myelin basic protein, ↓ galactocerebroside in oligodendrocytes |
| | ↑ Oxidative stress, ↑ ER stress, ↑ IL-6 and TNF-α in macrophages |
| | ↓ Tight junction proteins, ↓ synaptic proteins, ↑ TNF-α, IL-6 and IL-1β |
| **Atazanavir** | ↑ Oxidative stress, ↓ MAP-2, ↓ synaptophysin |

*Shah et al, Neurotox Res (2016) 30:677–697 691*

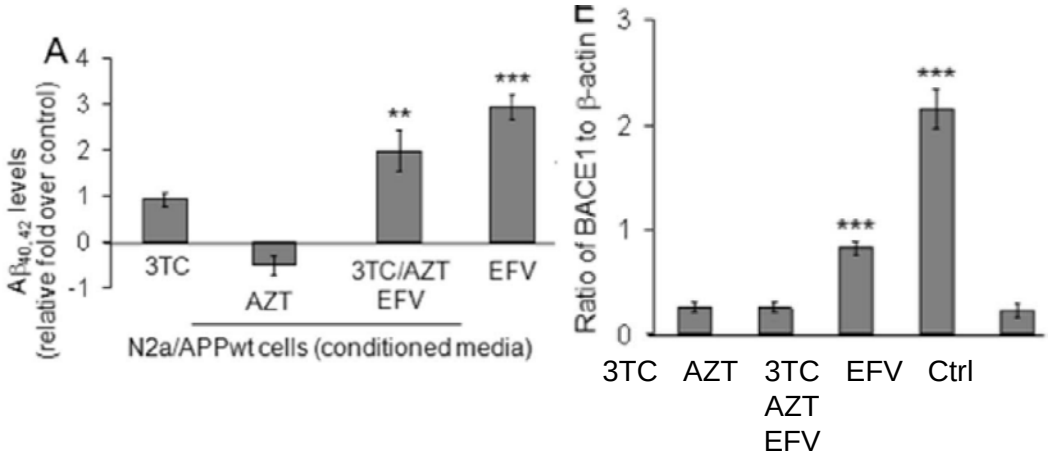
# ART Drugs Can Increase Amyloid-β & Reduce Microglial Phagocytosis




*Giunta et al, Molecular Brain 2011, 4:23*

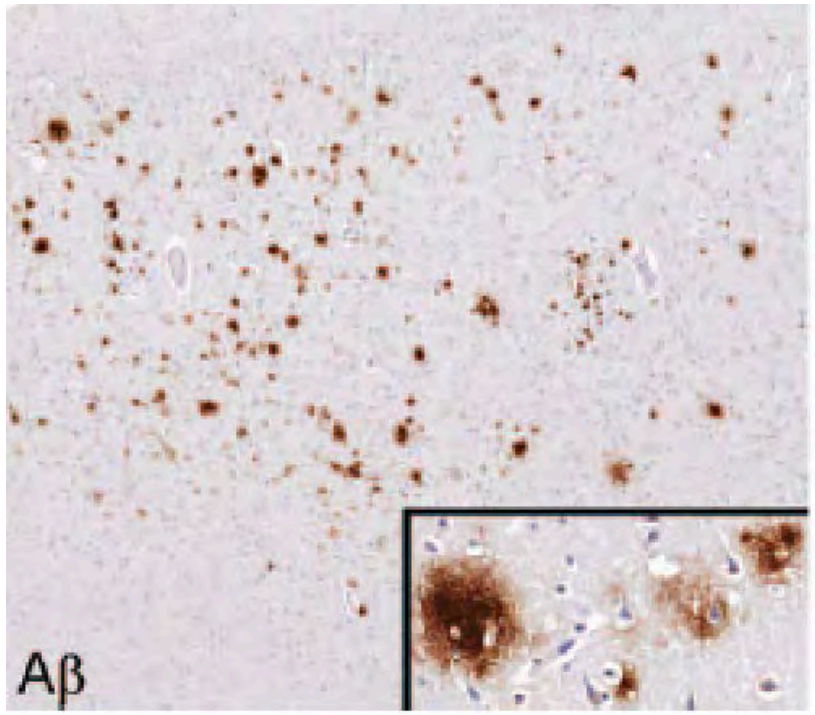



**EFV Reduces Microglial Phagocytosis of $A\beta_{1\text{-}42}$**

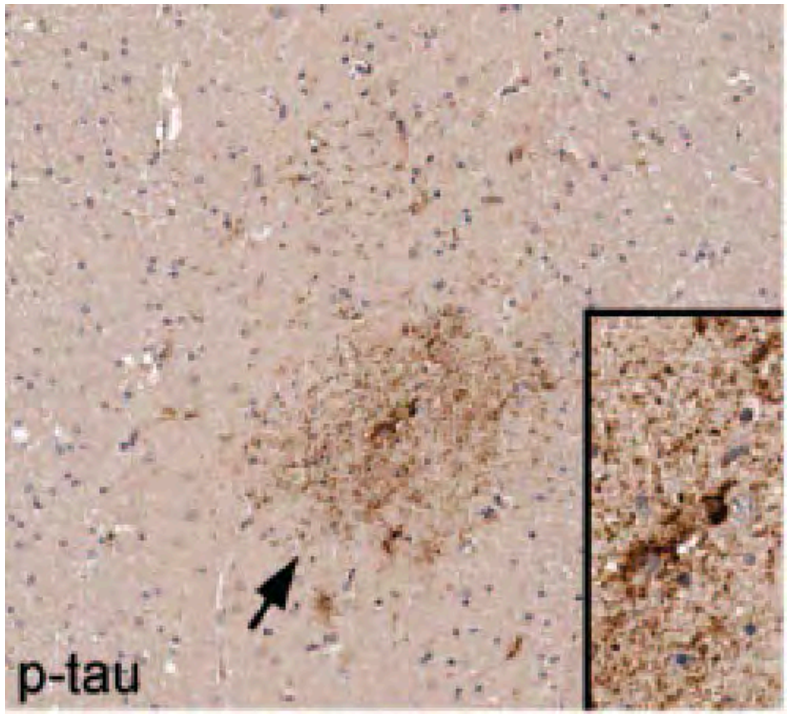



*Brown et al, PLoS ONE 2014, 9(4):* e95500

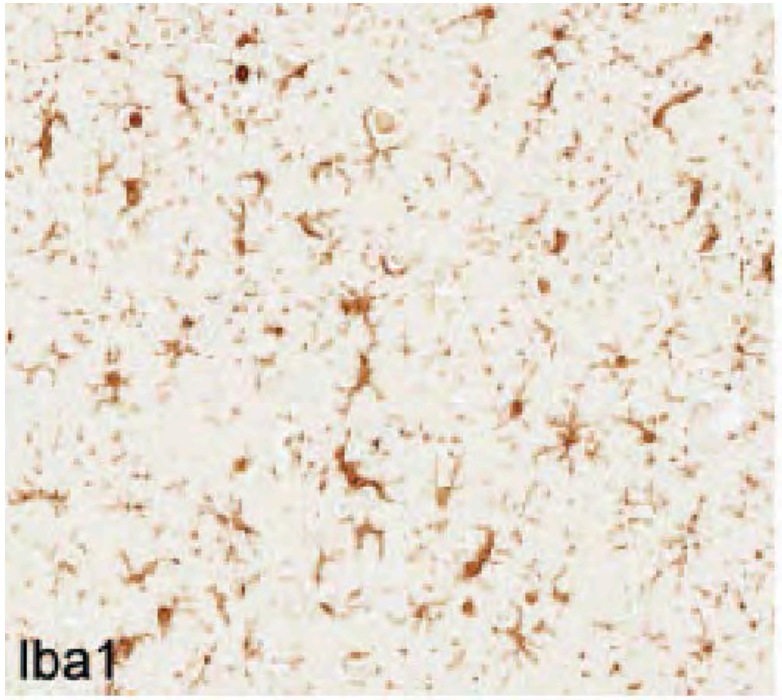
# Amyloid and Phospho-Tau Neuropathology May be Influenced by Antiretrovirals




**Tenofovir use prior to death associated with lower odds of amyloid β plaque deposition**
(OR 0.13, p=0.012)




**Darunavir use prior to death associated with higher odds of phopho-tau deposition in neurons**
(OR 15.3, p=0.0005)

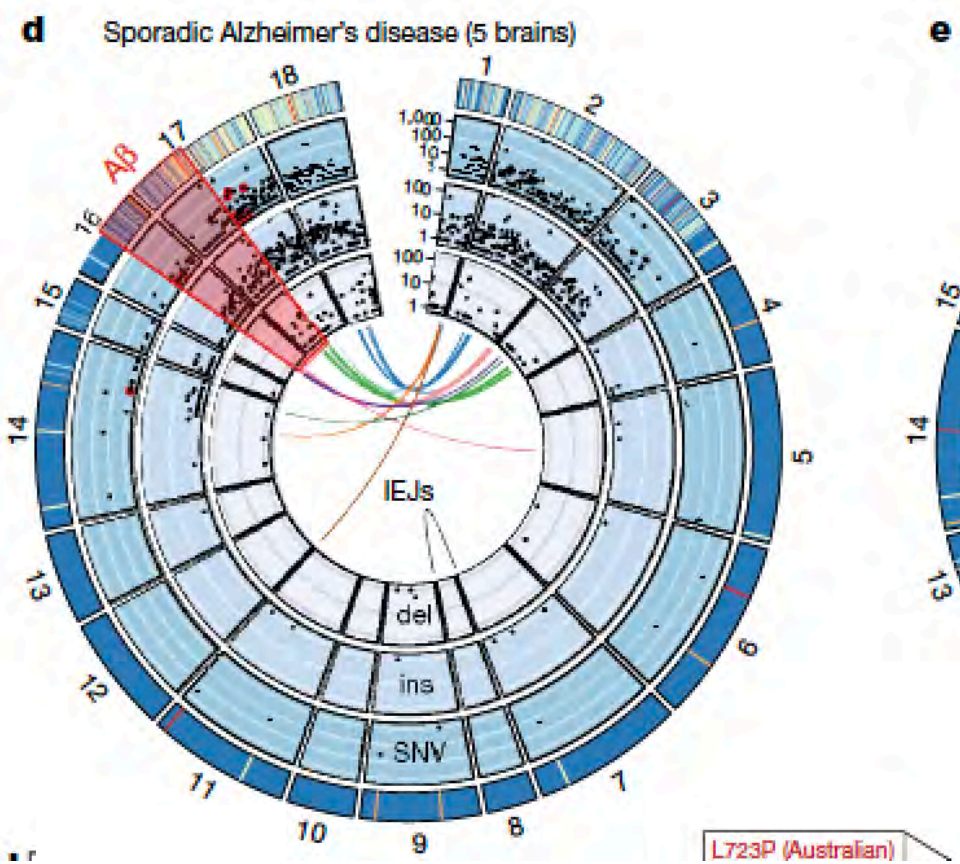


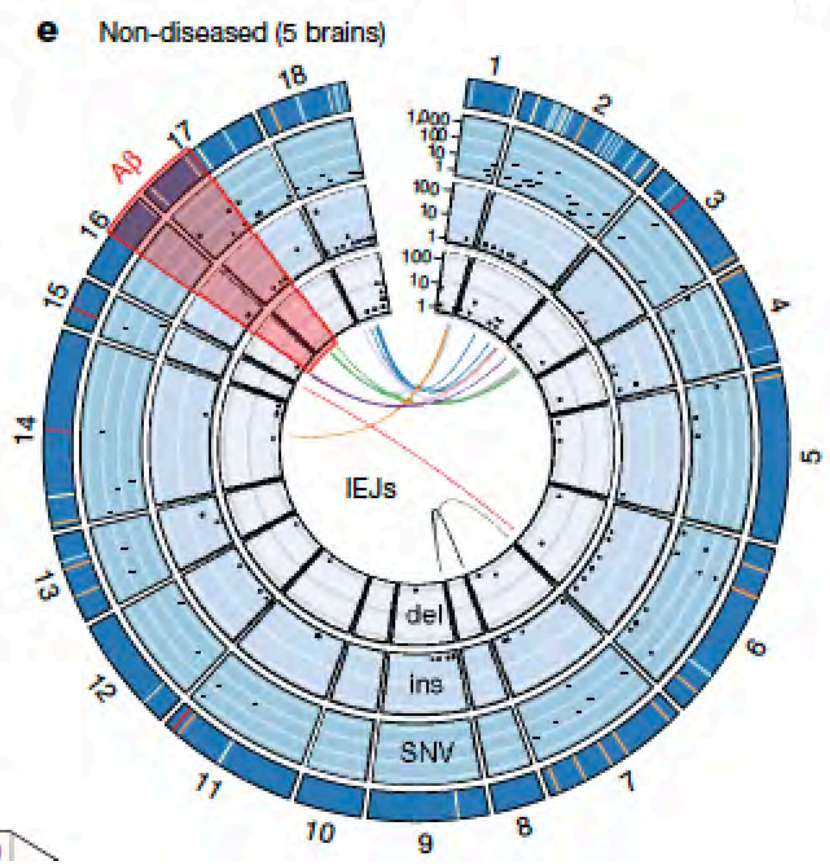

**Ritonavir use prior to death associated with higher odds of microgliosis**
(OR 4.96, p=0.023)

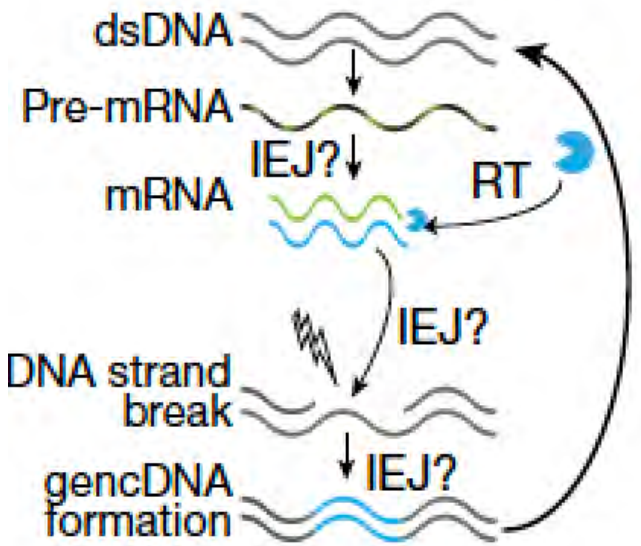
*Soontornniyomkij et al, AIDS 2018, 32: 2005–2015*

# Somatic *APP* gene recombination in Alzheimer's disease and normal neurons

Ming-Hsiang Lee[1], Benjamin Siddoway[1,3], Gwendolyn E. Kaeser[1,2,3], Igor Segota[1,3], Richard Rivera[1], William J. Romanow[1], Christine S. Liu[1,2], Chris Park[1,2], Grace Kennedy[1], Tao Long[1] & Jerold Chun[1]*



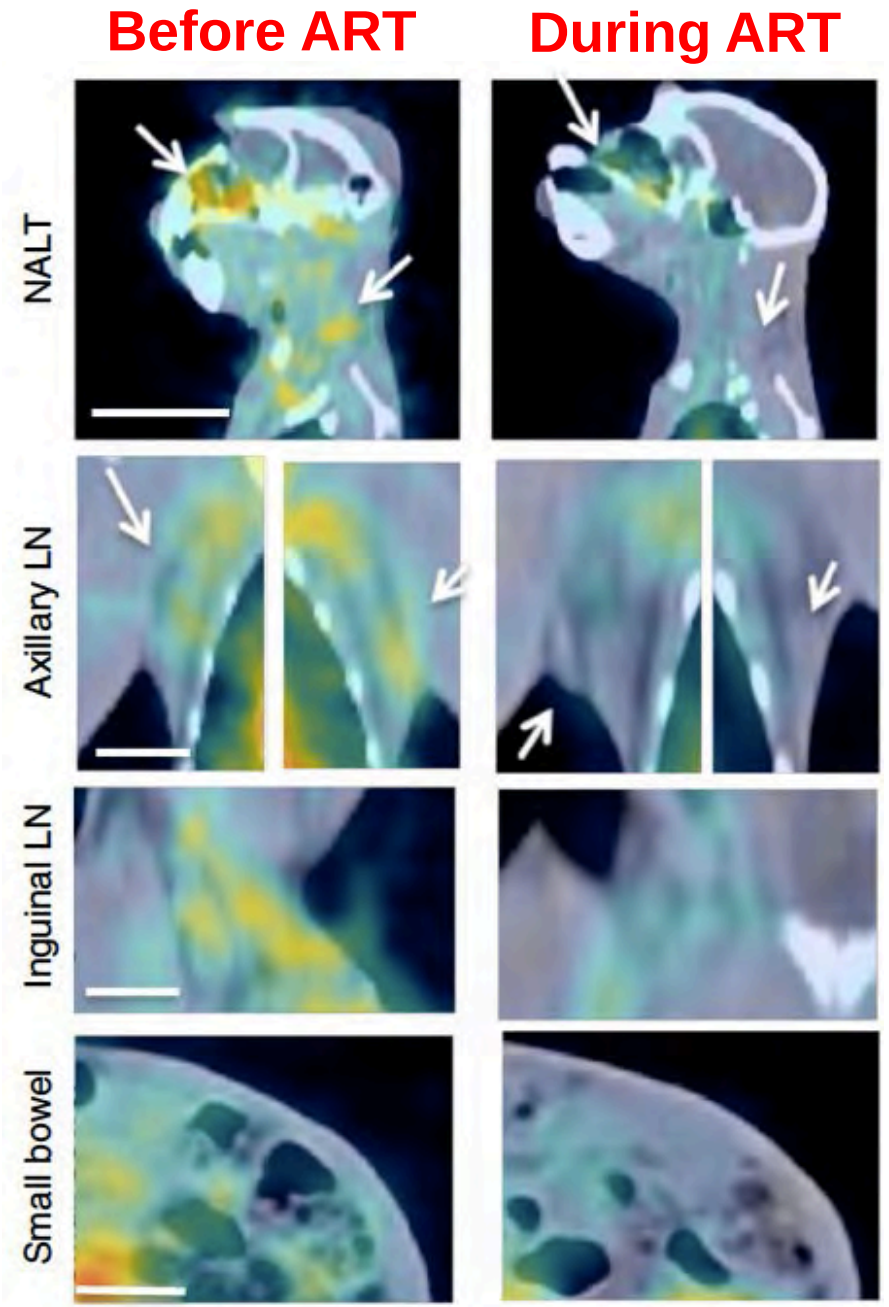




nature
International journal of science

https://doi.org/10.1038/s41586-018-0718-6

# SIV-Targeted ImmunoPET

- PEG-modified, $^{64}$Cu-labeled SIV Gp120–specific antibody
- Visualized by PET
- **Viremic animals:** Signals in the GI and respiratory tract, lymphoid tissues and reproductive organs
- **Aviremic animals:** Signals reduced but detectable in colon, lymph nodes, small bowel, nasal turbinates, genital tract and lung
- **Did not detect uptake in the CNS, "probably because of probe exclusion by the blood-brain barrier"**

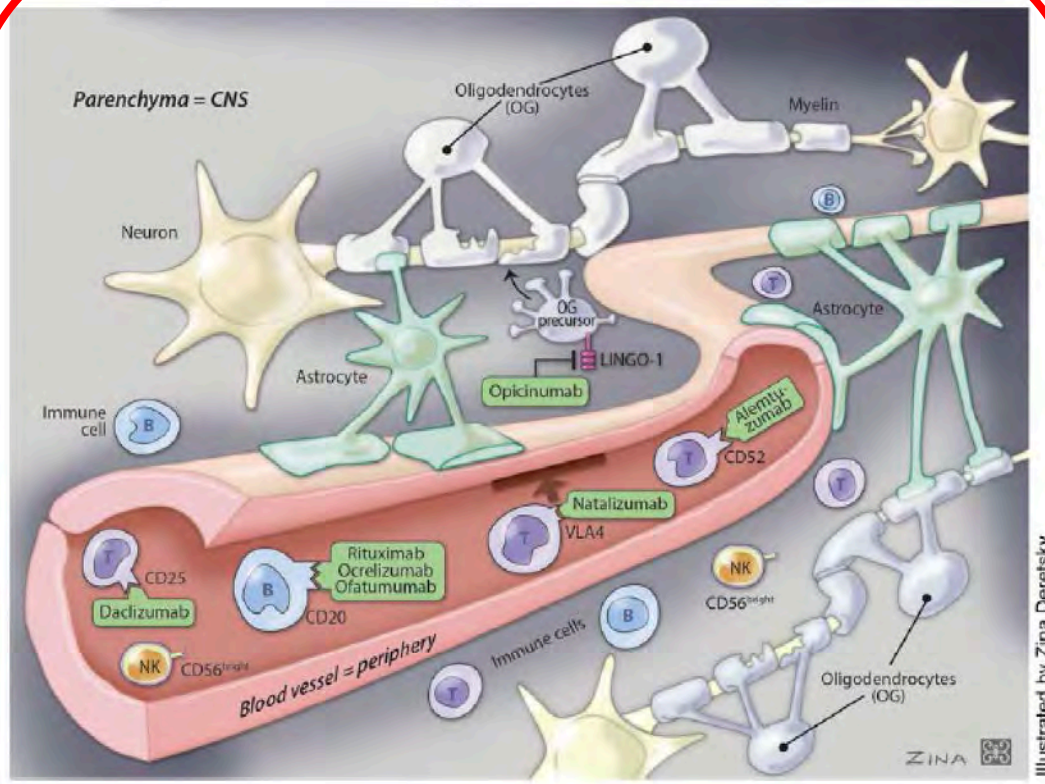



*Santangelo et al. Nature 2015, 12(5): 427-35*

# Monoclonal Antibodies Are Being Investigated For Alzheimer's Disease & Multiple Sclerosis

| Compound | Company | Epitope | Trial results |
|---|---|---|---|
| Bapineuzumab, humanized 3D6 | Janssen/Pfizer | Amino terminus | Phase 3 trials did not meet cognitive and functional endpoints |
| Solanezumab, humanized m266 | Eli Lilly | Central (amino acids 16 to 24), accessible only on soluble amyloid-β | Phase 3 trials did not meet functional endpoint; did meet cognitive endpoint in pooled analyses in mild AD |
| Gantenerumab, full human | Hoffmann-La Roche | Amino terminus and central portions of amyloid-β | Phase 2a trial showed reduction in brain amyloid β on PET |
| Crenezumab, humanized IgG4 | Genentech | Conformational epitopes, including oligomeric and protofibrillar forms | Phase 1 trial showed compound was safe and well-tolerated |
| BAN2401, humanized mAb158 | Eisai Inc. | Binds large-size amyloid-β protofibrils (>100 kDa) | Phase 1 trial showed compound was safe and well-tolerated |
| GSK 933776, humanized IgG1 | GlaxoSmithKline | Amino terminus | Phase 1 trial showed compound was safe and well-tolerated |
| AAB-003, Fc-engineered bapineuzumab | Janssen/Pfizer | Amino terminus | Phase 1 trial ongoing |
| SAR228810, humanized 13C3 | Sanofi | Protofibrils, and low molecular weight amyloid-β | Phase 1 trial ongoing |
| BIIB037/BART, full human IgG1 | Biogen Idec | Insoluble fibrillar human amyloid-β | Phase 1 trial ongoing |

Prins & Scheltens,
Alzheimer's Research & Therapy 2013, 5:56




Orthmann-Murphy & Calabresi,
Clinical Pharmacology & Therapeutics
2017, 101(1): 52-64

