

HIV Infection: A Model for the Use of Cannabinoid-based Anti-inflammatory Agents

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Disclosures

- **Research/Grants:** 1U01-DA044571-02 NIH/NIDA
Consequences of Marijuana use on Inflammatory
Pathways in HIV-Infected Youth

Learning Objective

1

Identify the inflammatory pathways associated with chronic HIV infection.



Learning Objective 2

Describe the mechanism in which cannabinoids may attenuate inflammation in people with HIV (PWH).



Learning Objective 3

Know the current therapeutic and recreational uses of cannabinoids among HIV-infected individuals.

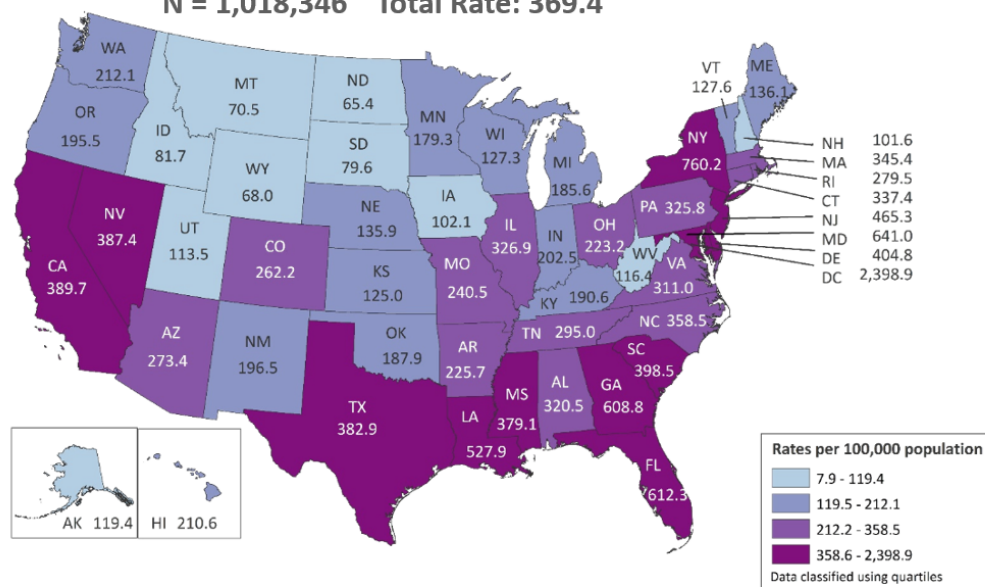


Adults and Adolescents Living with HIV 2018 Diagnosed HIV (2017)

Rates of Adults and Adolescents Living with Diagnosed HIV Infection, by Area of Residence,
Year-end 2017—United States and 6 Dependent Areas

N = 1,018,346 Total Rate: 369.4

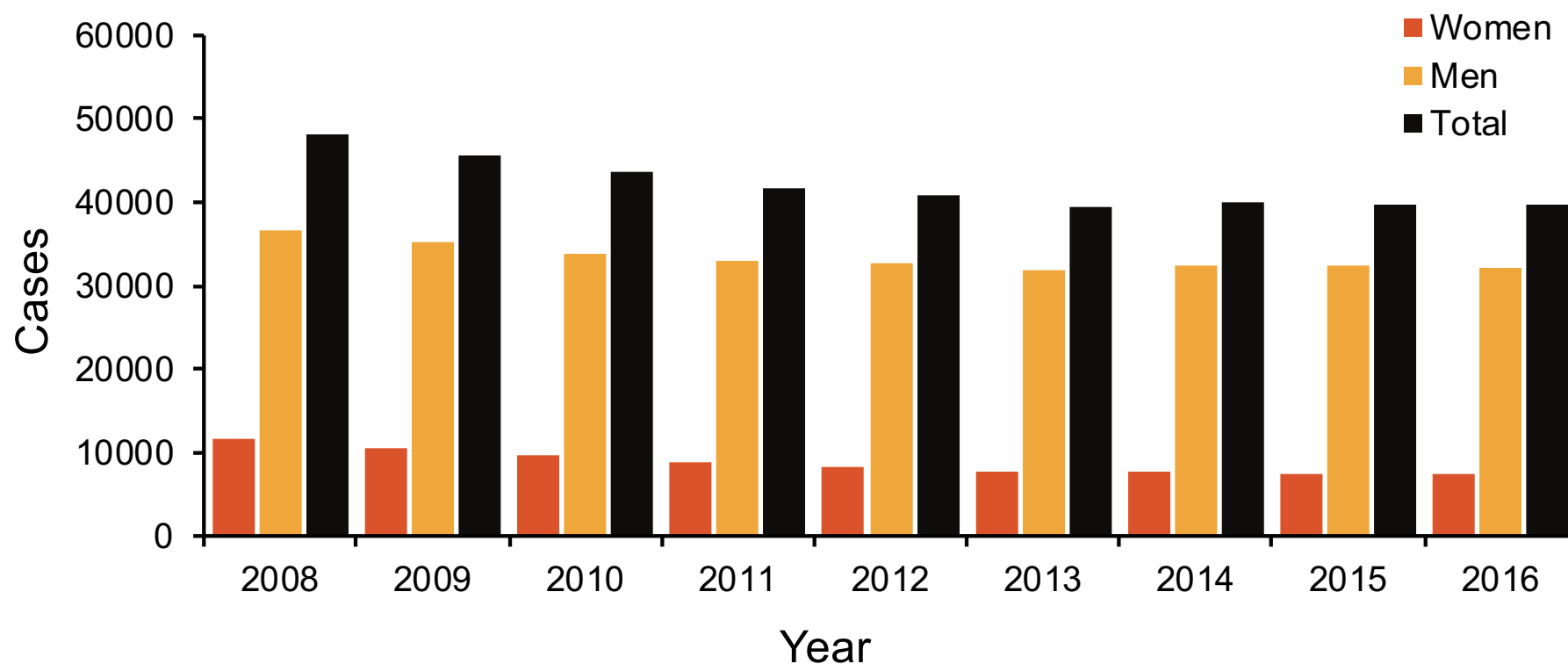
American Samoa	7.9
Guam	74.9
Northern Mariana Islands	34.8
Puerto Rico	553.5
Republic of Palau	50.1
U.S. Virgin Islands	610.8



HIV = human immunodeficiency virus.

Centers for Disease Control and Prevention. Available at <https://www.cdc.gov/hiv/pdf/library/slidesets/cdc-hiv-surveillance-maps-2018.pdf>. Accessed February 20, 2020. Note: Data are based on address of residence as of December 31, 2017 (i.e., most recent known address).

Total Cases of New HIV Diagnoses in the United States: 2008-2016



Data Source: AIDSVu.org. Emory University, Rollins School of Public Health. Accessed February 20, 2020.

