# The problems and promise of cannabis in HIV

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# Disclosures

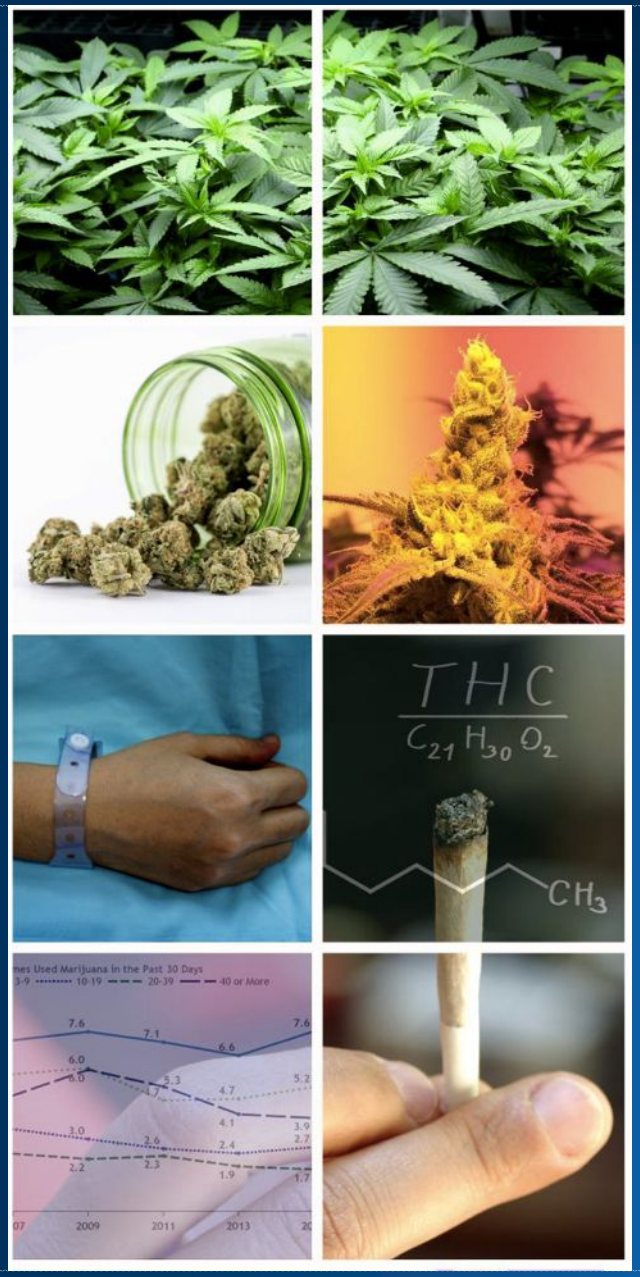
No financial interest or other relationship with any commercial interest

# Learning objectives

1. Review cannabis epidemiology
2. Compare and contrast cannabinoids
3. Review current science on the relevance of cannabis to the HIV epidemic
4. Describe the potential neuropsychiatric and health effects of cannabis use

# Outline

- Cannabis and cannabinoids
  - Endocannabinoids
  - Phytocannabinoids
  - Synthetic cannabinoids
- Cannabis and HIV outcomes
  - Observational studies
  - Clinical trials

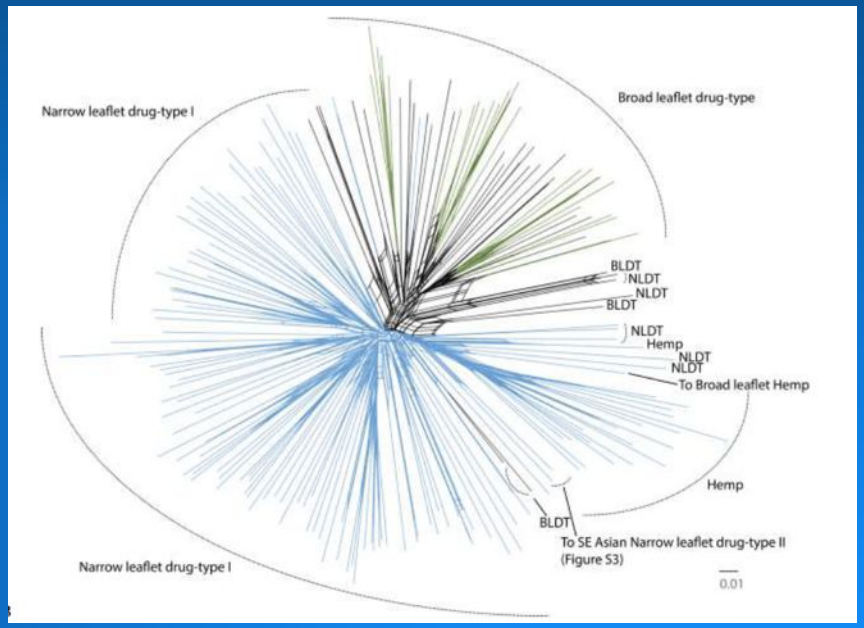



# Cannabis and cannabinoids

## Cannabis and its use

# Cannabis

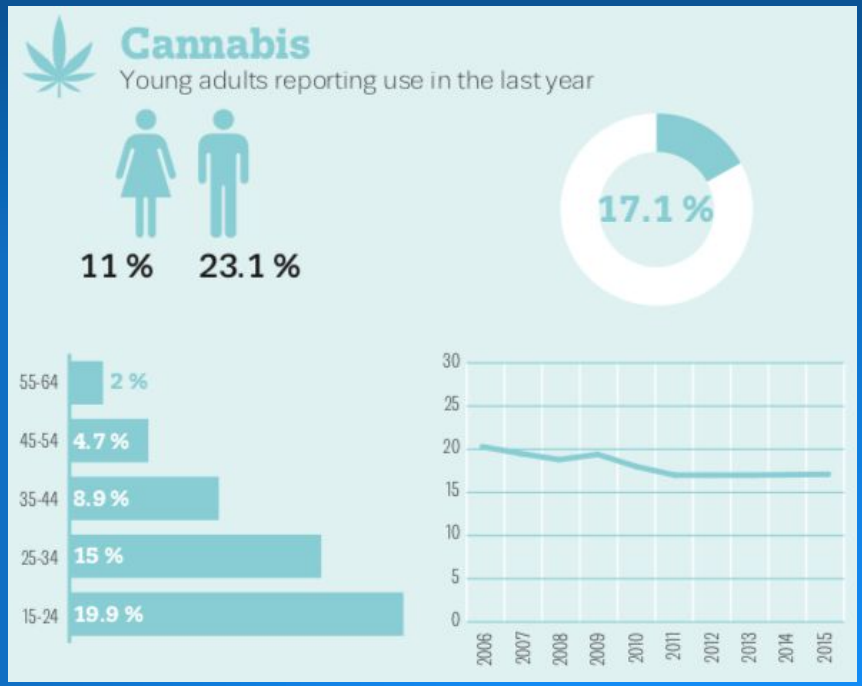
- 340 varieties of *Cannabis* plants
- Millennia of use and cultivation
- Inhaled or ingested for its psychoactive and therapeutic effects




Lynch et al. 2015

# Prevalence

- 2.7-4.9% 12-month adult prevalence of globally
- Most commonly used “illicit” drug, including in Spain
  - Increasing prevalence in the US
  - Stable prevalence in Spain




UNODC, 2015; EMCDDA 2017; Garin et al. 2015

# Prevalence in HIV (USA)

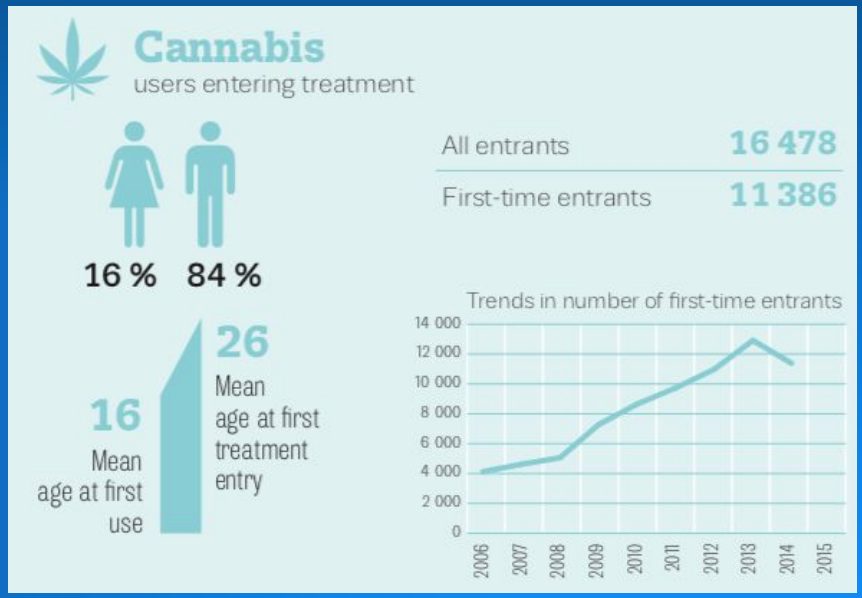
- 15% 1-month prevalence
  - Veterans; 2002-2010
- 24.3% 3-month prevalence
  - HIV primary care clinics (CNICS); 2005-2008
- 38.1% 12-month prevalence
  - HIV primary care clinics; 2003-2005
- 34.9% 12-month prevalence
  - National survey; 2005-2015
- 62% lifetime prevalence
  - HIV primary care clinics (CNICS); 2007-2014

| | Demographic subsample | Prior use of cannabis (%) |
|---|---|---|
| Aggregate sample | 10,652 | 6587 (62%) |
| *Patient demography* | | |
| Age group | | |
| 18–29 years | 1254 | 810 (65%) |
| 30–39 years | 2310 | 1465 (63%) |
| 40–49 years | 3901 | 2448 (63%) |
| 50+ years | 3187 | 1864 (59%) |
| Gender | | |
| Male | 8882 | 5815 (66%) |
| Female | 1770 | 772 (44%) |
| Race/ethnicity | | |
| Non-Hispanic White | 5278 | 3844 (73%) |
| Non-Hispanic Black | 3632 | 1788 (49%) |
| Hispanic | 1270 | 686 (54%) |
| Other | 472 | 269 (57%) |
| Transgender | | |
| Yes | 87 | 49 (56%) |
| No | 10,565 | 6538 (62%) |
| Sexual orientation ($n = 1716$) | | |
| Lesbian, Gay, or Homosexual | 1280 | 1007 (79%) |
| Straight or Heterosexual | 278 | 175 (63%) |
| Bisexual | 95 | 75 (79%) |
| "Something Else" | 34 | 29 (85%) |
| "Don't Know" | 29 | 12 (41%) |

Hartzler et al. 2017; Mimiaga et al. 2013; Adams et al. 2018; Pacek et al. 2018

# Cannabis use disorder

- 9 – 10% of regular cannabis users
- Growing proportion of first time entrants into treatment
- Evidence-based treatment
  - Cognitive Behavioral Therapy
  - Motivational Enhancement Therapy
- No significant impact of Screening, Brief Intervention, and Referral to Treatment (SBIRT) on cannabis "involvement scores" for PLWH




EMCDDA 2017; Dawson-Rose et al. 2017

# Cannabis use disorder in HIV

- 31% estimated prevalence of a cannabis use disorder
  - HIV primary care clinics (CNICS); 2007 and 2014
- Wide variation in prevalence depending on (4%-52%)

**Table 2** Substance use disorder prevalence by geographic site

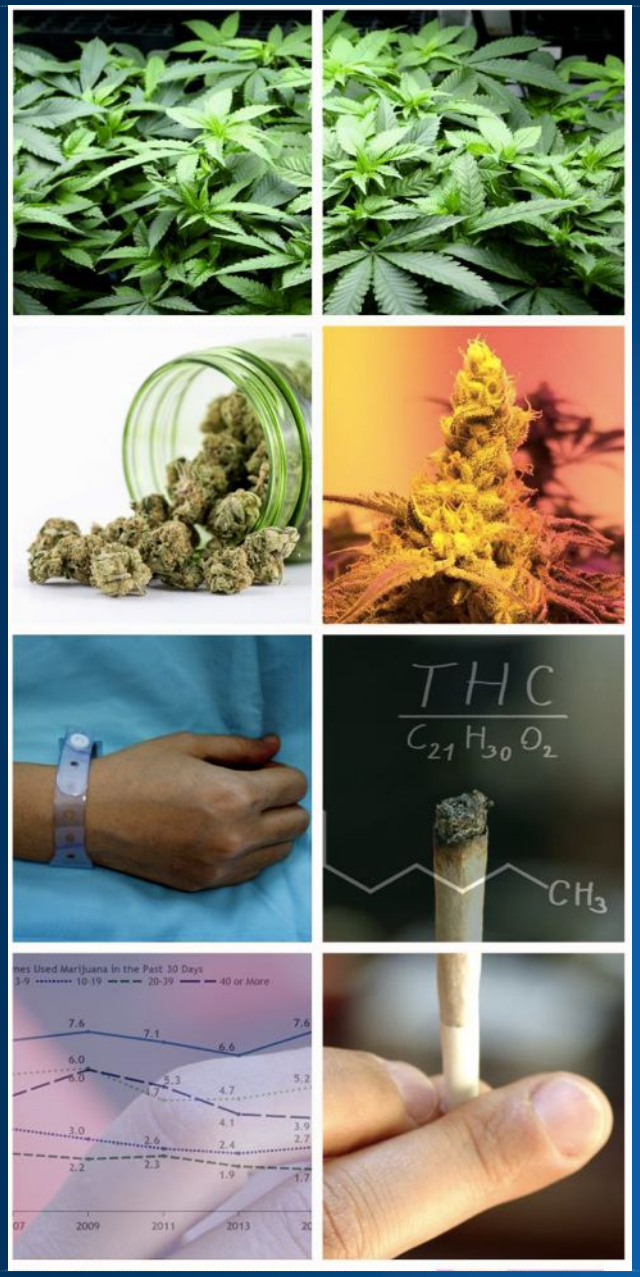
| | Site #1 (818) (%) | Site #2 (852) (%) | Site #3 (2580) (%) | Site #4 (3179) (%) | Site #5 (1161) (%) | Site #6 (706) (%) | Site #7 (1356) (%) | Aggregate (10,652) (%) |
|---|---|---|---|---|---|---|---|---|
| Any SUD | 60 | 21 | 39 | 48 | 71 | 34 | 61 | 48 |
| Alcohol UD | 27 | 13 | 16 | 18 | 21 | 14 | 22 | 19 |
| Cocaine UD | 13 | 7 | 11 | 8 | 17 | 7 | 18 | 11 |
| Marijuana UD | 36 | 4 | 26 | 29 | 52 | 24 | 42 | 31 |
| Methamphetamine UD | 14 | 1 | 4 | 17 | 31 | 2 | 21 | 13 |
| Opioid UD | 3 | 1 | 3 | 3 | 8 | 1 | 7 | 4 |