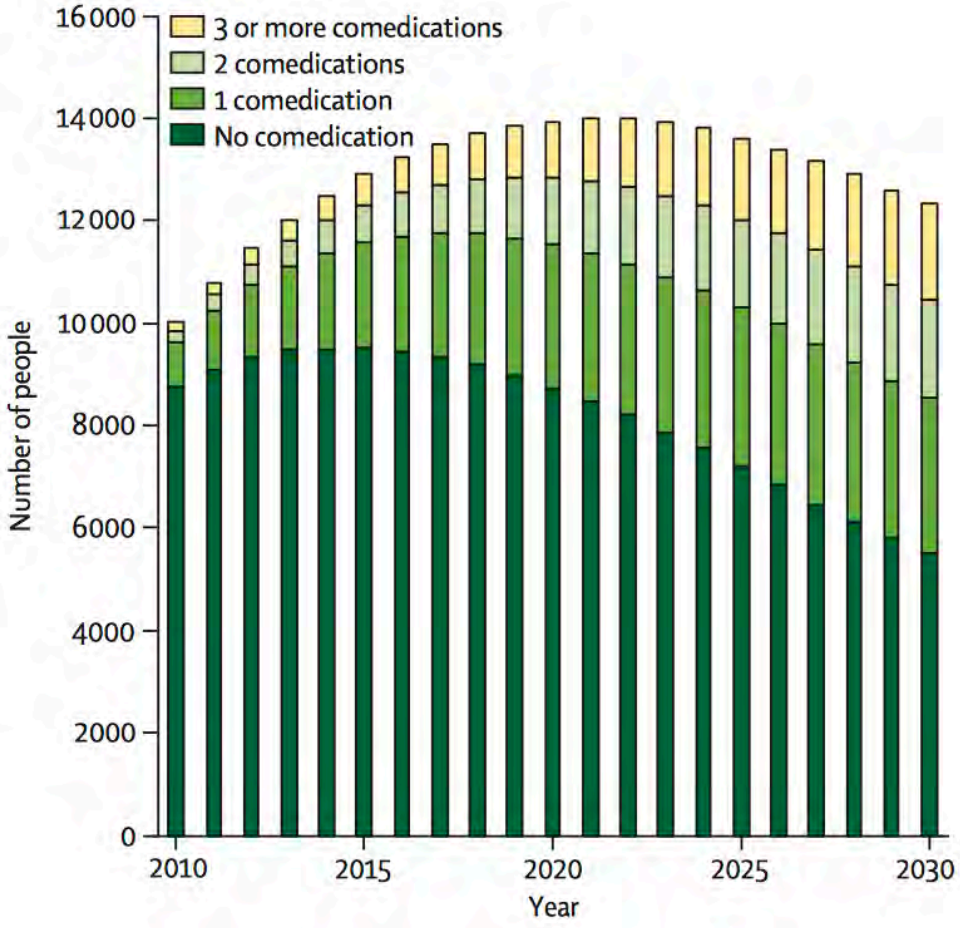
# Reduced Sensitivity to Broadly Neutralizing Antibodies in CSF-Derived HIV

- Near full-length HIV-1 envelope variants from paired CSF and blood plasma samples of 9 adults by SGA
- CSF compartmentalization in 55% (5/9)
- Autologous neutralization: No significant differences in sensitivity between CSF and blood viruses
- **BNAbs: Large differences between CSF and blood viruses with both compartmentalized and equilibrated CSF populations**

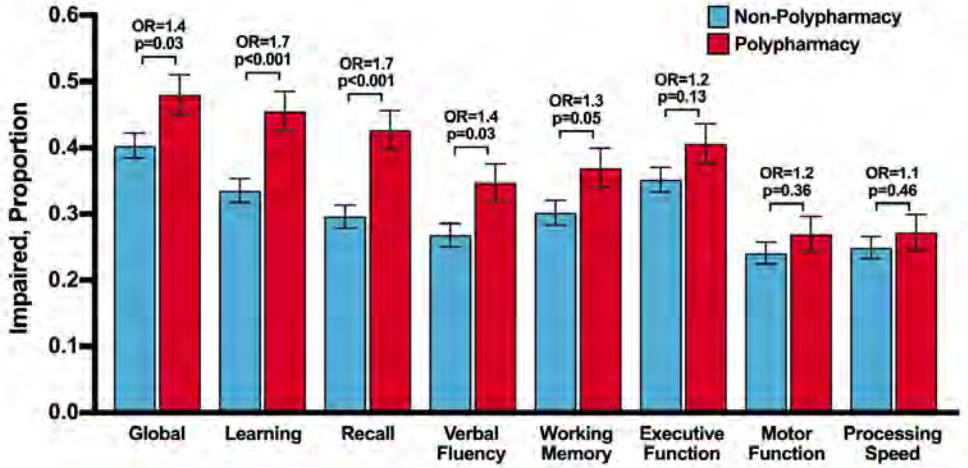
| | Compartmentalized | | | | | | Equilibrated | | |
|---|---|---|---|---|---|---|---|---|---|
| | KU | | | RO | | | BA | | |
| | blood | CSF | ratio | blood | CSF | ratio | blood | CSF | ratio |
| PGT121 | 0.023 | 0.201 | **x 9** | > 10 | 8 | x 1 | 1.493 | 0.015 | **x 99.5** |
| PG16 | 0.06 | 2.597 | **x 43** | > 10 | > 10 | - | 0.087 | 0.178 | x 2 |
| PGT145 | 4.267 | 0.539 | **x 8** | 0.13 | 0.023 | **x 5.5** | < 0.005 | 0.075 | **x 15** |
| VRC03 | > 10 | > 10 | - | > 10 | > 10 | - | 0.631 | > 10 | **x 16** |
| 8ANC195 | > 10 | > 10 | - | > 10 | 4.167 | x 2.5 | > 10 | > 10 | - |
| 10E8 | 1.37 | 1.626 | x 1 | 5.128 | 1.754 | x 3 | 1.449 | 3.333 | x 2.3 |
| sCD4 | 0.526 | 2.264 | **x 4** | 7.69 | 0.22 | **x 35** | 5.56 | 13.7 | x 2.5 |
| MVC | 2,58 | 2,58 | x 1 | 11,1 | 4,63 | x 2,6 | 4,57 | 2,8 | x 1,6 |
| | GK | | | KP | | | BL | | |
| | blood | CSF | ratio | blood | CSF | ratio | blood | CSF | ratio |
| PGT121 | > 10 | > 10 | - | > 10 | > 10 | - | 0.546 | 0.03 | **x 18** |
| PG16 | 0.04 | 0.01 | **x 4** | > 10 | > 10 | - | 0.496 | 0.24 | x 2 |
| PGT145 | 0.05 | 0.018 | x 3 | > 10 | > 10 | - | 1.449 | > 10 | **x 7** |
| VRC03 | > 10 | > 10 | - | > 10 | > 10 | - | 1.163 | 0.164 | **x 7** |
| 8ANC195 | > 10 | > 10 | - | > 10 | > 10 | - | 1.316 | 1.481 | x 1 |
| 10E8 | 3.7 | 4.17 | x 1 | 0.656 | 1.111 | x 1 | > 10 | 8.696 | - |
| sCD4 | 17.24 | 11.77 | x 1.5 | 1.31 | 28.57 | **x 22** | 6.67 | 20.41 | x 3 |
| MVC | 1,70 | 4,63 | x 2,7 | 10 | 5,23 | X 2 | 9,38 | 3,01 | x 3 |

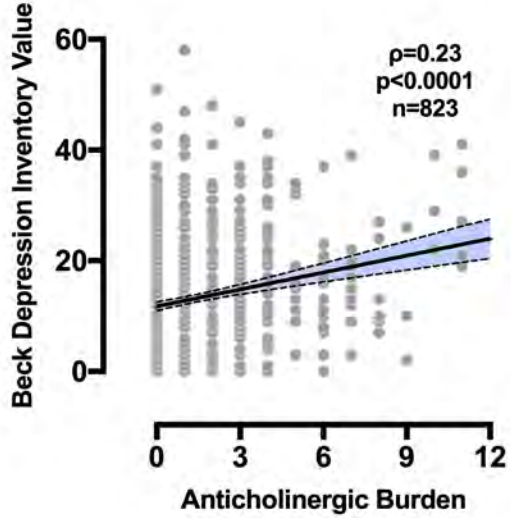
*Stefic et al, CROI 2016, Abstract 400*
*Stefic et al, PLoS ONE 2017, 12(8): e0181680*

# Risks of Polypharmacy in Aging PLWH




*Smit, et al Lancet Inf Dis 2015, 15(7):810-8*



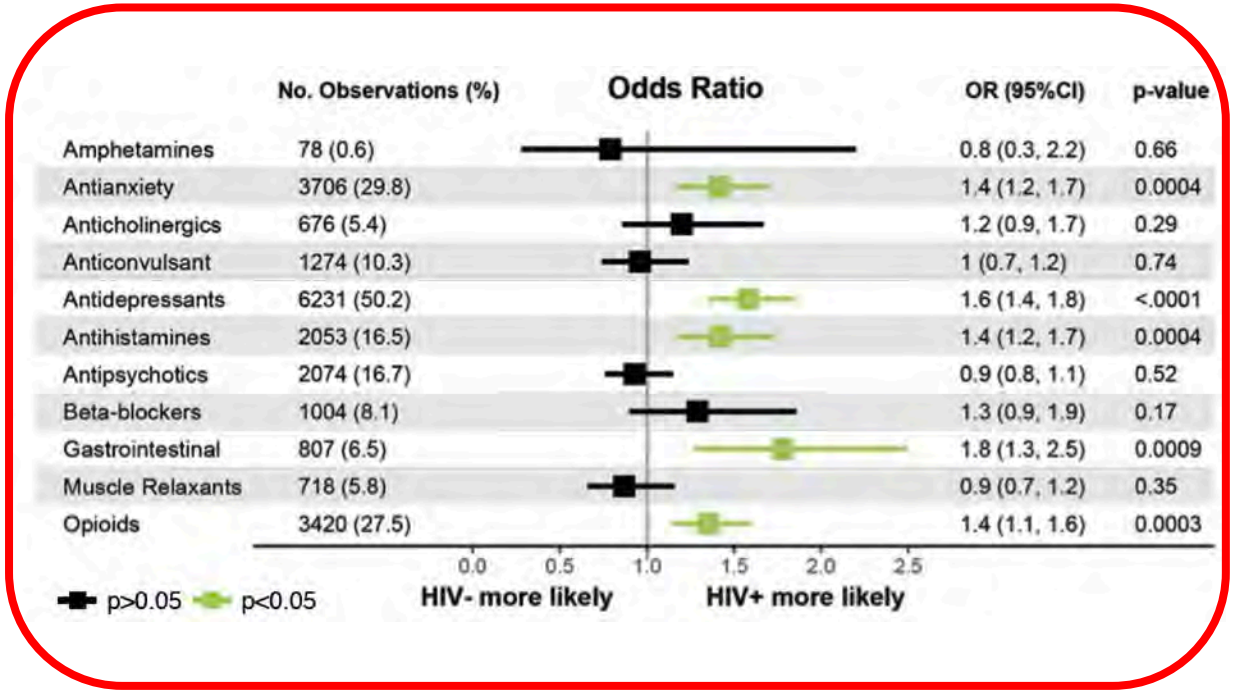



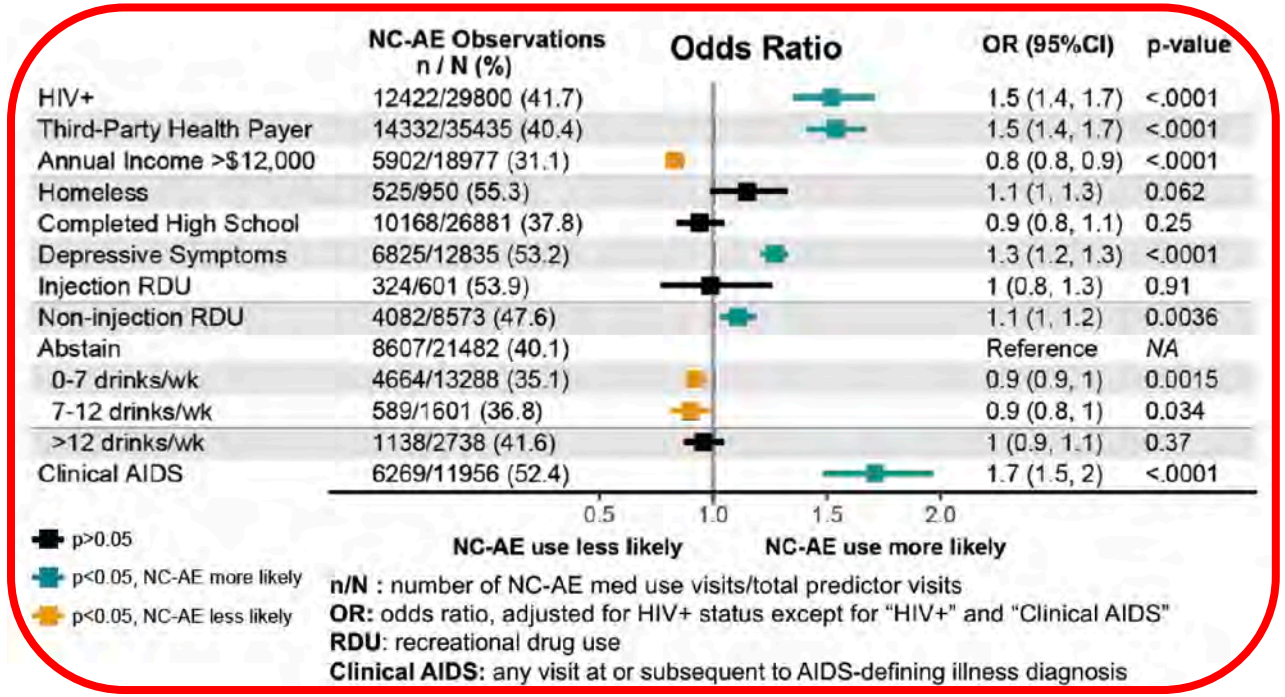

| | Learning | Executive Function | Working Memory | Recall | Processing Speed | Motor Function | Verbal Fluency |
|---|---|---|---|---|---|---|---|
| Anxiolytics | ** | ** | ** | ** | ** | - | * |
| Antipsychotics | ** | ** | ** | ** | - | * | ** |
| Opioids | ** | ** | ** | * | ** | * | - |
| Antimicrobials | ** | ** | - | ** | * | - | - |

** (Red): p < 0.01, * (Yellow): p < 0.05, - (Green): p > 0.10, statistical significance

*Ma, et al CROI 2019, Abstract 437*

# Women with HIV are More Likely to Use Other Medications Associated with NP-AEs




**n/N :** number of NC-AE med use visits/total predictor visits
**OR:** odds ratio, adjusted for HIV+ status except for "HIV+" and "Clinical AIDS"
**RDU**: recreational drug use
**Clinical AIDS:** any visit at or subsequent to AIDS-defining illness diagnosis

## NP-AE Drug Use and ART

| Outcome | OR (95% CI) | p-value |
|---|---|---|
| cART use | 1.46 (1.35-1.57) | <0.0001 |
| cART adherence | 1.03 (0.95-1.12) | 0.45 |
| Undectable viral load | 1.12 (1.05-1.19) | 0.0008 |

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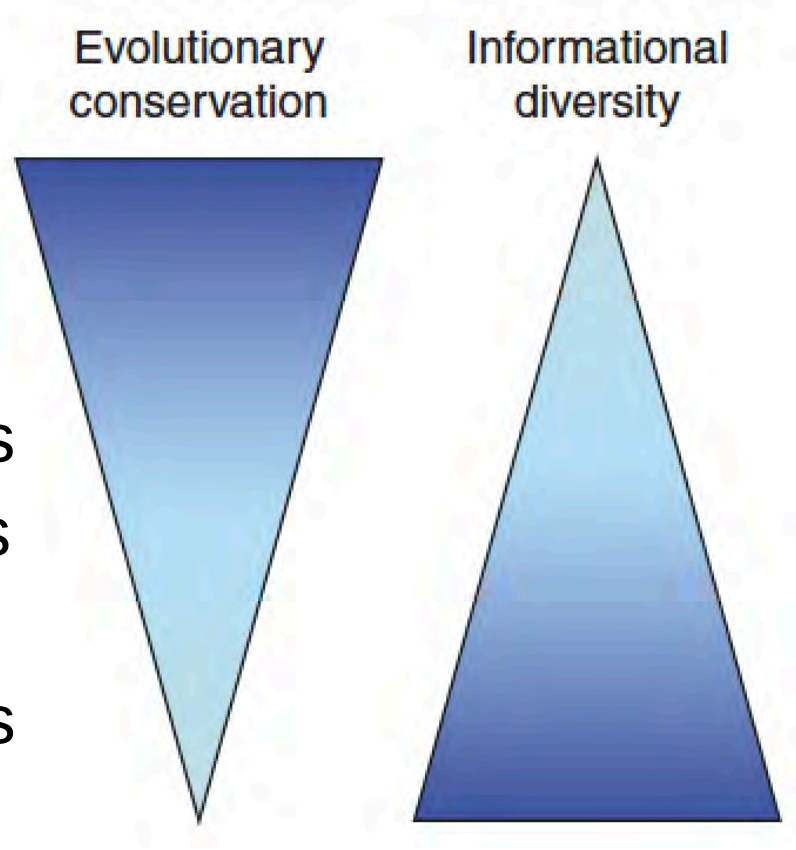
*Radtke, et al. CROI 2018, Abstract 401*

# Attack of the ’Omes

# ‘Omes Differ by Informational Diversity and Evolutionary Conservation

- **Genome:** DNA
- **Transcriptome:** mRNA, miRNA, others
- **Proteome:** Structural and functional proteins
- **Metabolome:** Energy flux, signaling proteins
- **Lipome:** Lipid-based membranes
- **Glycome:** Cell surface and secreted glycans

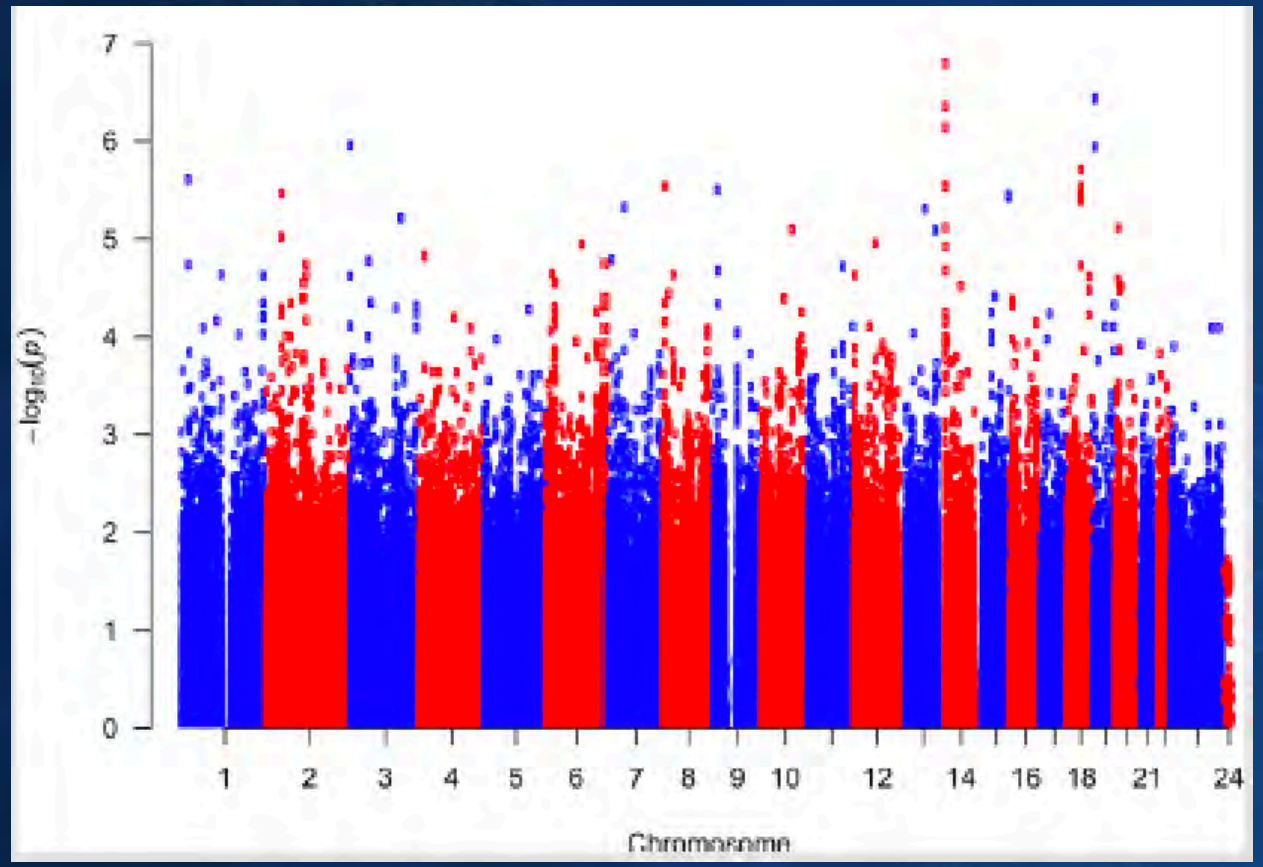


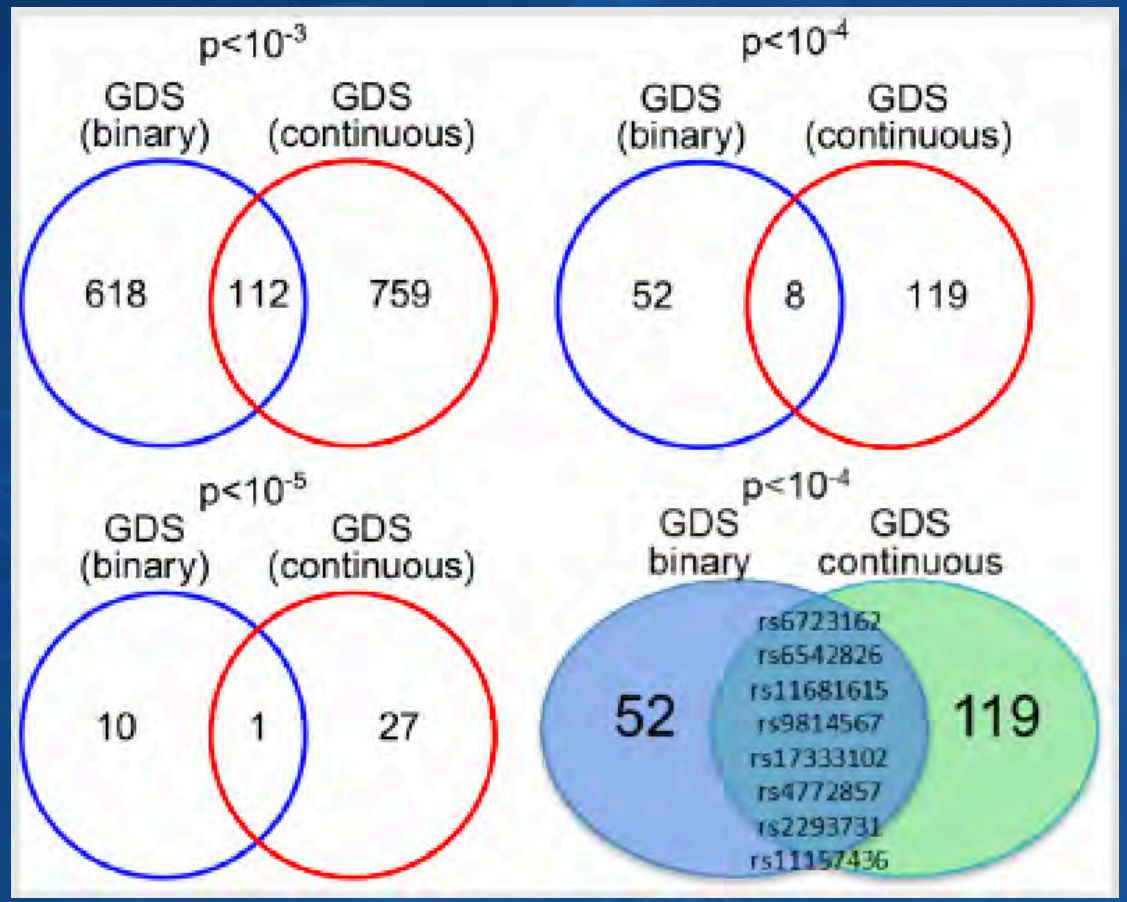

*Varki, A, Cold Spring Harb Perspect Biol 2011, 3:a005462*

*Giron et al, CROI 2019, Abstract 124*

# Genome

# Genomewide Association Study of HAND




*Jia et al, Am J Med Genetics 2017, 174(4):413-426*

**FAM155A**

# Biological Plausibility

- **T-Cell Receptor-α**
  - » One component of the αβ TCR heterodimer, involved in T-cell activation
  - » Knock-out mouse studies identified a role for TCRα in adult neurogenesis particularly in the hippocampus, which is commonly affected in HAND
- **SH3RF3**
  - » Involved in regulating endosome sorting and signaling (may be relevant to amyloid β clearance and accumulation)
  - » Associated with age of onset in familial Alzheimer's disease
- **FAM155A**
  - » Unknown function; Strongly associated with depression personality trait in the SardiNIA cohort, although this did not validate in the Baltimore Longitudinal Study of Aging