United States Epidemic: 2016

New HIV Diagnosis Across Age Groups



<u>AGES</u>	<u>NO.</u>	<u>RATE/100K</u>
15-19	1,698	8.0
20-24	7,084	33.4
25-29	7,510	31.2
30-39	9,631	~22.0
40-54	9,730	15.0
>55	3,715	~5.0
TOTAL	39,513	12.3

>40%

Centers for Disease Control and Prevention Report #27. 2015. Available at <https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2015-vol-27.pdf>. Accessed February 20, 2020.

High Marijuana Use Among People with HIV (PWH)

- Prevalence of marijuana use among PWH > 50% in adults enrolled in Canadian HIV clinical trial
- Among YWH enrolled in Adolescent Trials Network Study 071 (NICHD):
 - 49% used marijuana or marijuana plus tobacco regularly over the prior 3 months
 - 20% reported daily use
 - Results confirmed by toxicology to show concordance with self-report
 - High rates of alcohol use
 - <5% reported using opioids, methamphetamines, cocaine

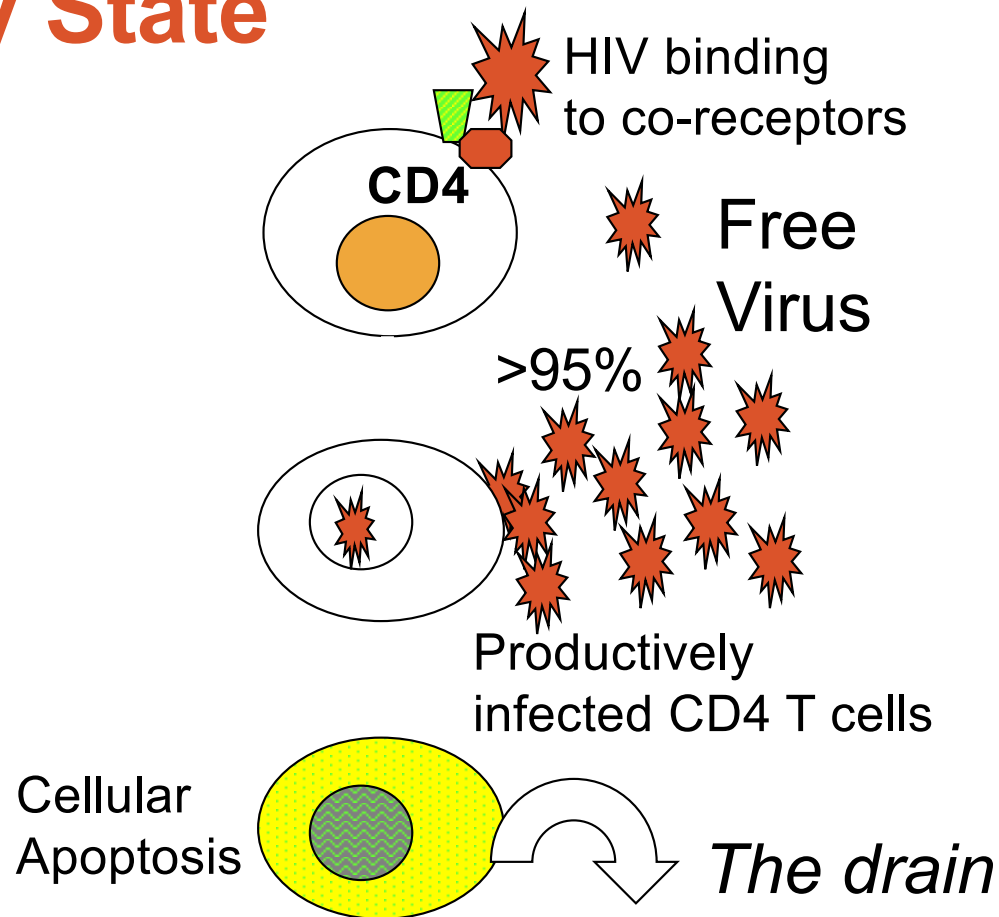
NICHD = National Institute of Child Health and Human Development; YWH = youth with HIV.
Costiniuk CT, et al. *Open Forum Infect Dis*. 2016;3(2):ofw050.; Nichols SL, et al. *Drug Alcohol Depend*. 2014;134:376-382.

Traditional Paradigm of HIV Immune Pathogenesis

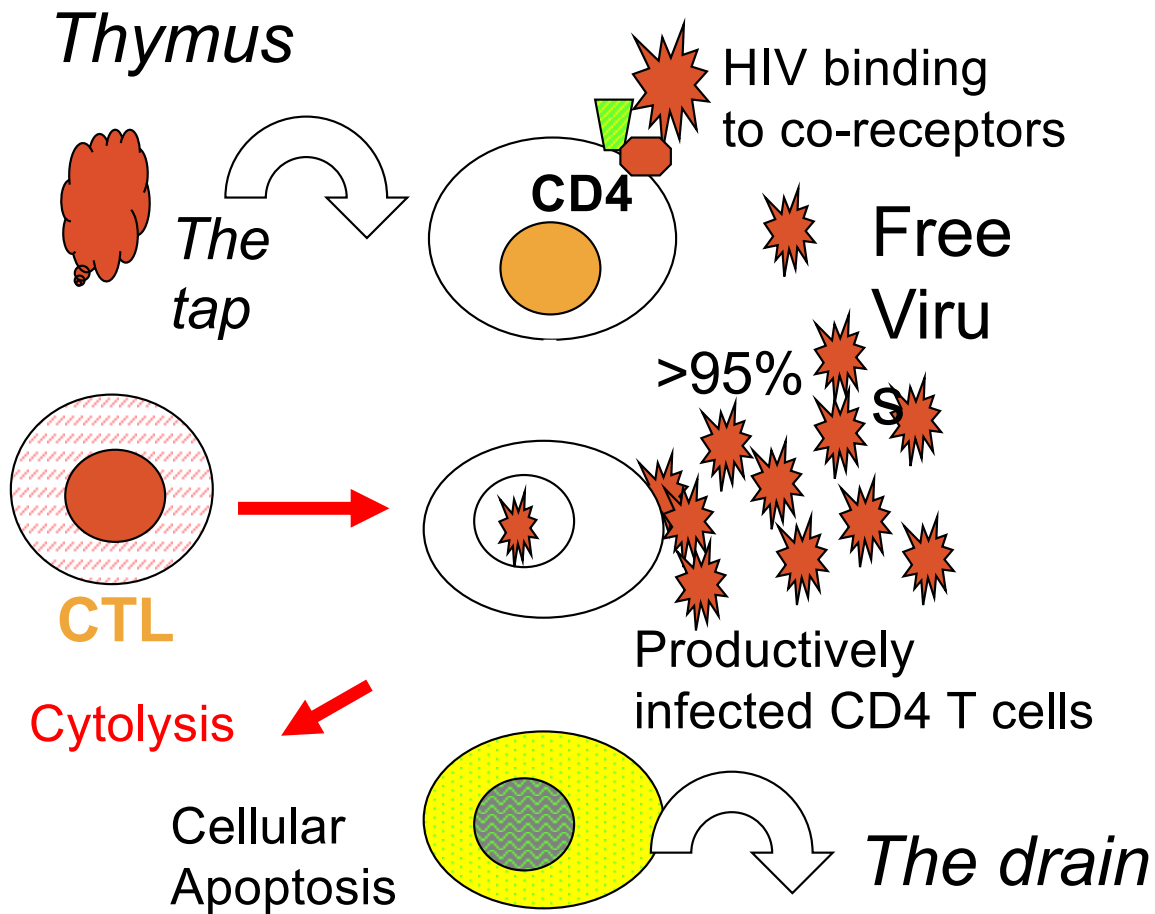
- Tap and drain T-cell dynamics
- Acute infection characterized by CD8 T-cell activation
- Slow/steady depletion of CD4 T-cell numbers and function over time
- Anti-retroviral therapy restores CD4 T-cells and corrects immunity

CD = cluster of differentiation.

