Decadimento cognitivo nel paziente HIV anziano

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Disclosure

- Paolo Bonfanti ha ricevuto grant da:

  - Gilead
  - ViiV
  - Jannsen
  - MSD
  - Pfizer
  - Astrazeneca

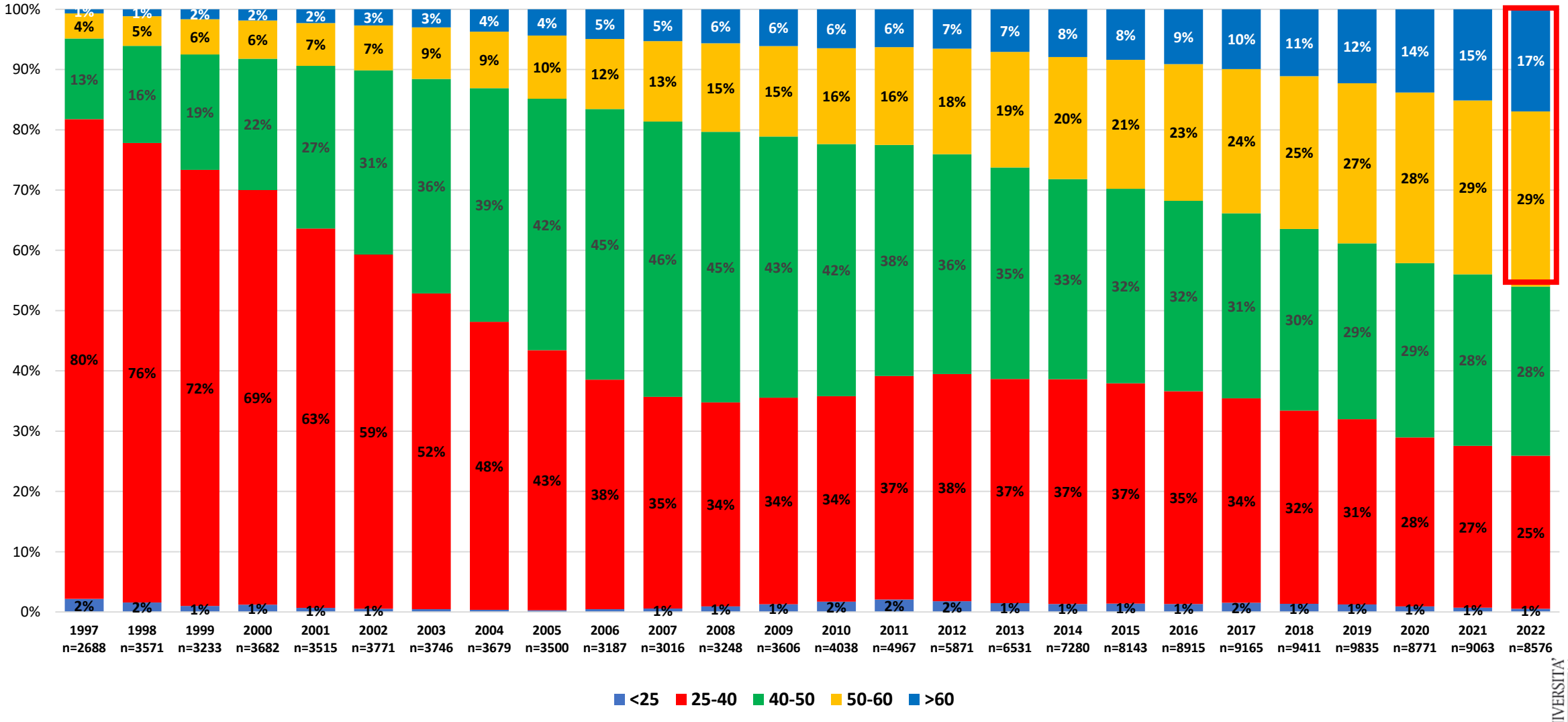
Outline

- Invecchiamento delle PWH
- Cognitive Impairment: definizioni
- Patogenesi e trend temporali nelle PWH
- Major Cognitive Impairment nelle PWH: primi dati epidemiologici

DECADIMENTO COGNITIVO NELLE PWH

INVECCHIAMENTO DELLE PWH

ICONA Cohort: age strata among patients in follow up



Dec 2022 Report: courtesy of Fondazione ICONA

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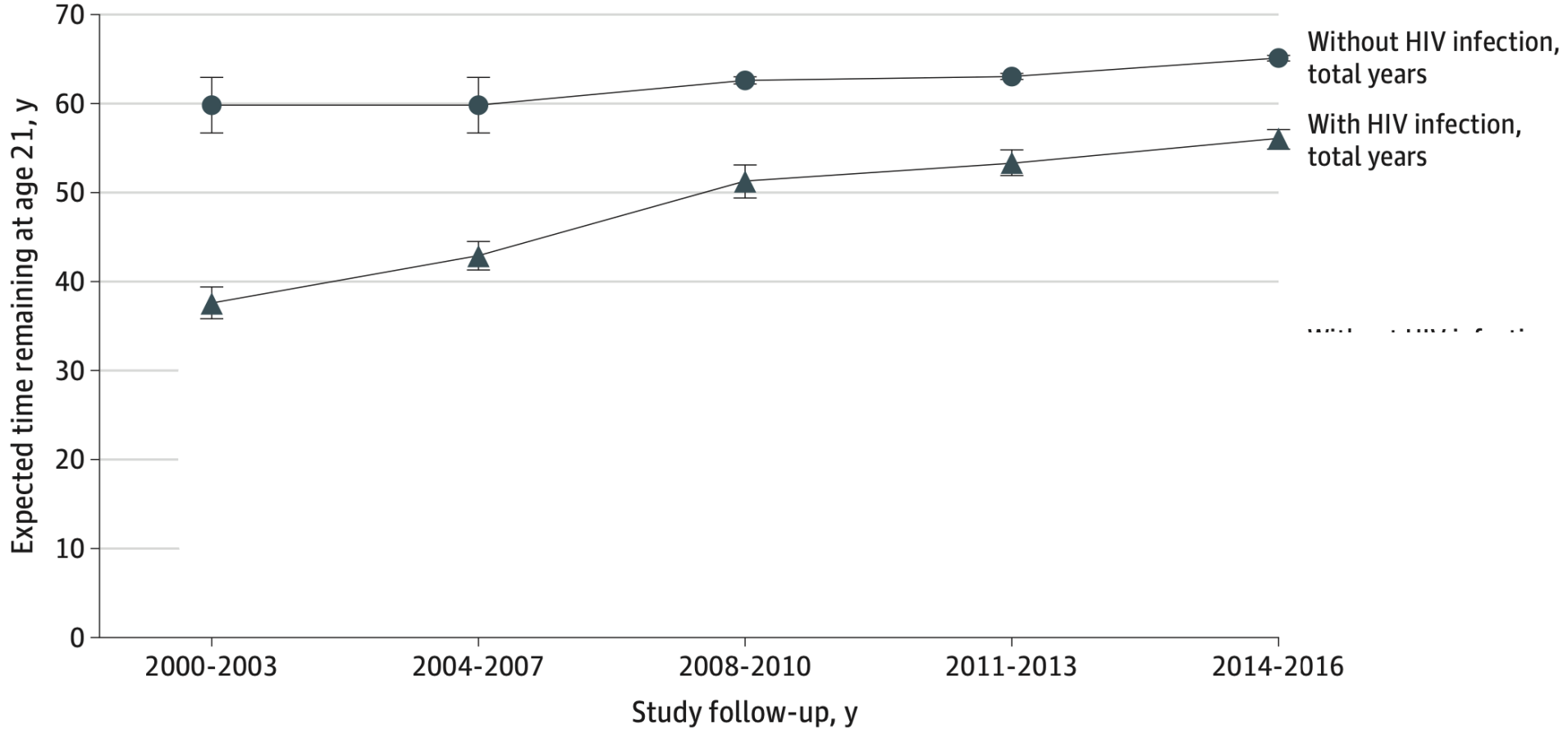
Overall and Comorbidity-Free Life Expectancy at Age 21 Years for Individuals With and Without HIV Infection