Hartzler et al. 2016

# Association with other conditions

- Other substance use disorders (including tobacco use disorders)
- Other mental health disorders
  - Mood disorders
  - Anxiety disorders
  - Psychotic disorders
- Individual and community factors

Pacek et al. 2018; Bruce et al. 2015

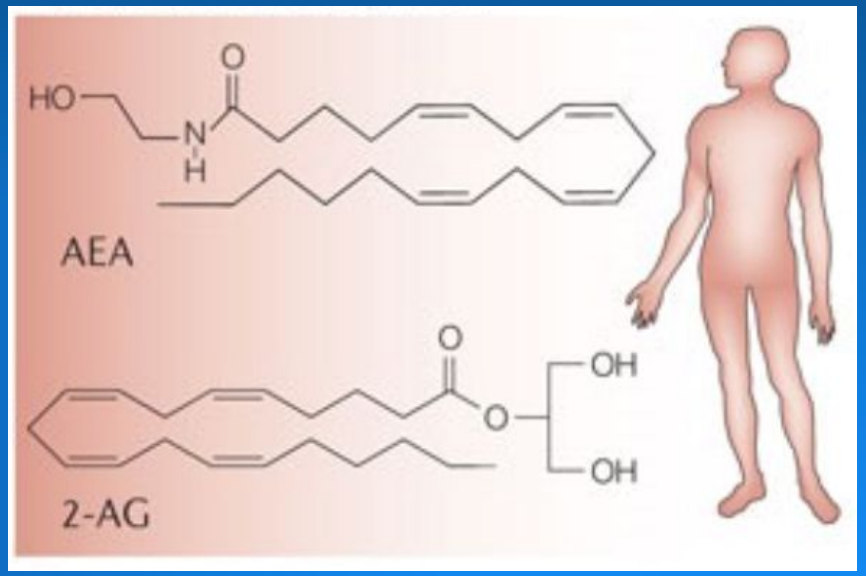



# Cannabis and cannabinoids

## Cannabinoids

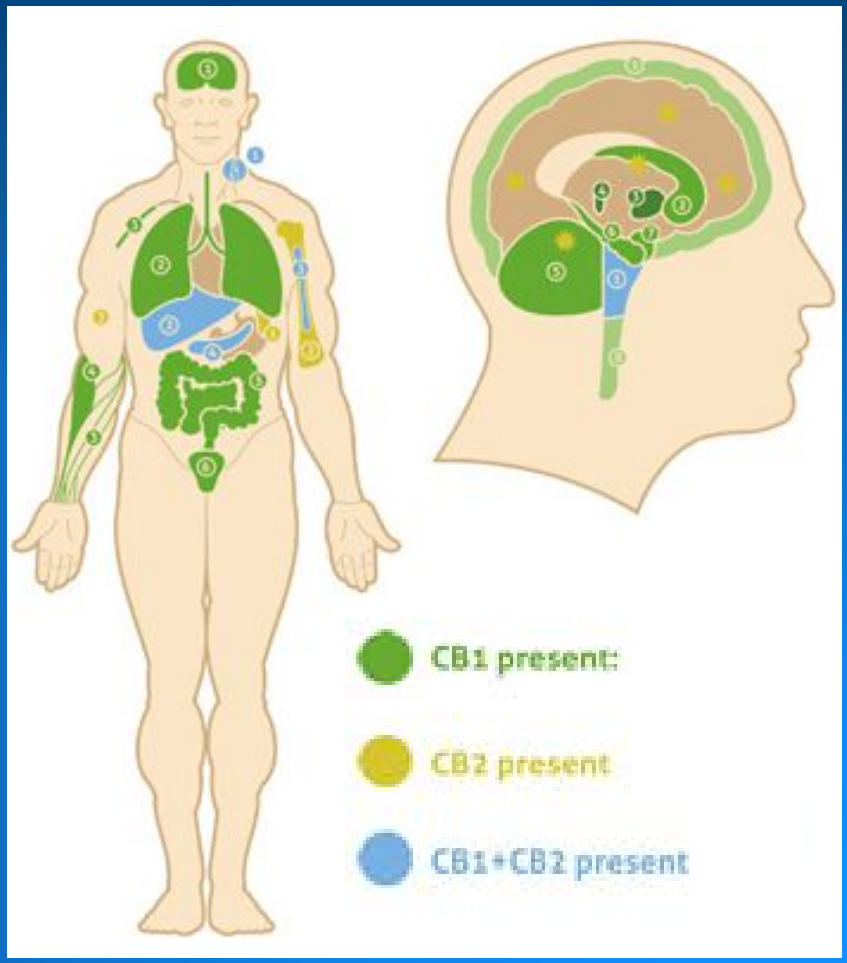
# Cannabinoids

- Endogenous cannabinoids
  - Anandamide
  - 2-arachidonoylglycerol
- Phytocannabinoids (Plant-derived)
  - Delta-9-tetrahyrdocannabinol (THC)
  - Cannabidiol
- Synthetic cannabinoids
  - Dronabinol (synthetic THC)
  - K2, Spice, and approximately 100 others



# Physiology

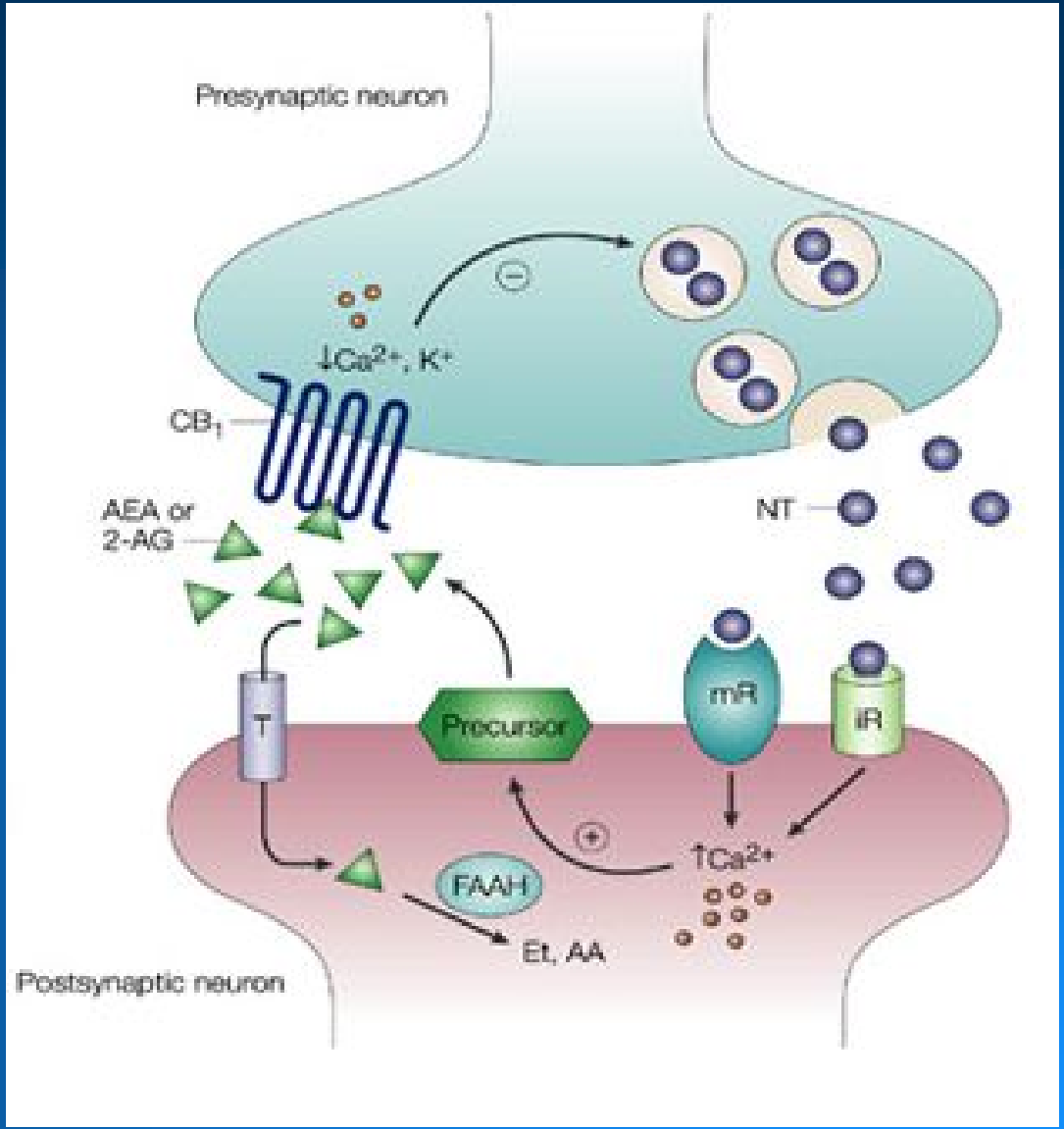
- Cannabinoids act on human cannabinoid receptors 1 and 2 (CB1 and CB2)
- CB1 is a G-protein coupled receptor, located in the CNS, and predominantly presynaptic




Elphick & Egertova 2001

# Synaptic activity

1. Cannabinoid interacts with CB1 on presynaptic neuron
2. CB1 activation inhibits adenylyl cyclase and decreases cellular cyclic adenosine monophosphate (cAMP)
3. Reduces membrane potentials
4. Inhibits neurotransmitter release




Guzman, Nature Reviews Cancer 2003

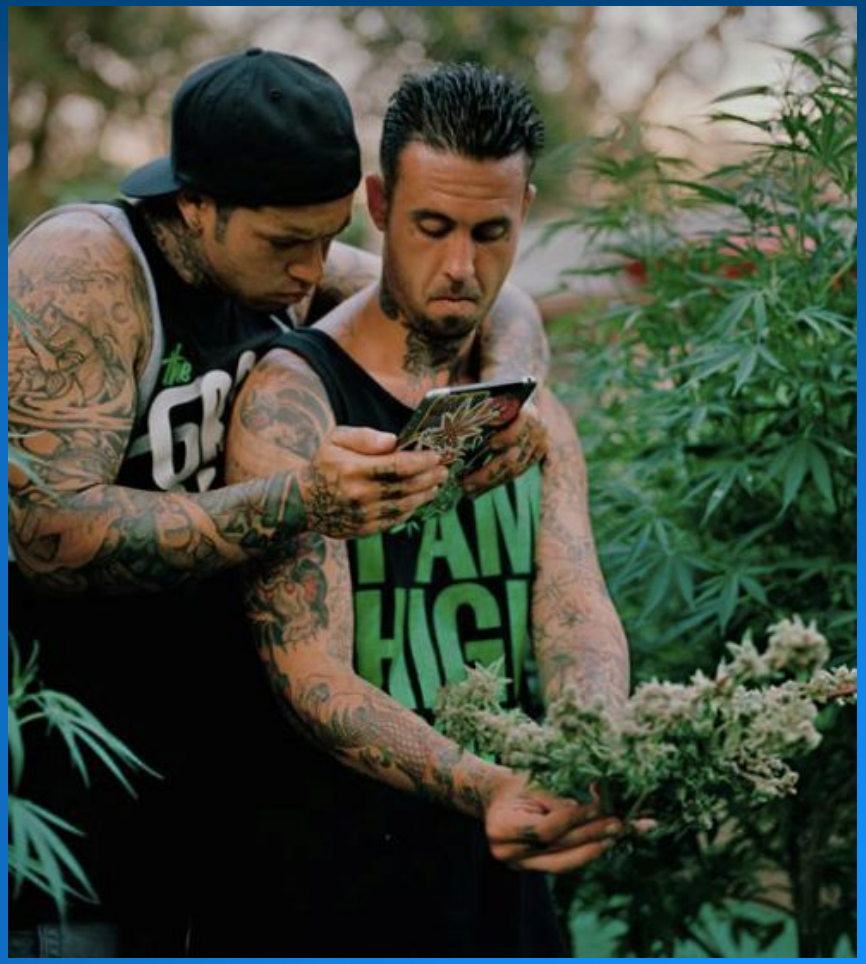
# Endocannabinoid effects

| | Cannabinoid | Action | Region | Effect |
|---|---|---|---|---|
| **Relax** | Anandamide | Inhibits GABA reuptake | Basal ganglia | Decrease locomotor activity |
| **Eat** | 2-AG | Inhibits NE release | Hypothalamus | Appetite stimulation |
| **Sleep** | 2-AG | Unknown | Hypothalamus | Promotes sleep states |
| **Protect** | Anandamide 2-AG | Inhibits NMDA receptors | Cortex | Neuroprotection |
| **Forget** | Anandamide 2-AG | Inhibits Glu and Ach release | Hippocampus | Inhibits Long-term Potentiation and memory |