HIV Steady State



HIV Steady State (cont.)

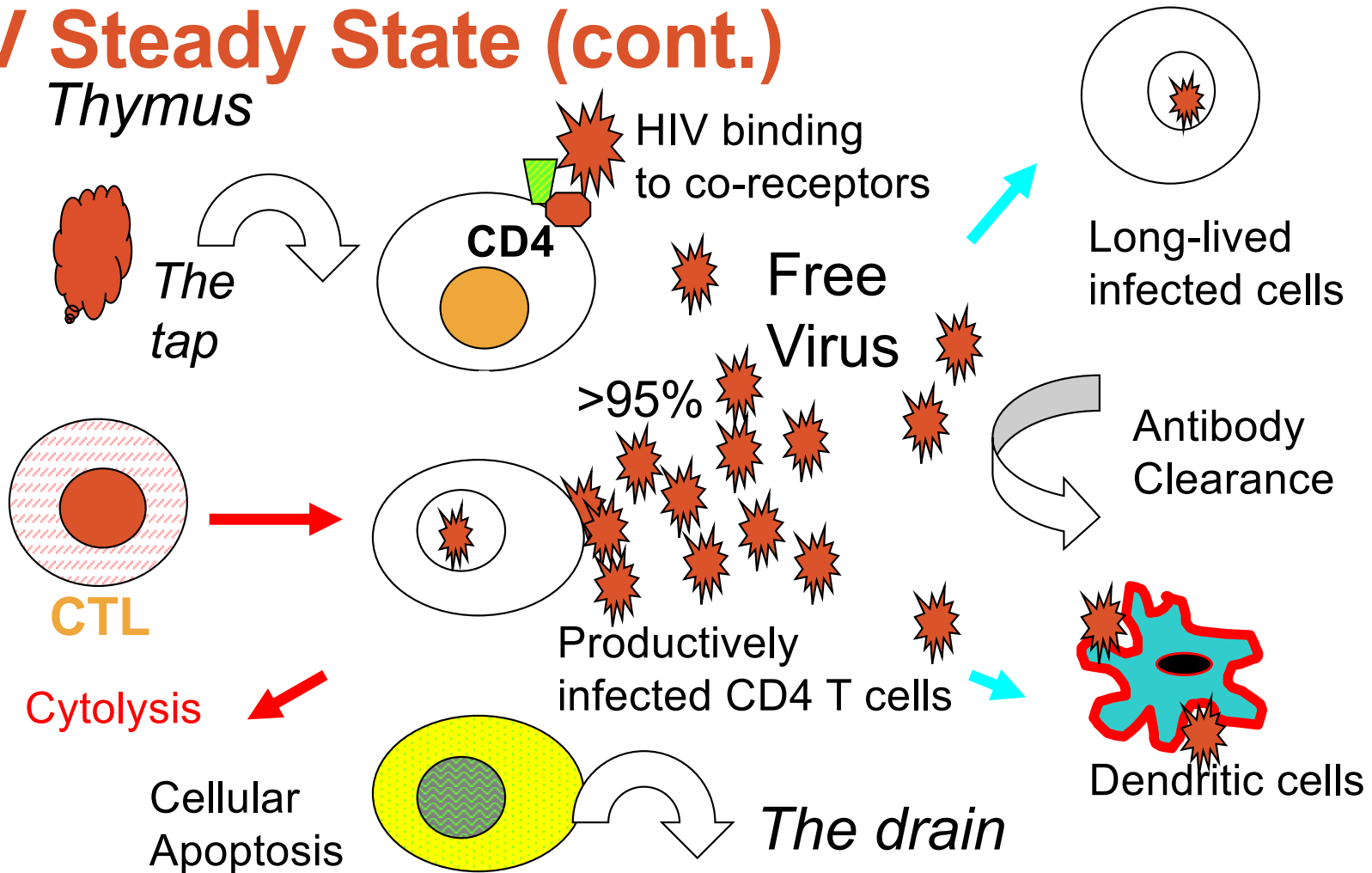


CTL = cytotoxic T cell.