- **Kaiser Permanente : 39000 individuals with HIV infection and 387785 matched uninfected adults**
- **ART initiation at a CD4 cell count of 500/μL or greater.**



Marcus JL et al, *JAMA Network Open 2020*

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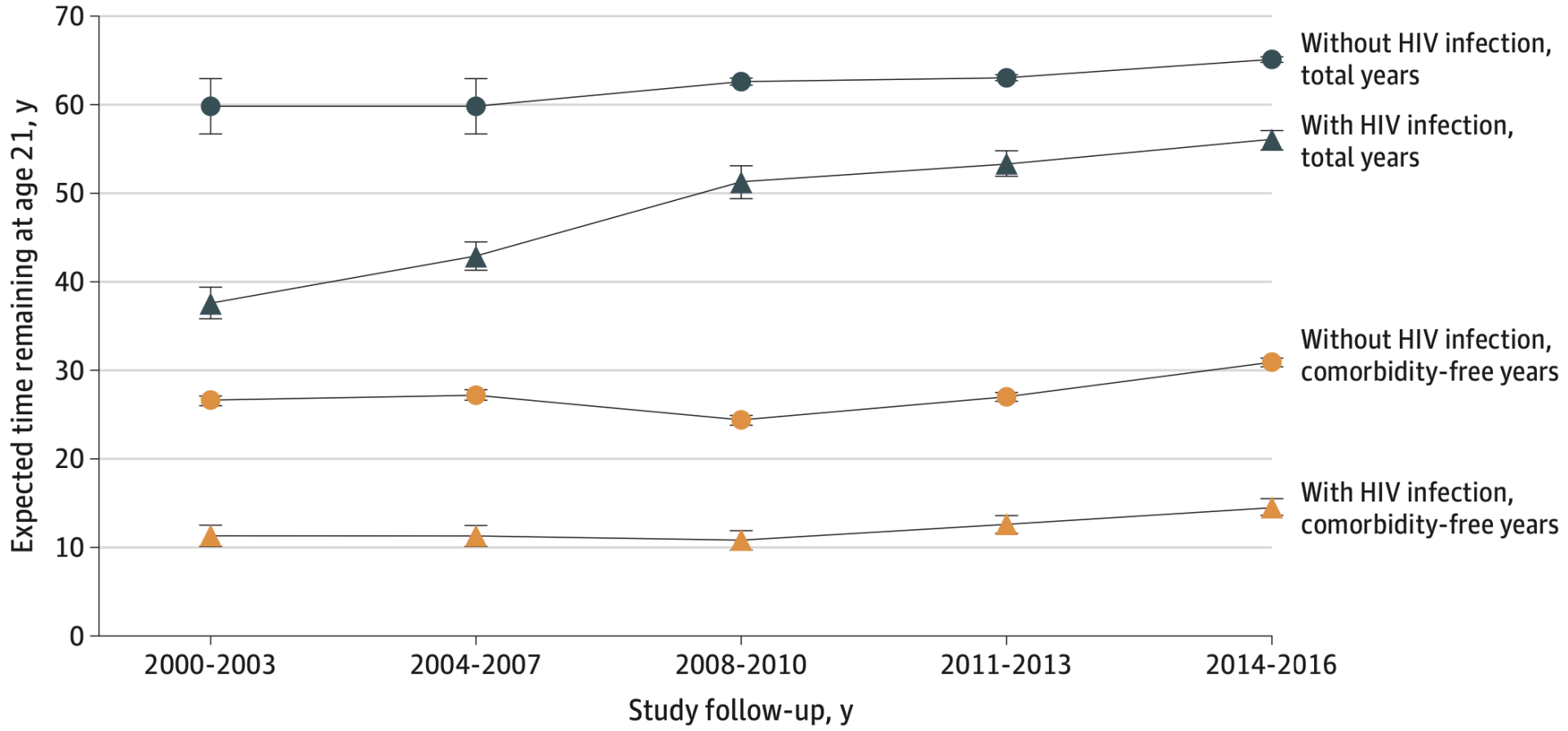
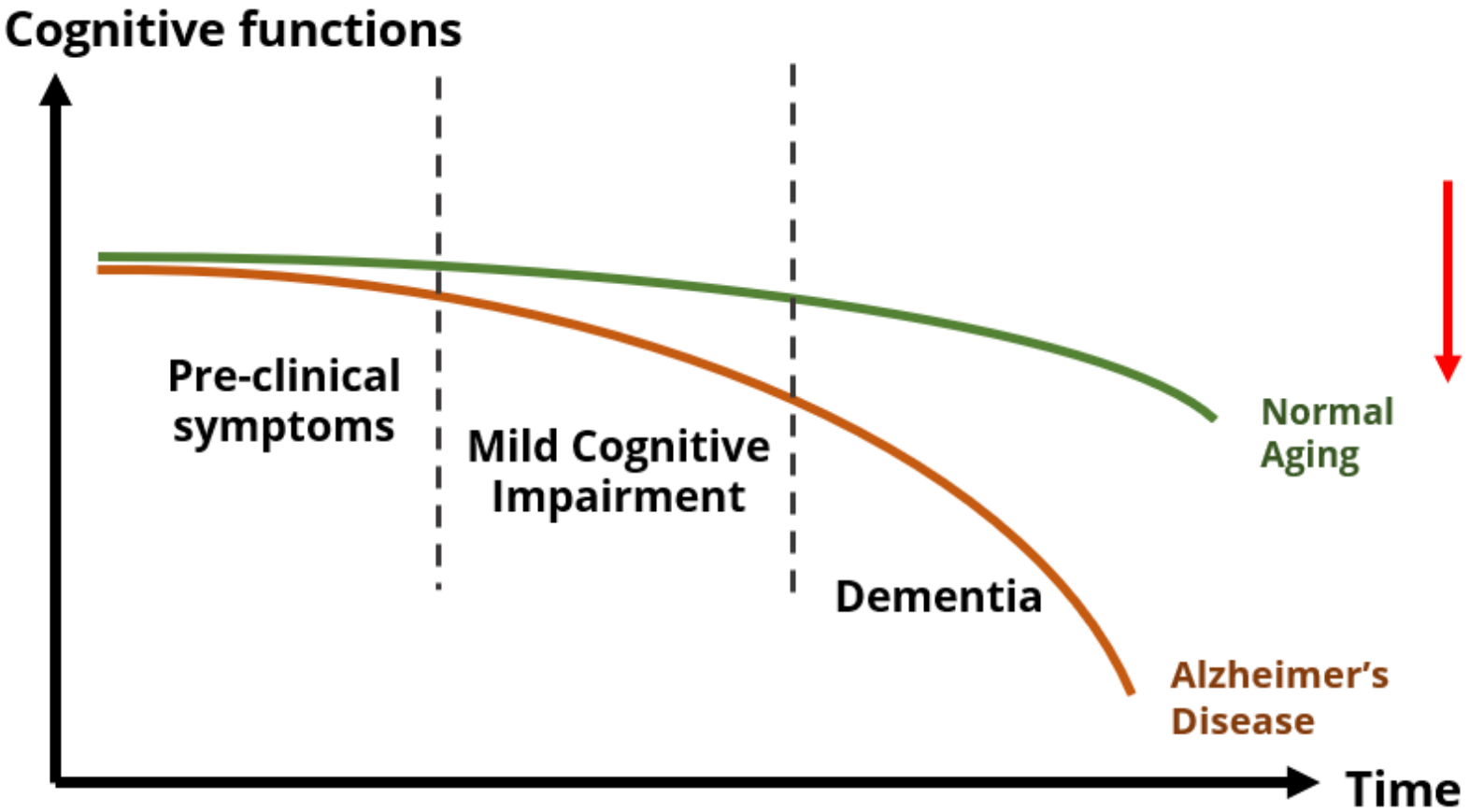