Di Marzo et al. 1998; Michoulam et al. 1998; Perez-Morales et al. 2013

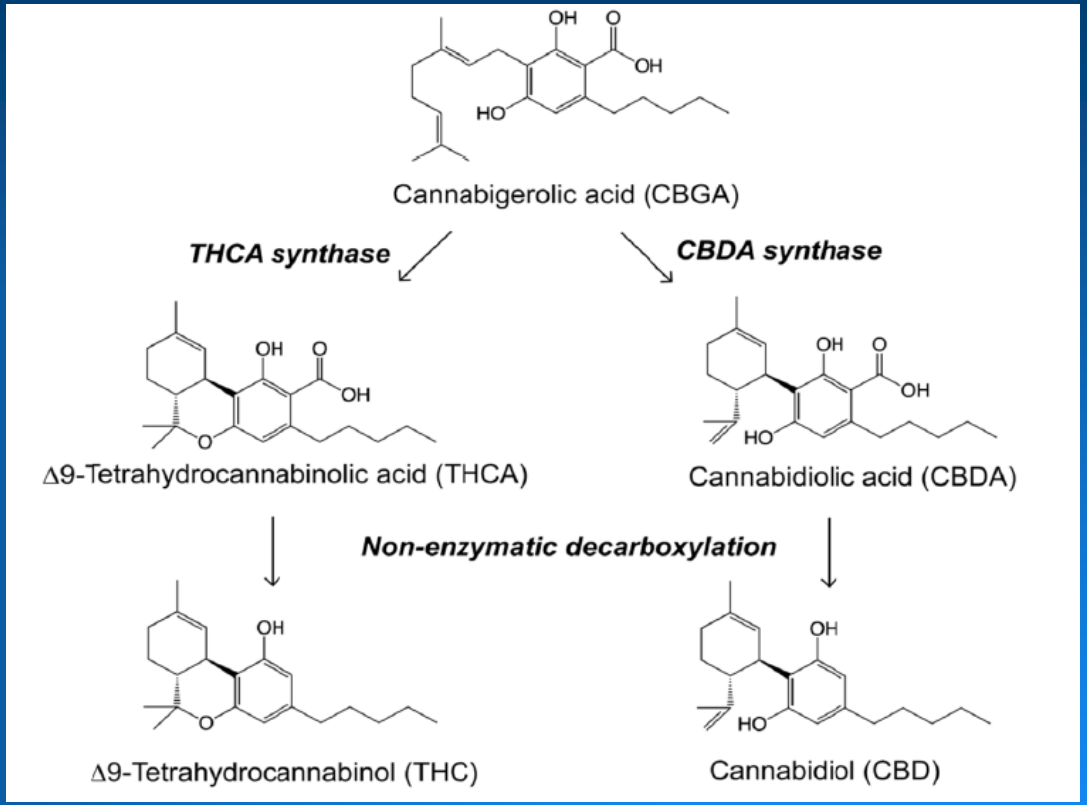
# Phytocannabinoids

- Endogenous cannabinoids
  - Anandamide
  - 2-arachidonoylglycerol
- Phytocannabinoids (Plant-derived)
  - Delta-9-tetrahyrdocannabinol (THC)
  - Cannabidiol
- Synthetic cannabinoids
  - Dronabinol (synthetic THC)
  - K2, Spice, etc.



# Phyto-cannabinoids

- Derived from plants (i.e., cannabis)
- 80+ cannabinoids
- Activity at the cannabinoid receptors
- “Entourage effect”




NAS 2017

# Psychoactivity (THC)

## Getting "high"

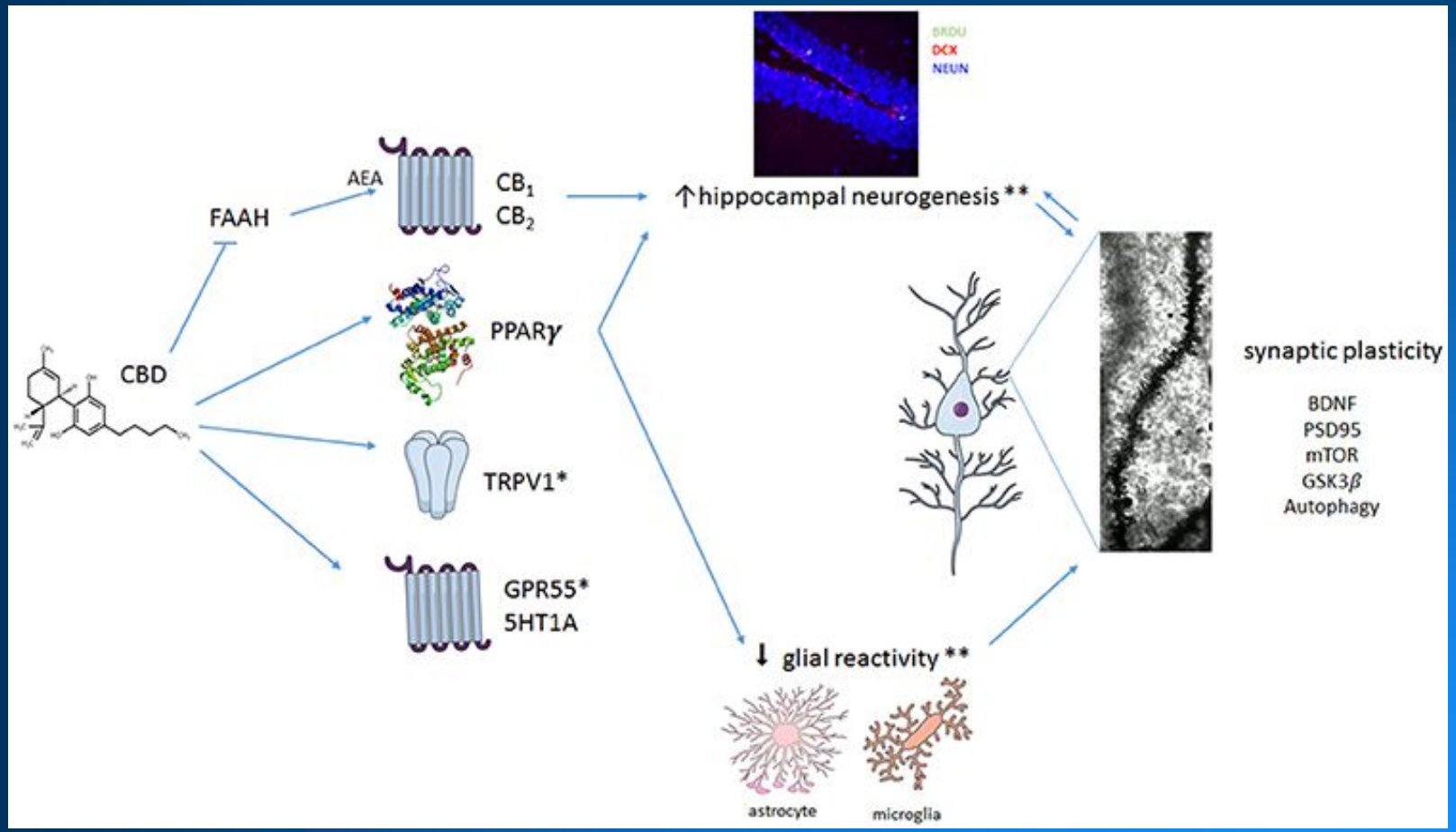
- Euphoria
- Sensory and perceptual changes
- Cognitive impairment

## Cannabinoid "tetrad"

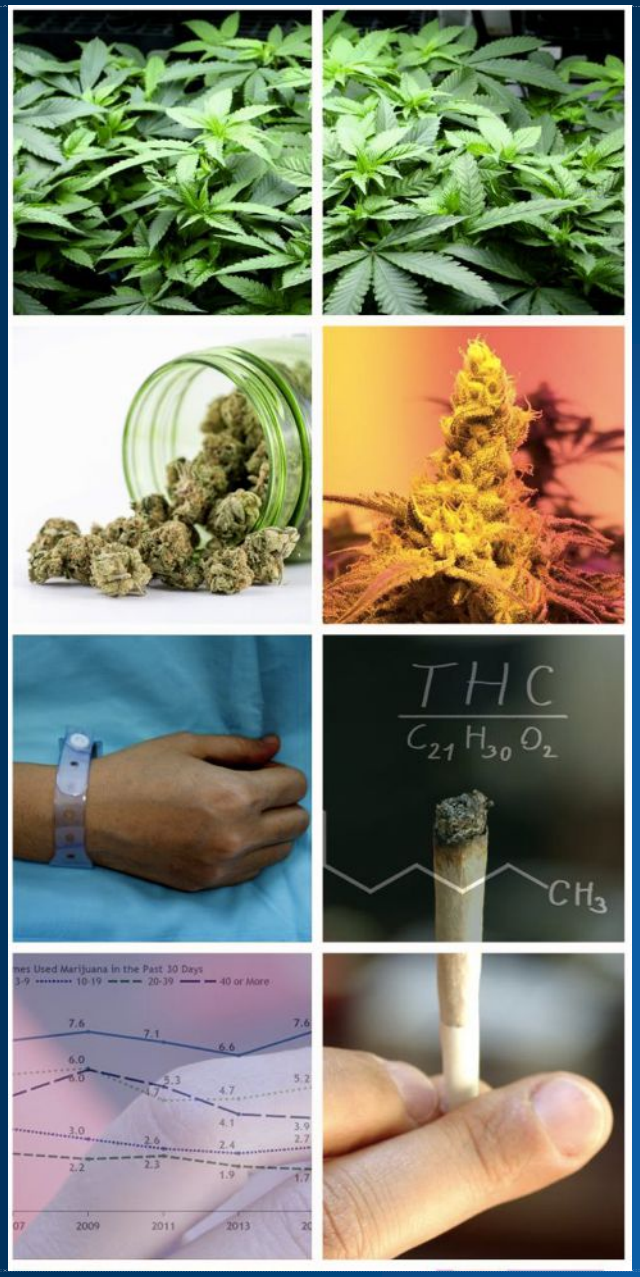
1. Analgesia
2. Catalepsy
3. Reduced spontaneous activity
4. Hypothermia

Abdulrahim et al. 2015; Castaneto et al. 2014

# Neuroprotective effects




Campos et al. 2017




# Cannabis and HIV

Observational studies

HIV continuum of care

# Cannabis-associated harms

| Conclusive | Moderate | Limited |
|---|---|---|
| Respiratory symptoms and more frequent chronic bronchitis episodes | Overdose injuries, including respiratory distress, among pediatric populations | Non-seminoma-type testicular germ cell tumors |
| Motor vehicle crashes | Lower newborn birth wt | Myocardial infarction |
| Development of schizophrenia or other psychoses | Mood, anxious, suicidal ideation, and suicide completion | Ischemic stroke or subarachnoid hemorrhage |
| *Less high school completion | Other substance abuse | Pregnancy complications |
| | | COPD |

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# HIV transmission

## Factors reducing risk

Homeless youth and MSM who use cannabis have less injection drug use or longer times to initiation of injection drug use

Reddon et al. 2018; Heinsbrook et al. in press

## Factors increasing risk

Youth, PLWH, heterosexual adults demonstrate more sexual risk behaviors (condomless sex, greater number of lifetime sexual partners) potentially mediated by:

- Decreased intentions to use HIV protection
- Lower self-efficacy
- Higher risk preference/hedonism

Cardoso & Malbergier 2015; Brodbeck et al. 2006

# HIV transmission risk

- Risky sex after controlled administration of 2.8% THC was considered less likely

Metrik et al. 2012

# HIV transmission

## Factors reducing risk

Lower HIV viral load among daily cannabis users newly diagnosed with HIV

Milloy et al. 2015

## Factors increasing risk

Greater probability of viral shedding in semen of virally suppressed MSM who use cannabis during sex

Ghosn et al. 2014

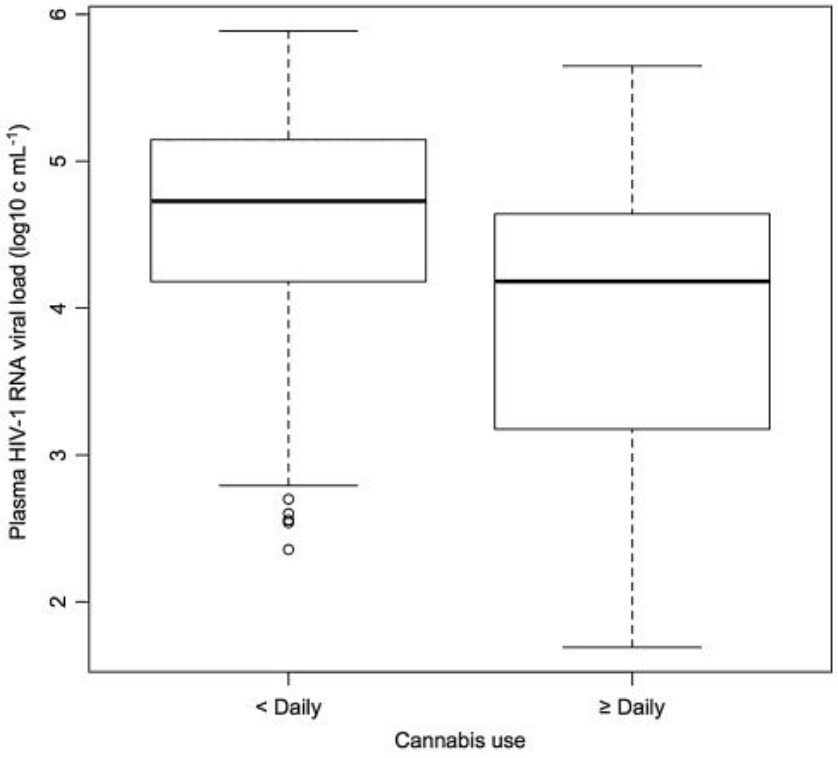
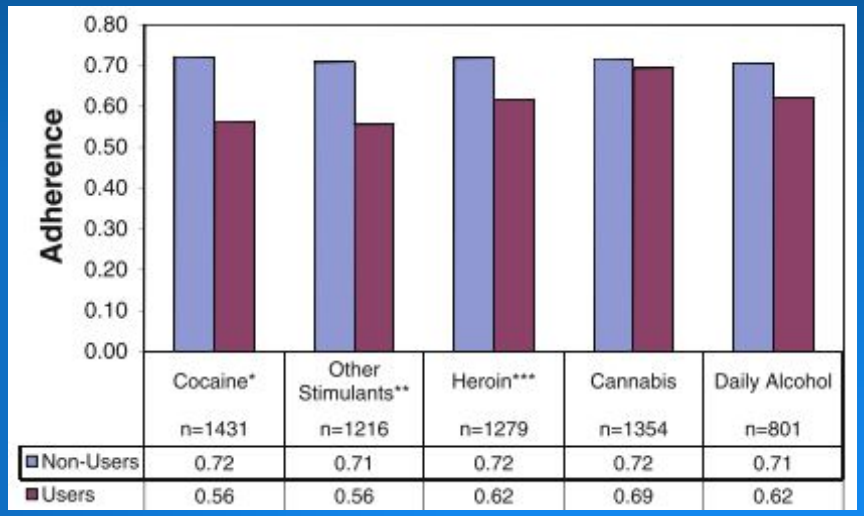