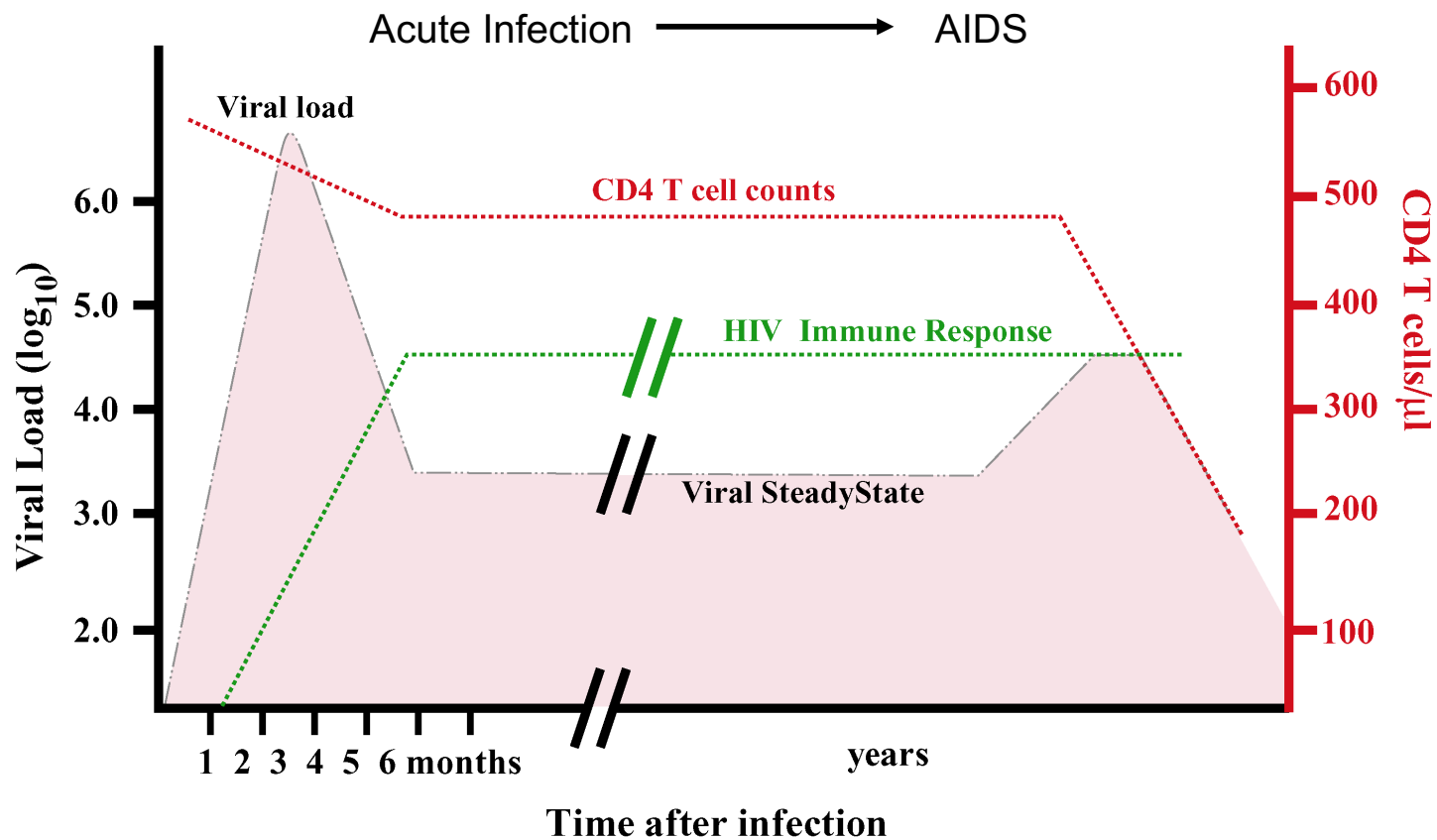
Sleasman JW, Goodenow MM. *J Allergy Clin Immunol*. 2003;111(2 Suppl):S582-592.

HIV Steady State (cont.)

Thymus



Clinical Disease Progression



AIDS = acquired immunodeficiency syndrome.
Sleasman JW, Goodenow MM. *J Allergy Clin Immunol.* 2003;111(2 Suppl):S582-592.

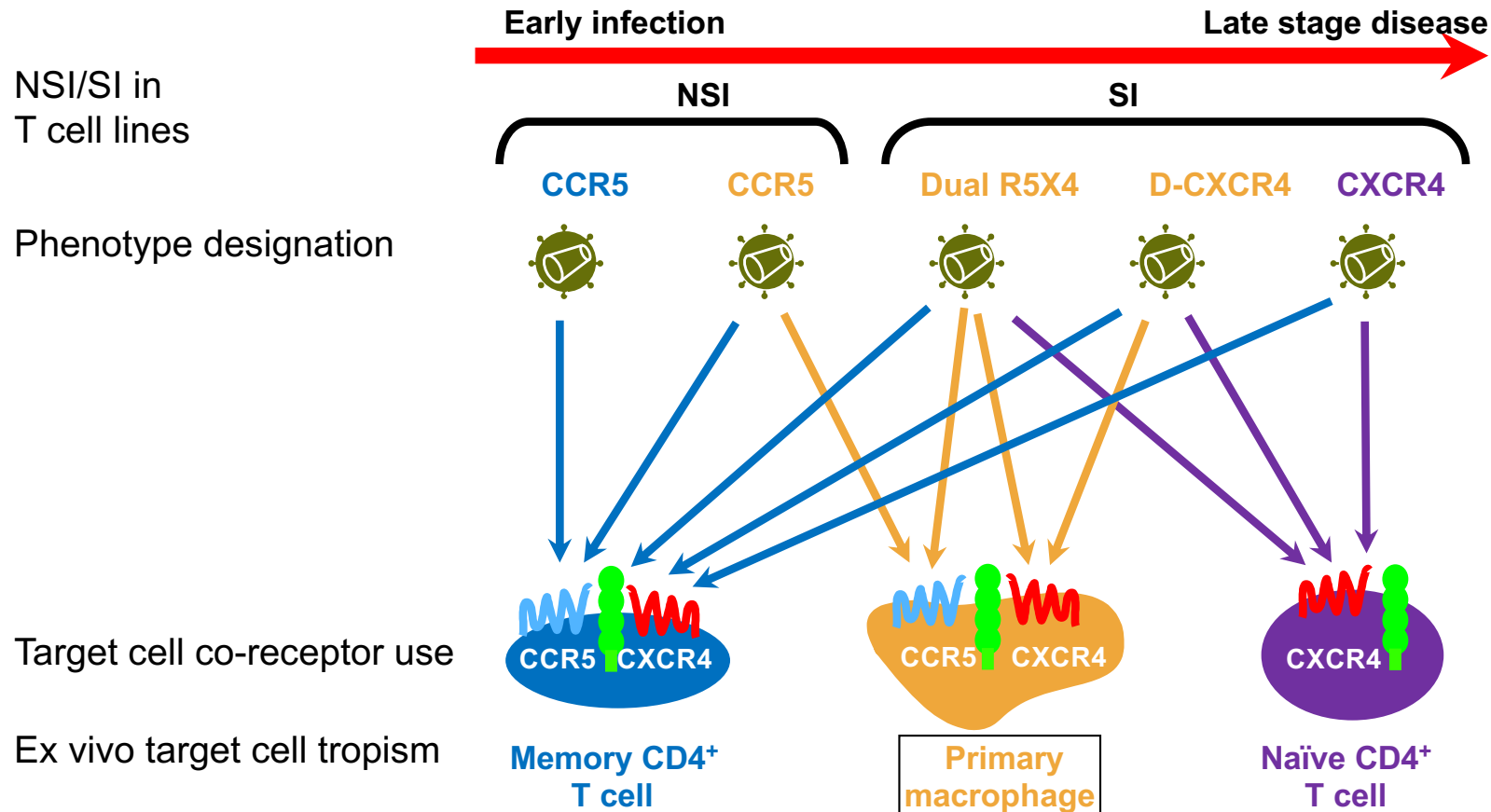
HIV Impact on Immune Function

- Only 0.01-1% CD4 T-cells productively infected by HIV
- Immune dysfunction begins early and persists throughout infection
- Control of viral replication by ART fails to completely restore functional immunity

ART = antiretroviral therapy.

Brenchley JM, et al. *Nat Immunol*. 2006;7(3):235-239.

Co-Receptor Use + Viral Tropism



CCR5 = C-C chemokine receptor 5; CXCR4 = C-X-C motif chemokine receptor 4; NSI = non-syncytium inducing; SI = syncytium inducing.
 Goodenow MM, Collman RG. *J Leukoc Biol.* 2006;80(5):965-972.