Marcus JL et al, *JAMA Network Open 2020*

DECADIMENTO COGNITIVO NELLE PWH

COGNITIVE IMPAIRMENT: DEFINIZIONI

Definitions



Sperling M et al, *Alzheimers Dement 2011*

Major Neurocognitive Disorder: Definitions

- While traditional definitions of dementia required a decline in at least two cognitive domains, the definition of **Major neurocognitive disorder (MND)** as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) only requires a substantial decline in a single cognitive area.
- **Mild cognitive impairment (MCI)** is an intermediate state between normal cognition and dementia in which there are objective cognitive impairments but no decline in overall level of function. While specific subtle changes in cognition can occur in normal aging, MCI can also be a precursor to dementia. At the same time, MCI may also represent a reversible condition in the setting of depression, as a complication of certain medications, or during the recovery from an acute illness.

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, 2013.

Diagnostic Criteria for Neurocognitive Disorders

Major neurocognitive disorder	Minor neurocognitive disorder
Significant cognitive decline in at least one cognitive domain as seen in *both* of the following: • Concerns expressed by the patient or reliable informant or as seen by the clinician • Objective neurocognitive testing/ assessments	Modest cognitive decline in at least one cognitive domain as seen in *both* of the following: • Concerns expressed by the patient or reliable informant or as seen by the clinician • Objective neurocognitive testing/ assessments
Interference with instrumental activities of daily living	Does not interfere with instrumental activities of daily living, but they require additional time and effort
Cannot occur exclusively during bouts of delirium	
Cannot be explained by another mental disorder	

Falk N et al, *Am Fam Physician 2018*

Major Neurocognitive Disorders: Classification

- **PRIMARY DEGENERATIVE DEMENTIAS**
  - **Alzheimer's disease**
  - **Frontotemporal dementia (ADRD)**
  - **Lewy body dementia (ADRD)**
  - **Parkinson Disease Dementia**
- **VASCULAR DEMENTIA**
- **SECONDARY DEMENTIA (HIV infection, PML)**

Epidemiology

- **Alzheimer disease** is the most common cause of dementia, as it is responsible for 70 to 80% of all cases of dementia. It can occur sporadically or be familial.
- **Vascular dementia** accounts for approximately 15% of all dementia cases. Its incidence increases with age and doubles every 5.3 years. Risk factors for vascular dementia include hypercholesteremia, diabetes mellitus, hypertension, and smoking.
- **Lewy body dementia** accounts for approximately 5% of dementia cases. The epidemiological data may not be completely accurate because the diagnosis of Lewy body dementia is often missed.
- **Parkinson disease dementia** accounts for approximately 10% of cases of dementia.
- **Frontotemporal dementia** is attributed to 25% of dementia cases in patients older than 65 years of age. It is, however, the second most common cause of dementia in patients younger than 65 years.

