

Practical training on diagnosis and management of clinical CNS problems in HIV-infected patients

Prevention of neurocognitive impairment in HIV-infected patients

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Potential causes/risk factors of cognitive decline in HIV+ persons

1. Direct HIV damage in CNS (HIV-associated NCI)
2. Previously established irreversible tissue damage by HIV or other causes (legacy effect)
3. Aging
4. Psychiatric disorders
5. Drugs, alcohol
6. Metabolic problems and cerebro-vascular disease
7. Alzheimer's and other neurodegenerative diseases
8. Drug toxicity (ART, other drugs) ?

How to prevent cognitive decline in HIV infection

- Prevent cause/risk factors of NCI
- Prevent process leading to NCI

Prevention of risk factors for cognitive decline

Preventable

- HIV replication and damage
- Drugs, alcohol
- Metabolic problems and cerebro-vascular disease
- Drug toxicity (ART, other drugs) ?

Possibly preventable

- Psychiatric disorders
- Alzheimer's and other neurodegenerative diseases

Non preventable

- Previously established irreversible tissue damage by HIV or other causes (legacy effect)
- Aging

Prevention of risk factors for cognitive decline

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- **Metabolic problems and cerebro-vascular disease**
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- **Aging**

Prevention of HIV replication and damage in CNS (HIV-associated NCI)

- ART
- ‘Neuro-active’ ART (with enhanced CNS penetration/efficacy) ?

Neuro-active ART

→ How to define?

→ In all patients?

→ In selected patients? Which patients?