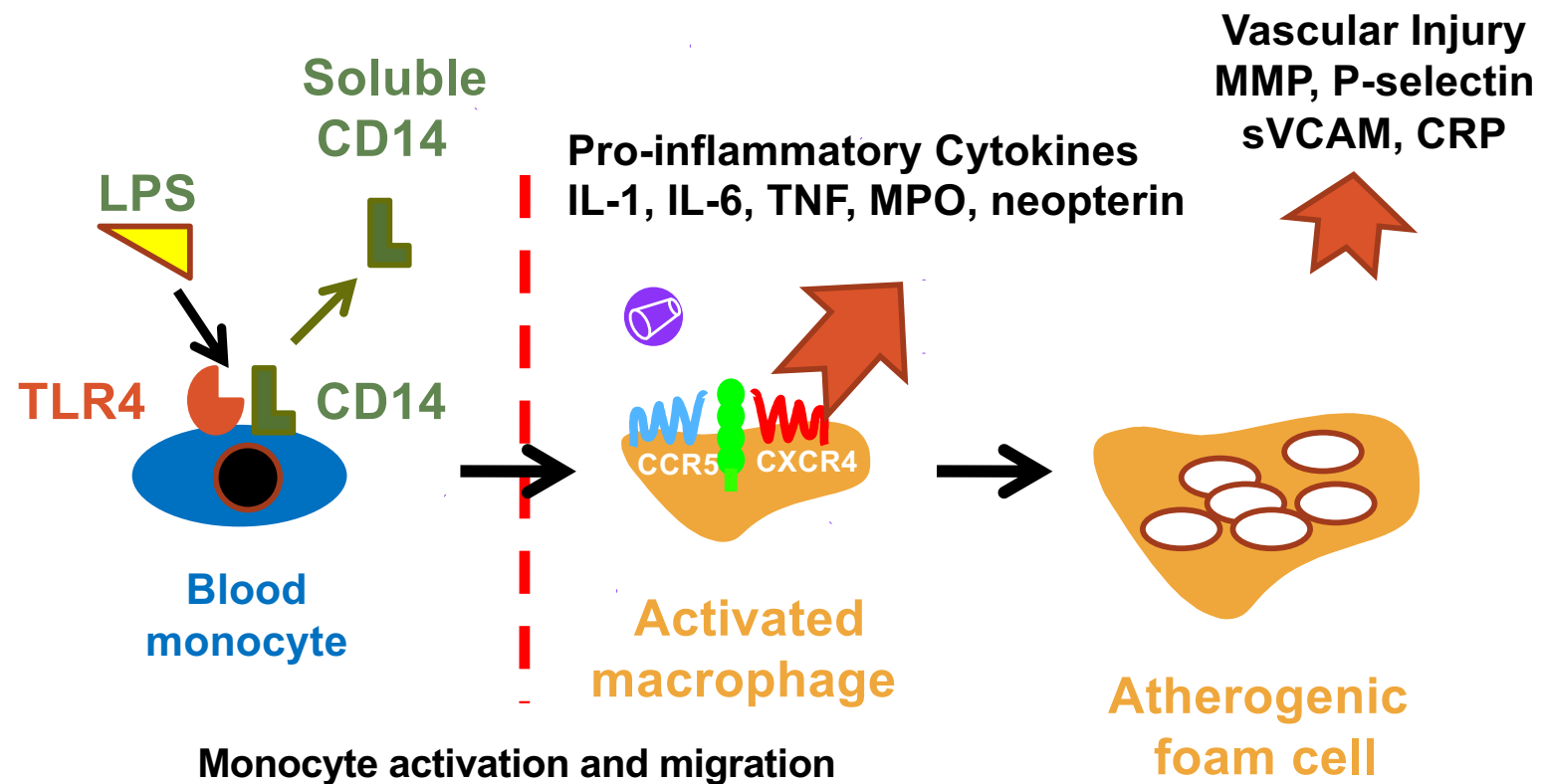
The Tsunami of Acute HIV Infection

- Between days 7 and 21, post infection, 30 – 60% of CD4, CD45RO, and CCR5 memory T-cells become infected
 - Peyer's patches, Inguinal and mesenteric LN
 - TH17 T-cells within the intestinal mucosa
- These cells are never totally replaced
- T-cell counts in the peripheral blood do not reflect the massive loss in the tissues

CCR5 = C-C chemokine receptor type 5; LN = lymph nodes.

Mattapallil JJ, et al. *Nature*. 2005;434(7037):1093-1097.; Veazey RS, et al. *Science*. 1998;280(5362):427-431.

Microbial Translocation of LPS Induces Activation of Monocyte/Macrophage



CRP = C-reactive protein; IL = interleukin; LPS = lipopolysaccharide; MMP = matrix metalloproteinase; MPO = myeloperoxidase; sVCAM = soluble vascular cell adhesion molecule; TNF = tumor necrosis factor.

Benchley JM, Douek DC. *Annu Rev Immunol.* 2012;30:149-173.

Chronic Macrophage Activation Impacts Clinical Outcomes in HIV-infected Individuals

- Macrophage activation (sCD14) best predictor of overall mortality in HIV-infected adults¹
- High levels of LPS and sCD14 correlates with extent of HIV encephalopathy²
- HIV-infected adults with elevated sCD14 have a 3-4-fold higher risk of atherosclerosis compared to adults with similar risk³

sCD14 = soluble cluster of differentiation 14.

1. Sandler NG, et al. *J Infect Dis*. 2011;203(6):780-790.; 2. Ancuta P, et al. *PLoS One*. 2008;3(6):e2516.; 3. Grunfeld C, et al. *AIDS*. 2009;23(14):1841-1849.

Increased Myocardial Infarction Rates and Cardiovascular Risk in HIV-infected Adults

- Adjusted for risk increased rates of:
 - HTN
 - DM
 - Dyslipidemia
- Rates of acute MI/1000
 - HIV negative/positive women
 - 4.9 vs 12.7
 - HIV negative/positive men
 - 10.5 vs 11.4 -smoking not factored in model

DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction.
Triant VA, et al. *J Clin Endocrinol Metab.* 2007;92(7):2506-2512.

Coronary Heart Disease (CHD) in HIV-Infected Adults

- Adjusted for risk, CHD is higher in younger HIV+ men (<34-years-old) and women (<44-years-old)
- ART and viral suppression does not impact (positive or negative) overall risk
 - Protease inhibitors did not result in higher CHD risk
- Conclusion: CHD is accelerated in HIV infection

Chronic Macrophage Activation and Neurocognitive Function

- Elevated plasma sCD14 levels are associated with impaired visuospatial memory in youth with HIV
- sCD14 positively associated with microstructural white matter damage
- TLR4 is expressed on microglia playing a role in neurodegenerative disease
- LPS activation of TLR4 reduces hippocampal pyramidal neuron dendrite length and impairs hippocampal-dependent spatial reference memory
- PET neuroimaging study of cognitively healthy HIV-infected adults shows increased translocator protein binding, a proxy measure of microglial activation

PET = positron emission tomography; TLR = toll-like receptors.