*Jia et al, Am J Med Genetics 2017, 174(4):413-426*

| Genes/processes dysregulated in HAND | Clinical phenotype(s) evaluated[1] | Study design(s) | Replication status[2] |
|---|---|---|---|
| *Nuclear genes* | | | |
| *APOE (E4 allele)* | AIDS with ADC/HAD±HIVE; non-AIDS with HAND±neuropathologic features | Autopsy (mostly case-control; one survival study with autopsy component; 2 uncontrolled); cross-sectional; longitudinal cohort | R |
| *TNFA* | HAD; HAD/ADC, or HIVE and/or HIV-LE | Autopsy case-control | NR |
| *MCP1/CCL2, CCR2* | HAD±HIVE or AIDS/ADC, *OR* change in executive functioning and processing speed between 2 consecutive visits up to 15 yrs apart; or NCI (clinical rating score≥5); HAE (children) | Retrospective case-control; longitudinal cohort±cross-sectional analysis | R (*MCP1*) NA (*CCR2*) |
| *MIP1A/CCL3* | HAD; AIDS with HAD; *OR* change in executive functioning and processing speed between 2 consecutive visits up to 15 yrs apart; *OR* risk of NCI | Retrospective case-control; longitudinal cohort | R |
| *SDF1* | Decline in NC test scores and/or brain growth failure in children; *OR* change in executive functioning and processing speed between 2 consecutive visits up to 15 yrs apart; *OR* prevalent NCI (adults); change in GDS or cross-sectional GDS in co-HCV+ | Longitudinal cohort with cross-sectional component; retrospective case-control | NR |
| *MBL2* | Changes in GDS or cross-sectional GDS in co-HCV+; *OR* change in executive functioning and processing speed between 2 consecutive visits up to 15 yrs apart; *OR* prevalent NCI (adults) | Longitudinal cohort with cross-sectional component | NR |
| *CCR5 (δ32 del)* | HAD/ADC; AIDS±HAD; decline in NC test scores and/or brain growth failure in children; NCI in children; GDS (change and cross-sectional) | Longitudinal cohort±cross-sectional component; case-control | R prior to 1991 only; NR in cART era |
| *COMT* | Executive functioning domain Deficit Scores±stimulant abuse; HAND: standardized NP domain T-scores | Retrospective/Case-control | NR |
| *DRD2, DRD3* | GDS≥0.5 (NCI); Global and cognitive domain T-scores in population with prevalent substance dependence | Cross-sectional/Case-control | R (DRD3 in substance users) |
| *HLA:DR, DQB1, A24, B27* | Time to CNS impairment ("deterioration in brain growth, psychological function and/or neurological status") | Pre-cART cross-sectional study; cART era case-cohort study; longitudinal cohort | R (*DR, B27*) NA (*DQB*) NR (*HLA A*) |
| *APOBEC3G* | Brain growth failure, with NCI defined differently based on age | Pre-cART pediatric cohort study | NA |
| *PKNOX1/PREP1* | AIDS with dementia | Retrospective case-control | NA |
| *YWHAE* | HAND | Cross-sectional study with HIV+/HIV- controls | NA |
| *Mitochondrial & nuclear DNA structural changes* | | | |
| 8-oxoG modification | HAND "screen", International HIV Dementia Score≤10 | Autopsy case-control | NA |
| Regulation of telomere length | Detailed NP test scores (global and ability domain scores)±history of chronic psychological trauma (Childhood Trauma Questionnaire Short Form) | Cross-sectional with HIV+/HIV- controls | NA |

**Neuro-degenerative**

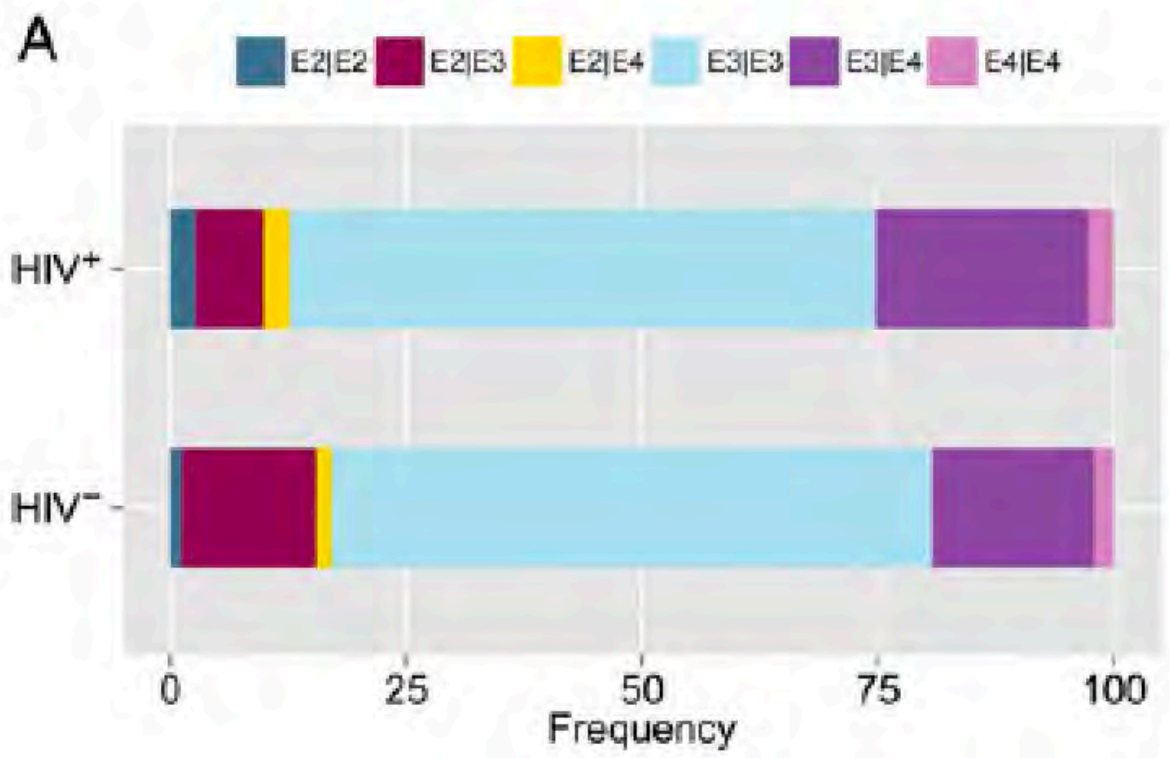
**Immune**

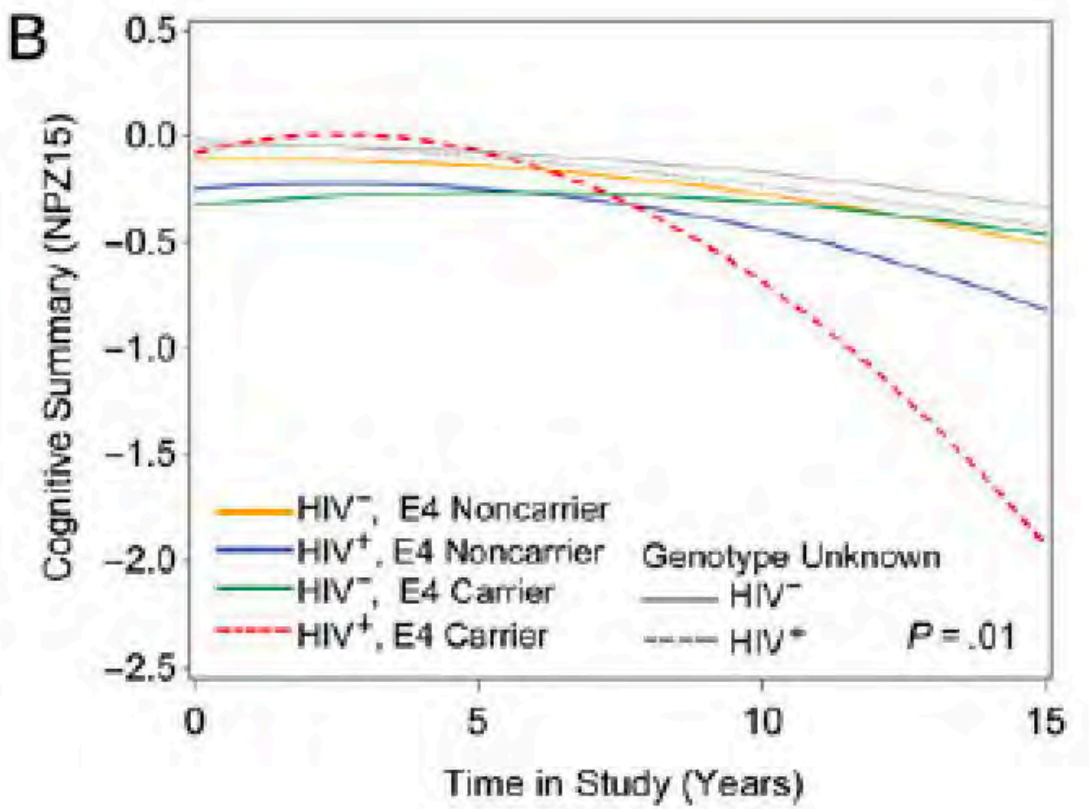
**Dopamine**

**Mitochondrial & Epigenetic**

*Kallianpur & Levine, Curr HIV/AIDS Rep (2014) 11:336–352*

# APOE ε4 Associated with Cognitive Decline in HIV+ Men in MACS



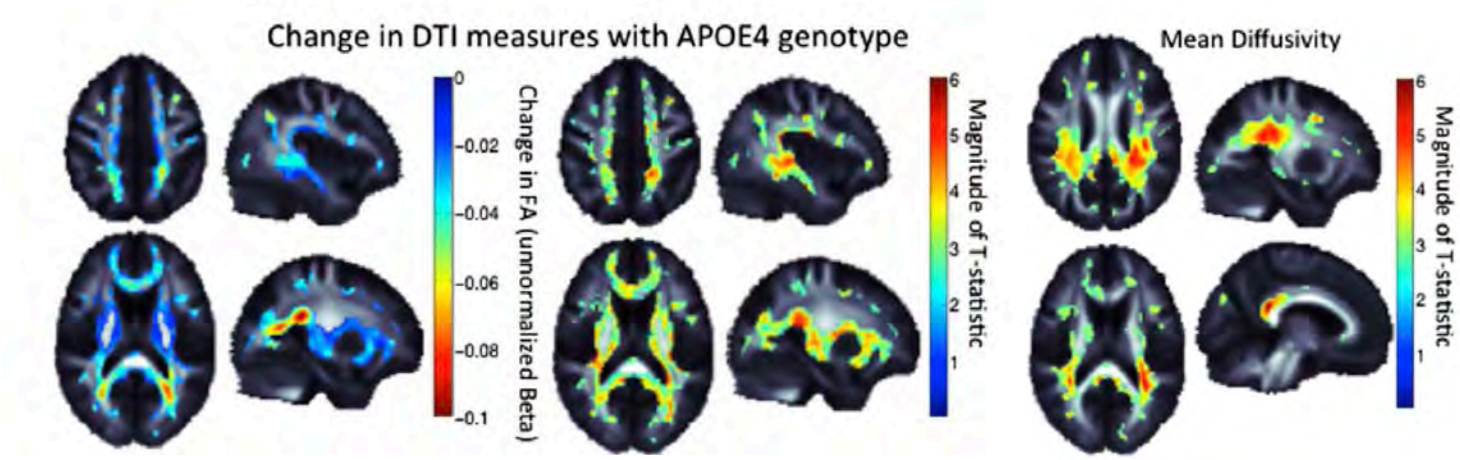




*Mukerji et al, Clinical Infectious Diseases 2016;63(8):1130–9*

# Evidence for APOE ε4 Vulnerability

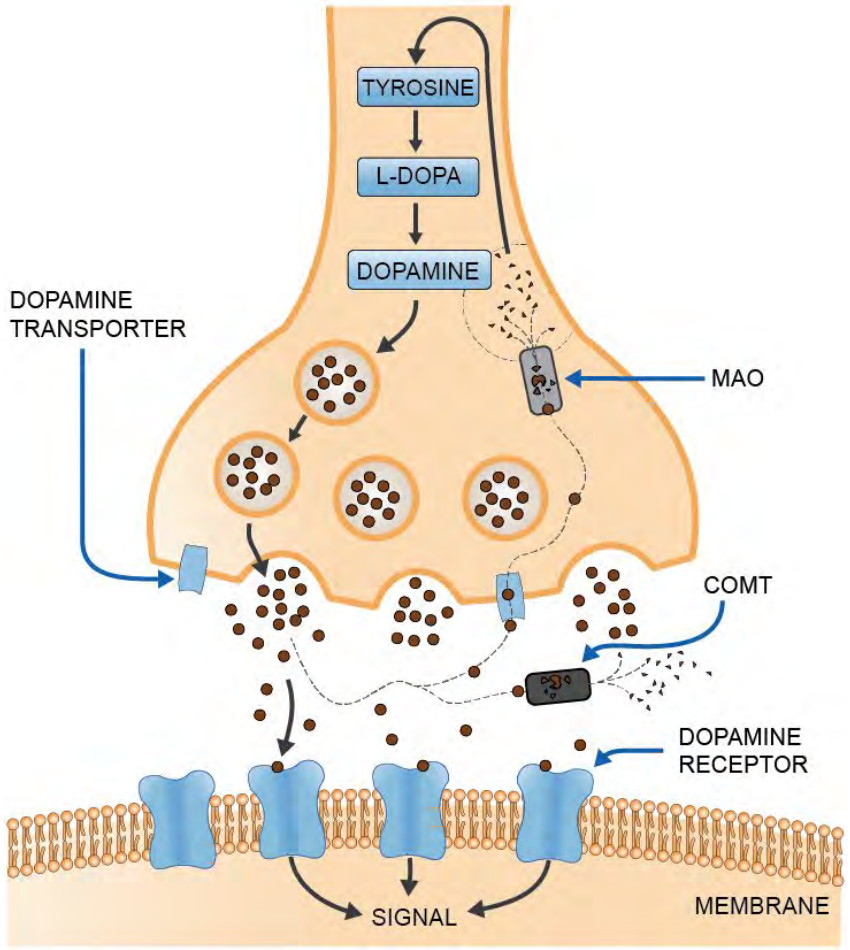
| Author | Year | Sample Size | Outcome | Association | Comment |
|---|---|---|---|---|---|
| **Morales** | 2012 | 36 | NCI<br>Memory Island test | No significant differences<br>Memory Island Test: p<0.05 | Women |
| **Hoare** | 2013 | 45 | NCI | Worse recall: p=0.05 | |
| **Wendelken** | 2016 | 76 | NCI | Worse executive fct, p=0.045 | Older than 60 |
| **Chang** | 2011 | 139 | NCI | HIV+ε4+: Worse verbal fluency, learning, executive function and memory | |
| **Joska** | 2010 | 144 | NCI | No significant differences | South Africa |
| **Chang** | 2014 | 177 | HAND | HIV x ε4 interaction: p=0.02 | |
| **Valcour** | 2004 | 182 | NCI | OR=2.9 (95% CI 1.03-8.24) | Only present in older pts |
| **Spector** | 2010 | 201 | NCI | OR=3.1, p=0.001 | Blood Donors in China |
| **Mukerji** | 2016 | 273 | Cognitive Decline | p=0.01 | Older than 50 |
| **Morgan** | 2013 | 466 | HAND | No differences ε4+ vs. ε4- | CHARTER |

# Evidence for APOE ε4 Vulnerability



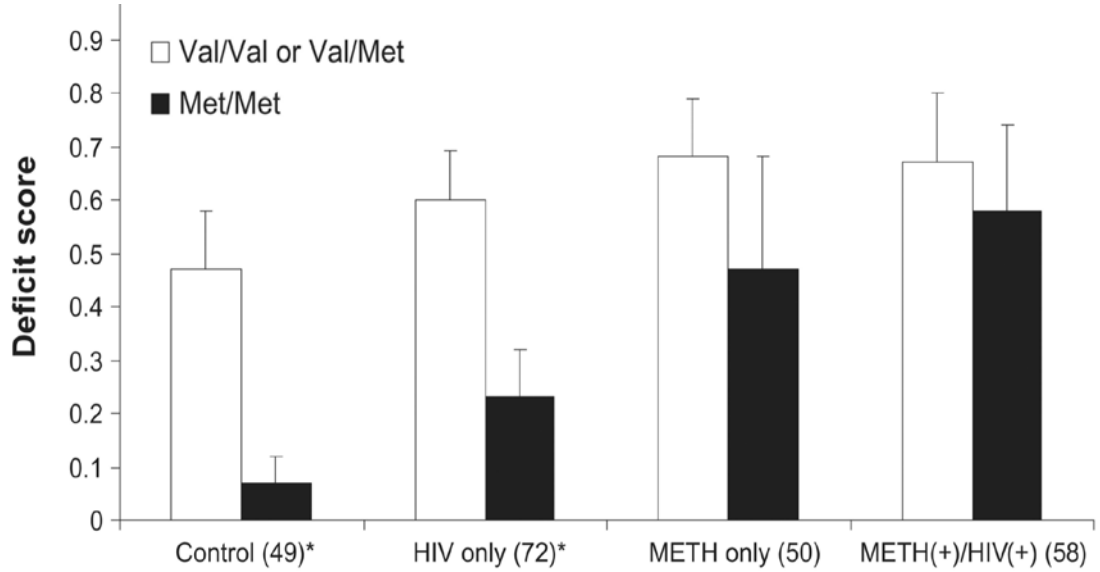

*Wendelken et al, J Acquir Immune Defic Syndr 2016; 73: 426–432*

| Author | Year | Sample Size | Outcome | Association | Comment |
|---|---|---|---|---|---|
| **Hoare** | 2013 | 45 | Diffusion Tensor Imaging | Corpus callosum, p=0.007 | |
| **Wendelken** | 2016 | 76 | Structural MRI and Diffusion Tensor Imaging | Corpus callosum, p=0.016 | |
| **Chang** | 2011 | 139 | Structural MRI | HIV x ε4 x age interactions: p value range 0.03 to 0.005 | |
| **Chang** | 2014 | 177 | MR Spectroscopy | HIV+ & HIV- ε4+: Lower mI | |
| **Cooley** | 2016 | 237 | Structural MRI | No differences ε4+ vs. ε4- | Stratified by age 50 |

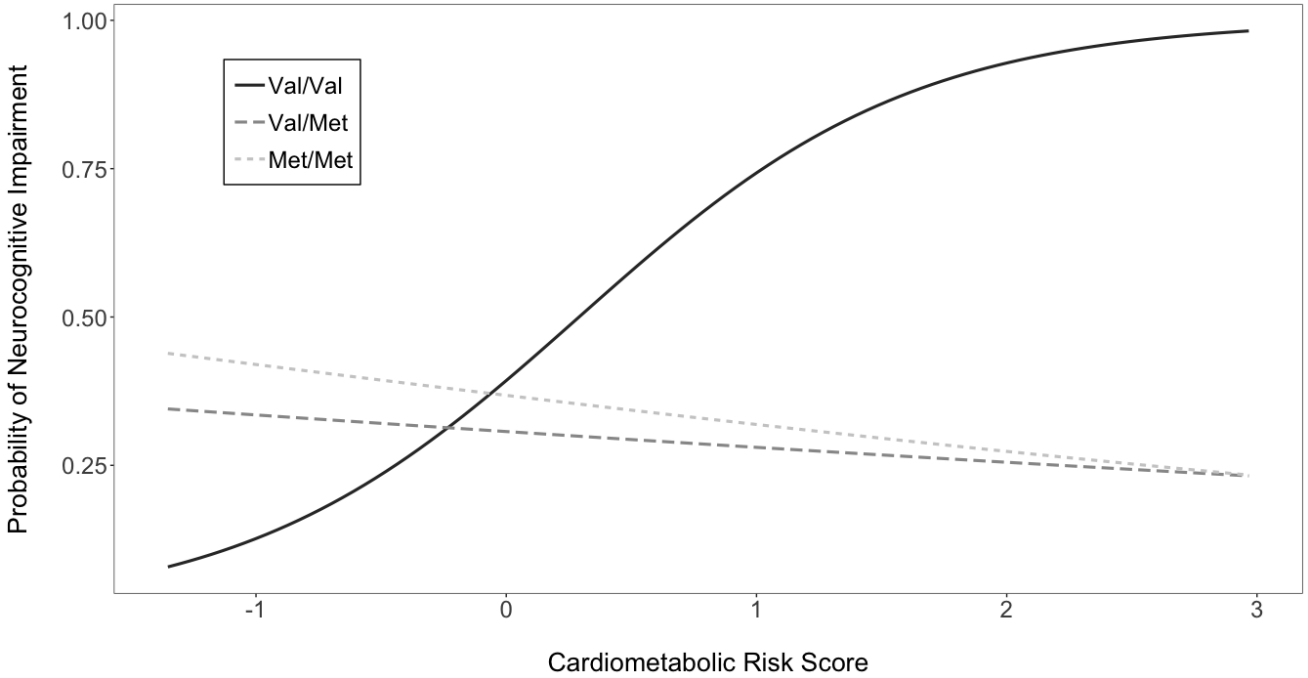



| Gene | Variant | Domain | OR | P value | MAF |
|---|---|---|---|---|---|
| DRD2 | rs6277 | Cognitive flexibility | 1.6 (1.2–2.6) | 0.004 | 0.23 |
| DRD2 | rs6277 | Executive Function | 3.3 (2.0–5.7) | 0.001 | 0.23 |

*Villalba et al. Behav Brain Funct (2015) 11:25*

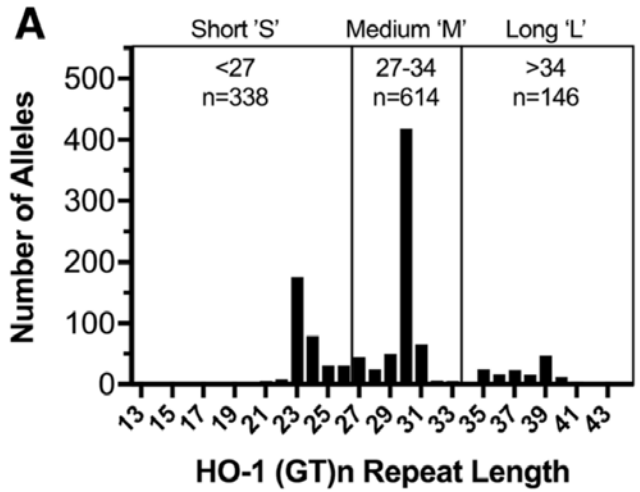


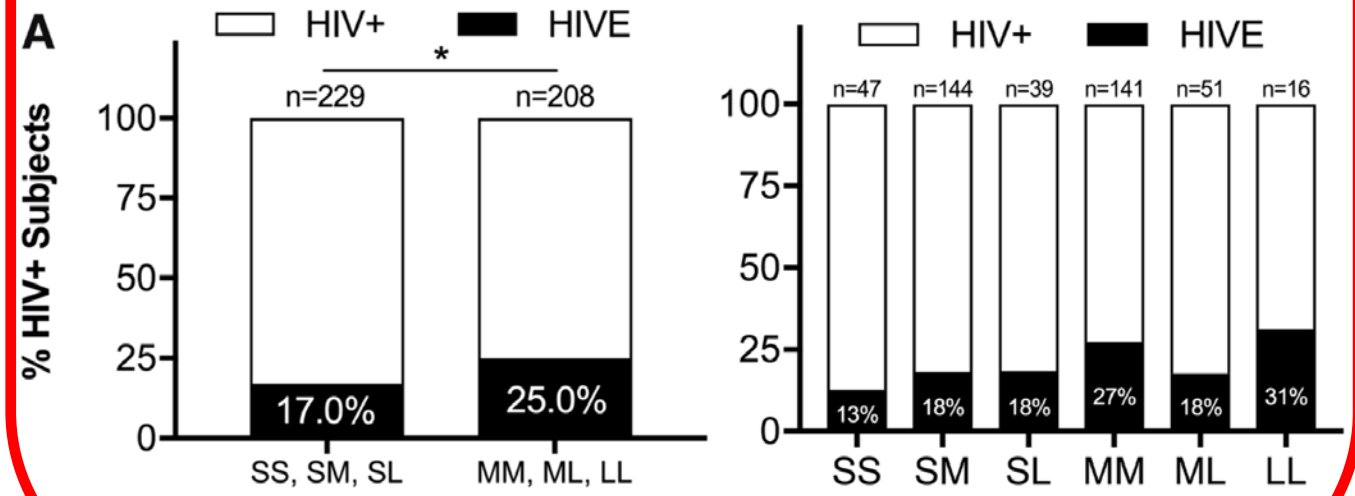

*Bousman et al. Neurobehav HIV Med; 2010: 1–11*



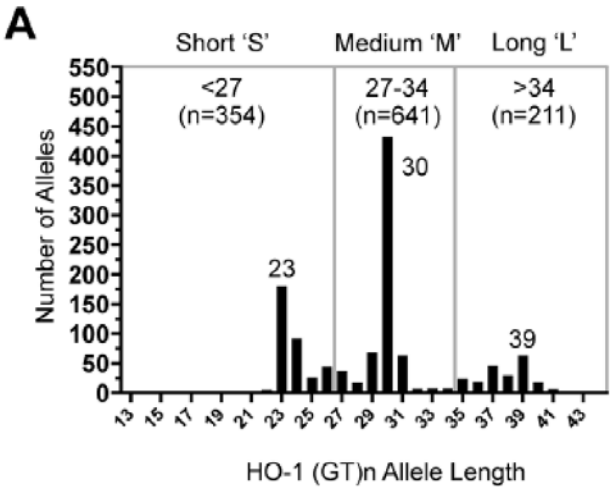

*Saloner et al, J Acquir Immune Defic Syndr. 2019 Apr 29*

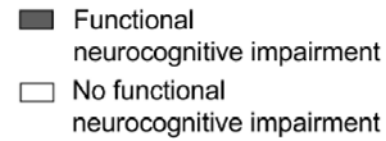
# Heme-Oxygenase-1 Promoter (GT)n dinucleotide repeat polymorphism, HIVE, & HAND