NCI and ART neuropenetration

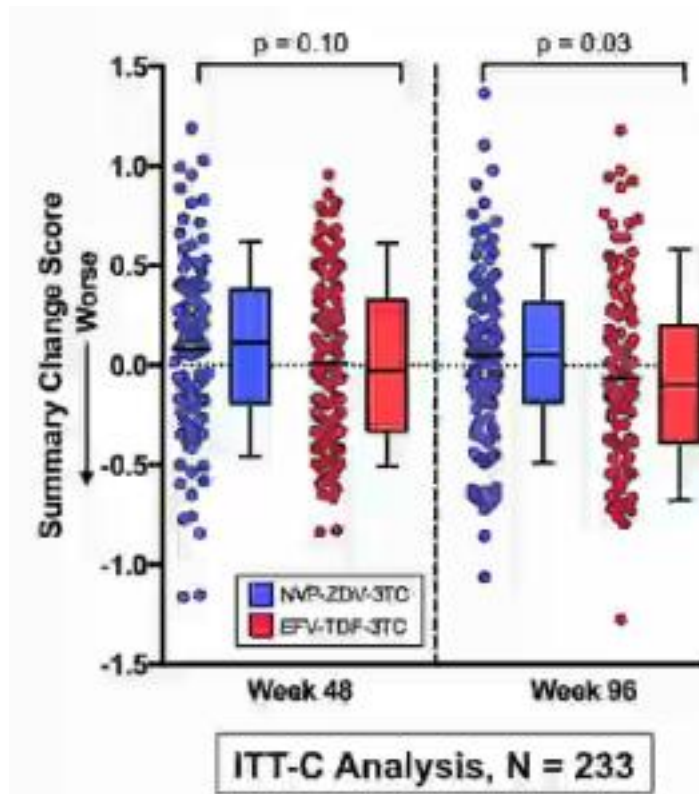
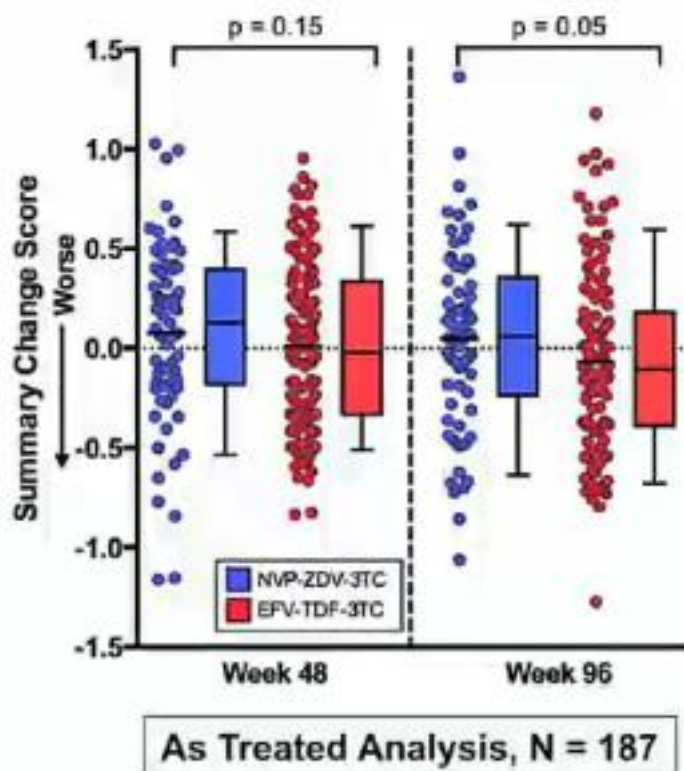
	Cysique	Tozzi	Smurzynski	Marra	Winston	Arendt	Garvey	Rourke	Ciccarelli	Robertson	Kahouadji	Ellis
Study	UCSD CIT	INMI	ALLRT	ACTG 736	ALTAIR	Dusseldorf NA Cohort	Imperial College, UK	OHTN Cohort Study	UCSC	ACTG 5199	INSERM	HNRPU/UCSD
Sample Size	37	185	2,636	26	30	3,883	101	545	101	860	54	49
CPE: CSF VL	Lower VL	No CSF	No CSF	Lower VL	No CSF	Lower VL	No CSF	No CSF	No CSF	No CSF	No CSF	No effect
Number of NP Tests	6	15	3	4	CogState	2	2	4	18	6	4	14
CPE: NP Tests	Better	Better	Better (only by >3 drugs)	Poorer	Poorer	Better	No effects	Not conclusive	Better	No effect	Poorer	No effect
Prospective	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Controlled	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes
Norms for NP Change	Yes	No	No	No	No	No	No	No	Yes	No	No	No

Cysique et al, Neurology 2009, 73(5):342-8; Tozzi et al, J Acquir Immune Defic Syndr 2009;52:56–63; Smurzynski et al, AIDS 2011;25:357- 365; Marra et al, AIDS 2009, 23(11):1359-66; Winston A, et al. Clin Infect Dis 2010;50:920-929; Arendt, et al. 18th CROI, Boston (MA, 2011. Poster #425; Garvey et al. HIV Clin Trials, 2011;12(6):333-338; Rourke SB, et al. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, 2011; Ciccarelli N, et al. Antiviral Ther, 2013; Robertson et al. Clin Infect Dis 2012;55(6):868–76; Kahouadji Y, et al. HIV Medicine 2012;14:311-315; Ellis et al. 20th CROI, Atlanta (GA), 2013; Abst#20.