**Figure 1.** *Box plot of human immunodeficiency virus (HIV)-1 RNA viral load observations stratified by cannabis use among 88 people who use illicit drugs with recent HIV infection.*

# Access to care and ART adherence

- No association with linkage to care (Lake et al. 2017)
- Associated with missed clinic visits but not retained in care (Kipp et al. 2017; Tarantino et al. 2018)
- No association with adherence in a sample of 119 HIV+ followed at Ramón y Cajal University Hospital, Madrid (González-Álvarez et al. 2017), a finding supported by a majority of other studies (Rosen et al. 2013; De Jong et al. 2005; Soto Blanco et al. 2005; Vidot et al. 2017; Slawson et al. 2014) but not African American youth in the US. (Gross et al. 2016)




Rosen et al. 2013

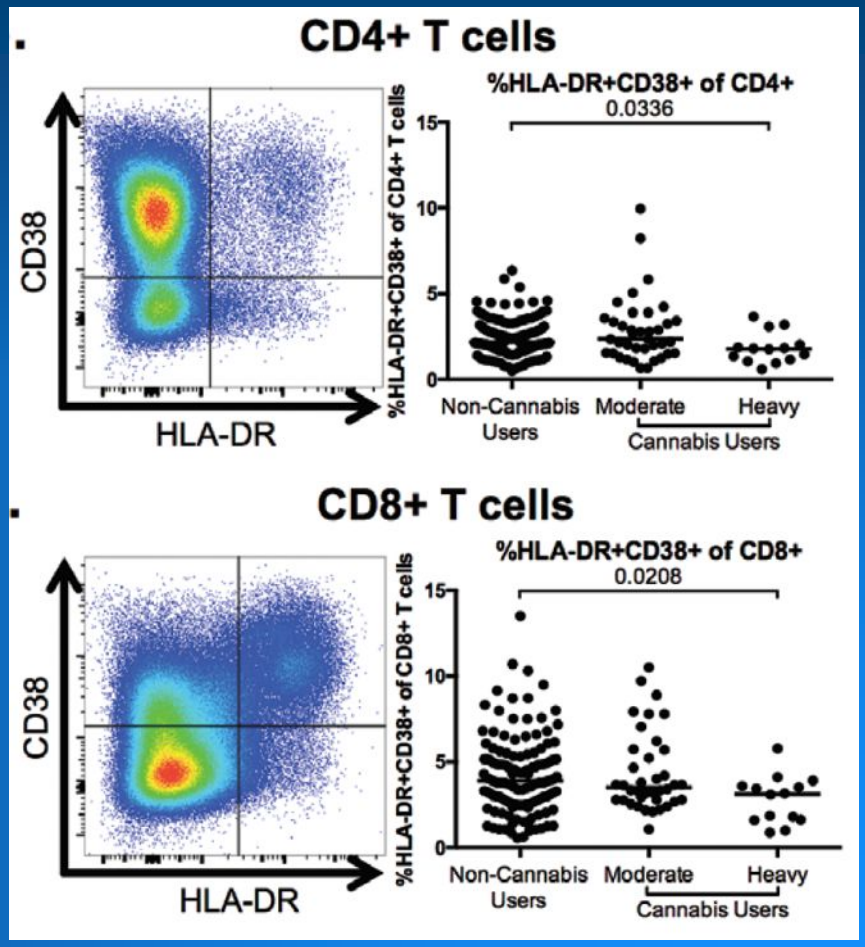
# Viral suppression

Results are mixed

- Cannabis dependence, but not cannabis use was associated with poorer adherence and higher viral load (Bonn-Miller et al. 2014)
- Cannabis use was associated with lower rates of viral suppression (Kipp et al. 2017)
- Cannabis use was associated with lower viral loads (Thames et al. 2015)

# Morbidity: Inflammation

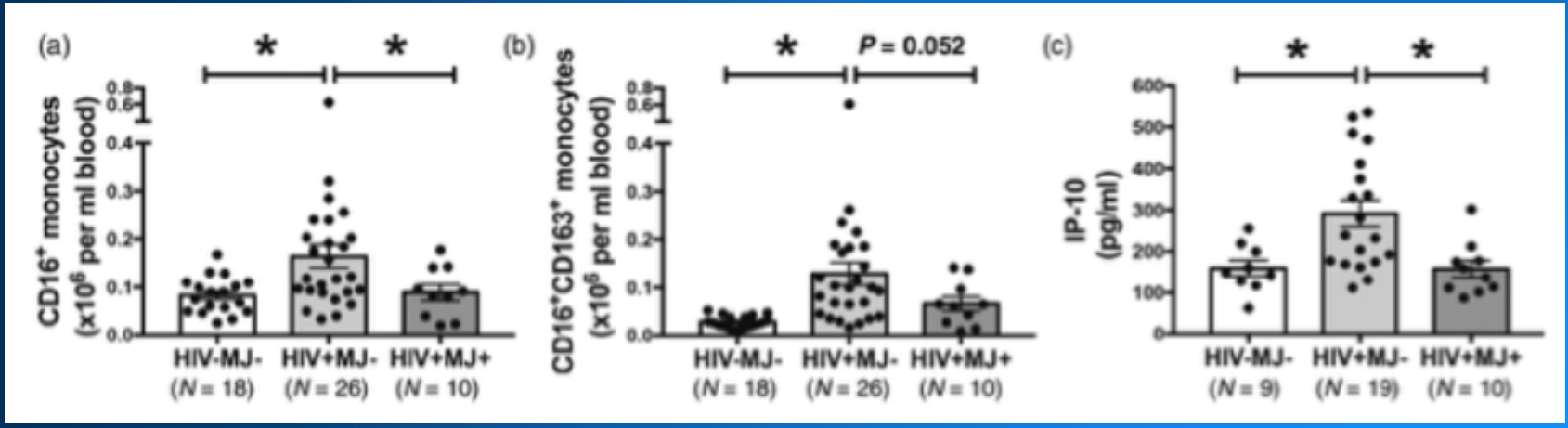
- Lower frequencies of activated (HLA-DR+CD38+) CD4+ and CD8+ T cells
- Lower frequencies of TNF-α+ B cells
- No differences in the frequency of IL-6+ B cells
- Lower frequencies of IL-23+ and TNF-α+ antigen presenting cells




Manuzak et al. 2018

# Morbidity: Inflammation

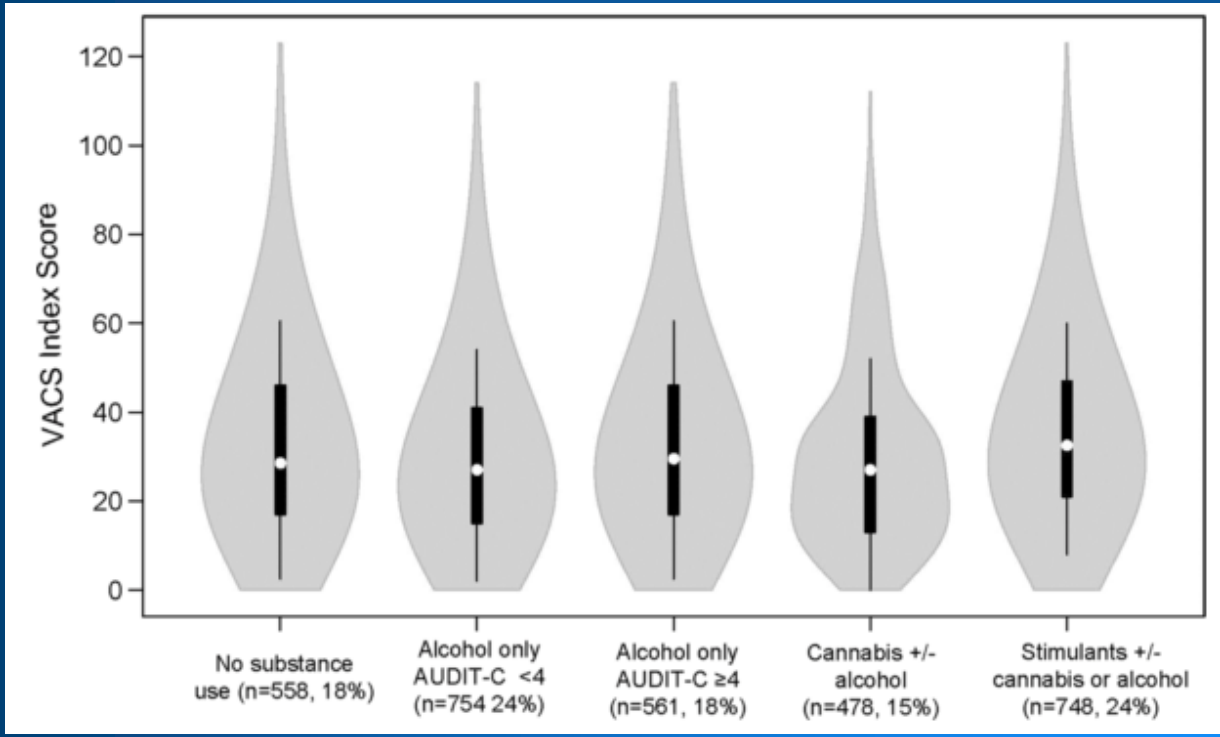
- Lower circulating CD16 monocytes and plasma IP-10 (implicated in neuroinflammation) among HIV+ cannabis users
- In-vitro THC treatment impaired CD16 monocyte transition to CD16 and IP-10.



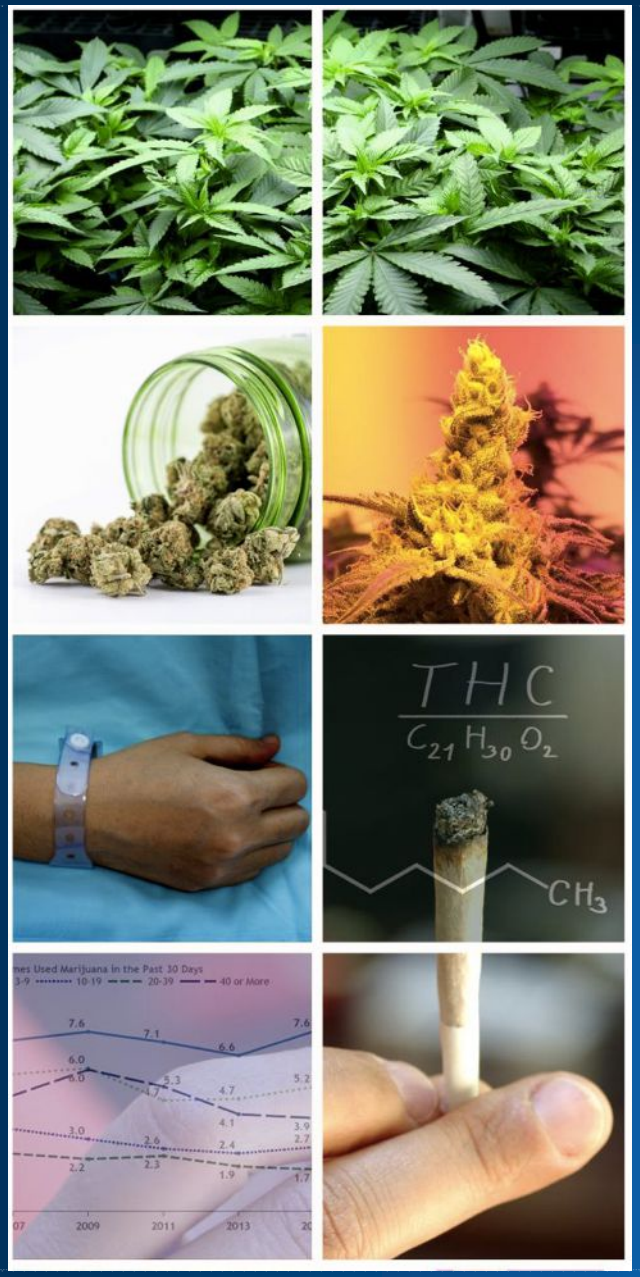

Rizzo et al. 2018; Manuzak et al. 2018

# Mortality

- Cannabis use [b =-0.97 (95% CI -1.93, 0.00), p = 0.048] was not associated with 5-year mortality risk among 3099 veterans followed from 2002-2010




Adams et al. 2017




# Cannabis and HIV

Observational studies

Morbidity and mortality

# Neuroimaging findings

- Independent effects of HIV and cannabis on brain structure
- There was an HIV x cannabis interaction on global cognition but not brain structure

Thames et al. 2017

# Cognitive impairment

**TABLE 2. Means for Neuropsychological Performance of Subgroups Stratified by Disease Status and Marijuana Use (MAR)**

| | HIV Negative | | HIV Asymptomatic | | HIV Symptomatic | | HIV[1] | MAR[2] | Interaction |
|---|---|---|---|---|---|---|---|---|---|
| | p < | | p < | | p < | | | | |
| | MAR- (n = 24) | MAR + (n = 49) | MAR- (n = 46) | MAR + (n = 79) | MAR- (n = 29) | MAR + (n = 55) | | | |
| Impairment[a] | 3.47 | 2.96 | 3.78 | 4.76 | 4.33 | 6.48 | 0.001 | 0.009 | 0.027 |
| PIQ Performance IQ | 107.73 | 106.54 | 105.47 | 102.46 | 100.42 | 98.86 | 0.003 | | |
| Trail Making A | 22.29 | 20.25 | 23.58 | 24.40 | 23.42 | 25.89 | 0.034 | | |
| Trail Making B | 50.41 | 51.83 | 56.62 | 62.78 | 59.44 | 70.32 | 0.002 | | |
| V Span Forward[b] | 6.24 | 6.04 | 6.19 | 5.98 | 5.71 | 5.64 | 0.012 | | |
| Pegboard D[c] | 60.80 | 65.08 | 66.25 | 66.56 | 67.51 | 69.10 | 0.001 | | |
| Pegboard ND | 67.55 | 70.42 | 72.86 | 70.98 | 75.15 | 73.38 | 0.013 | | |
| Figural Fluency | 51.64 | 52.04 | 46.69 | 47.20 | 47.99 | 45.59 | 0.006 | | |
| PASAT[d] | 38.21 | 44.00 | 40.30 | 35.59 | 37.48 | 30.96 | | 0.011 | |
| Reaction Time (msec) | 456.00 | 446.00 | 468.00 | 483.00 | 473.00 | 523.00 | 0.034 | | |
| SRT—Delay[e] | 11.42 | 11.57 | 11.09 | 10.28 | 10.56 | 9.21 | 0.001 | 0.033 | |