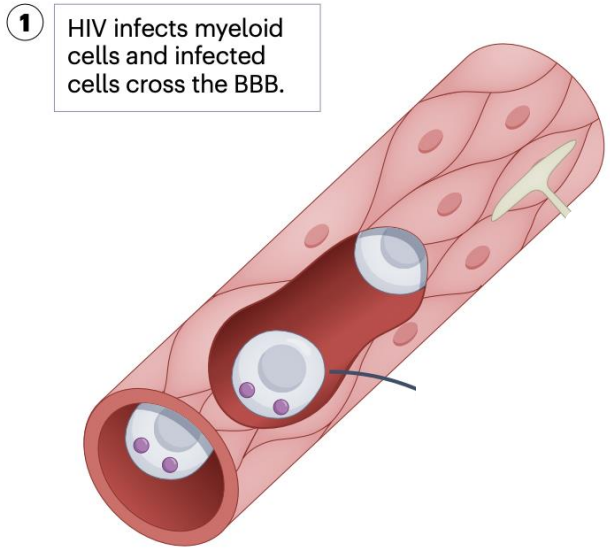
HIV-associated Neurocognitive Disorders (HAND)

	Neuropsychological Testing	Function
Mild Neurocognitive Impairment (MND)	Mild-moderately impaired in at least two cognitive domains	Typically mild to moderate impairment
HIV-associated Dementia (HAD)	More severely impaired in at least two cognitive domains	Typically more severe impairment
Asymptomatic Neurocognitive Impairment (ANI)	Any degree of impairment in at least two cognitive domains	No identified impairment

Antinori A et al, *Neurology 2007*

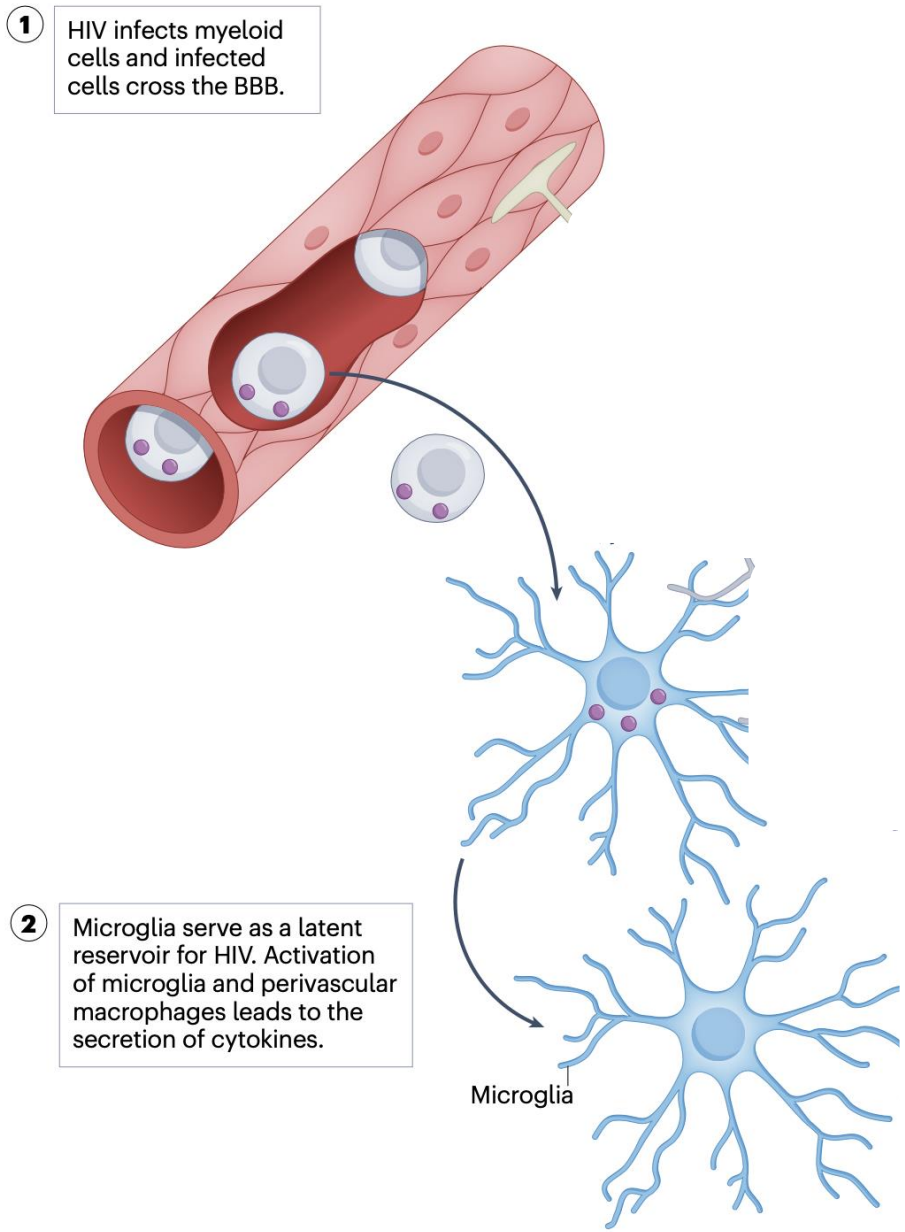
DECADIMENTO COGNITIVO NELLE PWH

PATOGENESI E TREND TEMPORALI



Hypothetical model of HIV-mediated myeloid cell and neuronal dysfunction in HIV-associated NCI.