(Courtesy of S. Letendre, 201

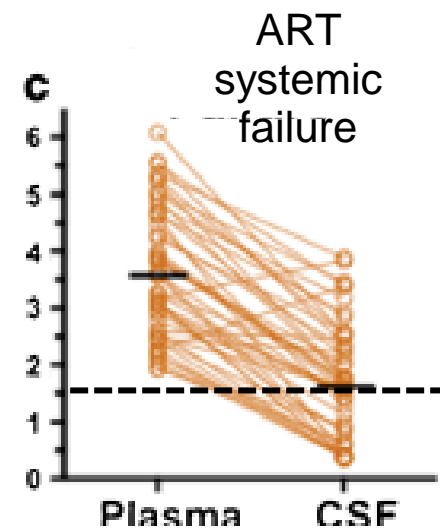
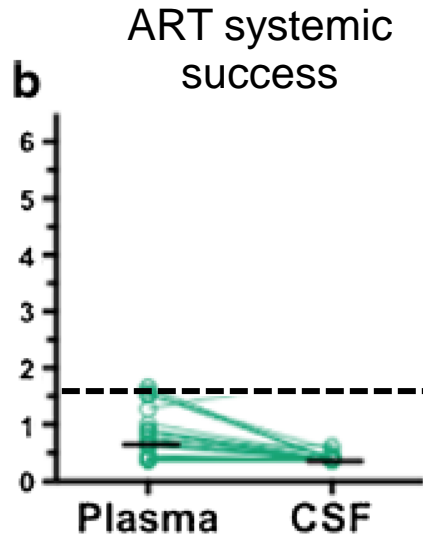
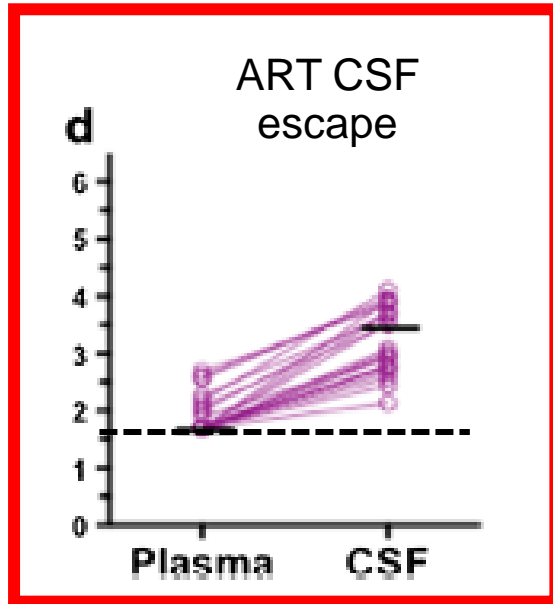
Randomized Clinical Trial of Antiretroviral Therapy for Prevention of HAND in naïve pts (Beijing, China)

NVP+AZT+3TC vs. **EFV+TDF+3TC**



- 1036 pts, no NCI
- 97-100% M, median CD4 235-222/ μ L, median logVL 4.2 c/mL
- 8 test battery

CSF viral escape



Ferretti F et al. Curr HIV/AIDS Rep 2015

- On ART > 6/9 months
- CSF VL > LLD (if plasma VL suppressed) or CSF VL > plasma VL (if plasma VL > 50)
- Symptomatic or asymptomatic

Possible risk factors for symptomatic CSF escape

- Presence and size of brain 'reservoir' (low nadir CD4 cells, previous HIV-E, previous CSF-escape)
- ARV drug resistance
- Inadequate ART adherence
- Inadequate efficacy of individual drugs/regimens
 - CNS 'penetration'
 - Efficacy in macrophages/microglial cells

In persons at risk:

→ Clinical monitoring for CSF escape?

→ ART with enhanced CNS penetration/efficacy?

Risk factors for cerebrovascular disease in the general population

Metabolic/physiological

- Hypertension
- Atrial fibrillation
- High blood cholesterol
- Being overweight or obese
- Diabetes

Modifiable behavioural

- Smoking
- Poor diet
- Lack of exercise
- Excessive alcohol consumption
- Stress