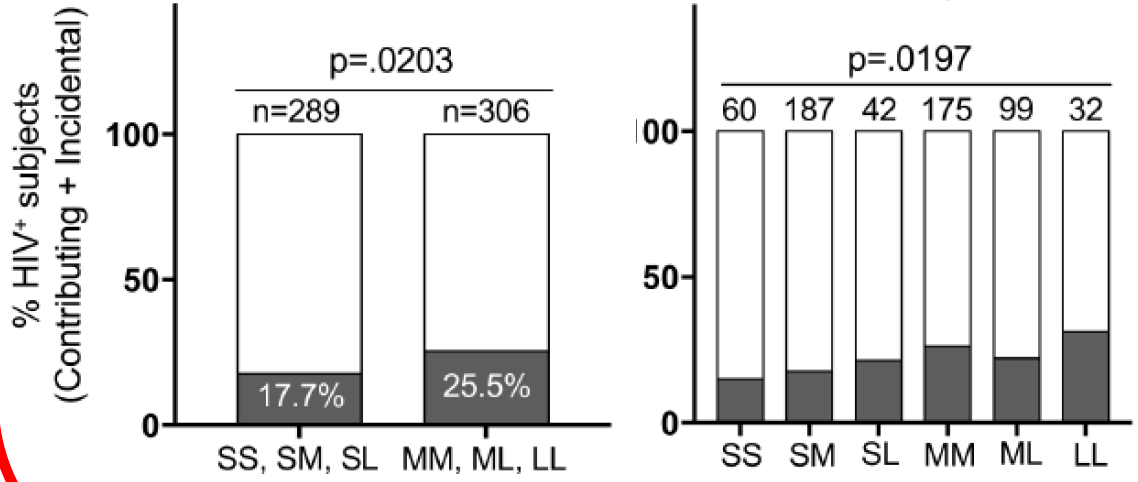



*Gill et al, Journal of Neuroinflammation (2018) 15:70*



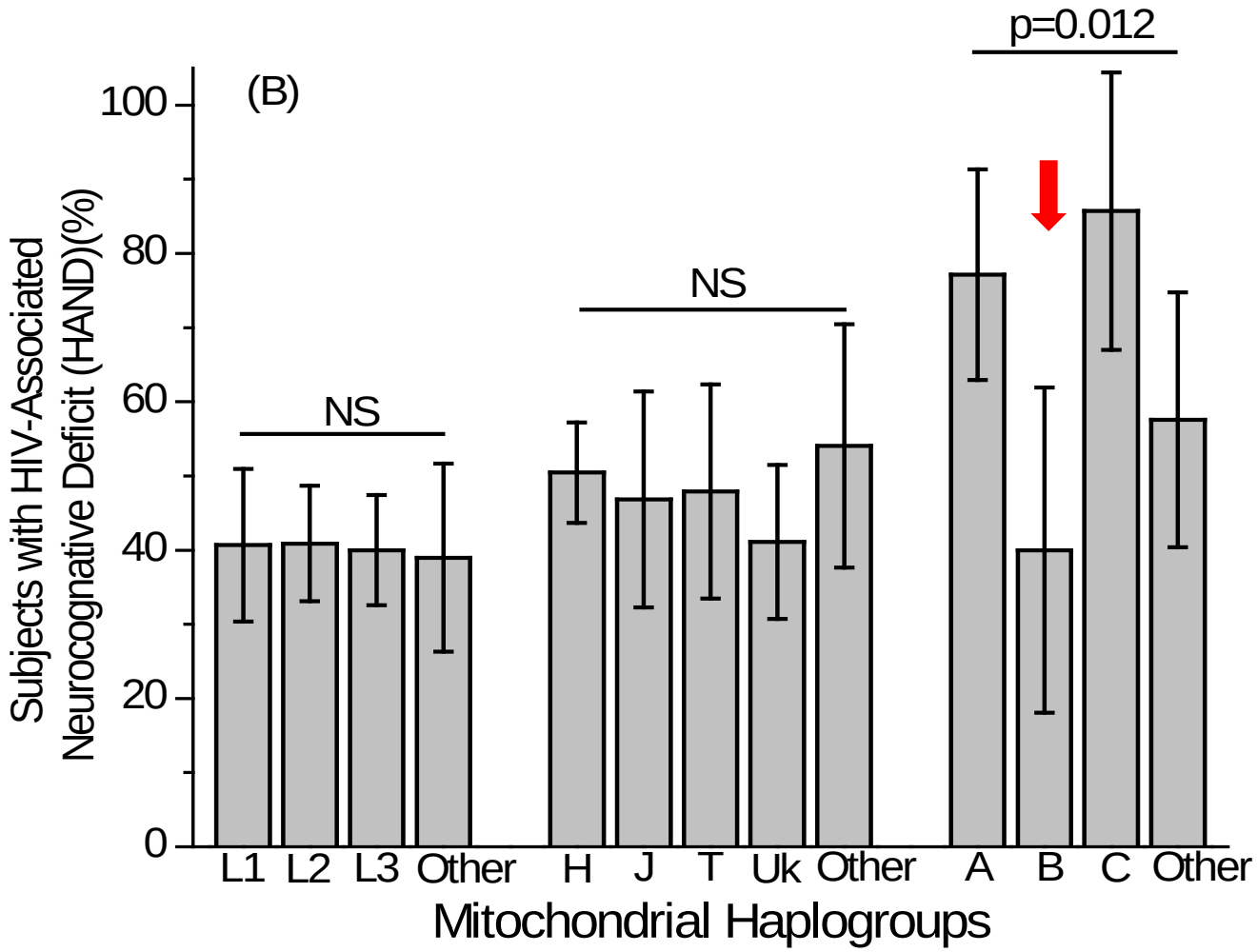

*Garza et al, Submitted 2019*

# Neurocognitive Impairment & HAND are More Frequent in Hispanic-ancestry Persons, but not mtDNA Haplogroup B

- **Post-mitotic, high-energy demands**
- **Neurodegeneration in inherited mtDNA diseases**
- **Mitochondrial link between neuroinflammation and neurodegeneration**

  Di Filippo, et al. *J Alzheimers Dis* 2010; Trudler, et al. *J Neural Transm* 2015
- **mtDNA haplogroups and AD/PD**

  Giannoccaro, et al. *Mov Disord* 2017

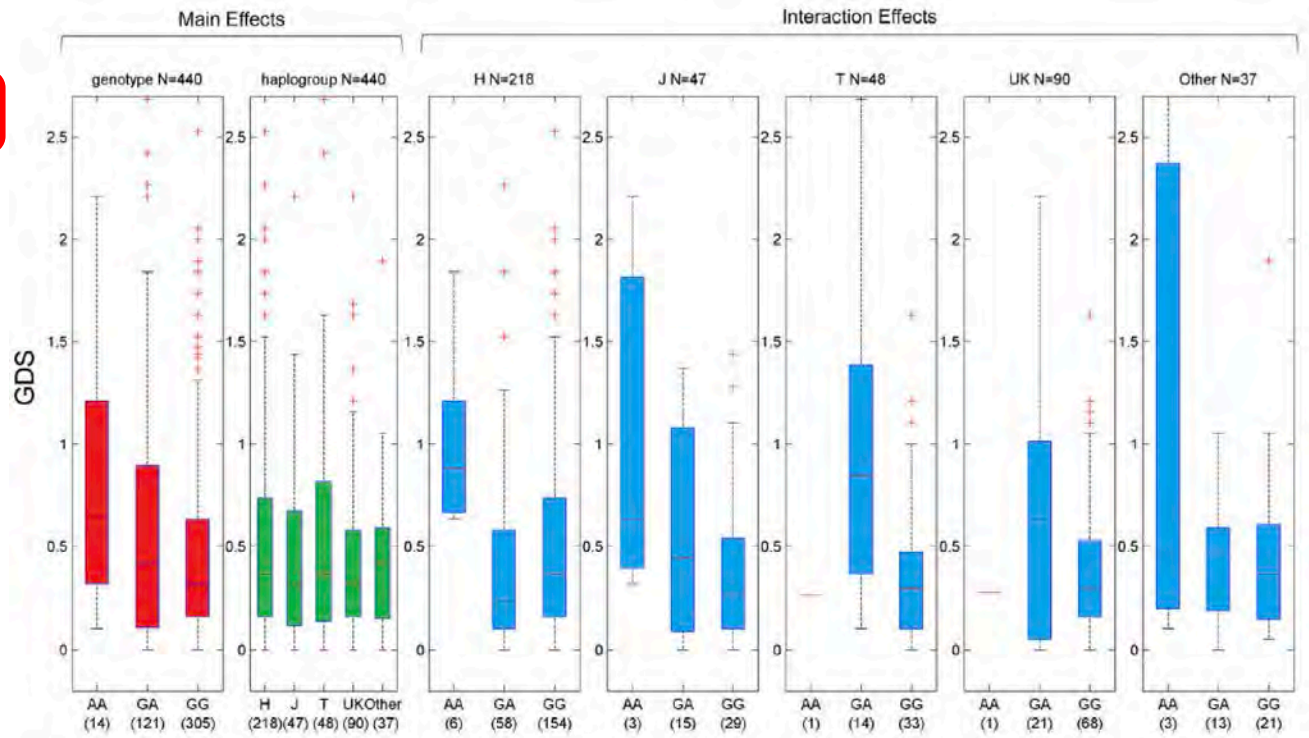



*Slide courtesy Todd Hulgan*

*Clin Infect Dis* 2015; 61(9): 1476-84

# Nuclear-Mitochondrial Interactions

| SNP | β (SNP) | β (MT) | Interaction P |
|---|---|---|---|
| rs17160128 | 0.3353 | 0.0268 | 0.00152 |
| rs12460243 | 0.3324 | 0.03294 | 0.00211 |
| rs17038463 | 0.5041 | 0.144 | 0.01999 |
| rs876084 | 0.008842 | 0.1305 | 0.1068 |
| rs1076546 | 0.2474 | 0.1334 | 0.1713 |
| rs12437004 | 0.248 | 0.1396 | 0.1923 |
| rs6723162 | -0.03417 | -0.1229 | 0.2266 |
| rs11681615 | -0.1184 | -0.03199 | 0.2464 |
| rs978490 | 0.3237 | 0.2019 | 0.2579 |
| rs2293731 | 0.2518 | 0.1474 | 0.2691 |
| rs795943 | -0.1168 | -0.02345 | 0.3423 |
| rs9814567 | -0.141 | -0.07142 | 0.3939 |
| rs2915495 | 0.08236 | 0.1751 | 0.399 |
| rs17154702 | -0.1892 | -0.1189 | 0.4305 |
| rs4772857 | 0.1444 | 0.08426 | 0.4368 |
| rs11157436 | 0.2578 | 0.1892 | 0.4679 |
| rs6542826 | -0.1017 | -0.06286 | 0.6197 |
| rs7840128 | 0.2039 | 0.09352 | 0.6417 |
| rs11915964 | -0.1279 | -0.09742 | 0.7081 |
| rs829418 | 0.2453 | 0.211 | 0.7812 |



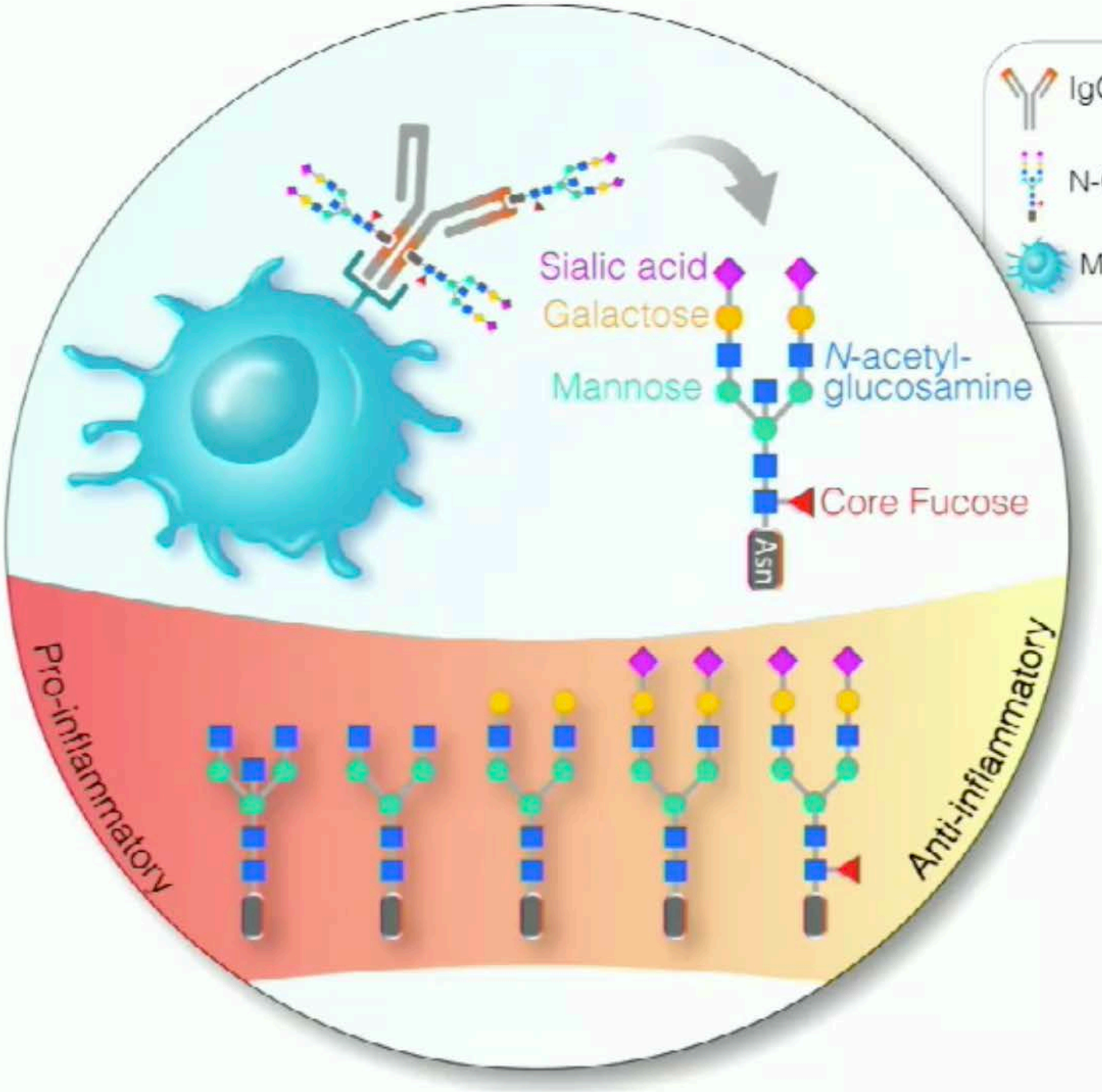

Bonferroni-Corrected P value Threshold=0.0025

- FBN3 is a fibrillin, an extracellular matrix protein that is involved in microfibril formation. FBN3 is highly expressed in the brain (unlike FBN1 and FBN2) and is involved in maintaining BBB integrity

*Smieszek et al, Mitochondrion 46 (2019) 247–255*

# Glycome

# Glycosylation of Secreted Proteins/Antibodies Mediates Inflammatory Responses

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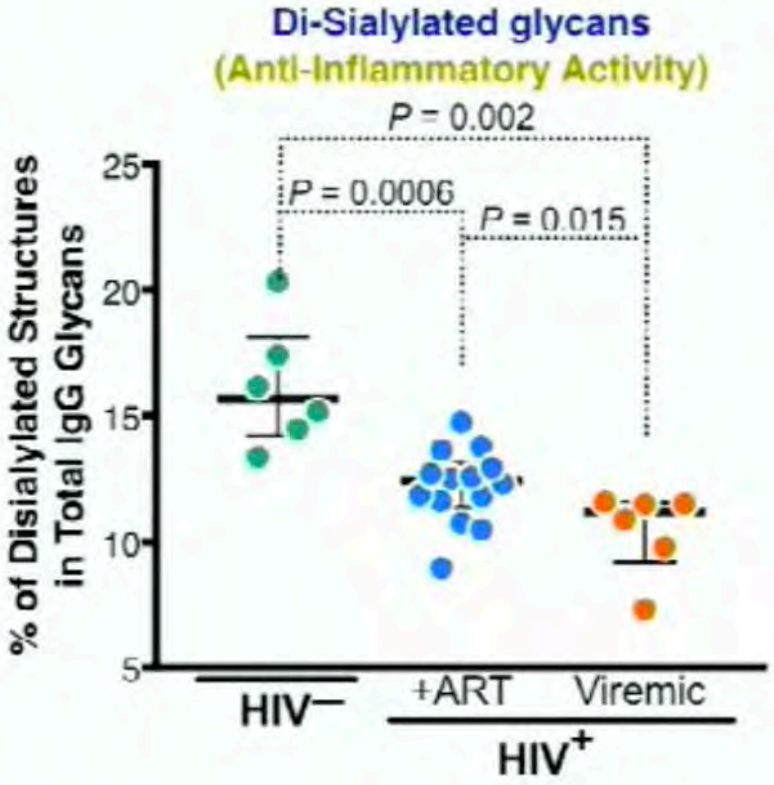
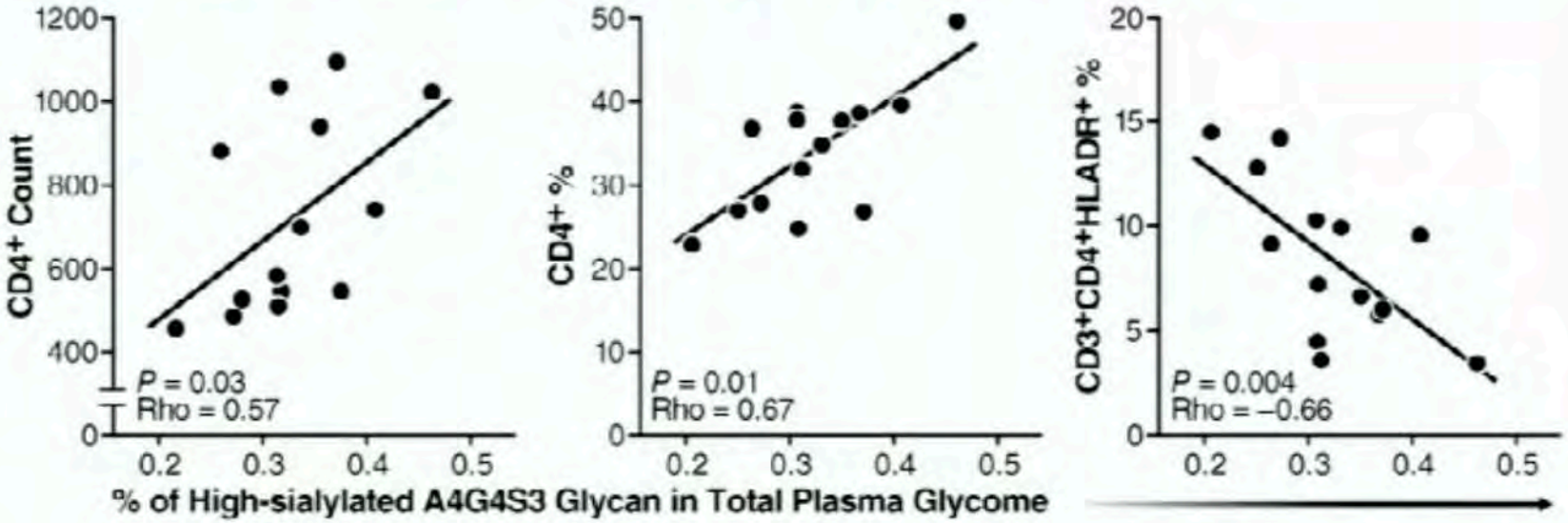
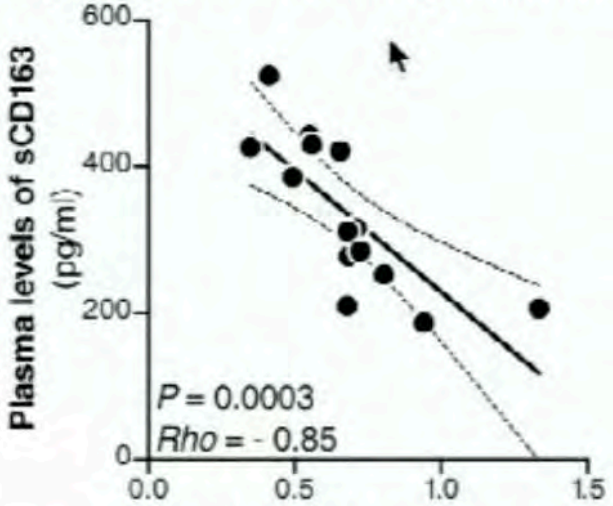
*Giron et al, CROI 2019, Abstract 124*