[1]Main effect for HIV disease status, [2]Main effect for Marijuana Use (≤12 per year versus ≥ 52 per year)
[a]Summary impairment score (number of test in the impaired range)
[b]Visual Span Forward (from Wechsler Memory Scale-Revised)
[c]Grooved Pegboard Test (Dominant and Non-Dominant Hand)
[d]Paced Auditory Serial Addition Test (number correct, 2.4 second intertrial interval)
[e]Selective Reminding Test—delayed recall

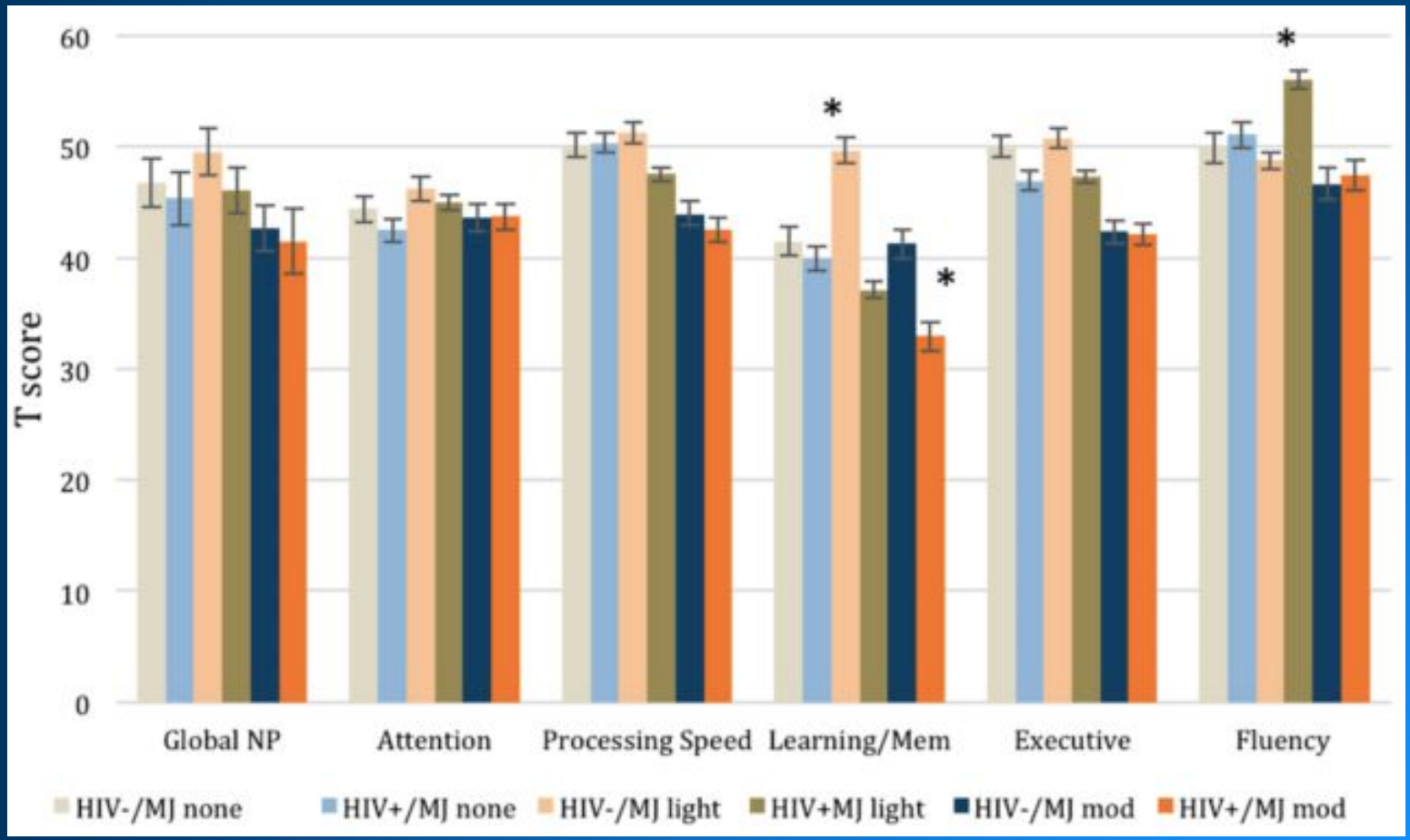
Cristiani et al. 2004

# Self-report of cognitive function

| | Medical Outcomes Study-HIV CF4 $\beta$ (95% CI) | Montreal Cognitive Assessment Memory $\beta$ (95% CI) |
|---|---|---|
| Current cannabis use | -0.36 (-0.64, -0.07) | 0.00 (-0.03, 0.02) |
| Lifetime cannabis use | 0.03 (-0.22, 0.29) | 0.01 (-0.01, 0.03) |

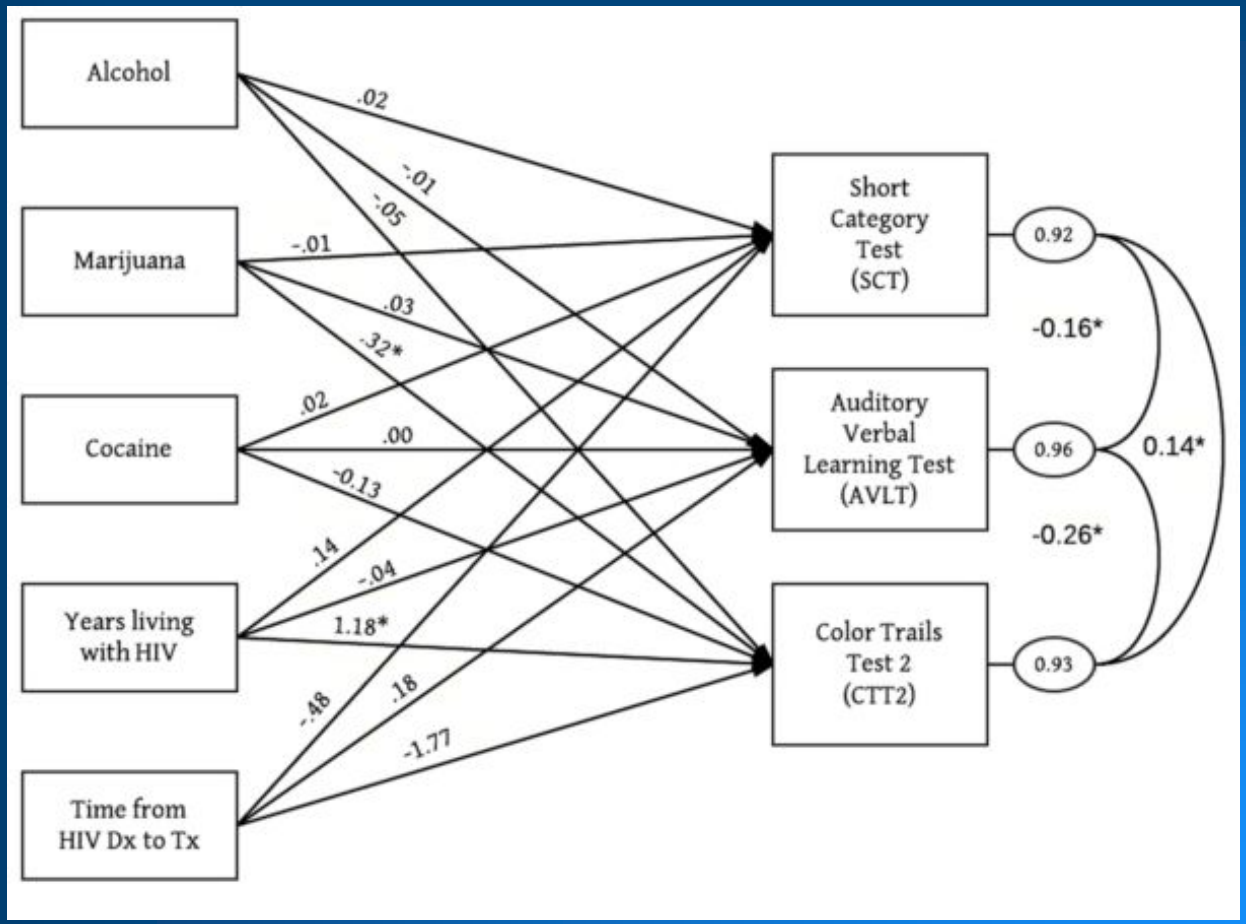
Lorkiewicz et al. 2017

# Learning and memory




Thames et al. 2015

# Attention, executive function, and information processing




Attonito et al. 2014

# Learning and memory

**Table 2** Series of logistic regression models predicting neurocognitive impairment by domain (N = 69)

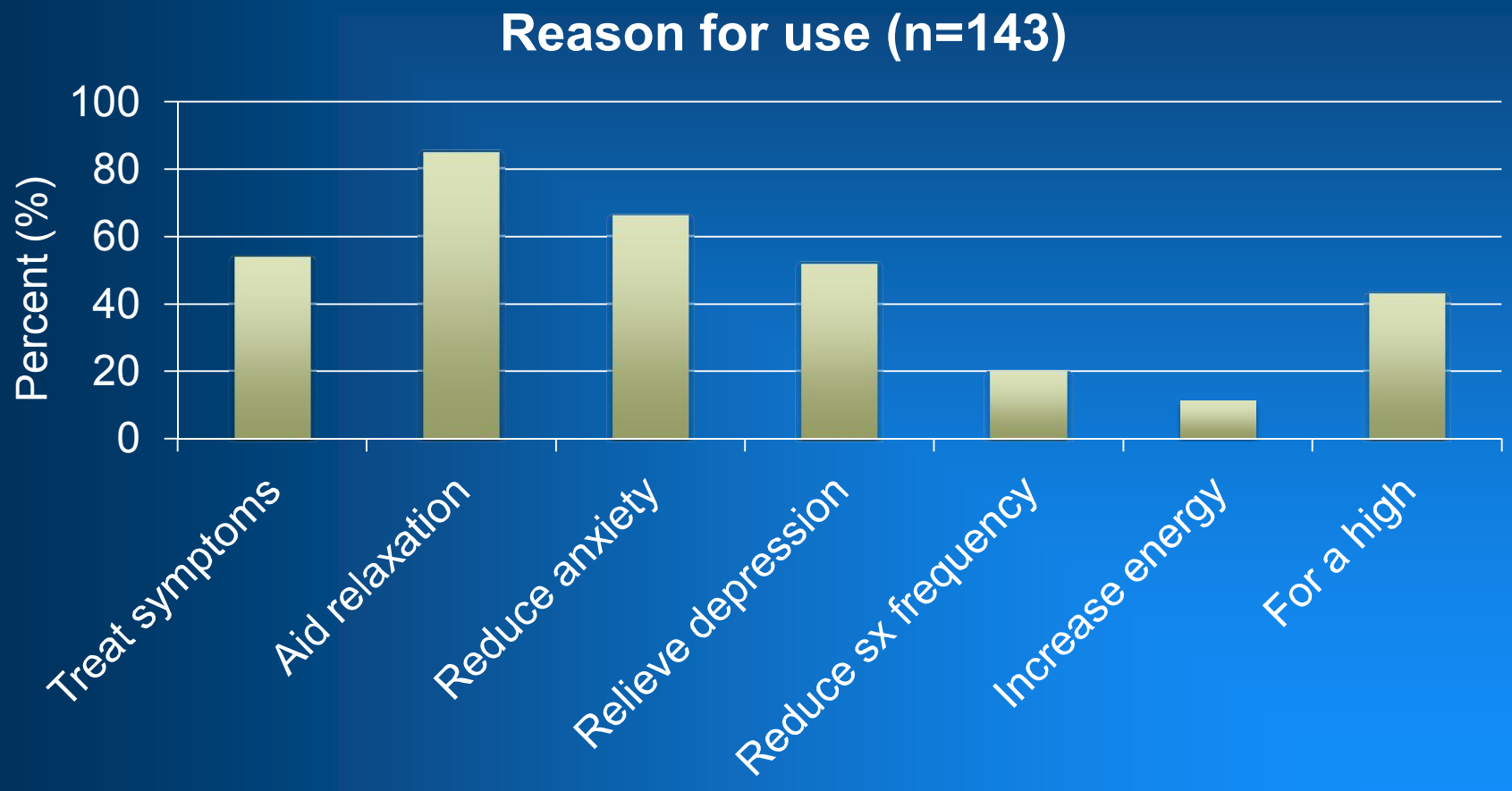
| | Percent impaired | Odds ratio (95% CI) | p value |
|---|---|---|---|
| Learning | | | |
| Early onset | 75 | 8.46 (1.93–37.02) | 0.005 |
| Late onset | 20 | 0.71 (0.17–2.97) | 0.634 |
| Non-marijuana | 26 | | |
| Memory | | | |
| Early onset | 58 | 3.95 (1.04–15.04) | 0.044 |
| Late onset | 27 | 1.03 (0.27–3.90) | 0.971 |
| Non-marijuana | 26 | | |
| Attention/working memory | | | |
| Early onset | 8 | 0.11 (0.01–0.93) | 0.043 |
| Late onset | 27 | 0.44 (0.12–1.61) | 0.215 |
| Non-marijuana | 45 | | |