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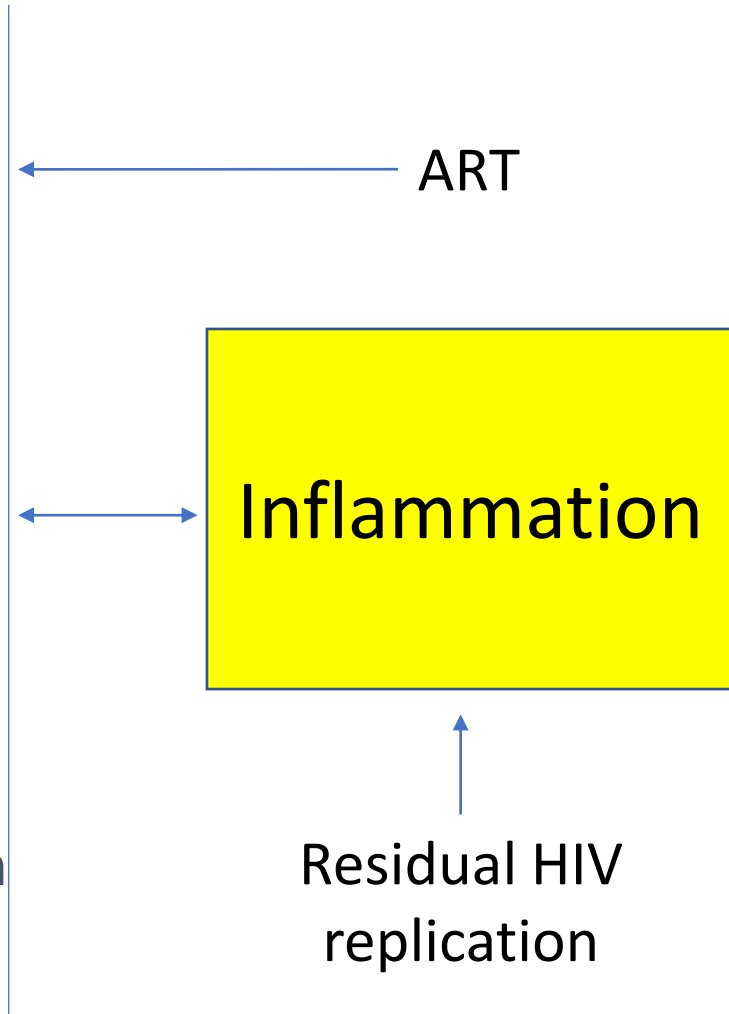
Risk factors for cerebrovascular disease in HIV infection

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**Prevention of
cerebrovascular disease**
through adoption of an
healthy life style

Prevention of Cognitive Decline in Older Healthy Adults

1. Possible pharmacological interventions
2. Cognitive training – mental exercises
3. Physical exercises

Prevention of cognitive decline in the elderly by pharmacological interventions

- Cholinesterase inhibitors and NMDA-glutamate receptor antagonists (donepezil),
- Hormonal therapies (Estrogen, Testosterone, Dehydroepiandrosterone),
- Miscellaneous substances like Ginkgo biloba, Vitamins (vitamin B6, E, omega-3 fatty acid), candesartan, naproxen, rofecoxib, celecoxib, and rivastigmine

“There is no consistent evidence of benefit for any pharmacologic agent in preventing cognitive decline in healthy older adults”

Computerised cognitive training interventions

Measured parameter or a particular tool	URL of the website presenting the particular software tool
1 Time of reaction	http://www.brainmetrix.com/brain-reflection/
2 Measuring of the efficiency of reflex	http://www.brainmetrix.com/reflex-test/
3 Simple test of short term memory	http://www.brainmetrix.com/memory-test/
4 Test for ability to divided attention	http://www.militantplatypus.com/games/gamepage.php?game=divided+attention#
5 Test for selective attention	http://www.mindmagician.org/vidsimons1.aspx
6 Test for perceptivity	http://www.mindgames.com/mindgame.php?mind=Relax&game=131
7 The online Stroop effect tests	http://www.onlinestrooptest.com/stroop_effect_test.php https://faculty.washington.edu/chudler/words.html
8 Test of efficiency of logical thinking	http://brainpages.org/seesaw-logic/
9 An example of a computerizing comprehensive system realizing the cognitive training (partly free access)	http://www.lumosity.com/
10 An example of a free, open website that contains sets of games helpful for the realization of cognitive training (partly free access)	http://www.mindgames.com/
11 Basic information about so called „brain games” on example of “Big Brain Academy” tested by authors of cited paper [40]	http://www.bigbrainacademy.com/
12 The free access website of so called “Brain Age” discussed in the cited paper [29]	http://www.freebrainagegames.com/
13 Basic information about so called “Tetris game”, which is compared to above mentioned “Brain Age” by Nouchi et al. [40]	http://www.tetrisfriends.com/
14 The website.: ” Cogtest – The definitive solution for cognitive testing. Tower of London”, which enable to comprehend the Tower of London task proposed as cognitive training by Rainville et al. [41]	http://cogtest.com/tests/bacs_nonint/tlflash1.html
15 Advices for people counteracting the symptoms of dementia	http://www.alz.org/we_can_help_brain_health_maintain_your_brain.asp