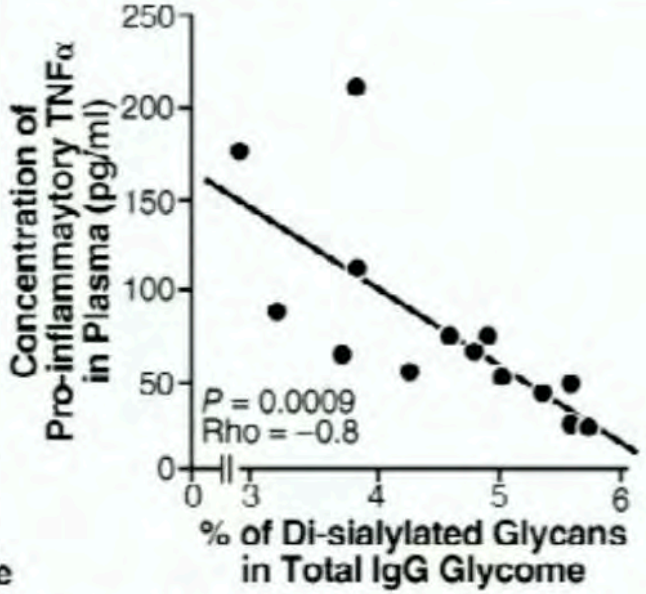
*Colomb et al, Curr HIV/AIDS Rep, 2019*

# HIV Infection is Associated With an ART-irreversible State of Hypo-Sialyation of Circulating Glycoproteins




*Giron et al, CROI 2019, Abstract 124*
*Vadrevu et al, J Leukocyte Biol 2018*

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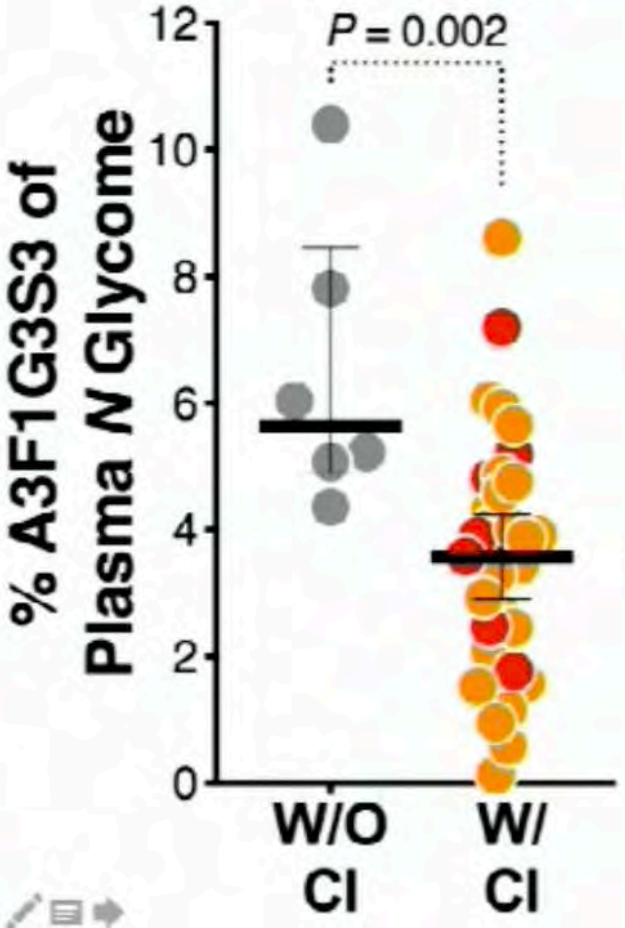
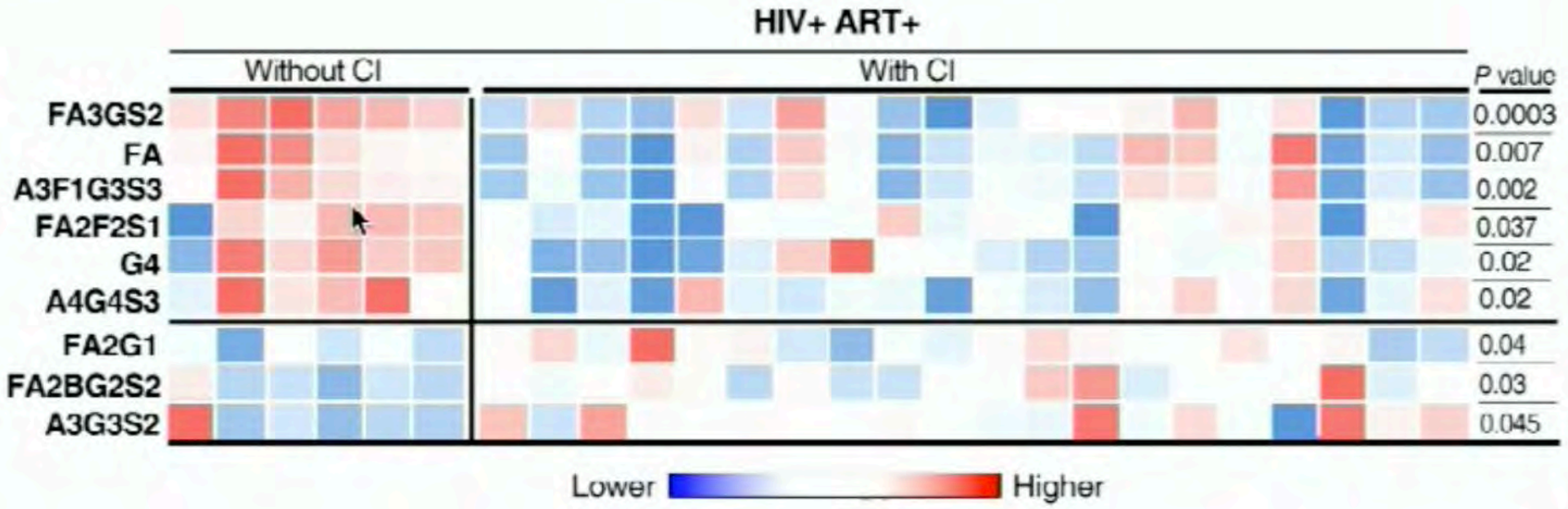
**HIV+ Individuals on Suppressive ART**

# Hypo-sialylation Is Linked to Neurological Impairment in *Total Plasma Glycome*

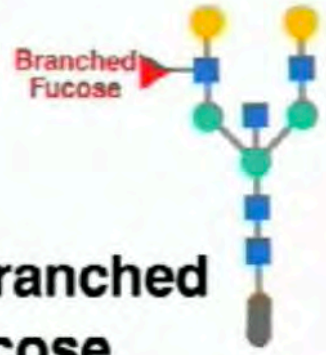



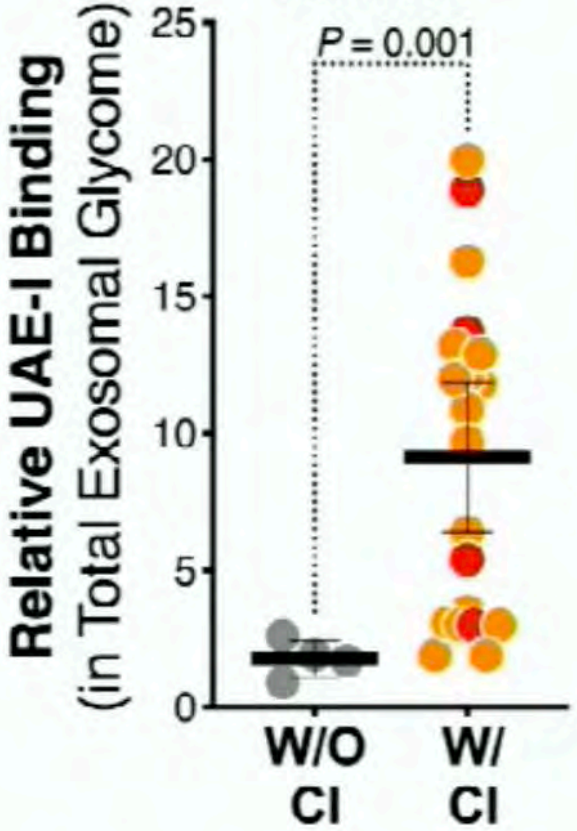

CROI Conference on Retroviruses and Opportunistic Infections

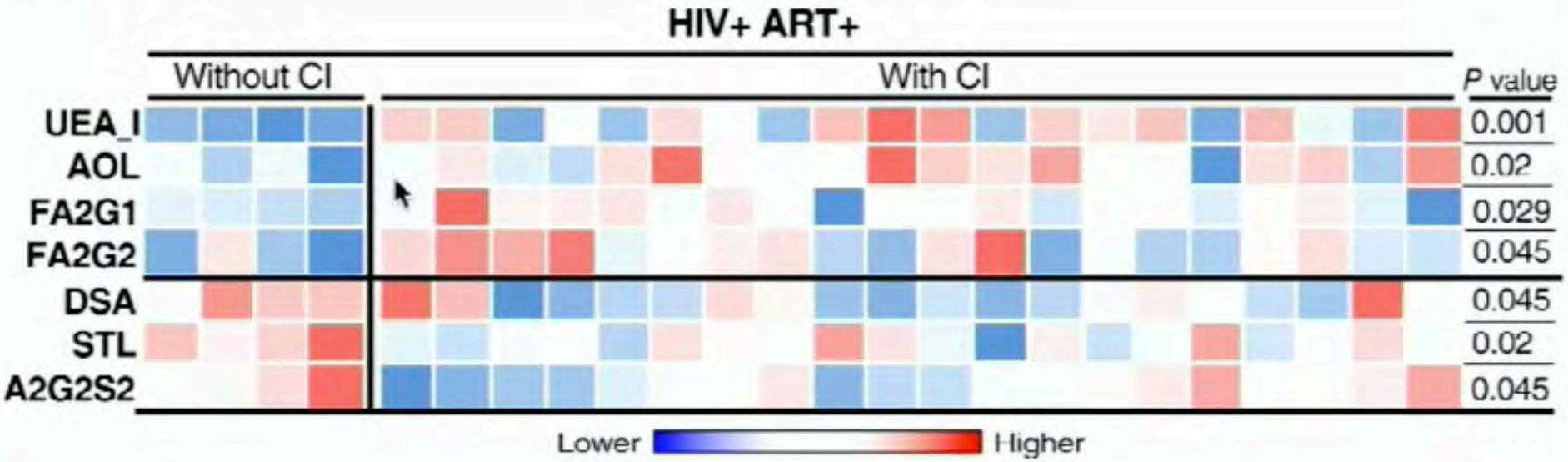
*Giron et al, CROI 2019, Abstract 124*

# Fucosylation Is Linked to Neurological Impairment in Total *Exosomal Glycome*




α1-2 Branched Fucose

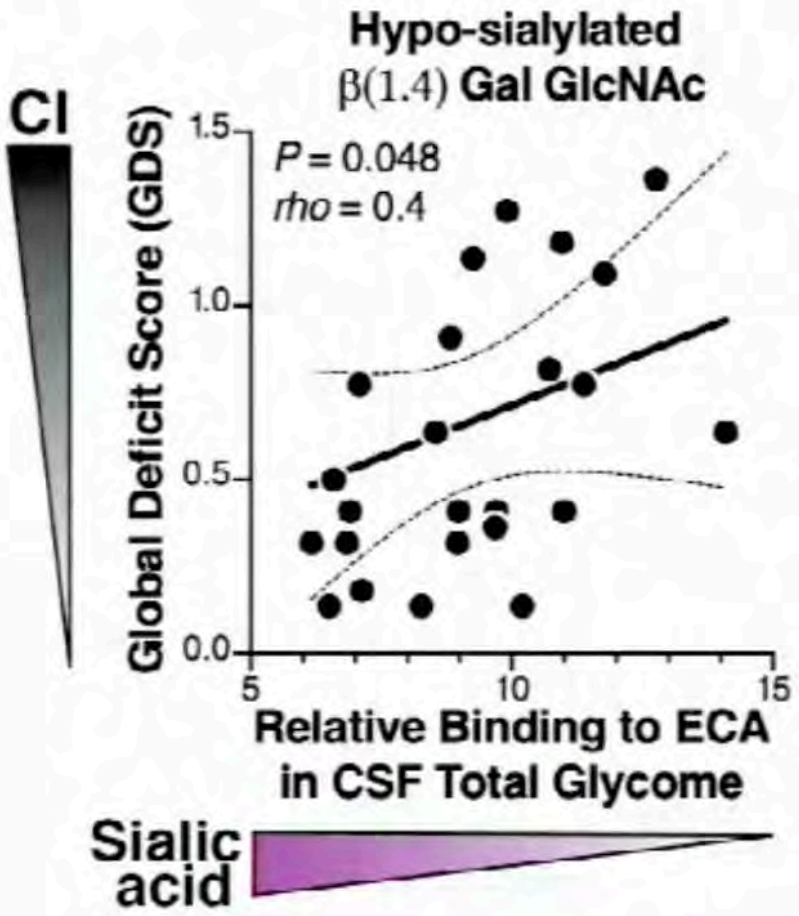


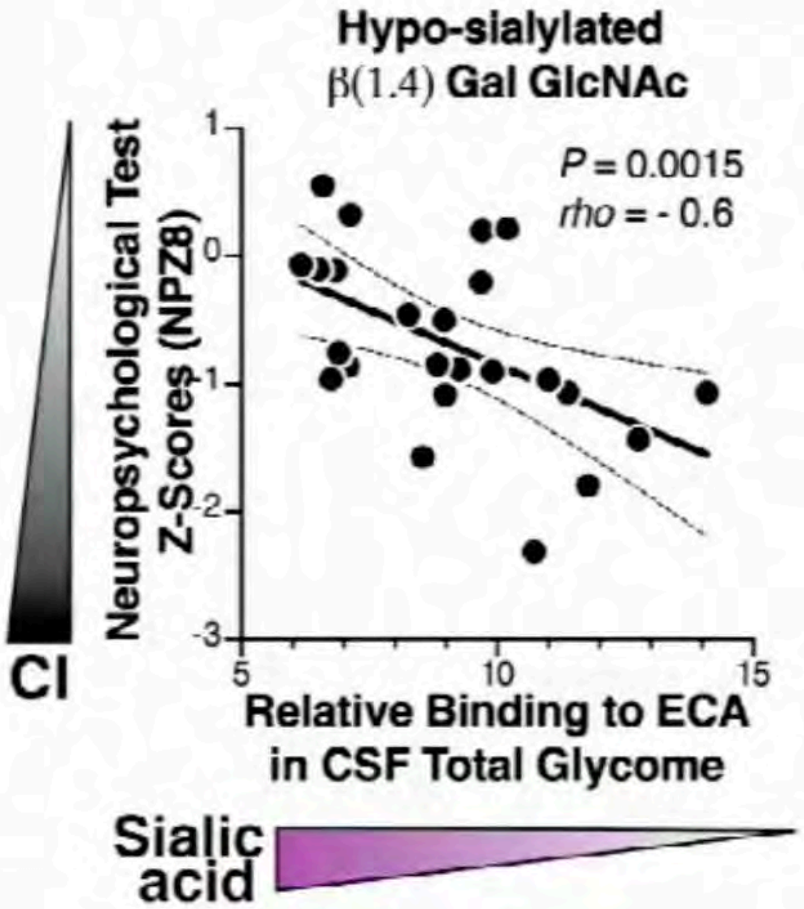




CROI Conference on Retroviruses and Opportunistic Infections

*Giron et al, CROI 2019, Abstract 124*

# Hypo-sialylation Is Linked to CI in *CSF Glycomes*


HIV+ Individuals on Suppressive ART with CI

*Giron et al, CROI 2019, Abstract 124*

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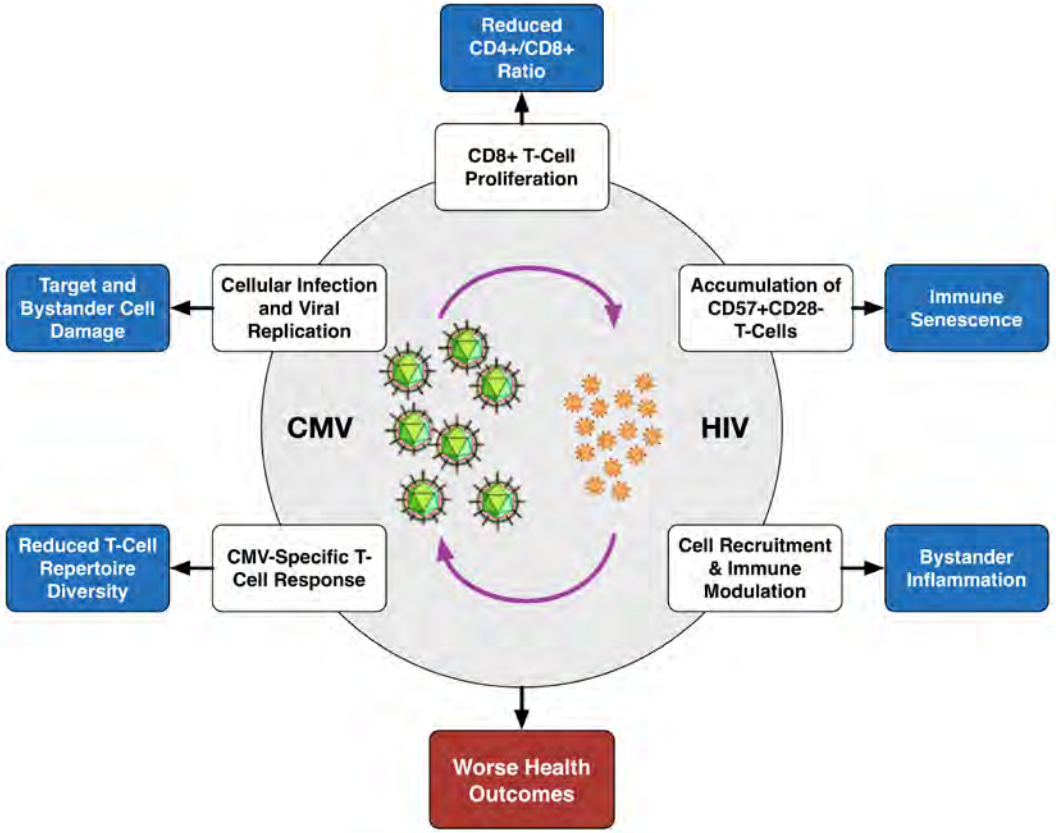
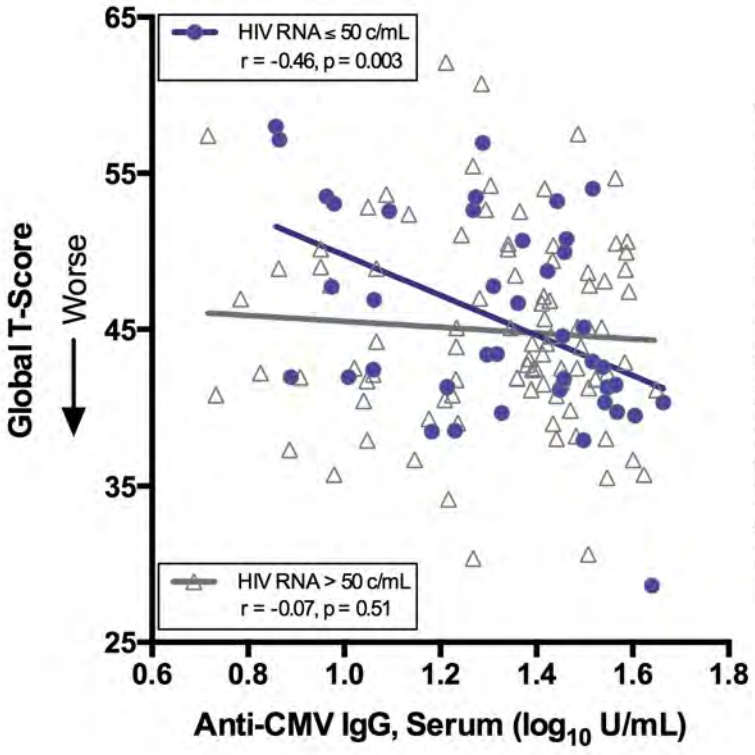
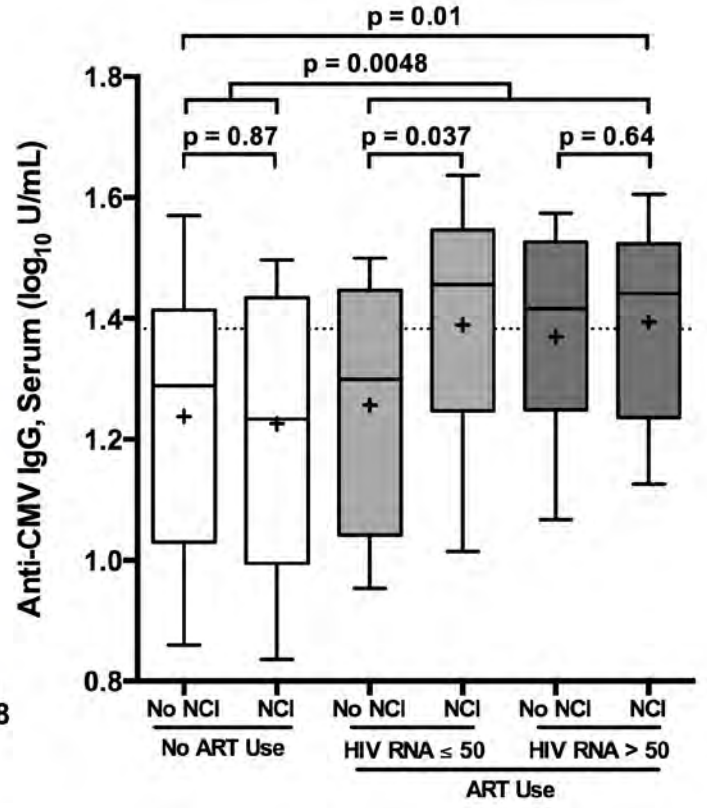
# Virome