Ellis RJ et al, *Nat Rev Neurol 2023*



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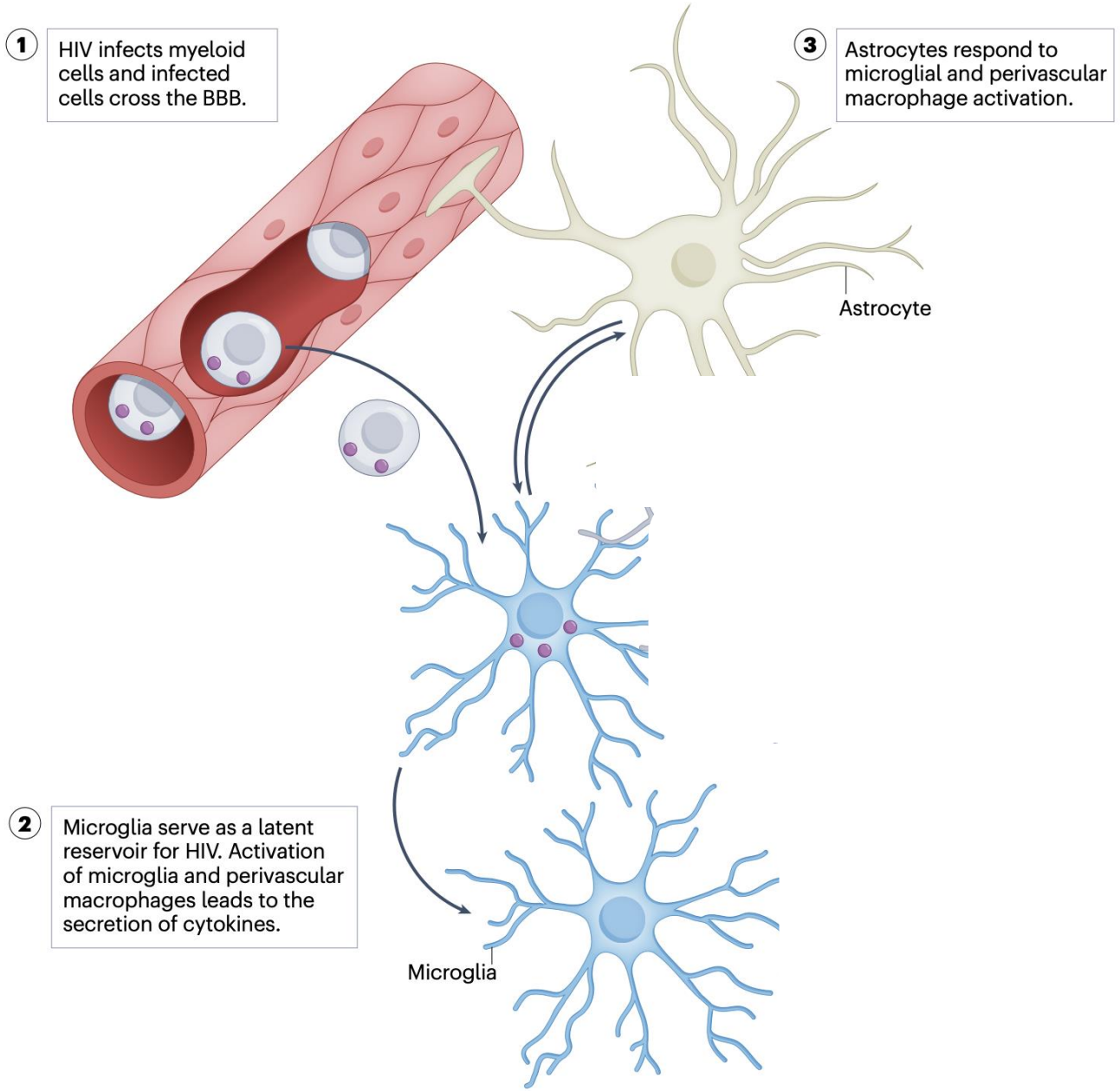

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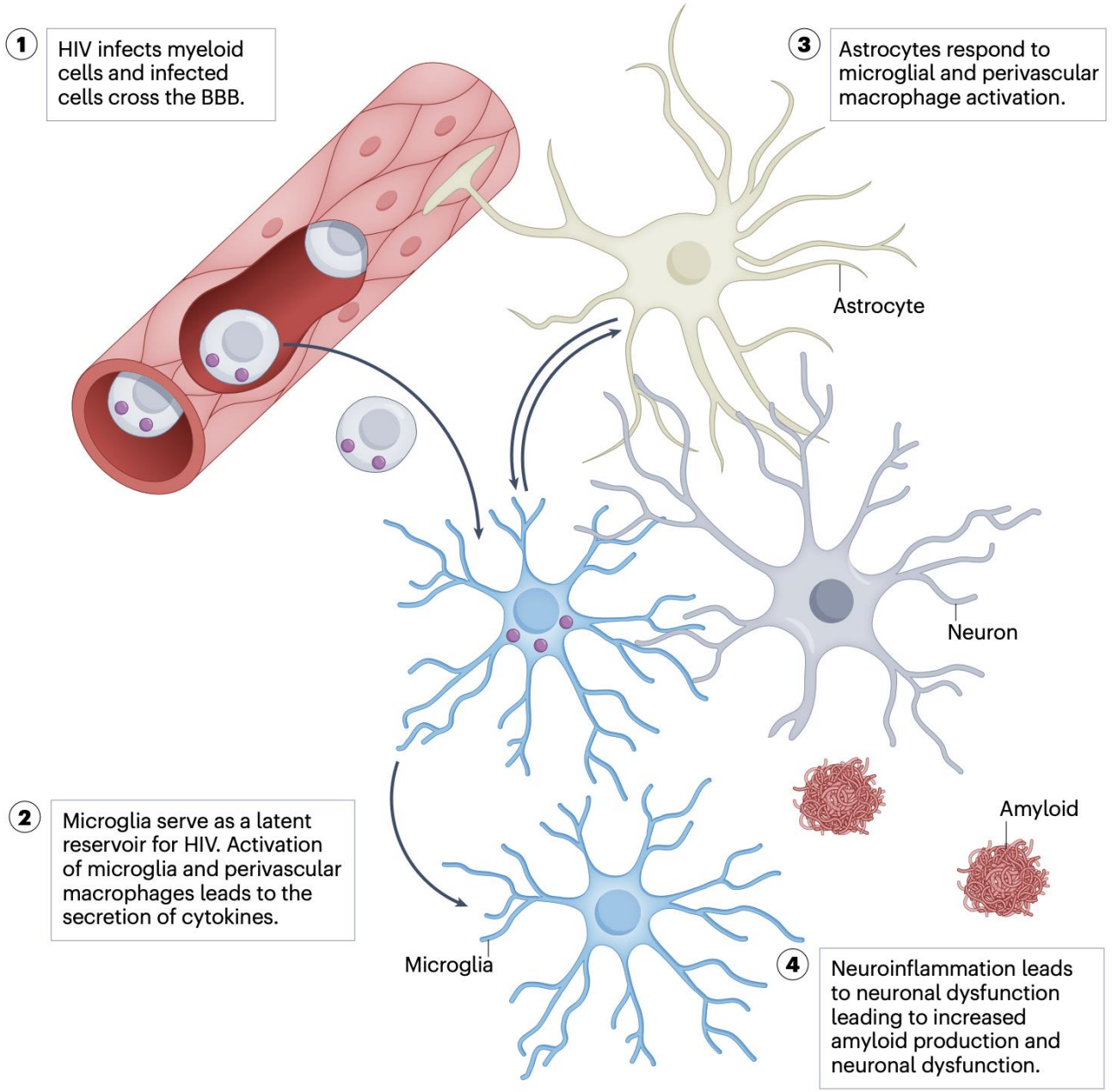