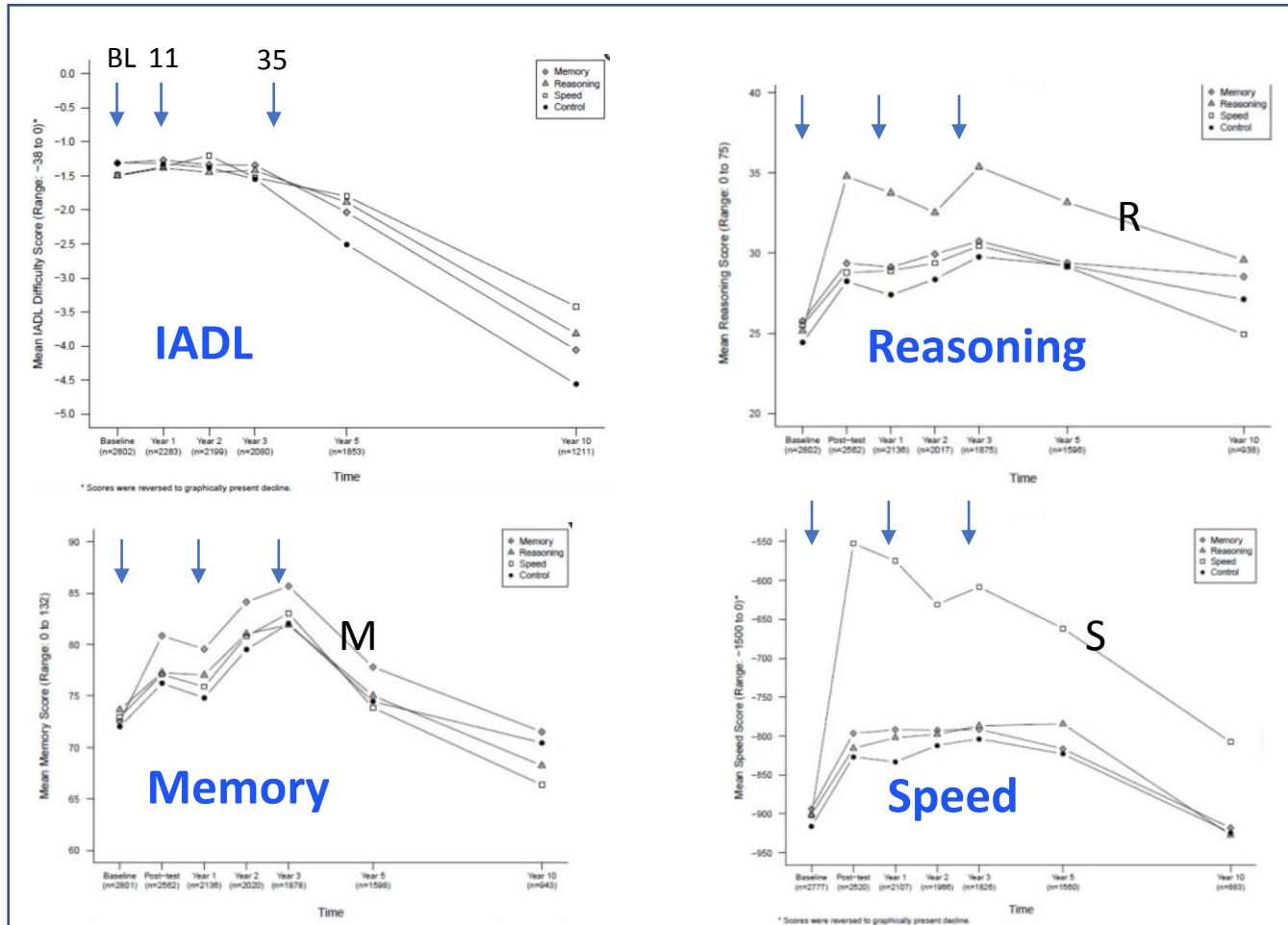
Cognitive training interventions

But there are many common, natural, demanding intellectual tasks that are performed by some people with willingness and interest.

Examples: reading novels, writing memories or autobiography, learning a foreign language, playing board games, traveling...

Prevention of cognitive decline in the elderly by cognitive training

Interventions: 10-session training for memory, reasoning, or speed-of-processing.; 4-session booster training at 11 and 35 months



The ACTIVE study

- 2832 persons
- mean BL age 73.6
- 4 training groups
 1. Reasoning
 2. Memory
 3. Speed
 4. Controls