Sklaski et al. 2018

# Summary of observational studies

- Associated with HIV transmission risk, but perhaps mediated by other factors
- Association with poorer viral suppression, possibly in setting of heavy use or dependence
  - Why do studies of adherence suggest otherwise?
- Neurocognitive are minimal and results vary:
  - Cannabis use characteristics: amount, duration, age of onset, recency
  - Characteristics of the cohort: era, prevalence of other drugs, proportion of medicinal users
- Limitations of these studies include their observational nature, limited information on cannabinoid concentrations, dosages, routes of administration and possible contaminants

# Medicinal cannabis use in PLWH

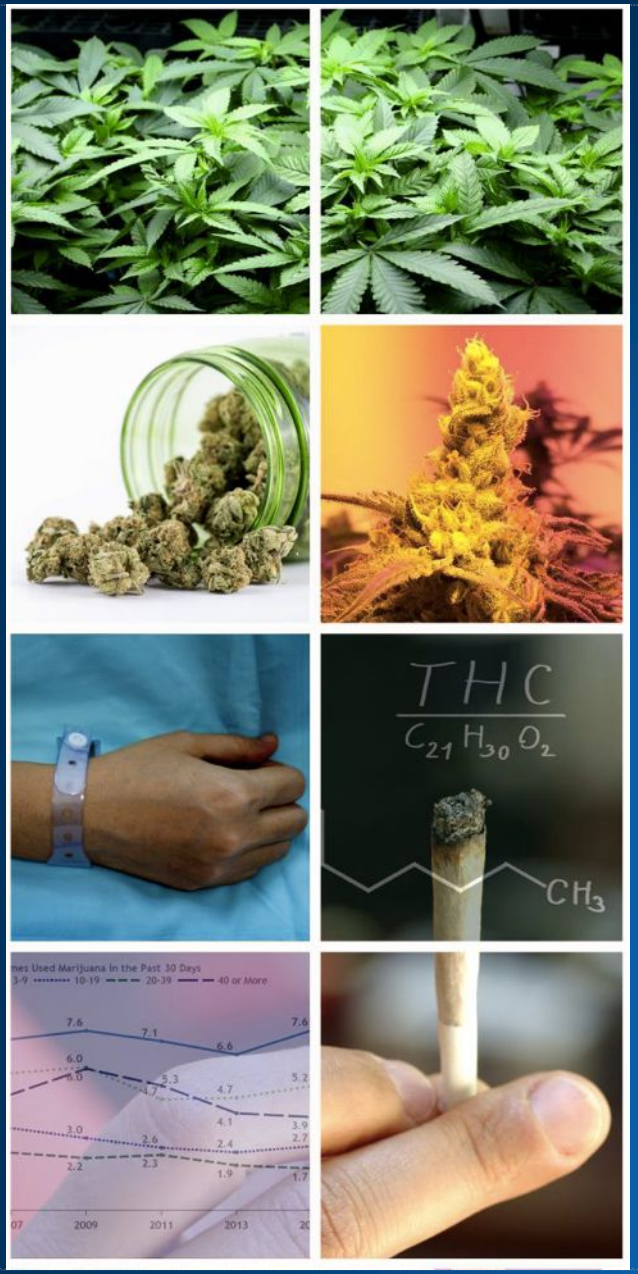



*Source: Woolridge, et al. 2005*

# HIV+ cannabis users more likely to endorse medicinal cannabis use

- No impact
  - Some recreational use
- Positive impact
  - Some recreational use
  - **Medicinal use**
- Negative impact
  - Some recreational use (Cannabis use disorder)

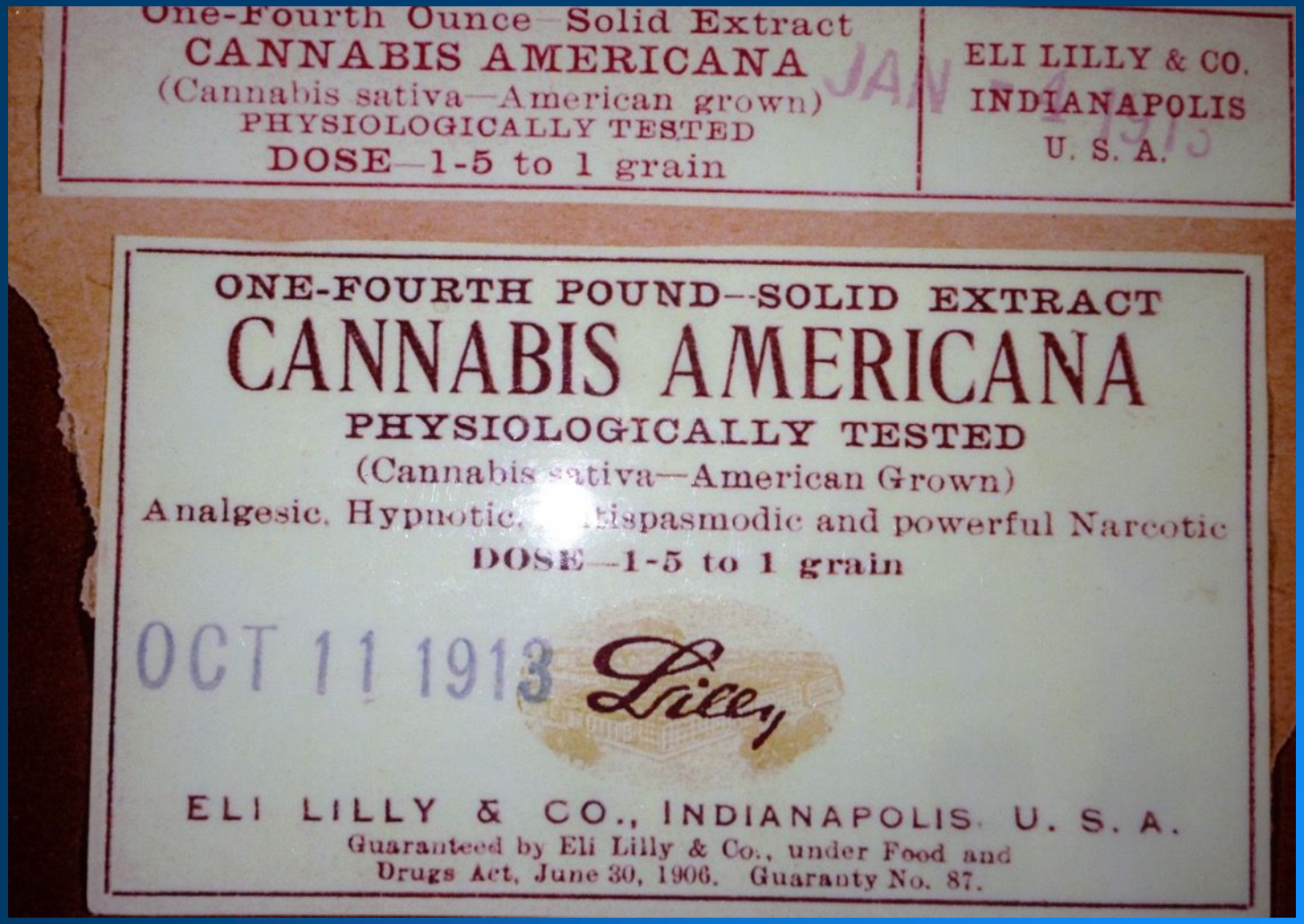

Pacek et al. 2018; Towe et al. 2018




# Cannabis and HIV

## Clinical trials

# Cannabis: not a new medicine

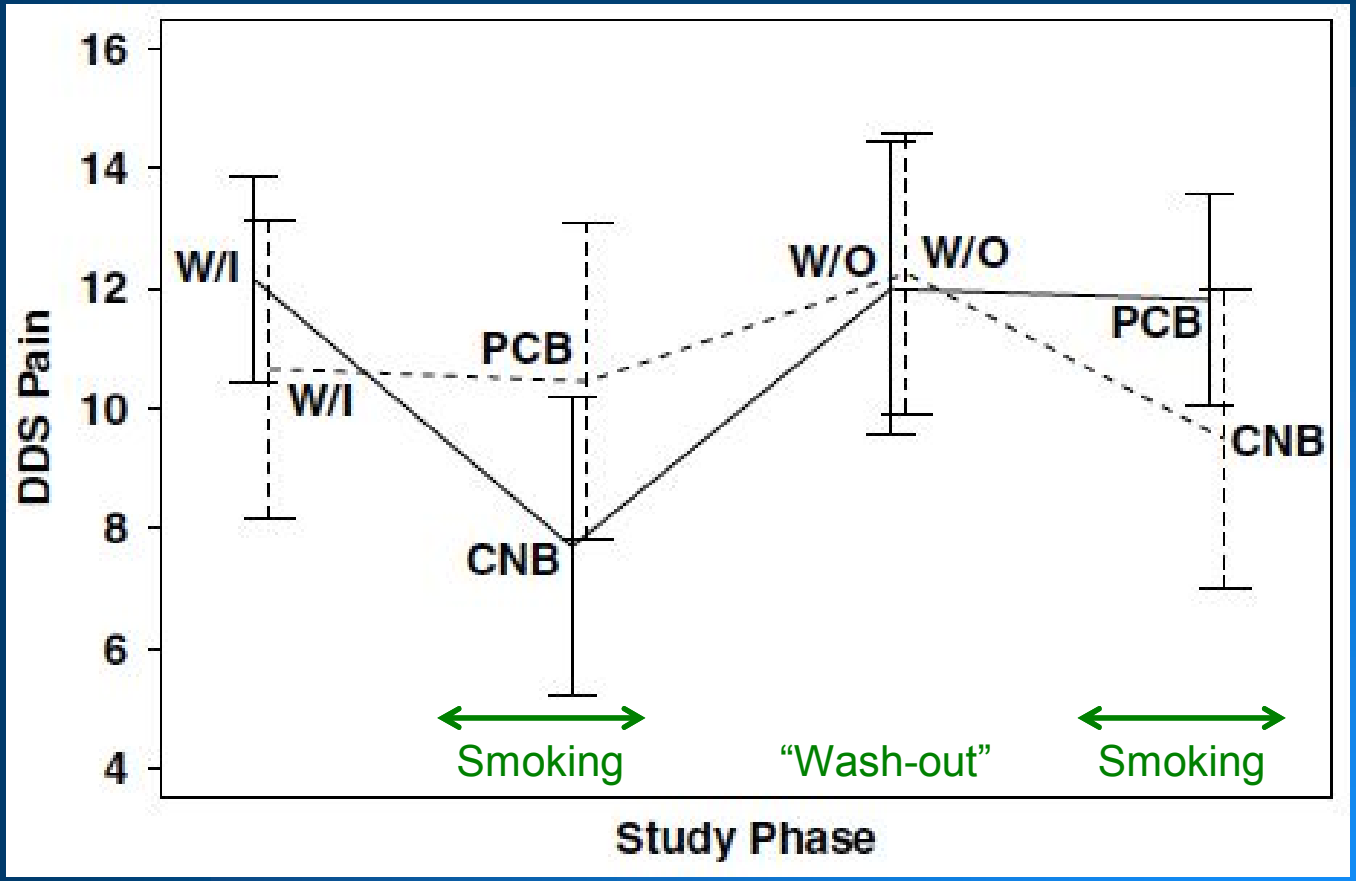


# Evidence for a benefit of cannabis

| Conclusive | Moderate | Limited |
|---|---|---|
| Chronic pain | Sleep (short-term) | HIV/AIDS wasting |
| Nausea | | Tourette syndrome |
| Spasticity in multiple sclerosis (patient report) | | Spasticity in multiple sclerosis (clinician rating) |
| *Severe intractable epilepsy (cannabidiol) | | Anxiety related to public speaking (cannabidiol) |
| | | PTSD |
| | | Outcomes after TBI |
| | | *Schizophrenia (cannabidiol) |

NAS 2017

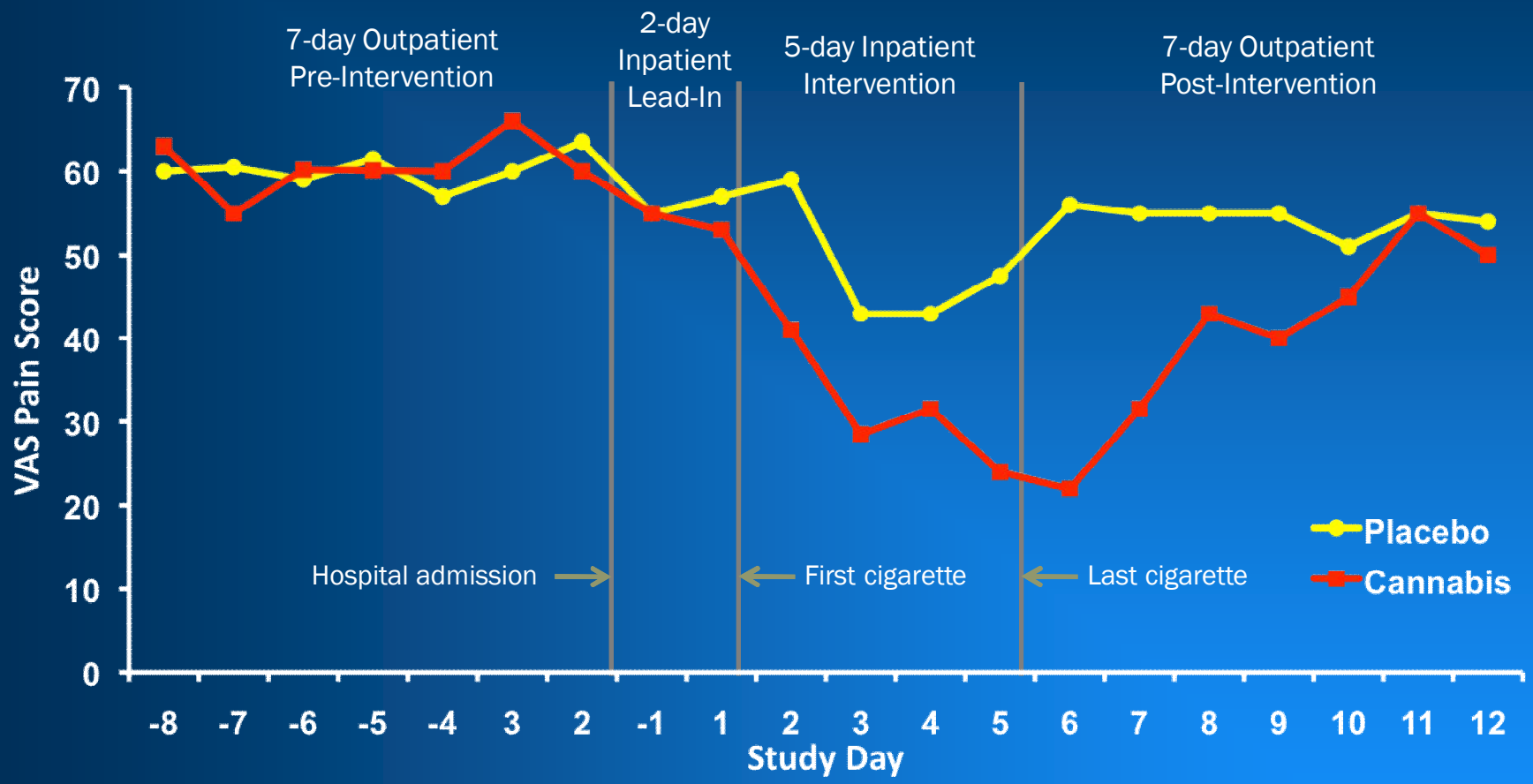
# Cannabis improves HIV neuropathy




Placebo controlled double blind randomized crossover trial of 1 – 8% THC and placebo MJ cigarettes administered 4x/day for 5 days.