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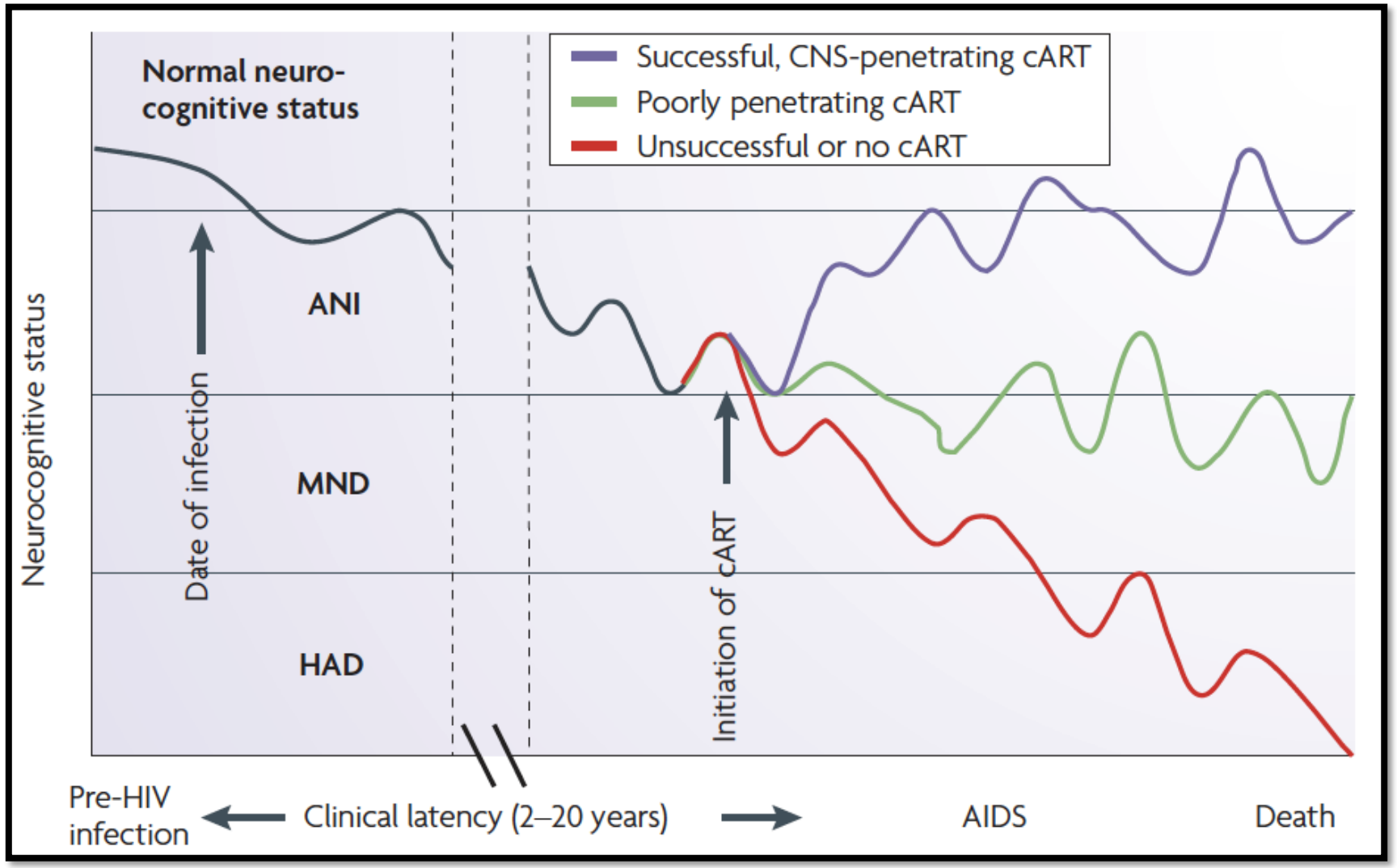
HIV neurocognitive impairment and the effects of cART



Ellis R et al, *Nat Rev Neurosci 2007*

CNS penetration effectiveness score (CPE score)

Antiretroviral Drug Class	4 (Very Good)	3 (Good)	2 (Fair)	1 (Poor)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Adefovir Tenofovir Zalcitabine
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease Inhibitors (PIs)	Amprenavir-r Indinavir-r	Amprenavir Danmavir Darunavir Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanarir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Integrase Inhibitors		Elvitegravir Raltegravir		
Entry Inhibitors		Maraviroc Vicriviroc		Enfuvirfide T-1249

Borrajo A et al, *Microrganisms 2021*

Global prevalence and burden of HIV-associated neurocognitive disorder

	ANI				MND				HAD			
	No. of studies	Prevalence, % (95% CI)	I^2, %	Subgroup difference	No. of studies	Prevalence, % (95% CI)	I^2, %	Subgroup difference	No. of studies	Prevalence, % (95% CI)	I^2, %	Subgroup difference
Overall	50	23.5 (20.3–26.8)	94.7	—	48	13.3 (10.6–16.3)	95.4	—	52	5.0 (3.5–6.8)	94.5	—
Year of study				0.736				0.120				0.320
Before 2012	6	21.8 (13.1-32.0)	92.3	—	6	20.3 (11.0–31.6)	93.9	—	7	8.3 (1.9–18.1)	96.4	—
2012 or later	44	23.7 (20.2–27.3)	94.8	—	42	12.4 (9.6–15.6)	95.5	—	45	4.6 (3.0–6.4)	94.2	—
Proportion on ART				0.237				0.365				0.028
Naive	4	15.0 (6.5–23.6)	91.6	—	4	23.3 (8.1–43.2)	96.8	—	6	13.1 (4.7–24.7)	95.8	—
0–70	3	25.2 (14.3–36.1)	86.3	—	3	20.7 (6.5–40.1)	94.8	—	4	7.6 (1.5–17.5)	93.5	—
70–90	13	24.8 (19.0–30.6)	94.4	—	13	13.8 (9.6–18.5)	92.7	—	13	3.9 (2.3–5.9)	83.8	—
>90	22	24.5 (19.5–29.6)	95.8	—	20	11.9 (9.2–14.7)	88.2	—	20	2.6 (1.5–3.9)	84.1	—