- Cognitive intervention resulted in less decline in self-reported IADL
- Reasoning and speed, not memory, training resulted in improved targeted cognitive abilities for 10 ys

WHO recommendations of physical activity for health adults aged 18-65

→ At least **150 minutes** of **moderate-intensity aerobic** physical activity throughout the week

or

→ At least **75 minutes** of **vigorous-intensity aerobic** physical activity throughout the week

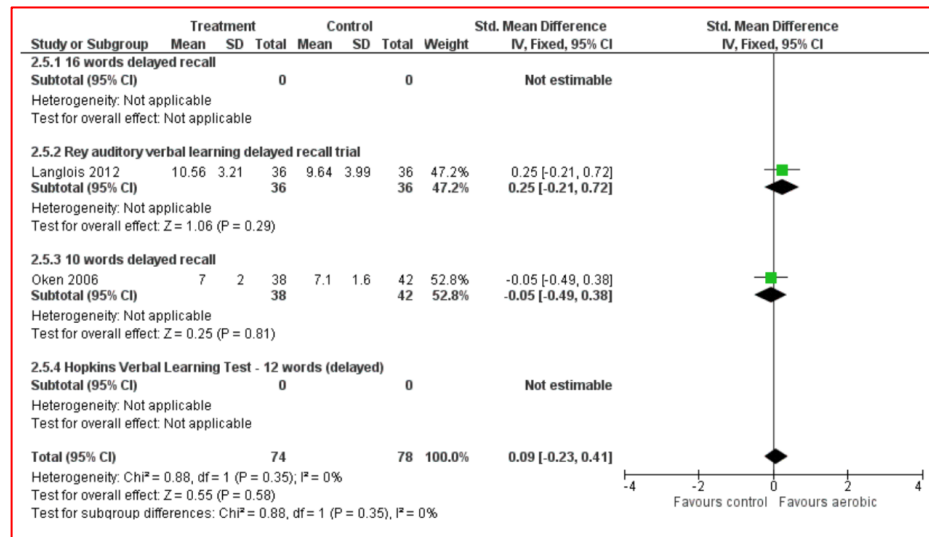
Applicable to (based on literature evidence):

- Cardiorespiratory health (coronary heart disease, CVD, stroke, hypertension)
- Metabolic health (diabetes, obesity)
- Bone health (osteoporosis)
- Breast and colon cancer
- Depression