# CMV is Associated with Worse Neurocognitive Performance



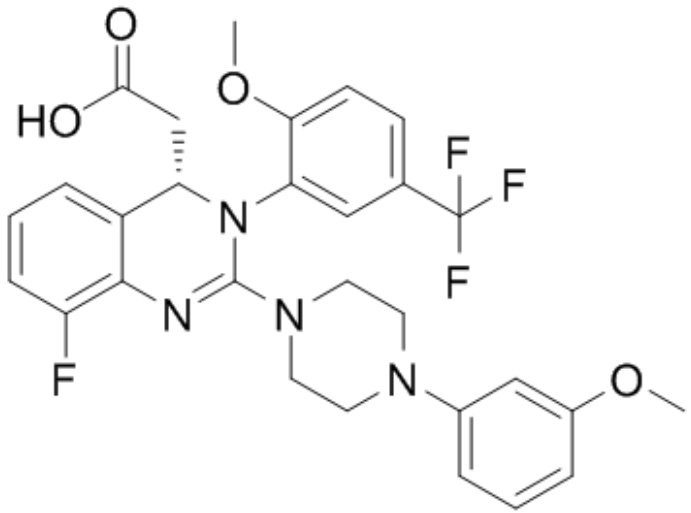



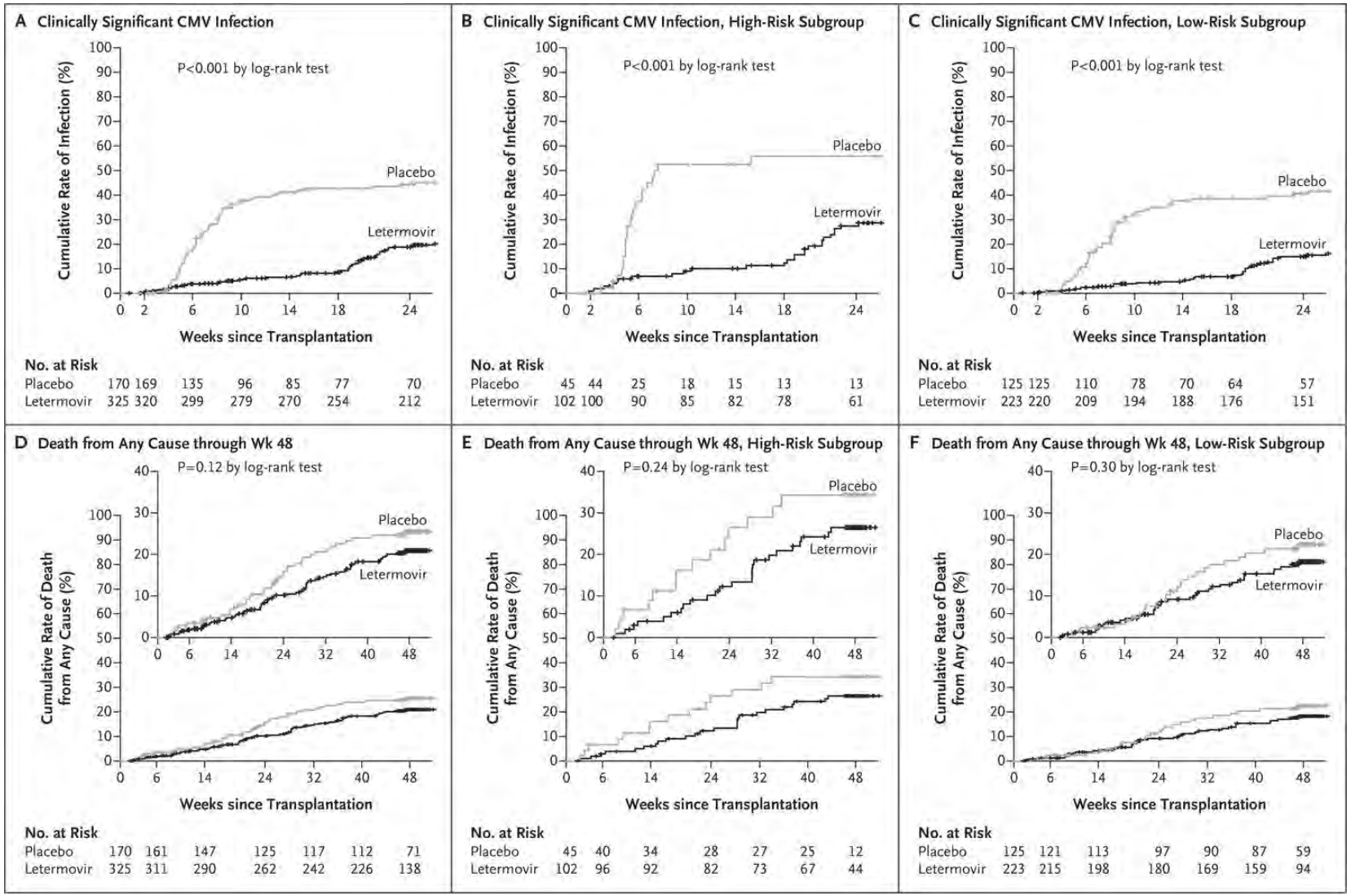

*Gianella & Letendre, J Infect Dis 2016*

*Letendre, et al, Clin Infect Dis. 2018;67(5):770-777*

# Letermovir for Prevention of CMV Morbidity

## Letermovir

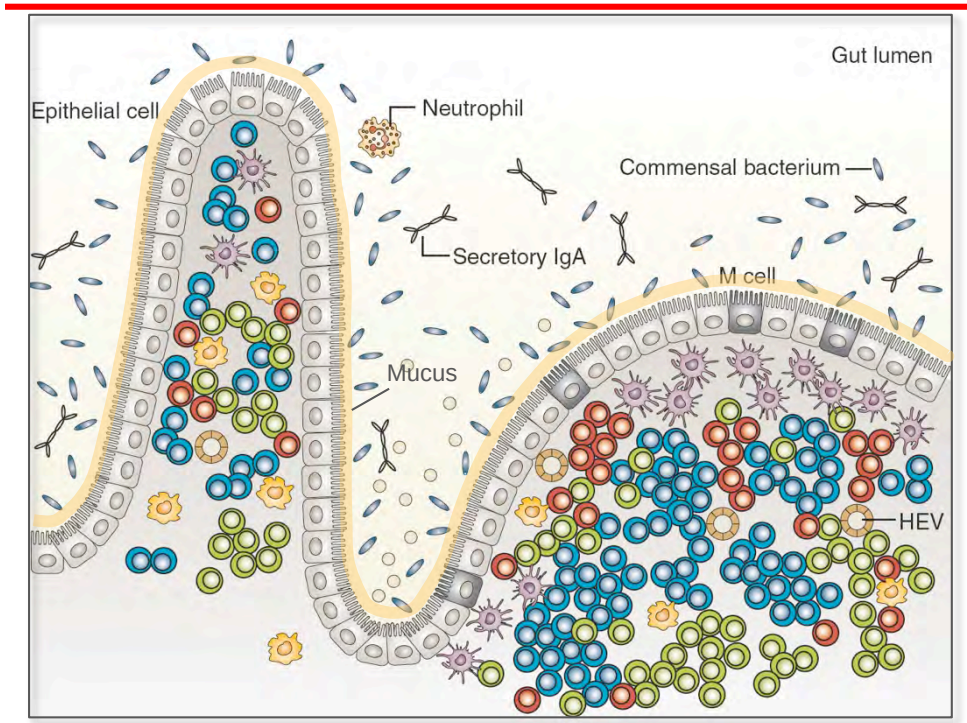



*Marty FM et al. N Engl J Med 2017;377:2433-2444.*

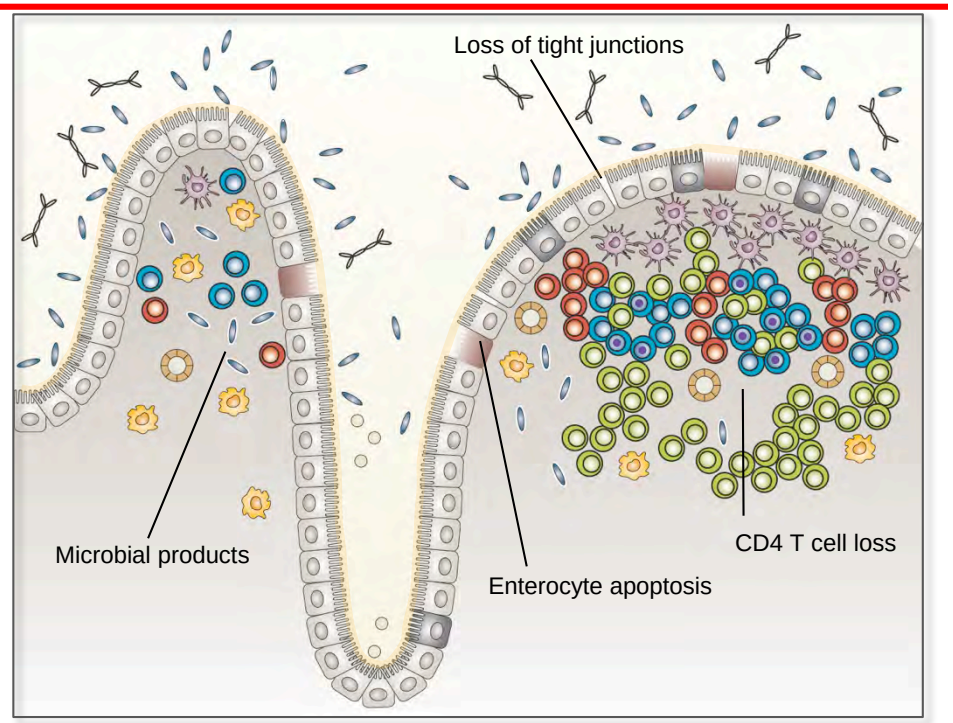
# Microbiome

# The GALT Provides HIV with Abundant Target Cells




**Healthy Gut**

- Majority of CD4+ T cells in body
- Tight epithelial junctions, mucus
- Antimicrobial peptides, antibodies, cells
- Cross-talk between microbes and epithelial cells and immune cells




**HIV-Infected Gut**

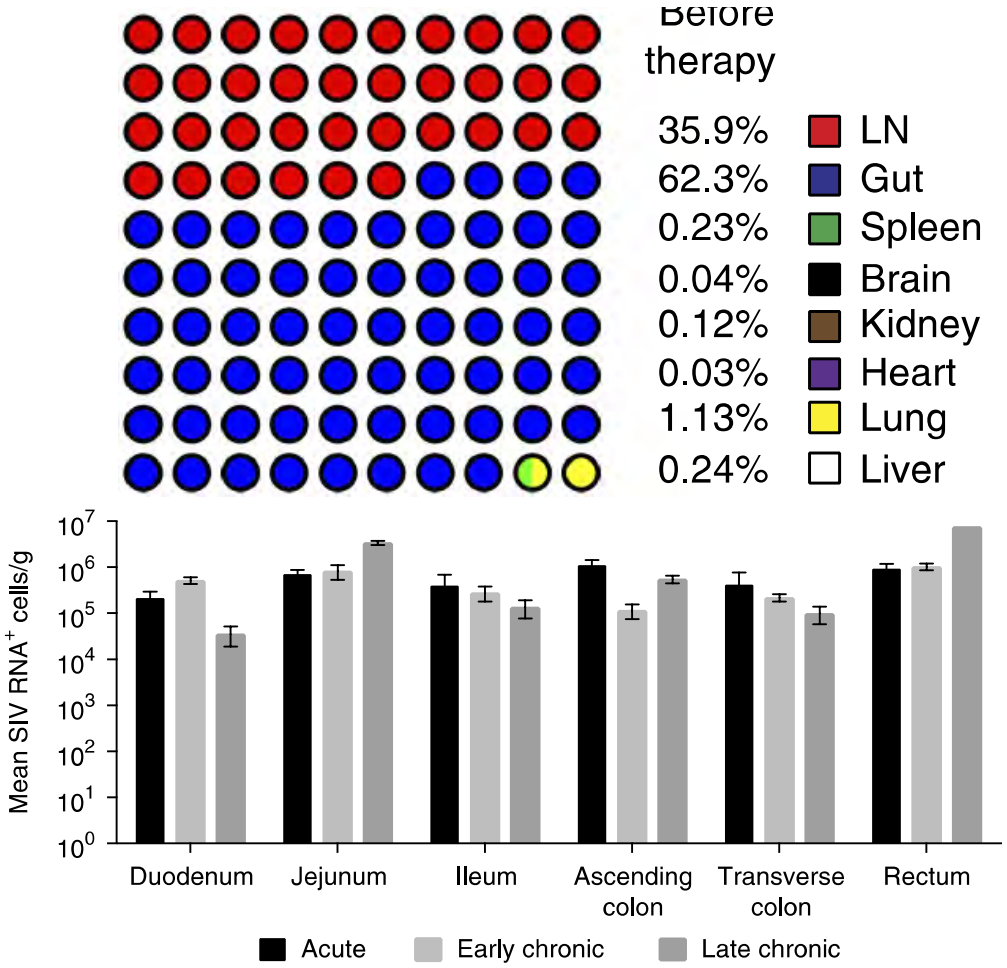
- Massive loss of CD4+ T cells
- Enteropathy
- 2-10x increased permeability
- Translocation of microbial products
- Systemic immune activation

*Slide Courtesy Netanya Utay, M.D.*

*Brenchley and Douek, Mucosal Immunology, 2008*

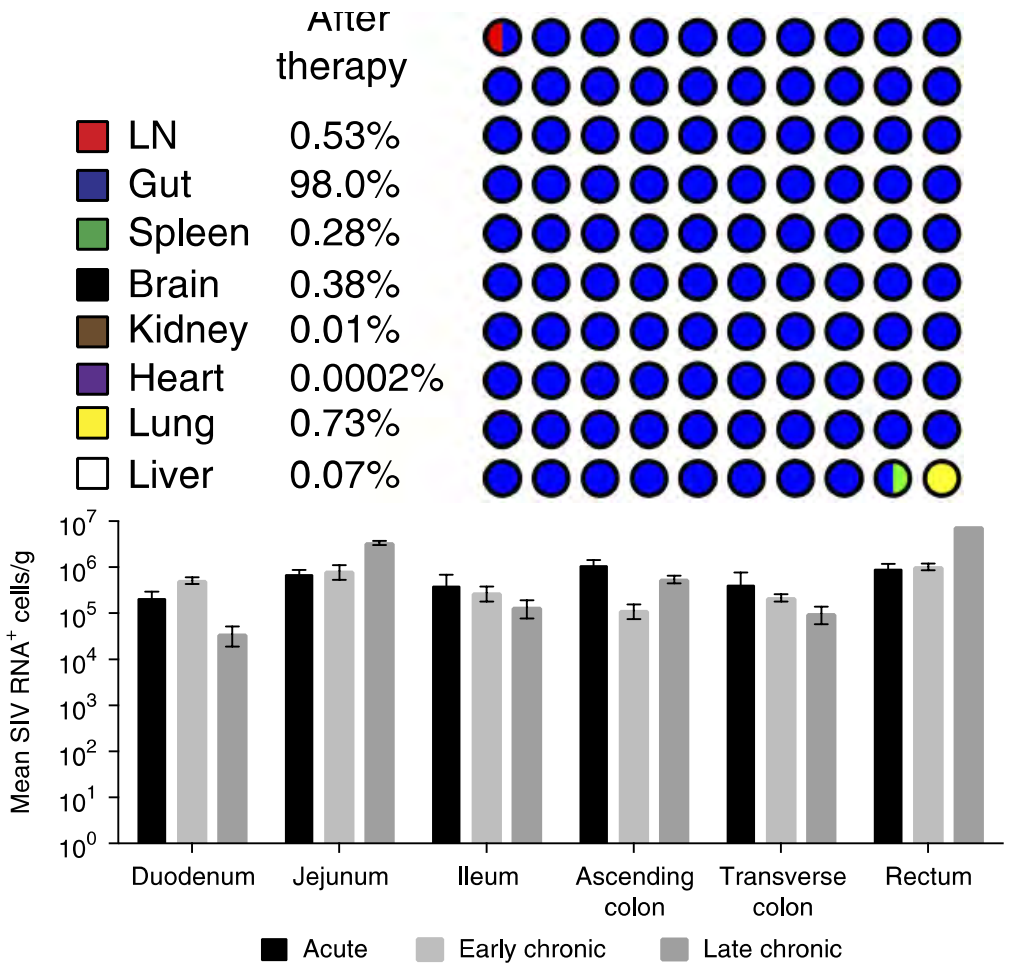
# HIV in the Gut

## Without ART




**62% of vRNA+ cells are in the gut**

## With ART



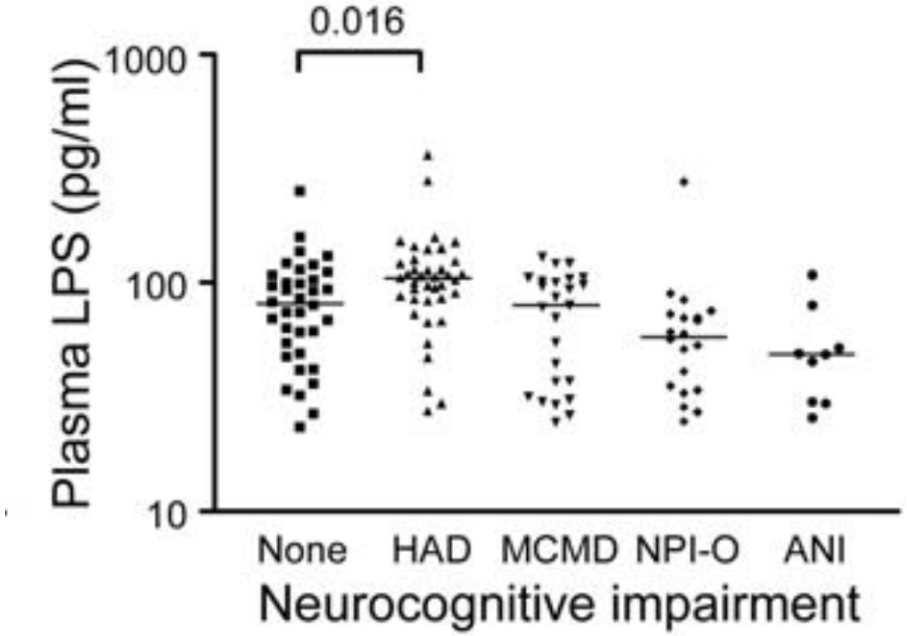

**98% of vRNA+ cells are in the gut**

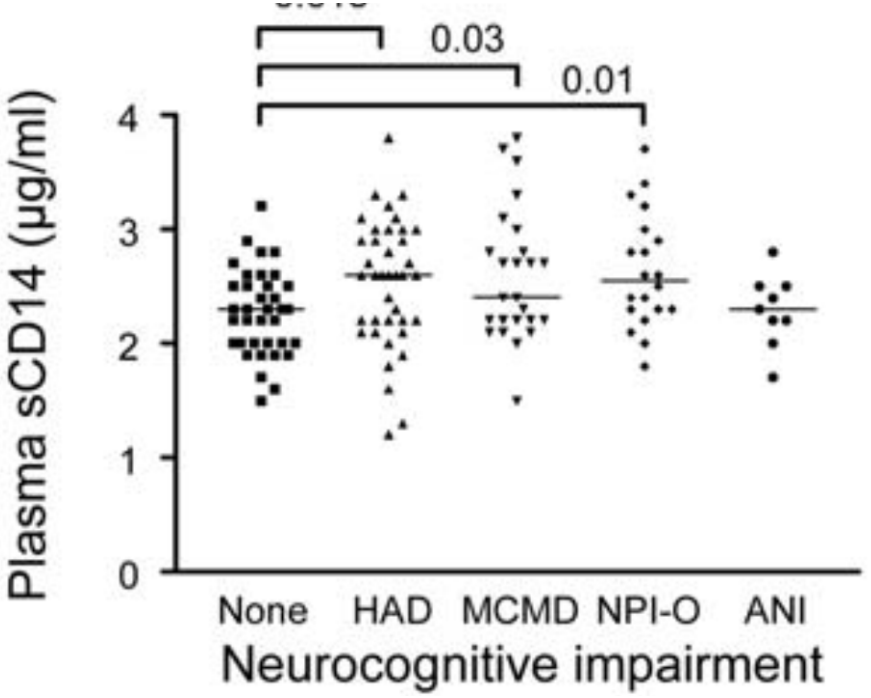
*Slide Courtesy Netanya Utay, M.D.*

*Estes, Nat Med, 2017*

# Microbial Translocation and NCI

- **LPS and sCD14 levels are higher in people with HAD than with no impairment**
- **sCD14 levels are also higher in people with mild neurocognitive disorder and neuropsychiatric impairment due to other conditions**
  - Not asymptomatic neuropsychiatric impairment



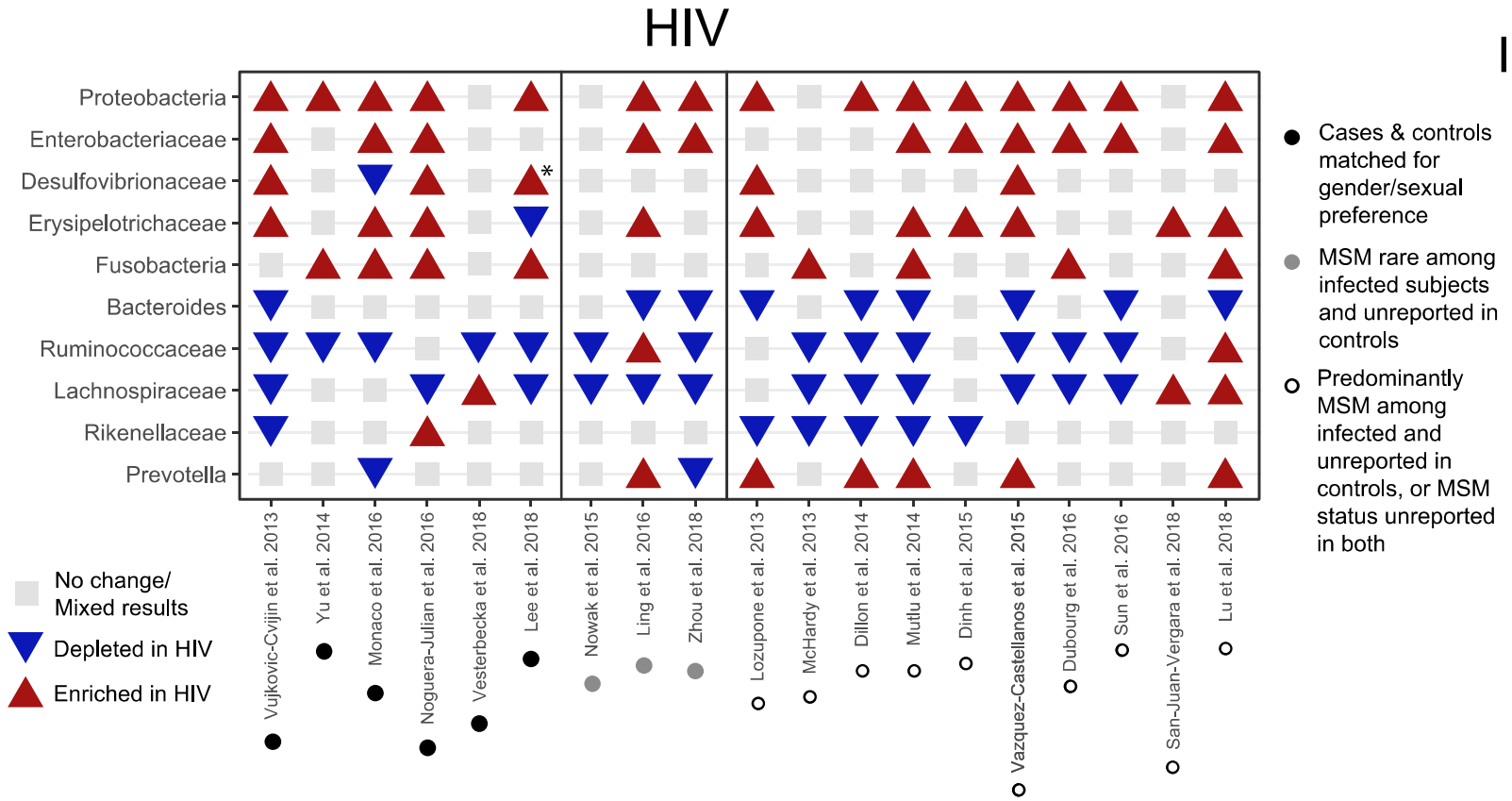




*Slide Courtesy Netanya Utay, M.D.*

*Ancuta, AIDS, 2008*

# Alterations in Gut Microbiome in PLH

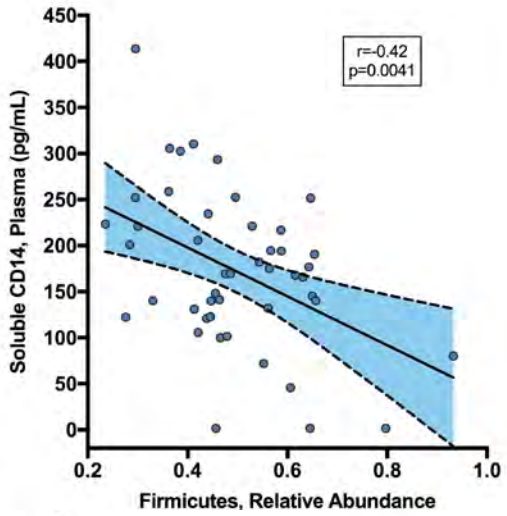
- **$10^{12}$ bacteria live in GI tract**
- **Diversity is key to a healthy microbiome**
- **Finding are variable, but generally PLH have**
  - Less diversity
  - More Proteobacteria, Enterobacteriaceae, Fusobacteria
  - Less Ruminococcaceae and Lachnospiraceae

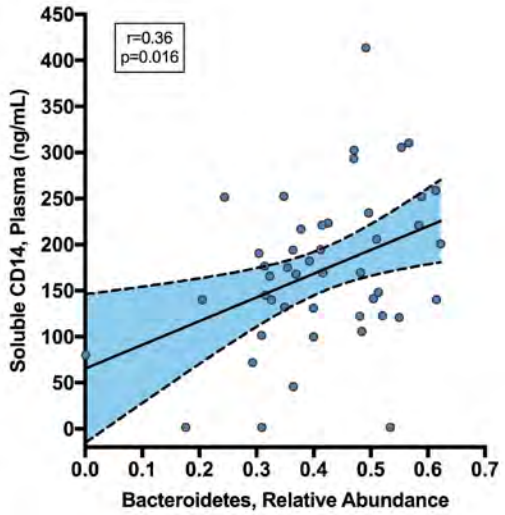


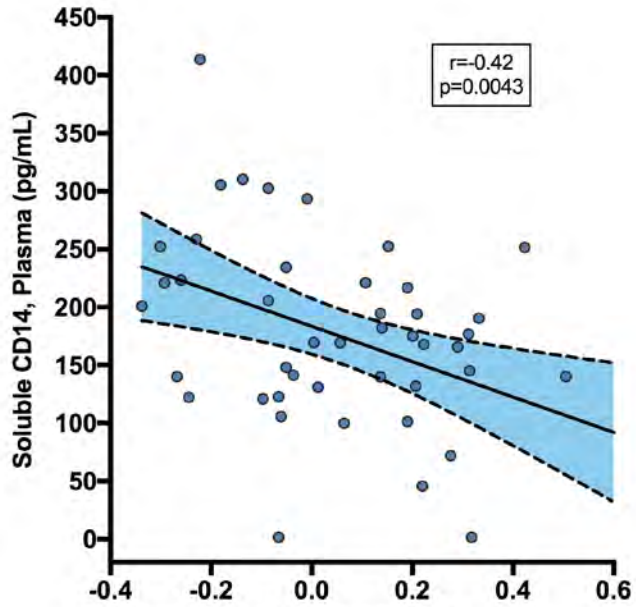

*Slide Courtesy Netanya Utay, M.D.*

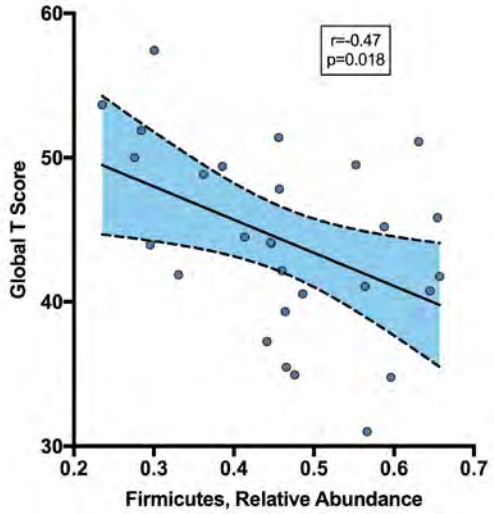
*Vujkovic-Cvijin, Curr HIV/AIDS Rep, 2019*