*Source: Ellis et al. Neuropsychopharmacology 2009*

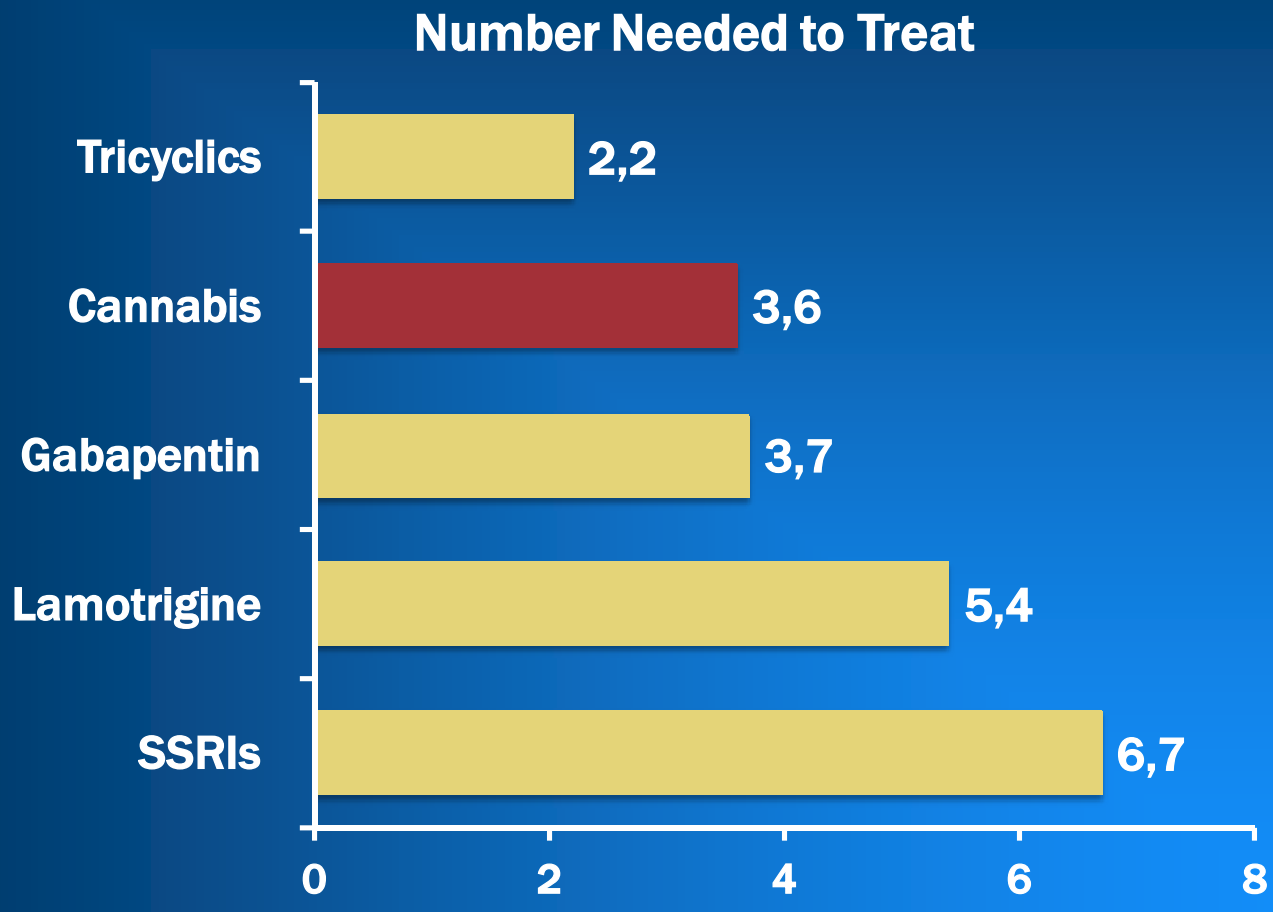
# Cannabis improves HIV neuropathy




Placebo controlled double blind randomized trial of 4% THC containing vs 0%THC MJ cigarettes administered 3x/day for 5 days.

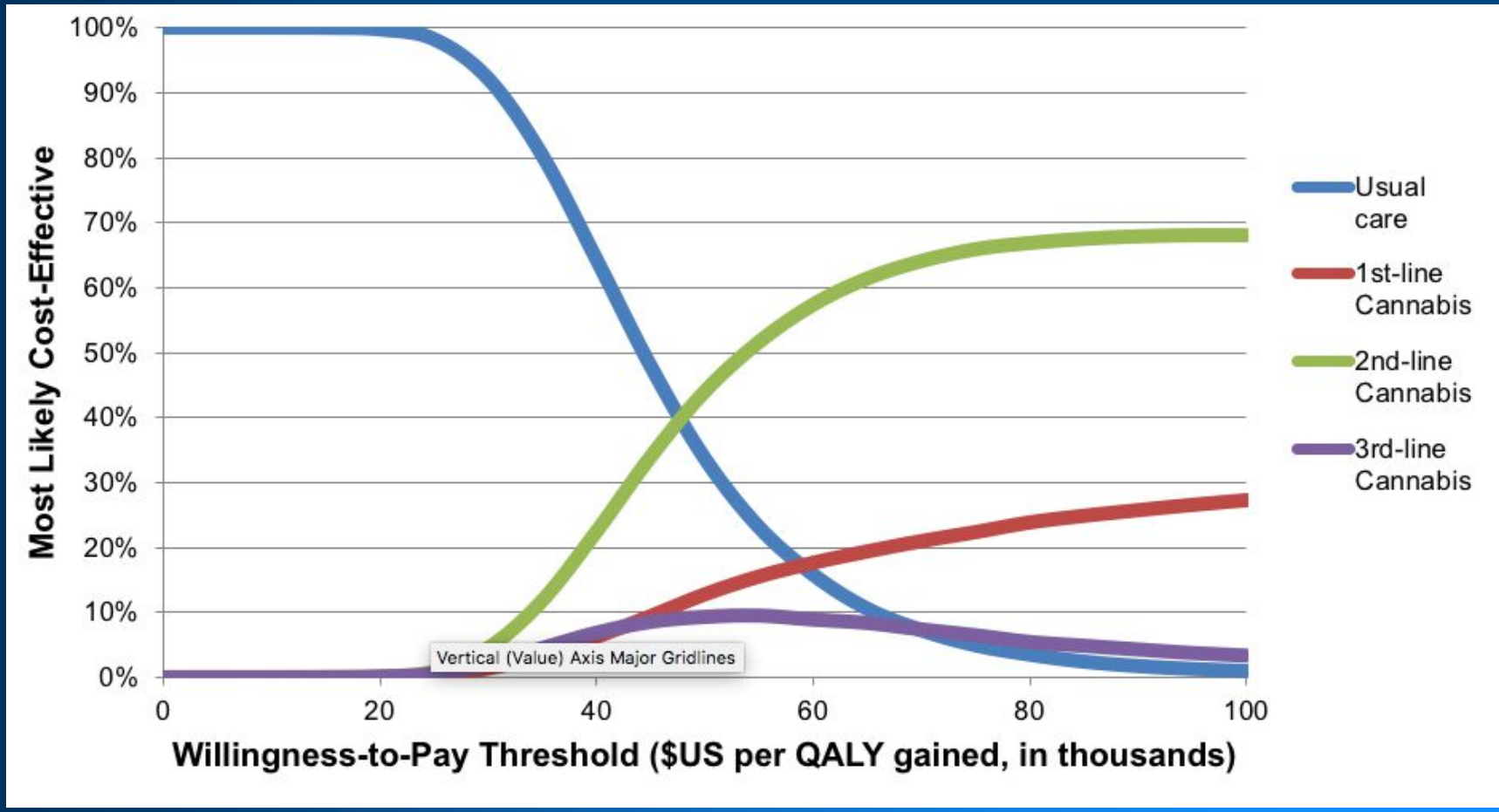
*Source: Abrams, D. I. et al. Neurology 2007;68:515-521*

# Common Analgesics for Neuropathic Pain



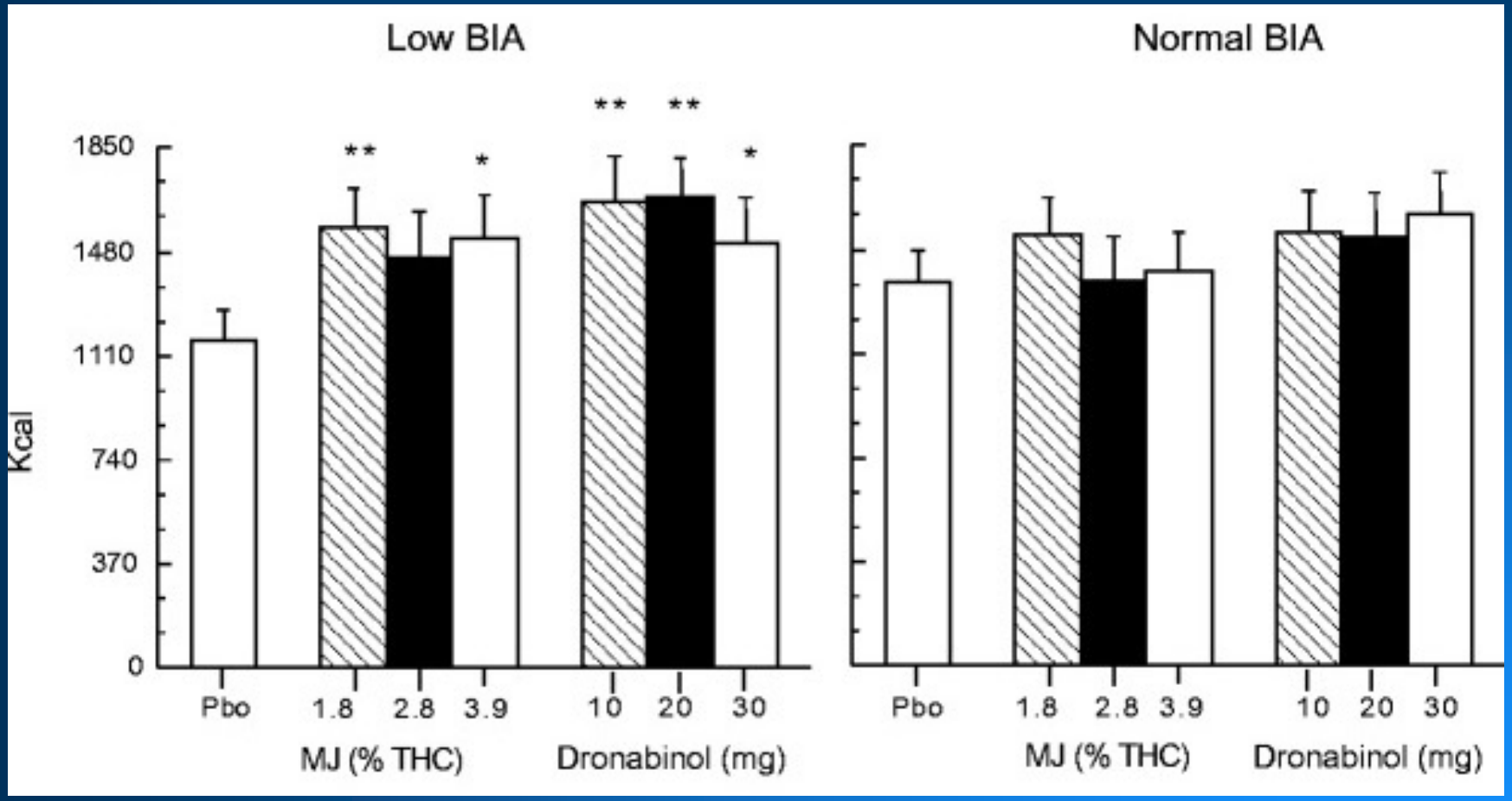

*Number Needed to Treat to to achieve a 30% reduction in pain.