Wang Y et al, *Neurology 2020*

Neurocognitive performance and depressive symptoms at baseline and 12 years later of the two age groups

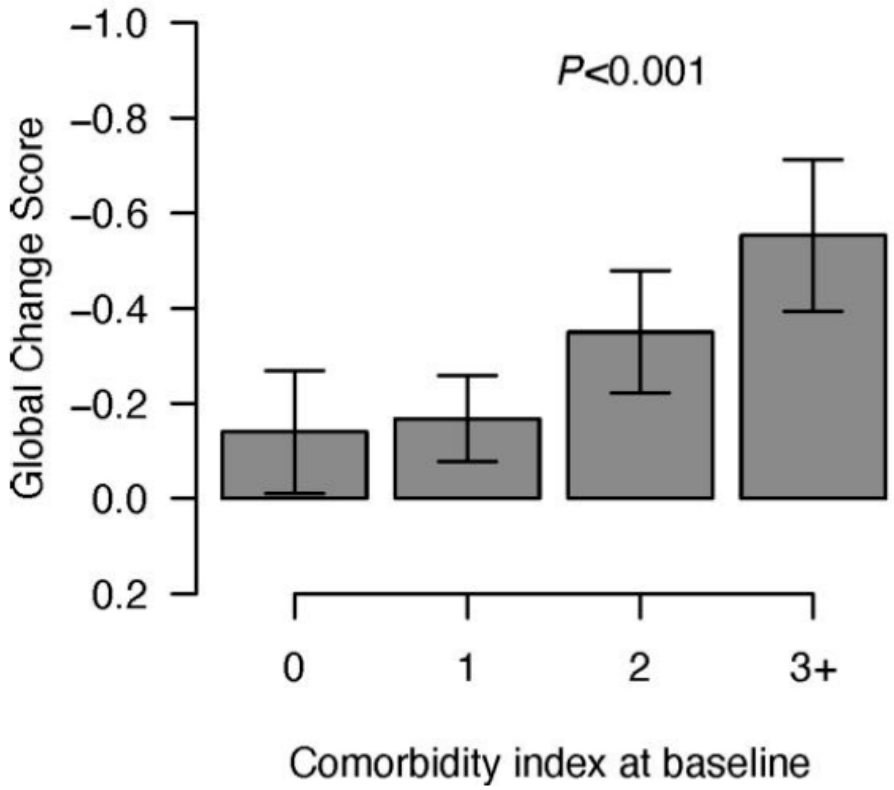
- Results of comprehensive assessments over 12 years of 402 people with HIV in the CNS HIV ART Effects Research (CHARTER) programme, who at follow-up were composed of younger (<60 years) and older (≥60 years) subgroups.
- Test scores were automatically converted to demographically corrected standard scores (T-scores). These were then converted to deficit scores, which were summarized as a Global Deficit Score (GDS), which reflects the number and severity of neurocognitive impairments on the entire test battery.
- **Based upon GCS , 23.7% declined, 70.0% remained stable, and 6.2% improved**

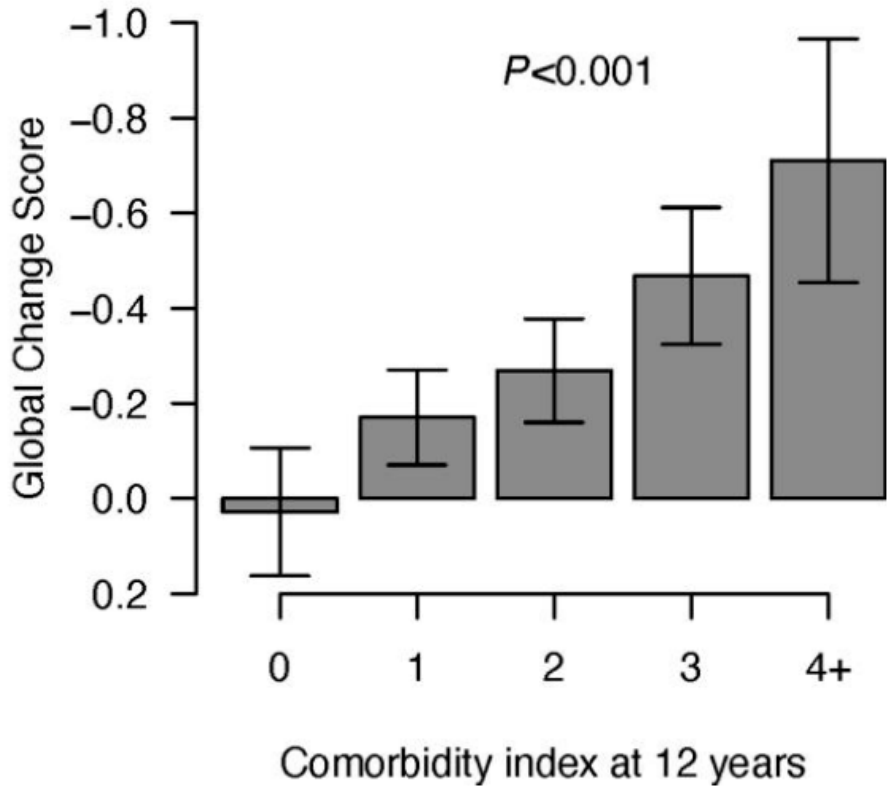
	Younger (<60 years)		Older (≥60 years)		Age group	Visit	Age group × Visit	Group contrasts[a]
	(*n* = 260)		(*n* = 142)		*P*-value	*P*-value	*P*-value	
Characteristic	Baseline (1)	12 years (2)	Baseline (3)	12 years (4)				
Age, years	39.2 (5.30)	51.8 (5.47)	51.5 (4.59)	64.4 (4.34)	<0.001	<0.001	0.018	1 < 2,3; 4 > 2,3
Education, years	12.8 (2.53)	Unchanged	13.5 (2.73)	Unchanged	0.005	No test	No test	1 < 3
Sex, male	197 (75.8%)	Unchanged	110 (77.5%)	Unchanged	0.81	No test	No test	No diff.
Race, Black	118 (45.4%)	Unchanged	67 (47.2%)	Unchanged	0.75	No test	No test	No diff.
Ethnicity, Hispanic	32 (12.3%)	Unchanged	11 (7.8%)	Unchanged	0.18	No test	No test	No diff.
WRAT-III	92.3 (15.3)	92.5 (15.4)	91.6 (17.7)	92.1 (18.2)	0.68	0.63	0.57	No diff.
Global Deficit Score[b]	0.50 (0.50)	0.53 (0.57)	0.51 (0.46)	0.55 (0.54)	0.59	0.88	0.82	No diff.
Global impairment	116 (44.6%)	104 (40.5%)	65 (45.8%)	65 (46.4%)	0.81	0.25	0.39	No diff.
BDI-II	13.5 (10.8)	9.55 (9.35)	13.2 (11.0)	9.83 (10.0)	0.77	<0.001	0.66	1 > 2; 3 > 4
BDI-II >13	109 (41.9%)	71 (28.1%)	60 (42.3%)	40 (29.0%)	0.95	<0.001	0.99	1 > 2; 3 > 4