Aerobic exercise to improve cognitive function in older people without known cognitive impairment

- Meta-analysis of 12 trials including 754 participants, 8-26 weeks in duration
 - Aerobic exercise vs. any active intervention
 - Aerobic exercise vs. no intervention
- **no evidence of benefit from aerobic exercise in any cognitive domain**

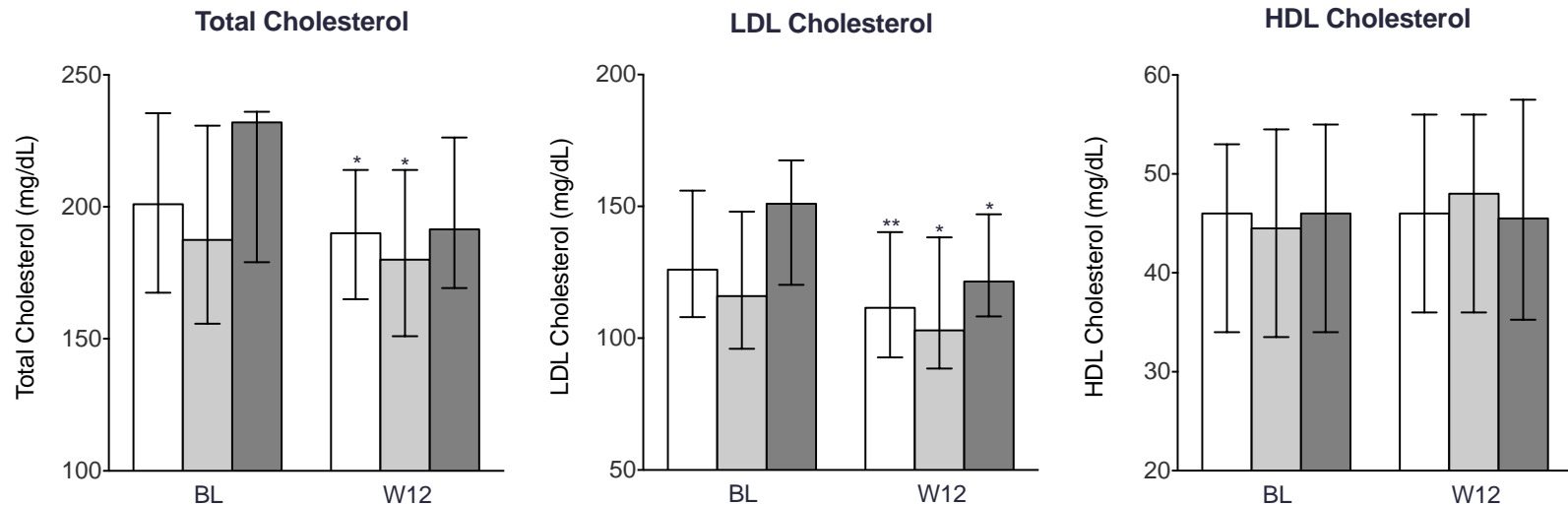
Example: Aerobic exercise versus no intervention, outcome: memory functions



The effect of a 12-week brisk walking program (60 min 3 times a week) on cholesterol level

□ All ■ Walk ■ Walk-strength

*: $p < 0.05$; **: $p < 0.01$ (Wilcoxon; median, IQR)



The effect of a 12-week brisk walking program (60 min 3 times a week) on soluble and cell inflammatory markers