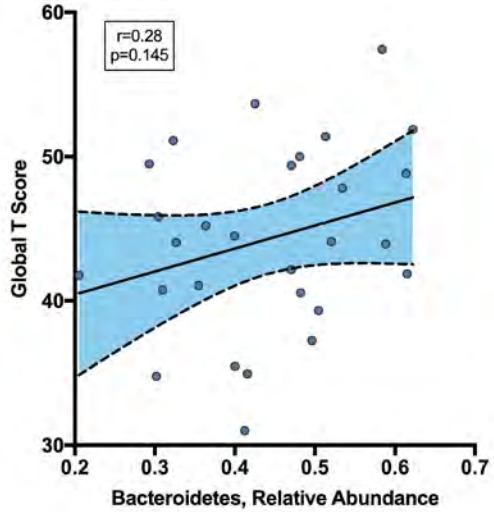
# Gut Microbiome, sCD14, and HAND

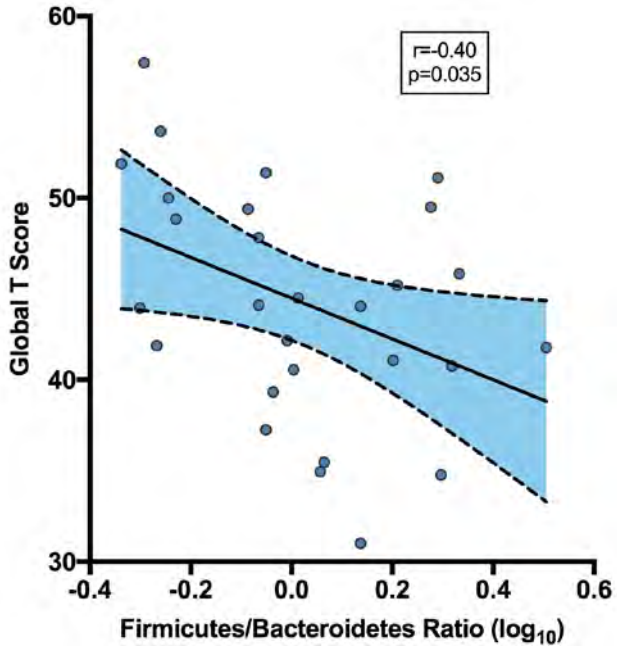


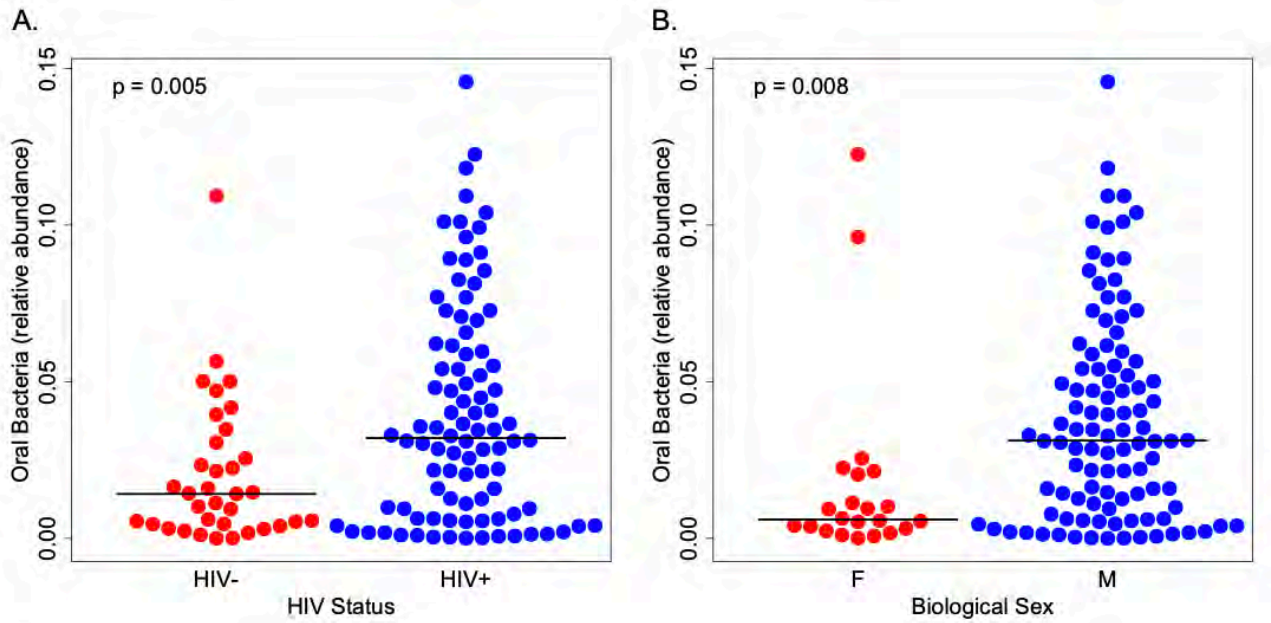



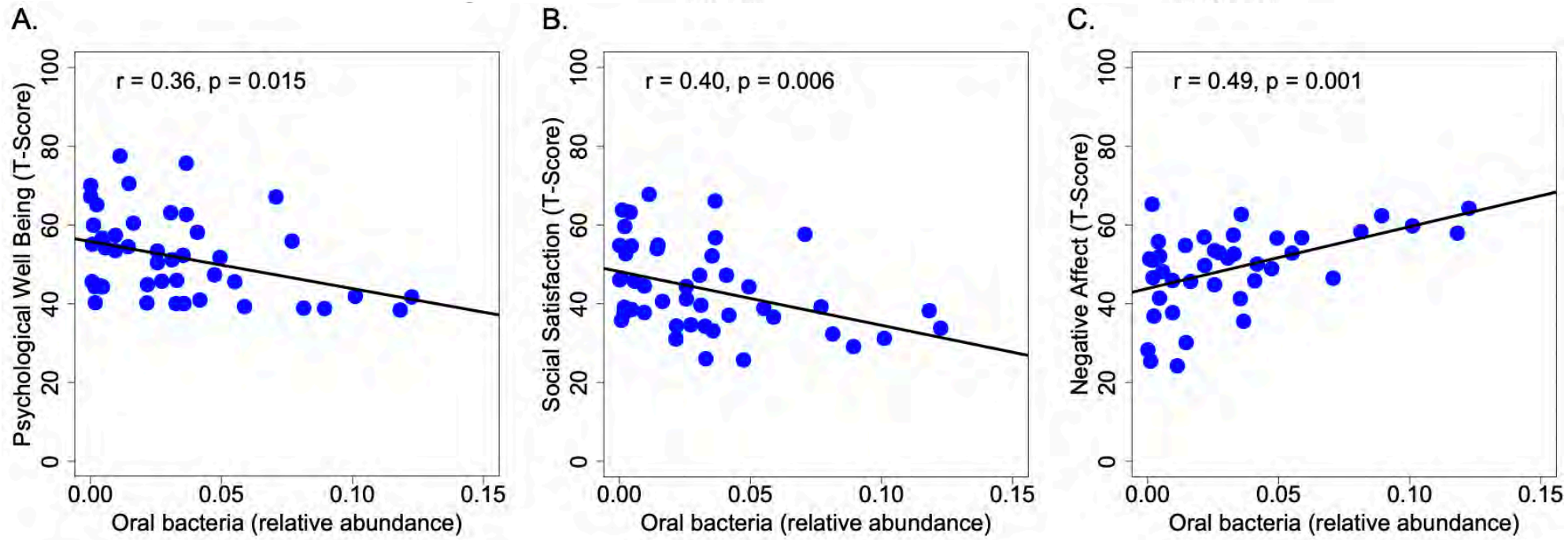




CROI
Conference on Retroviruses and Opportunistic Infections

*Perez Santiago et al, CROI 2017, Abstract 390*

# Gut Dysbiosis and NIH Toolbox Emotional Battery

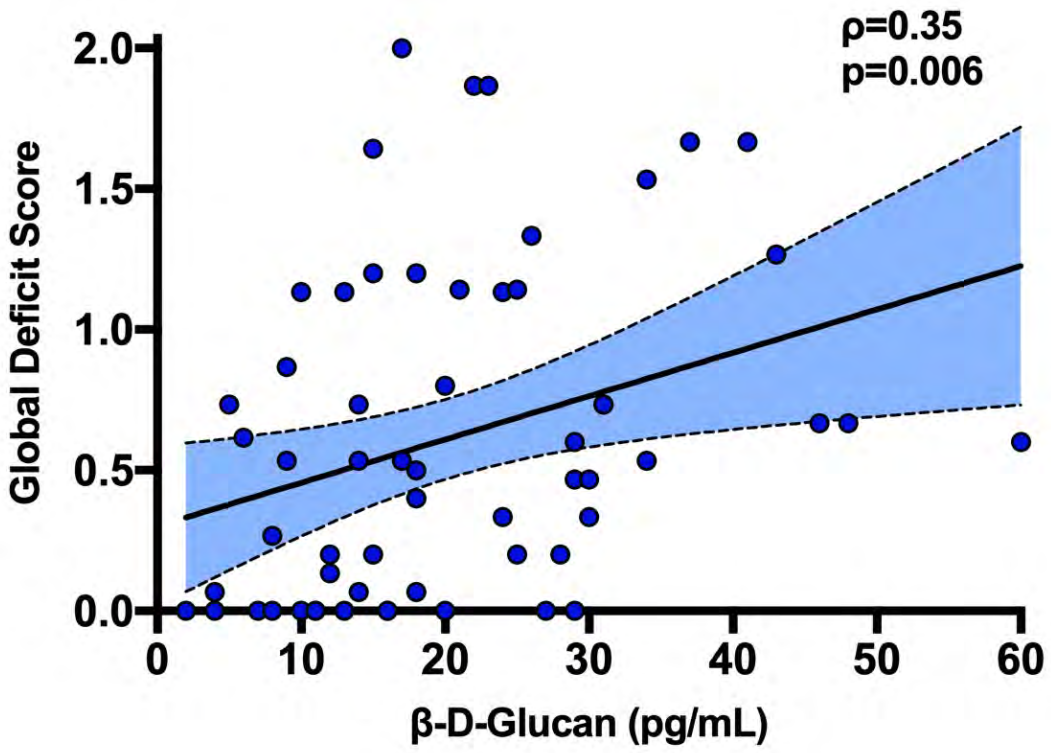


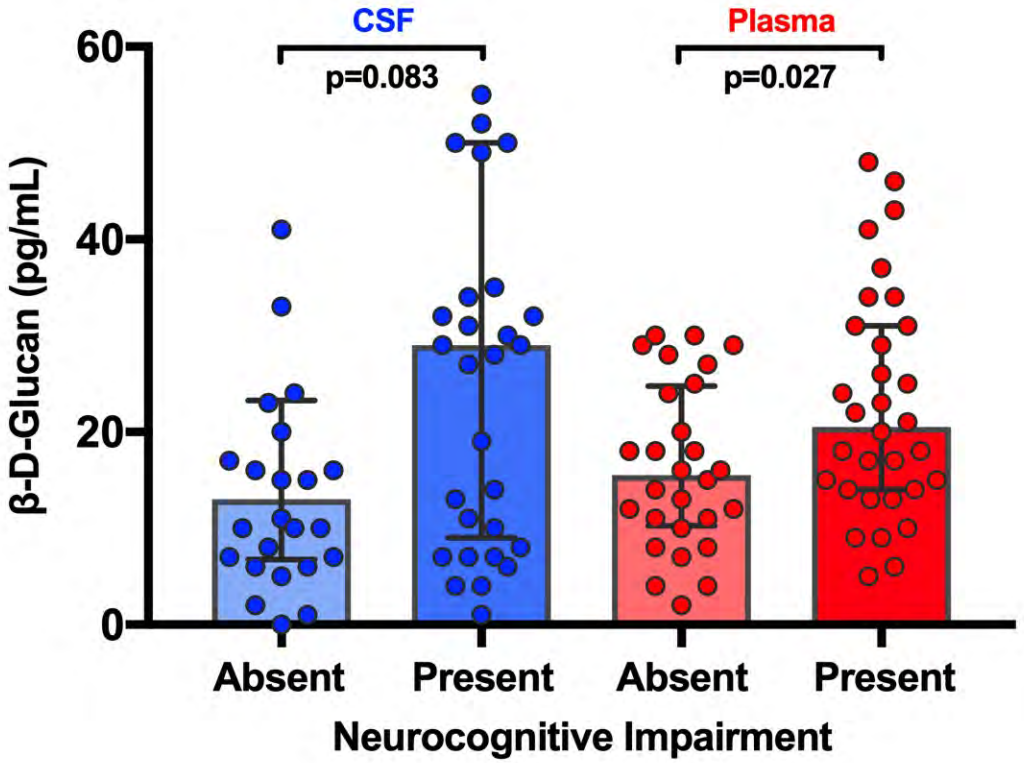




SNIP

*Perez Santiago et al, Society on Neuroimmune Pharmacology 2019*

# Fungal Translocation as an Indicator of Gut Permeability



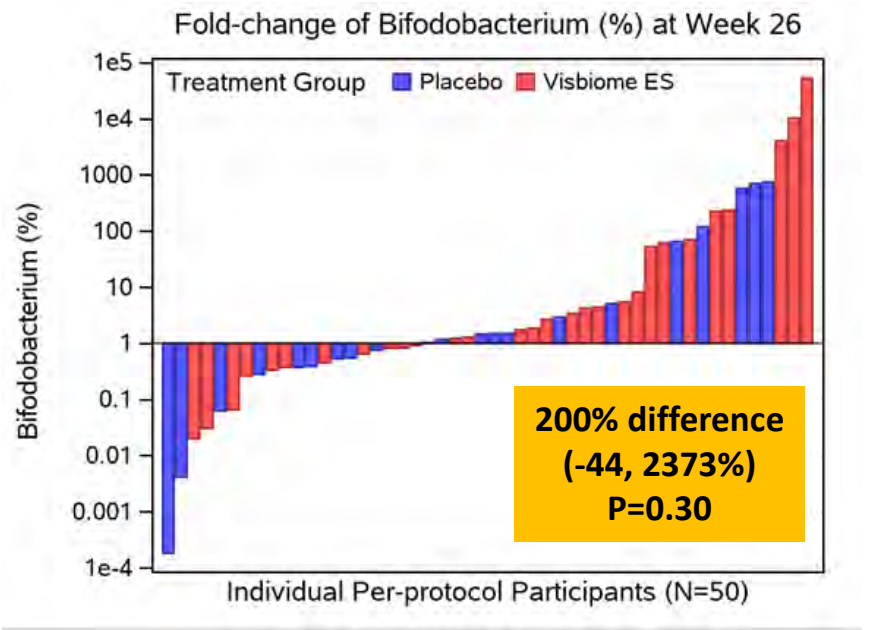



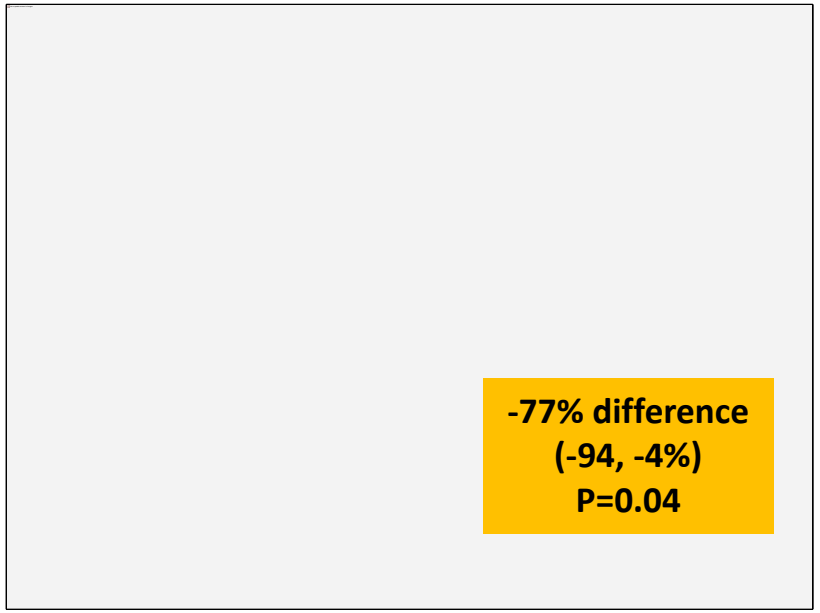

CROI
Conference on Retroviruses and Opportunistic Infections

*Hoenigl et al, CROI 2019, Abstract 410*

# Targeting Microbial Translocation

- In A5286, rifaximin, a luminal antibiotic, did not decrease sCD14 or IL-6 levels
- In A5296, sevelamer did not decrease LPS, sCD14, or IL-6
- In non-human primate studies, probiotic (Visbiome) + prebiotic (inulin) increased gut CD4 T cell frequency and function



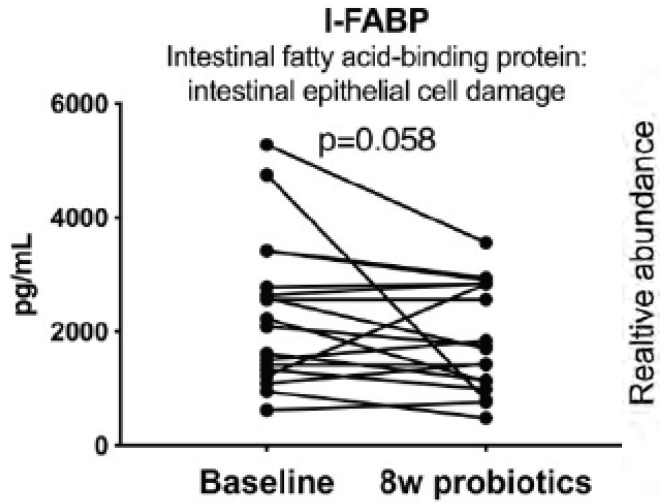

*Slide Courtesy Netanya Utay, M.D.*

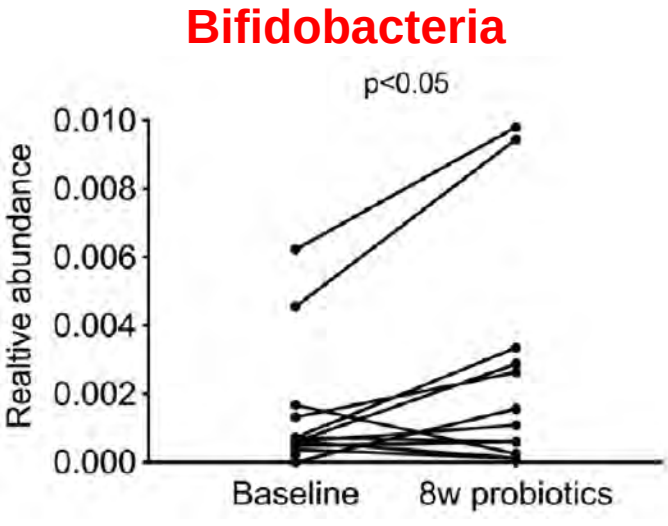
*Tenorio, JID, 2015; Sandler, JID, 2014; Klatt, J Clin Invest, 2013*

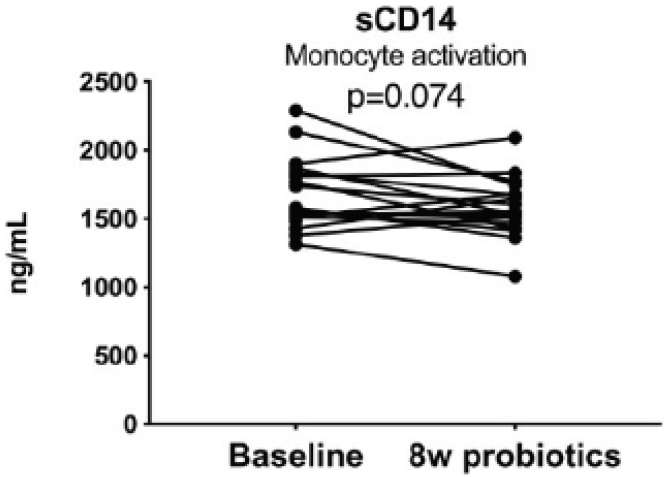
# Probiotic Clinical Trial in Immunologic Non-Responders

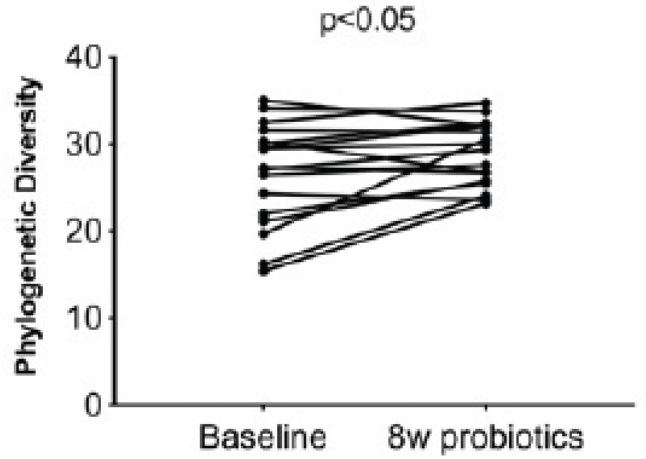
CROI Conference on Retroviruses and Opportunistic Infections

- **Nadir CD4 ≤ 157/µL, Current CD4 ≤ 374/µl**
- **Idoform Travel Probiotic**
  - Lactobacillus rhamnosus,
  - Lactobacillus acidophilus,
  - Bifidobacterium,
  - Lactobacillus bulgaricus,
  - Streptococcus thermophilus
- **Decreased IFA-BP, sCD14, LBP**
- **Increased Bifidobacteria & alpha diversity**