Kim-Chang JJ, Donovan K, Loop MS, Hong S, Fischer B, Venturi G, Garvie PA, Kohn J, Rendina HJ, Woods SP, Goodenow MM, Nichols SL, Sleasman JW. *AIDS*. 2019;33(15):2363-2374.

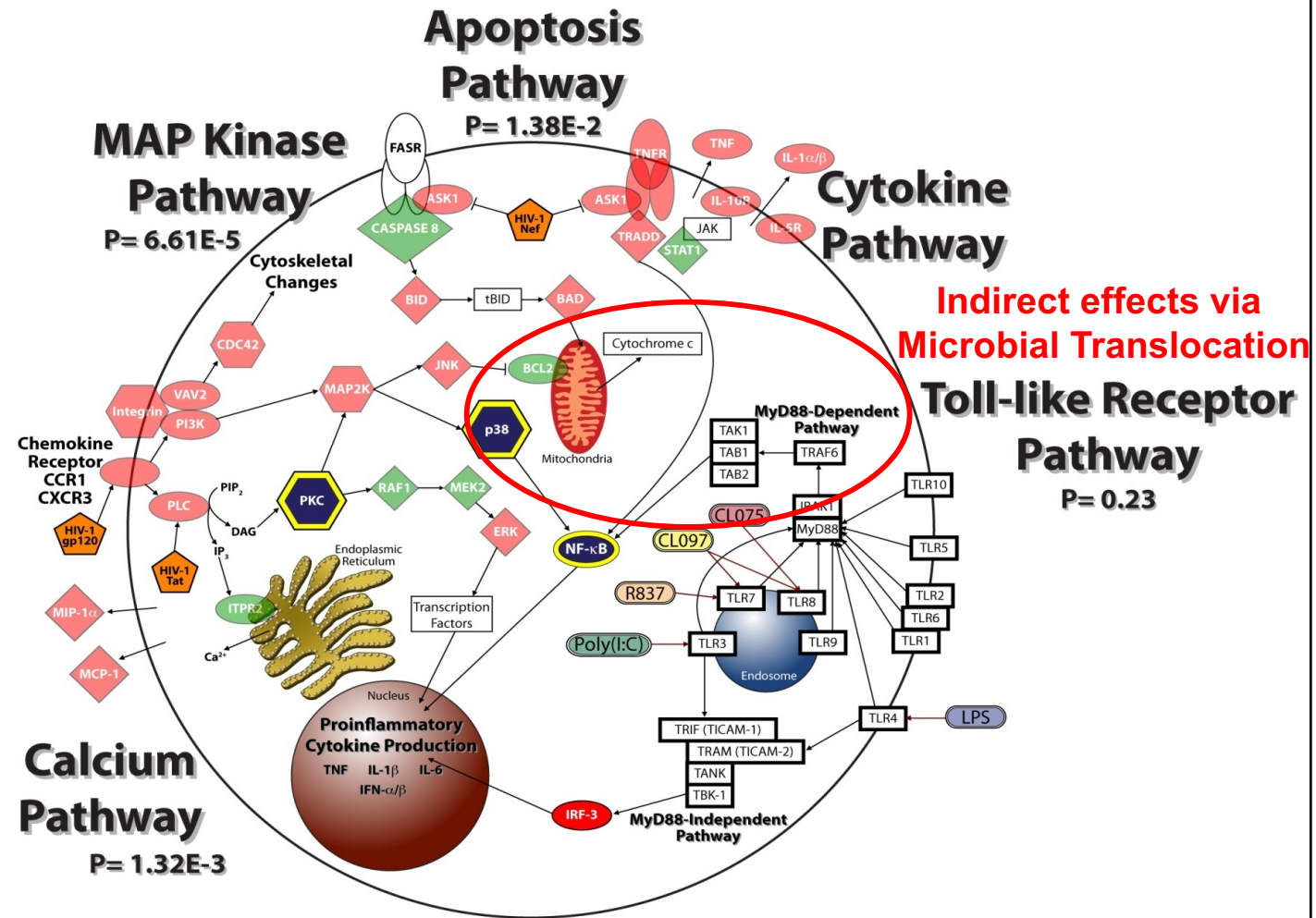
Complications of HIV Across the Lifespan



- HIV infection in youth results in chronic inflammatory state
- Impacts across the lifespan
- Results in persistent disorders including
 - HIV associated neurocognitive impairment
 - Cardiovascular disease
 - Bone and metabolic dysfunction

HIV Induces Macrophage Activation Through Multiple Pathways

Direct effects via viral infection



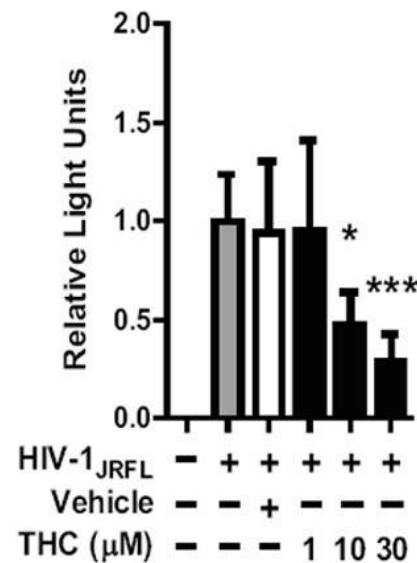
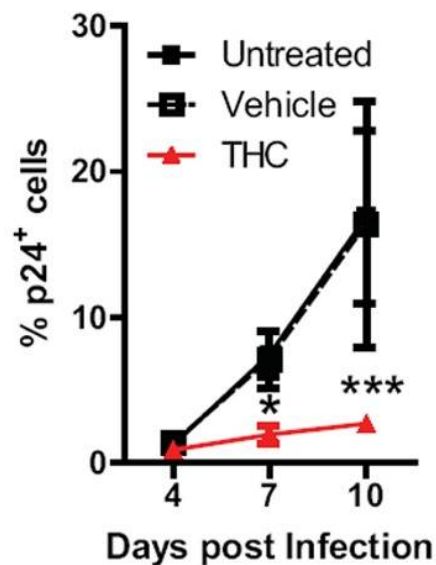
The Case for Cannabinoids as Therapeutics in HIV Infection

- LPS potent stimulator of cannabinoids receptors
- THC reduces TNF, GM-CSF, and IL-6 production in vivo and in vitro (contradictory murine/human studies)
- THC exposure impairs monocyte derived dendritic cell differentiation and T-cell activation
- CB2 receptor agonists reduce in vitro Tat chemokine-driven microglial and macrophage cell migration

CB2 = cannabinoid receptor type 2; GM-SCF = granulocyte-macrophage colony-stimulating factor; THC = tetrahydrocannabinol.
Cabral GA. *J Neuroimmune Pharmacol.* 2006;1(3):280-295. Klein TW. *Nat Rev in Immunol.* 2005;5(5):400-411.