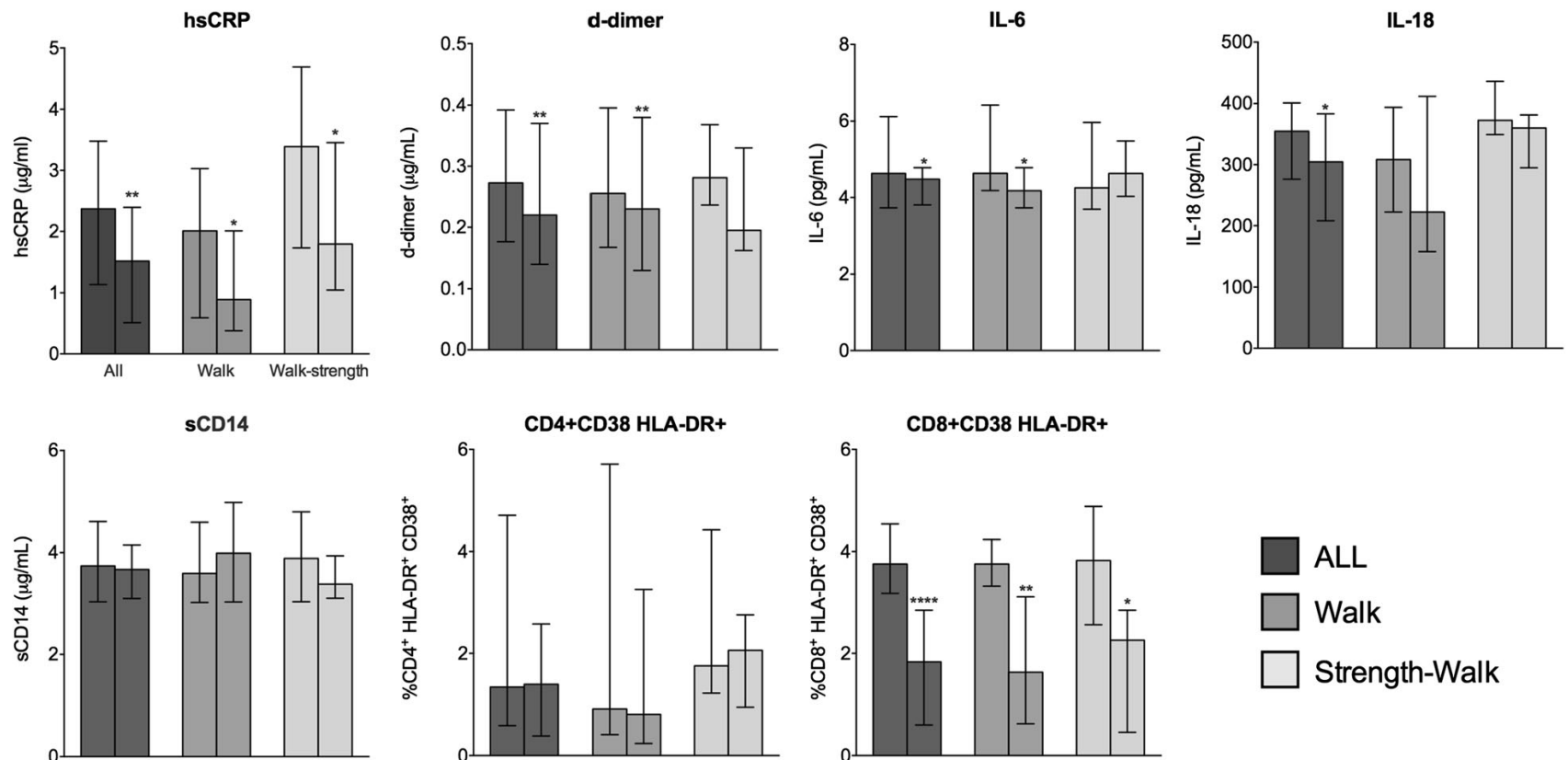


Fig. 2 Soluble and cell inflammatory markers at baseline (BL) and week-12 (W12)

Conclusions, suggestions, questions

Many possible interventions
to prevent cognitive decline
in HIV infection

HIV specific

- ART
- 'Neuro-active'
ART in rare
selected
situations ???

General

- Life-style changes
- Programmes
specifically suited
to HIV patients ???