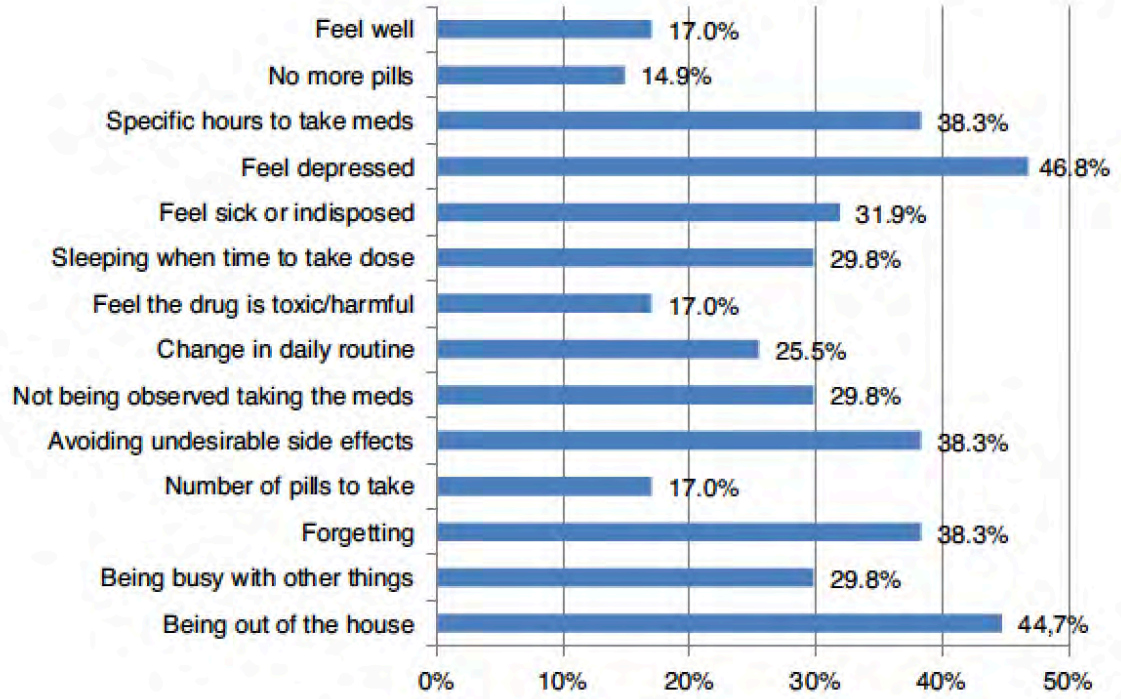




*Slide Courtesy Netanya Utay, M.D.*

*Meyer-Myklestad, CROI 2019*

# Thinking Outside the Cognitive Box

# Depression Influences Adherence, Disease Progression, and Mortality

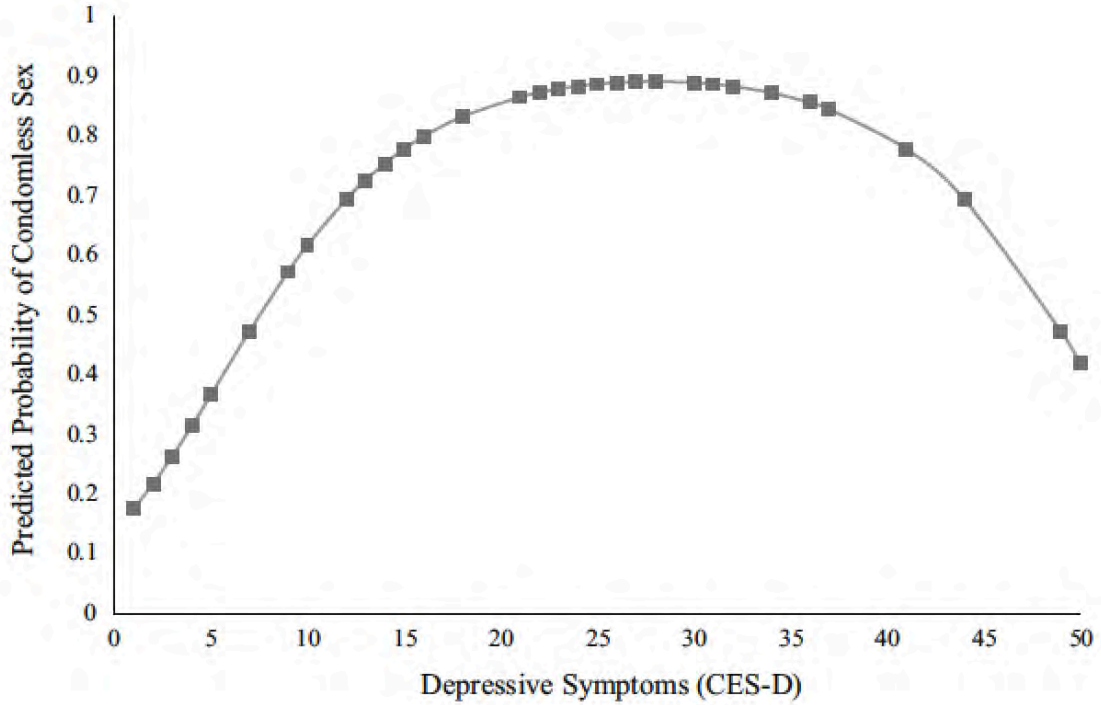


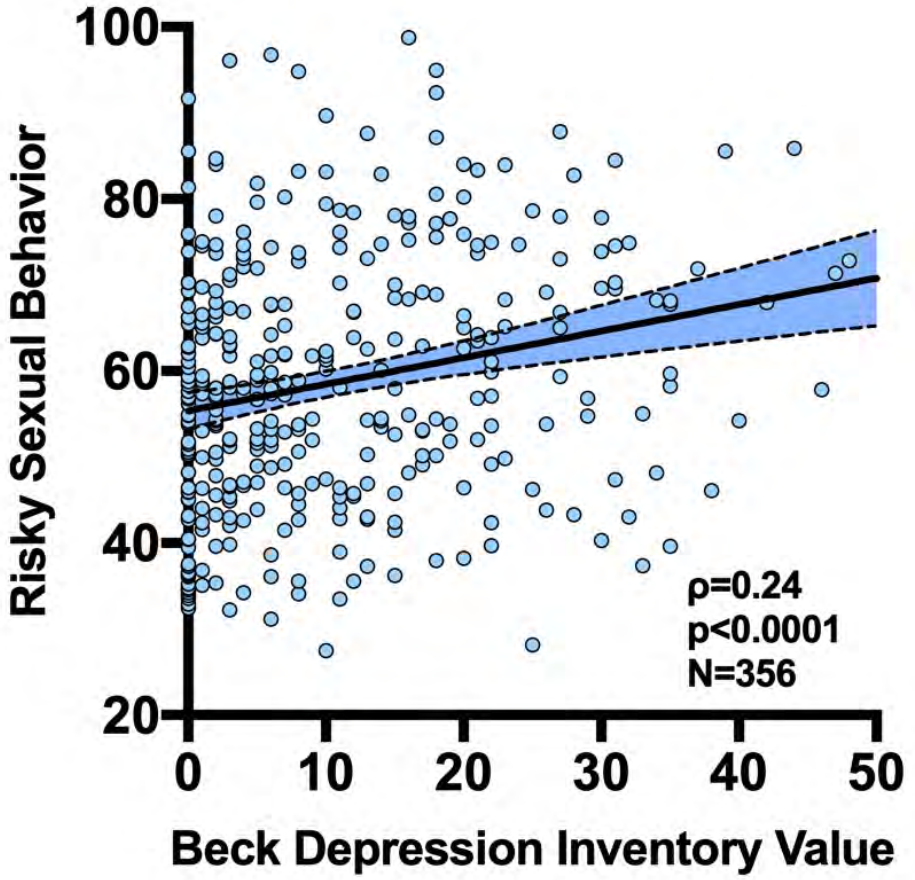

| Outcome[a] | Effect Estimate (95% CI) | |
|---|---|---|
| | Per 25% Increase in % of Days With Depression | Comparing Those Always Depressed With Those Never Depressed |
| All-cause mortality, hazard ratio[b] | 1.19 (1.05-1.36) | 2.02 (1.20-3.42) |
| Risk of missing a scheduled appointment, risk ratio[c] | 1.08 (1.05-1.11) | 1.37 (1.22-1.53) |
| Risk of having an unsuppressed viral load, risk ratio[c] | 1.05 (1.01-1.09) | 1.23 (1.06-1.43) |

| Studies | Effect of MD in HIV disease progression: HAART era |
|---|---|
| Evans *et al.*, 2002[112] | ↓NK, ↑ viral load, ↑ activated CD8 |
| Ironson *et al.*, 2005[62] | ↓CD4, ↑ viral load |
| Ickovics *et al.*, 2001[29] | ↓CD4 |
| Alciati *et al.*, 2007[113] | ↓NK, failure of NK to be restored |
| Cruess *et al.*, 2005[114] | ↑NK with improvement of MD |
| Cook *et al.*, 2004[115] | AIDS-related deaths in women |
| Leserman, 2008[116] | ↓CD4, ↑ viral load, greater risk of mortality |
| Schuster *et al*, 2012[117] | (i) Faster progression to AIDS through elevating cortisol secretion mechanisms; (ii) ↓CD4, ↑ viral load, medication-resistant strains of HIV through poor medication adherence |
| Grossman and Potter, 1999[118] | HIV replication through increasing of norepinephrine |

*Betancur et al, Braz J Infect Dis 2017; 21(5):507–514*
*Arseniou et al, Psych Clinic Neurosci 2014; 68: 96–109*
*Pence et al, JAMA Psychiatry 2018 75(4): 379–385*

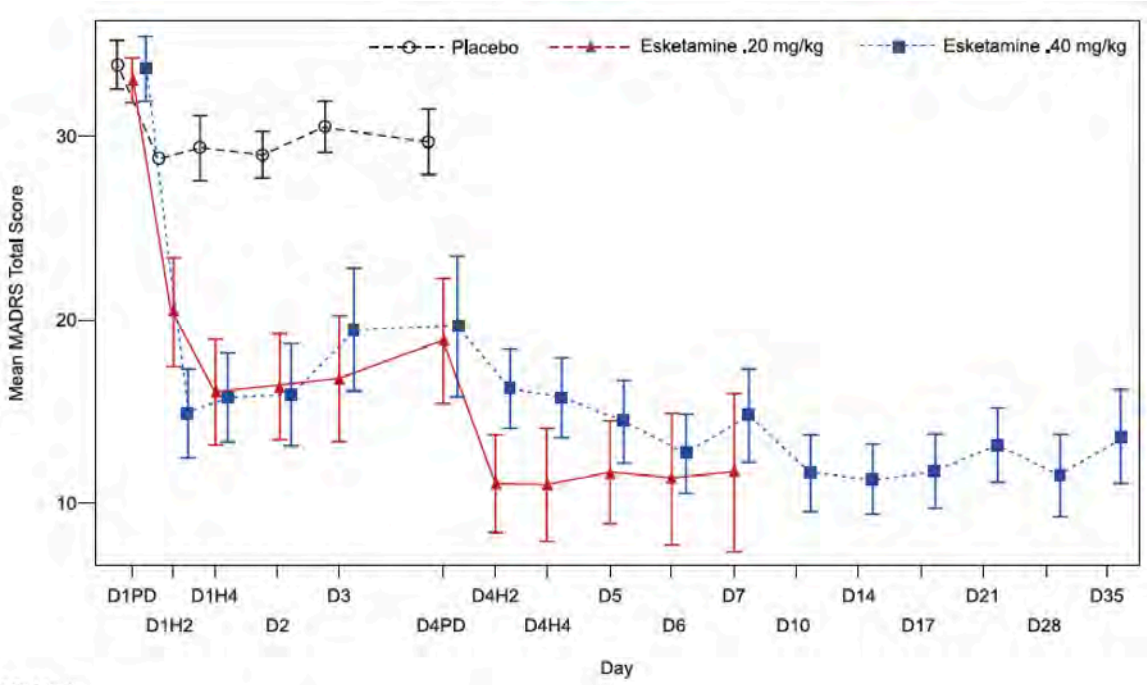
# Depression and Risky Sexual Behavior



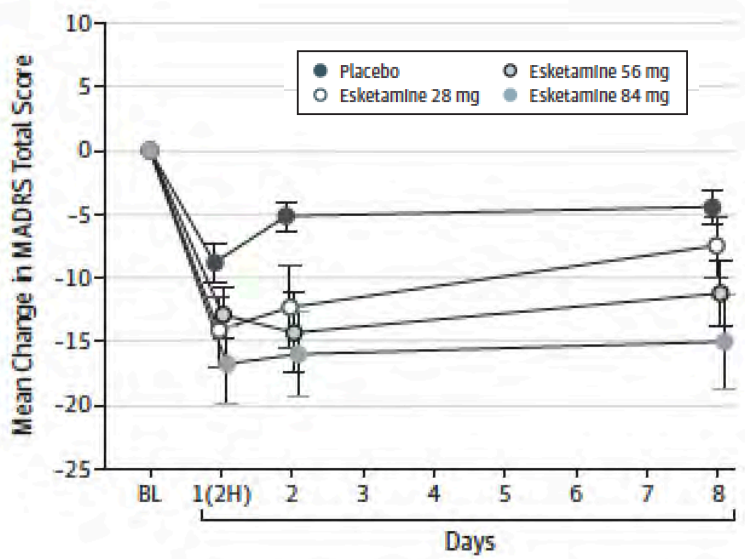

*Babowitch et al, Arch Sex Behav (2018) 47:2035–2040*

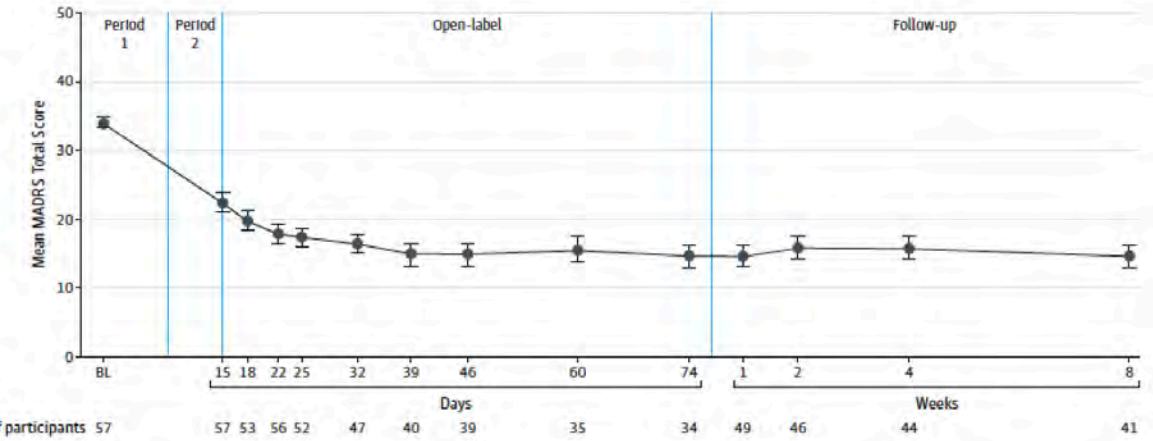
# Esketamine Trial Data




| Number of Subjects | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 10 | 10 | 10 | 10 | 10 | 10 | | | | | | | | | | |
| Esketamine .20 mg/kg | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | | | | | |
| Esketamine .40 mg/kg | 11 | 11 | 11 | 11 | 11 | 11 | 20 | 20 | 20 | 19 | 20 | 29 | 29 | 27 | 29 | 28 | 27 |

MADRS: Montgomery–Åsberg Depression Rating Scale




*Singh et al, http://dx.doi.org/10.1016/j.biopsych.2015.10.018*

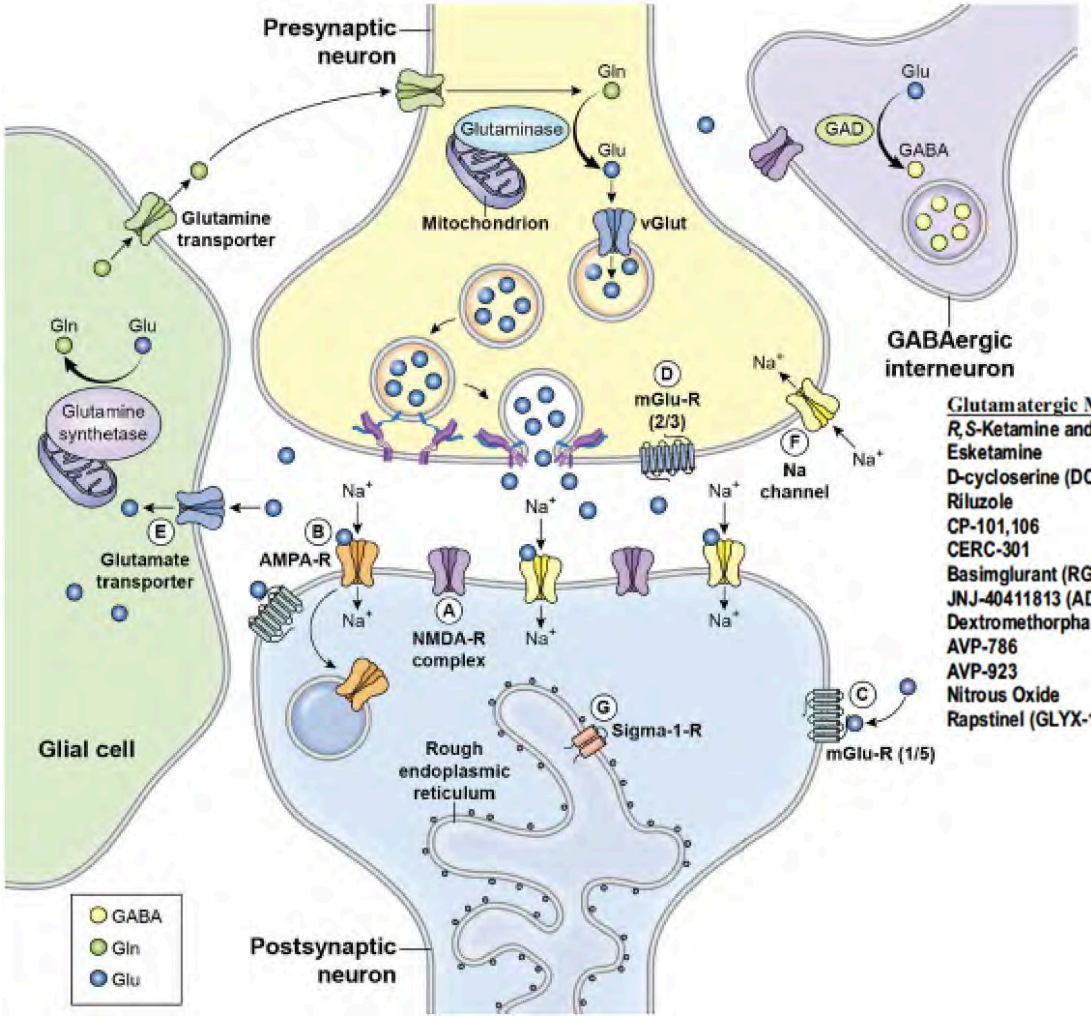
*Daly et al, JAMA Psychiatry. 2018;75(2):139-148*

Drugs (2017) 77:381–401
DOI 10.1007/s40265-017-0702-8

REVIEW ARTICLE

# Ketamine and Beyond: Investigations into the Potential of Glutamatergic Agents to Treat Depression

Marc S. Lener[1] · Bashkim Kadriu[1] · Carlos A. Zarate Jr[1]



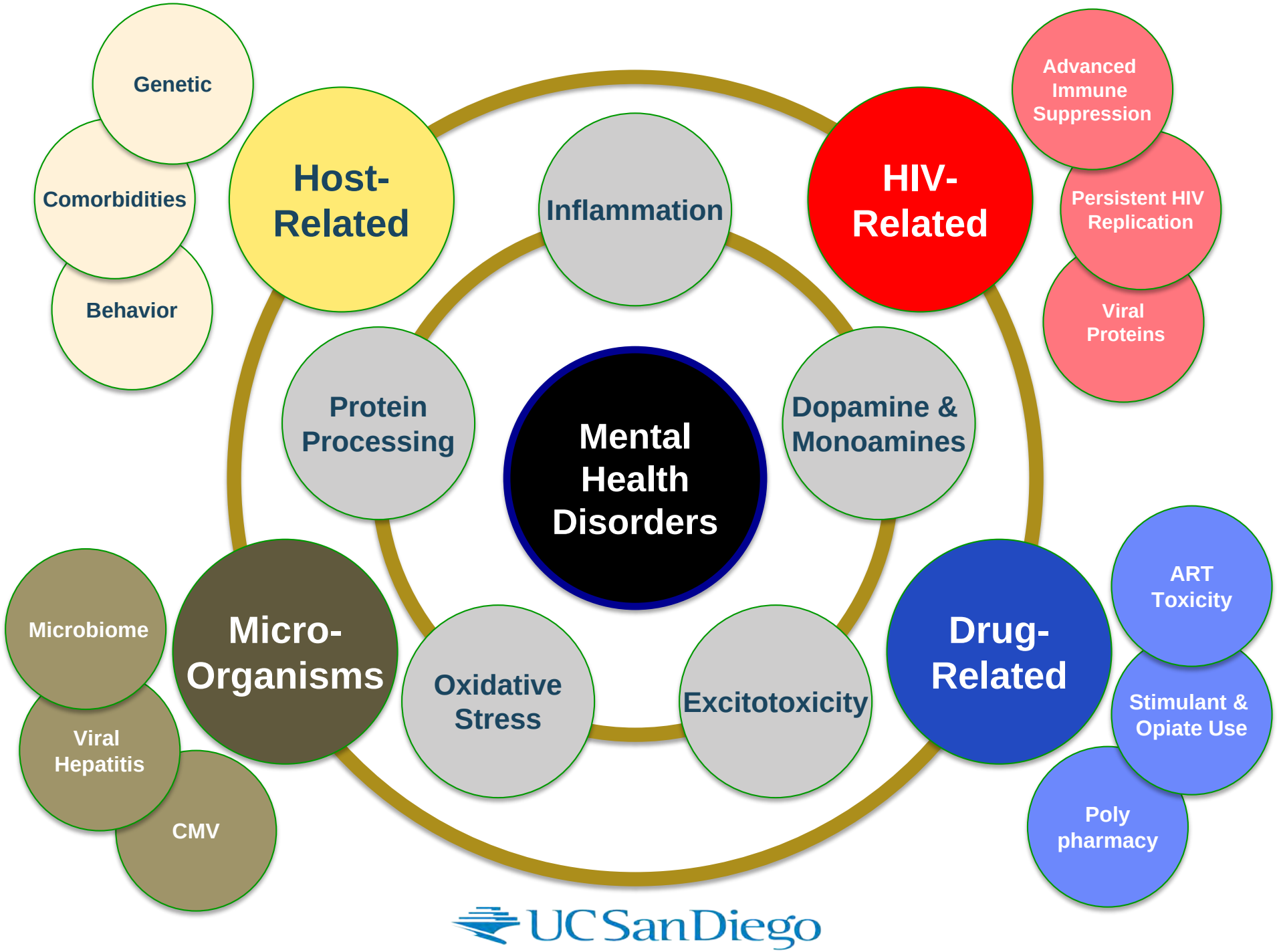

| Glutamatergic Modulating Agent | Molecular Target*: |
|---|---|
| *R,S*-Ketamine and Metabolites | A, B |
| Esketamine | A |
| D-cycloserine (DCS) | A |
| Riluzole | E, F |
| CP-101,106 | A,G(?) |
| CERC-301 | A |
| Basimglurant (RG7090) | C |
| JNJ-40411813 (ADX-71149) | D |
| Dextromethorphan | A, G |
| AVP-786 | A, G |
| AVP-923 | A, G |
| Nitrous Oxide | A |
| Rapstinel (GLYX-13) | A |

# A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems

Samuel T. Wilkinson[1,2] and Gerard Sanacora[1,2]

[1] Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA
[2] Connecticut Mental Health Center, New Haven, CT, USA

| Compound, route of administration | Pharmacology | Sponsor | Phase | Comments |
|---|---|---|---|---|
| Ketamine, various | Nonselective, noncompetitive NMDAR antagonist | Multiple | N/A | Several small trials from academia; unlikely to be studied as a monotherapy in Phase III clinical trials required to receive FDA approval |
| Esketamine, intranasal | Nonselective, noncompetitive NMDAR antagonist | Janssen | III | Breakthrough Therapy Designation in 2013 for TRD and Breakthrough Therapy Designation in 2016 for MDD with imminent risk of suicide; 4–5 x NMDAR-binding potency compared with (*R*)-ketamine; several positive studies reported, with one study among older patients that did not meet statistical significance for its primary endpoint |
| Lanicemine/AZD-6765, intravenous | Low trapping NMDAR antagonist | AstraZeneca/ BioHaven | IIb | Mixed results in two Phase II studies |
| Traxoprodil/CP-101,606, intravenous | NMDAR antagonist at NR2B subunit | Pfizer | II | Positive Phase II study reported; no additional studies registered |
| EVT-101 | NMDAR antagonist at NR2B subunit | Evotec/La Roche | II | Phase II trial terminated early, placed on clinical hold by FDA (clinicaltrials.gov) |
| Rislenemdaz/CERC-301/ MK-0657, oral | NMDAR antagonist at NR2B subunit | Cerecor | II | At least one Phase II trial did not show separation from placebo |
| AVP-786, oral | Nonselective antagonist of NMDAR | Avanir/Otsuka | II | Combination of dextromethorphan and quinidine. Phase II trial completed in February 2016; no additional studies for mood disorders registered as of March 2018. |
| AXS-05, oral | Nonselective antagonist of NMDAR | Axsome | III | Combination of dextromethorphan/ bupropion; Fast Track Designation by FDA |
| Rapastinel/GLYX-13, intravenous | Partial functional agonist at glycine site of NMDAR | Allergan | III | Fast Track Designation for MDD in 2014; Breakthrough Therapy designation in 2016 |
| Apimostinel/NRX-1074/ AGN-241660, oral | Reported to be a functional antagonist at Glycine B site of NMDAR | Allergan | II | Company press release reports that NRX-1074 showed rapid antidepressant efficacy in initial single-dose Phase II study in patients with MDD |
| AV-101, oral | Selective agonist at glycine site of NMDAR NR1 subunit | VistaGen | II | Fast Track Designation for MDD in 2018 |
| NRX-100/NRX-101, oral | Partial NMDAR agonist at glycine site | NeuroRx | III | Ketamine (NRX-100) followed by D-cycloserine plus lurasidone (NRX-101) to sustain effects in suicidal bipolar depression |
| AGN-241751 | NMDAR modulator | Allergan | II | Fast Track Designation by FDA in 2018 |
| Basimglurant/ RO4917523, oral | Negative allosteric modulator of $mGluR_5$ | Hoffmann-La Roche | IIb | Phase IIb study did not show separation from placebo |
| Decoglurant/RG1578/ RO4995819 | Negative allosteric modulator of $mGluR_{2/3}$ | Hoffmann-La Roche | II | Removed from Roche pipeline as reported by company in 2015 |
| Tulrampator/CX-1632/S-47445 | Positive allosteric modulator of AMPAR | RespireRx | II | Completed Phase 2 trial in TRD; no results reported to date. |
| Riluzole, oral | Glutamate release inhibitor/ up take facilitator | Multiple | II | Mixed results, among randomized clinical trials: three negative studies (incl. NCT00376220); one positive study |
| Brexanolone/SAGE-547, intravenous | Positive allosteric modulator of $GABA_A$ receptor | Sage | III | PPD with two positive Phase III trials; Breakthrough Designation for MDD |
| Ganaxolone, intravenous | Positive allosteric modulator of $GABA_A$ receptor | Marinus | II | Treatment of PPD |
| SAGE-217, oral | Positive allosteric modulator of $GABA_A$ receptor | Sage | II | Fast Track Designation by FDA in 2017 with a positive Phase II trial |


Genetic
Comorbidities
Behavior
Host-Related
Inflammation
HIV-Related
Advanced Immune Suppression
Persistent HIV Replication
Viral Proteins
Protein Processing
Mental Health Disorders
Dopamine & Monoamines
Microbiome
Viral Hepatitis
CMV
Micro-Organisms
Oxidative Stress
Excitotoxicity
Drug-Related
ART Toxicity
Stimulant & Opiate Use
Poly pharmacy
UC San Diego

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UC San Diego

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- David Moore
- Tom Marcotte
- Cris Achim
- Asha Kallianpur
- Todd Hulgan
- Jennifer Iudicello
- Brookie Best
- Edmund Capparelli
- Davey Smith
- Mariana Cherner
- Debra Rosario
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