Cannabinoids Reduce in vitro Susceptibility to HIV Infection

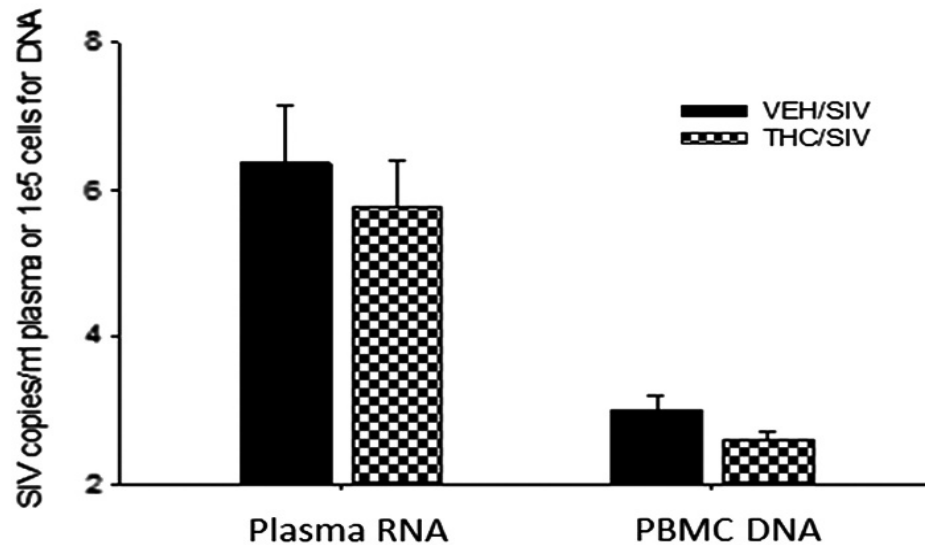
- Attenuation of CXCR4-tropic viral infection of CD4 T cells
- Reduces viral entry into monocyte derived macrophages



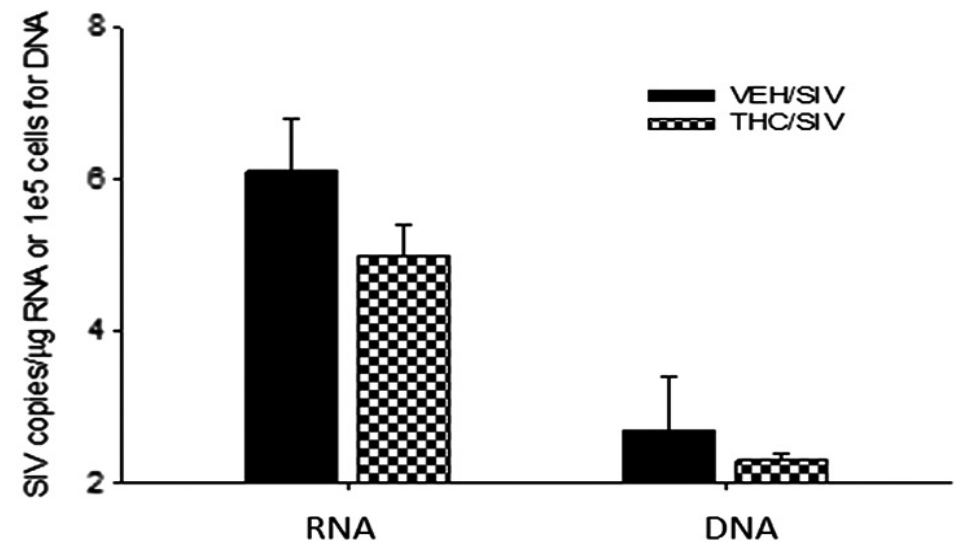
Constantino CM, et al. *PLoS One* 2012;7(3):e33961.; Williams JC, et al. *J Neuroimmune Pharmacol.* 2014;9(3):369-370.

THC Modulates SIV in Macaques Gut

Circulating SIV Levels at Necropsy

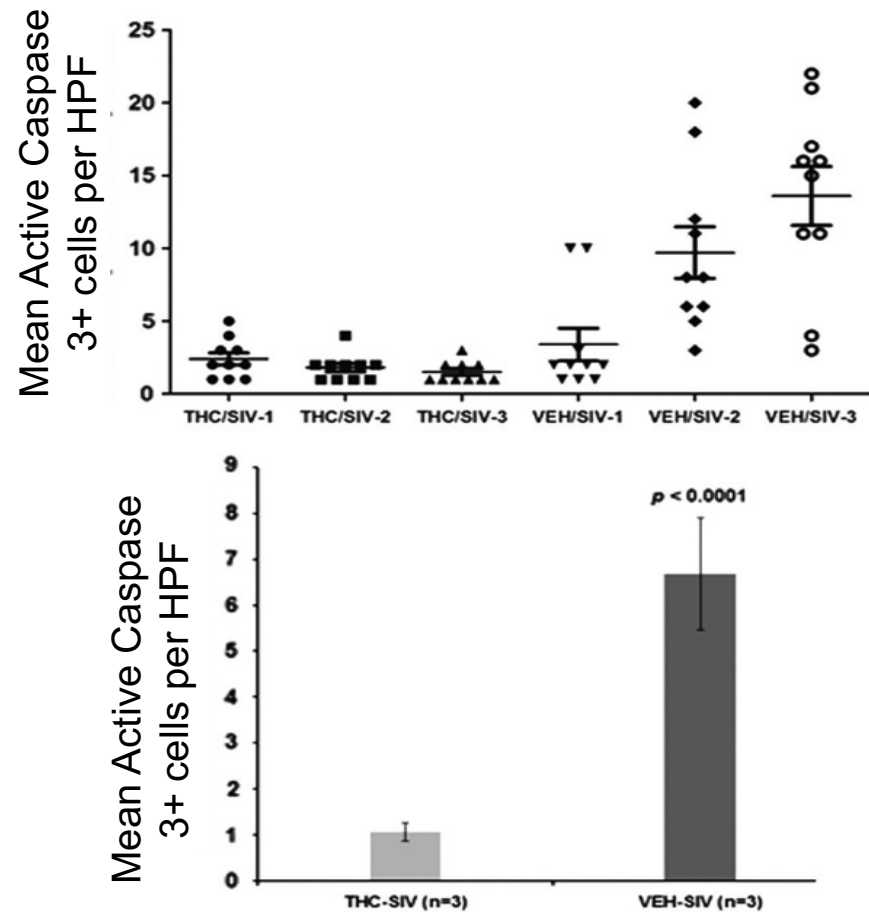
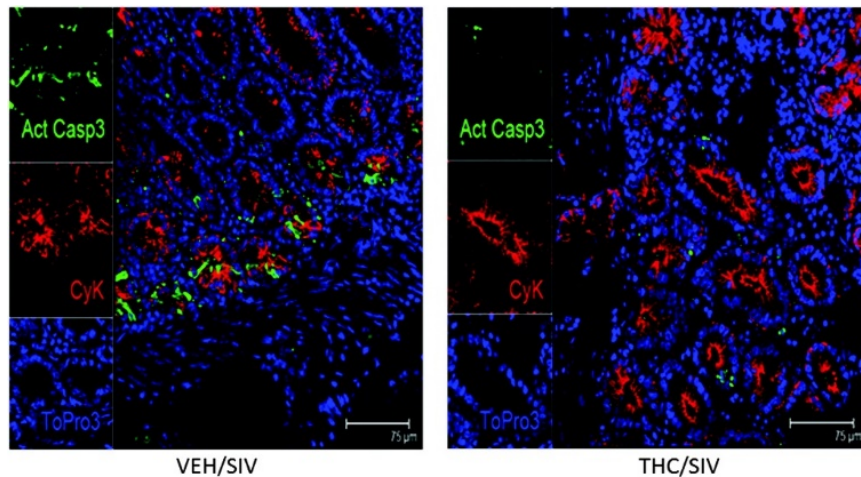