# Cannabis is cost-effective




*Source: Tyree, G. et al. under review*

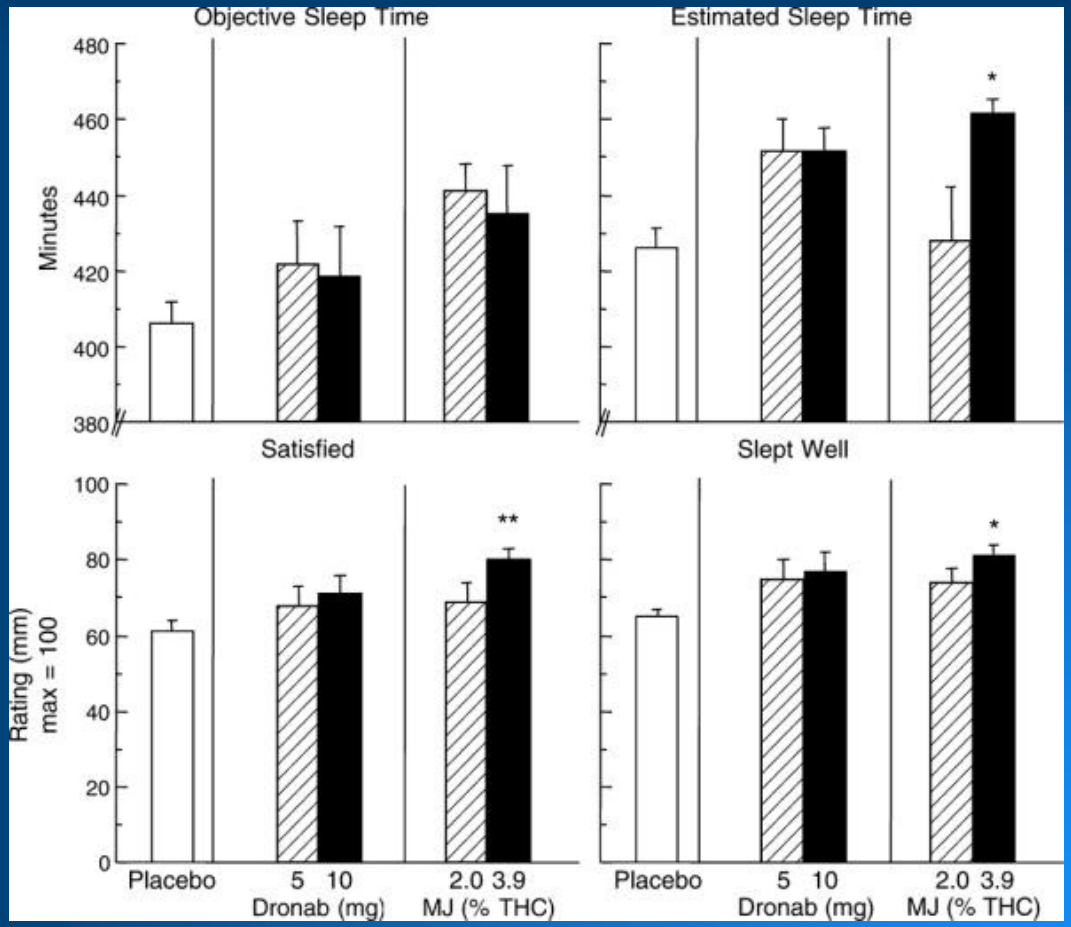
# Cannabis helps PLWH gain weight




Daily marijuana or dronabinol over 8 days. Bioelectrical impedance analysis (BIA) is a measure of muscle mass.

*Source: Haney, et al. Psychopharmacology 2005*

# Cannabis helps PLWH sleep

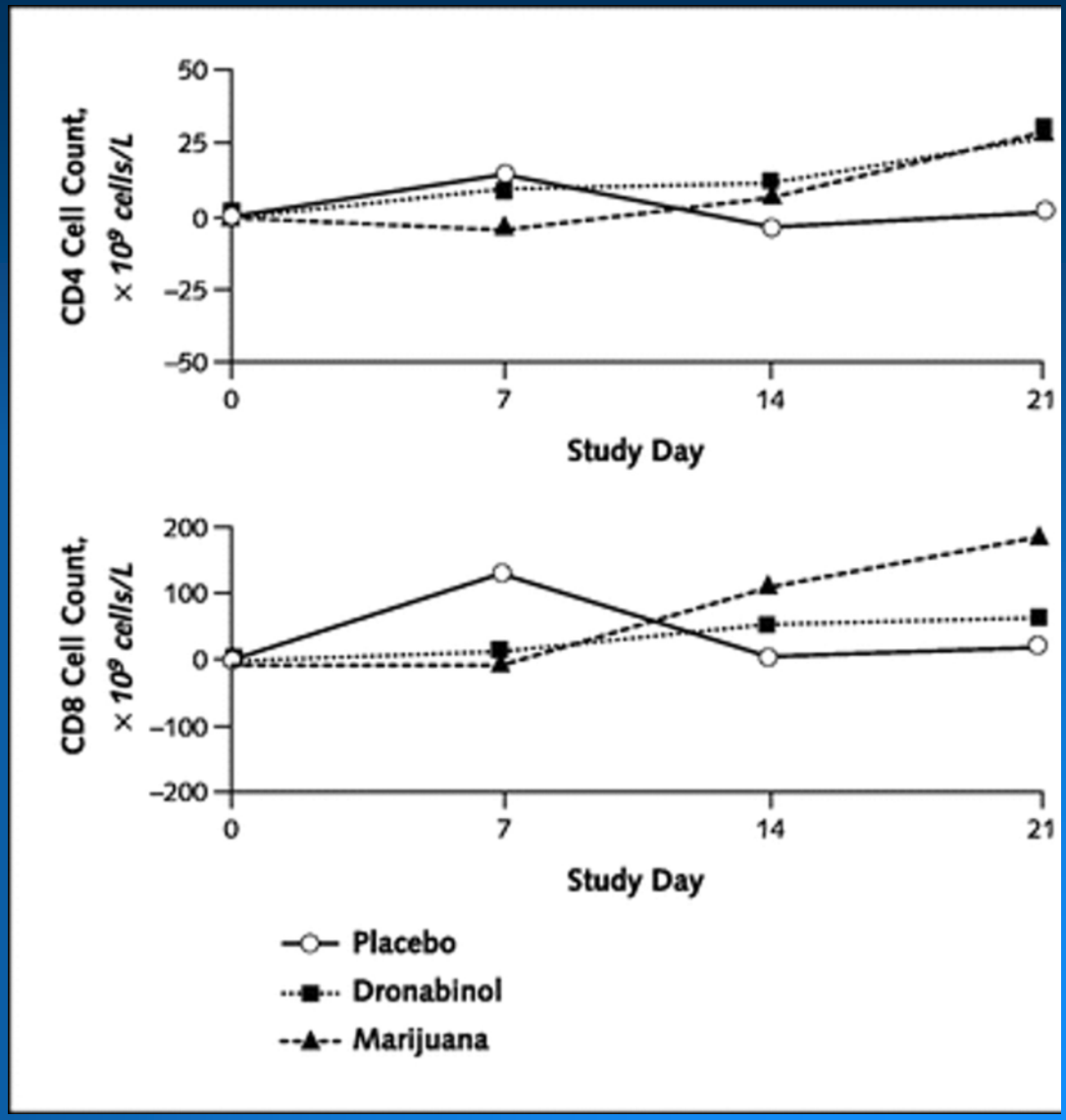



Dronabinol (5 and 10 mg) and marijuana (2.0% and 3.9%) administered 4 times daily for 4 days, but only 1 drug was active per day

*Source: Haney et al. JAIDS 2007*

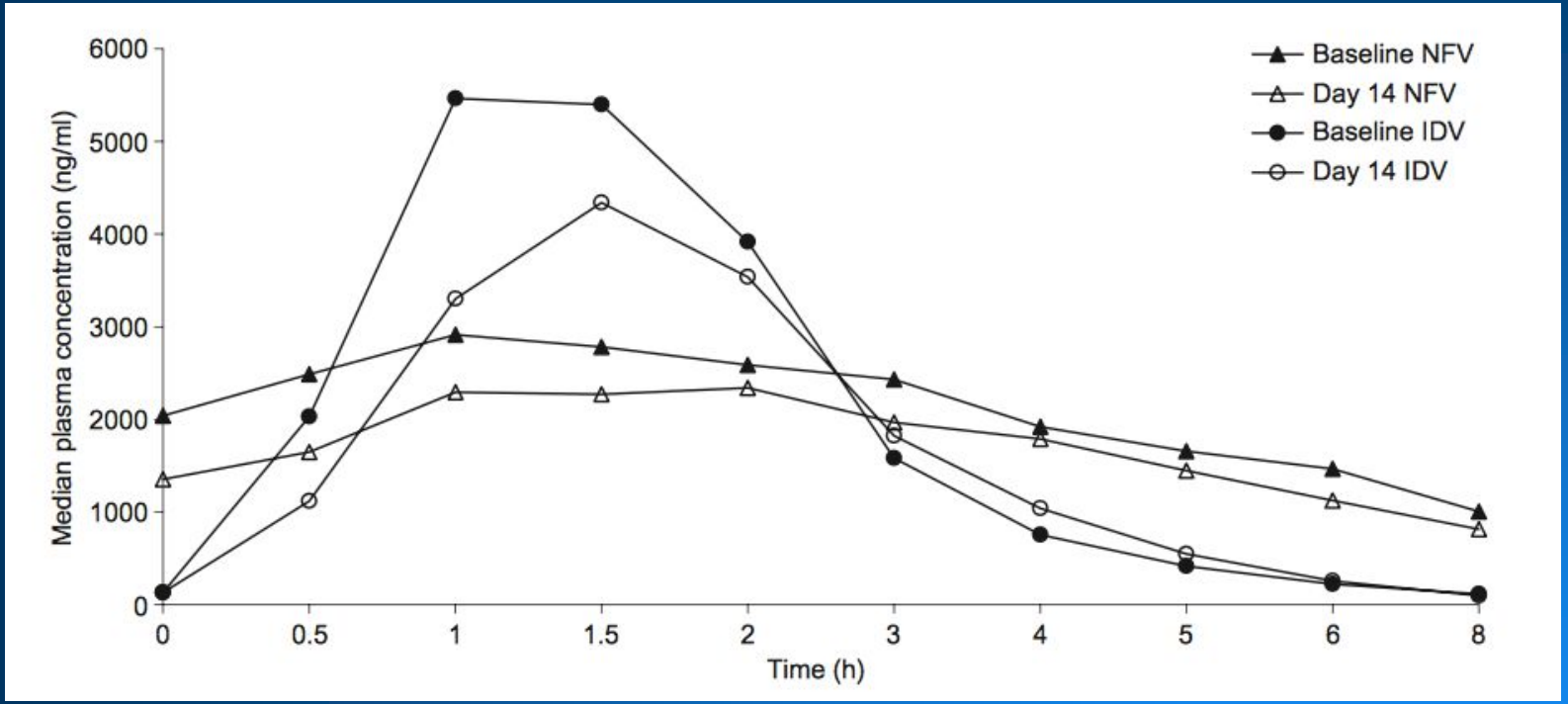
# Cannabis and T-cells

- No impact on CD4 or CD8 count
- No impact on viral load



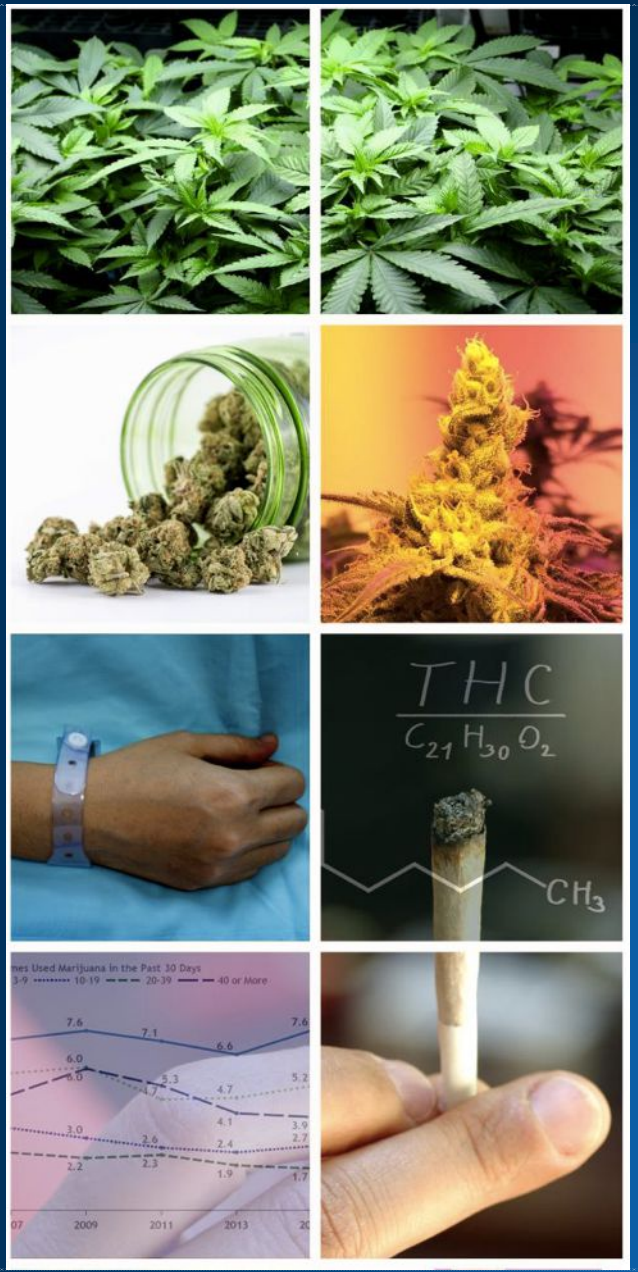

*Source: Abrams, et al. 2002 & 2003*

# Cannabis and ART




- In vitro evidence of inhibition of CYP3A and CYP2C
- Statistically significant reductions in indinavir (but not nelfinavir) concentrations in vivo suggests induction of CYP-450 enzymes

Kosel et al. 2002




# Summary and conclusions

# Cannabis: Good or bad?

Neither and both.

How do we come to terms with the apparent duality?

- Examine contextual factors
- Consider cannabis's impact on health and functioning
- Conduct additional controlled research

# Resources

- The Health Effects of Cannabis and Cannabinoids. National Academies of Sciences, Engineering, and Medicine (Free):
  - https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state
- Monitoring Health Concerns Related to Marijuana in Colorado: 2016. State of Colorado (Free):
  - https://www.colorado.gov/pacific/cdphe/marijuana-health-report
- Wilsey, et al. (2015) The Medicinal Cannabis Treatment Agreement: Providing Information to Chronic Pain Patients Through a Written Document. Clin J Pain.
- The University of California Center for Medicinal Cannabis Research (Free / Link to Research):
  - http://www.cmcr.ucsd.edu
  - cmcr@ucsd.edu

# Center for Medicinal Cannabis Research

Thank you!

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