Duodenal SIV Levels at Necropsy



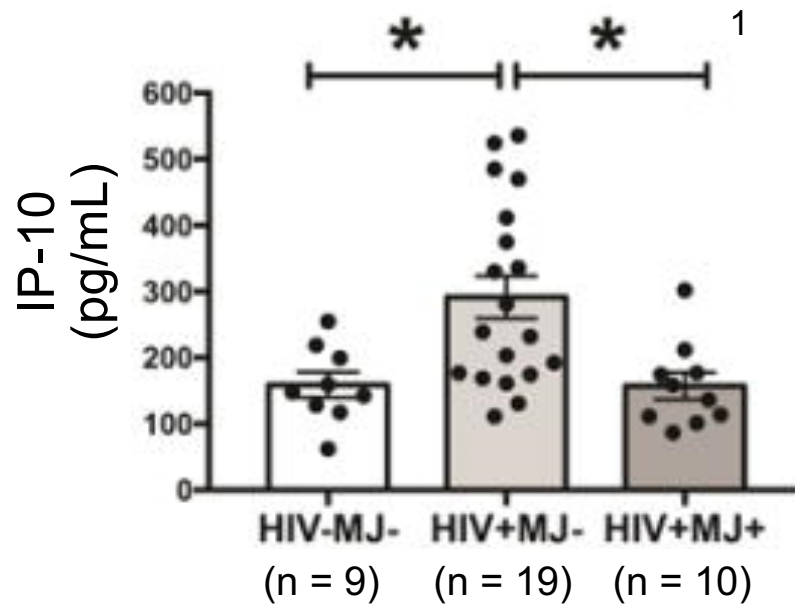
DNA = deoxyribonucleic acid; PBMC = peripheral blood mononuclear cell; RNA = ribonucleic acid; SIV = simian immunodeficiency virus; VEH = vehicle.
Molina PE, et al. *AIDS Res Hum Retroviruses*. 2014;30(6):567-578.

THC Modulates SIV in Macaques Gut (cont.)



Molina PE, et al. *AIDS Res Hum Retroviruses*. 2014;30(6):567-57

Marijuana Use Lowers Macrophage Activation in Adults with HIV



- Fewer circulating activated monocytes
- Lower levels of plasma and inducible IP-10 (CXCL10) in PWH compared to controls¹
- Suppression of α IFN induced T cell activation²
- Compared to non-users, heavy marijuana use in PWH:³
 - Have lower CD38/DR+ activated T cells
 - Decreased TNF α expression by antigen presenting cells

CXCL10 = C-X-C motif chemokine 10; IP-10 = interferon γ -induced protein 10; MJ = marijuana.

1. Rizzo MD, et al. *AIDS*. 2018;32(4):419-429.; 2. Henriquez JE, et al. *J Pharmacol Exp Ther*. 2018;367(1):49-58.; 3. Manuzak JA, et al. *Clin Infect Dis*. 2018;66(12):1872-1882.

Current Status of Cannabinoids as Therapeutic Agents for HIV/AIDS

- Most studies focus on chronic pain or appetite stimulations as outcomes
 - Utilize THC or dronabinol
- Few randomized trials
 - Short duration, small numbers for participants
- No studies have included long term outcomes
- Studies not performed in the context of antiretroviral therapy

Study Outcomes

- Small placebo-controlled trial showed that 13/25 participants had >30% reduction in HIV-associated sensory neuropathy¹
- There are no apparent short-term adverse effects of cannabinoids in PWH²
 - No impact on viral replication or CD4 T-cell counts
- Minimal impact on protease inhibitor pharmacokinetics

1. Abrams DI, et al. *Neurology*. 2007;68(7):515-521.; 2. Abrams DI, et al. *Ann Intern Med*. 2003;139(4):258-266.

Oral Cannabinoids in PWH

- *BMJ Open*: Oral cannabinoids in people living with HIV on effective antiretroviral therapy: CTN PT028 – study protocol for a pilot randomized trial to assess safety, tolerability and effect on immune activation.
- Randomized clinical trial design of oral capsules
- Both Δ^9 -tetrahydrocannabinol and cannabidiol included at different dosing regimens
- Projected Outcomes: quality of life, cognition, mood, and extent of immune activation

Conclusions

- So far, there is little evidence for the therapeutic use of cannabinoids in the treatment of HIV/AIDS
- Based on human observational studies, ex vivo studies, and animal models there is strong evidence that cannabinoids could be effective
- Cannabinoids appear to be safe for PWH
- Observational cohort studies are difficult to interpret due to the effect of ART, HIV replication, and other substance use
- The use of CBD as an anti-inflammatory is moving forward in pilot clinical trials

Additional Abbreviations

ASK1 = apoptosis signal-regulating kinase 1
BAD = BH3 interacting-domain death agonist
BCL2 = B-cell lymphoma 2
Ca = calcium
DAG = dystroglycan
ERK = extracellular receptor kinase
FASR = Fas receptor
IRF = interferon regulatory factor
ITP = inositol 1,4,5-triphosphate receptor, type 2
JAK = janus kinase
JNK = jun N-terminal kinases
MCP = membrane cofactor protein
MEK2 = mitogen-activated protein kinase kinase 2
MIP = major intrinsic protein
NF- κ B = nuclear factor kappa-light-chain-enhancer

PIP = prolactin-inducible protein
PKC = protein kinase C
SR = serine and arginine-rich
STAT1 = Signal transducer and activator of transcription 1
TAB = TGF-beta activated kinase
TAK = tat-associated kinase
TBK = TANK-binding kinase
TICAM = TIR-domain-containing adapter molecule
TRADD = Tumor necrosis factor receptor type 1-associated DEATH domain
TRIF = TIR-domain-containing adapter-inducing interferon- β
VAV2 = guanine nucleotide exchange factor

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