Heaton RK et al, *Brain 2023*

GCS by comorbidity indices at baseline and at 12 Years

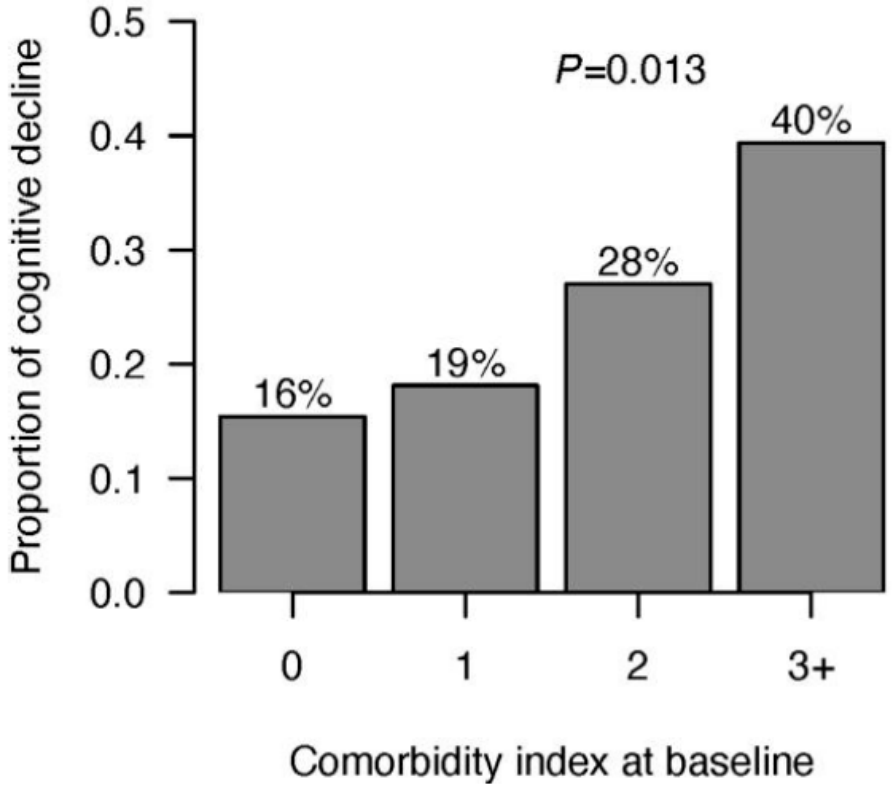
Based only upon categorical predictors, **two new indexes** were created that are simply the counts of the **categorical risk conditions** at baseline (hypertension, CPD, BDI-II>13, lifetime cannabis use disorder, AST>40, and total serum protein <7.1) and at 12 years (diabetes, CPD, the combination of pre-frailty and frailty, BDI-II>13, low haematocrit, and lifetime cannabis use disorder).

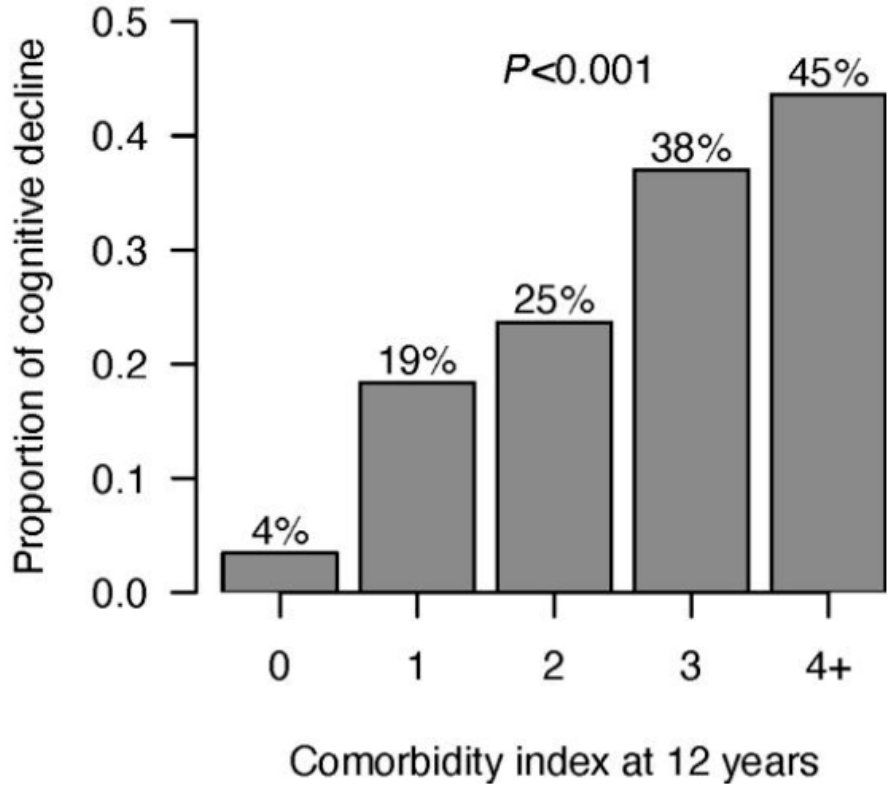




Heaton RK et al, *Brain 2023*

Proportion of decliners by number of comorbidities at baseline and at weeks 12





Heaton RK et al, *Brain 2023*

Moving on From HAND: Why We Need New Criteria for Cognitive Impairment in PWH and a Proposed Way Forward

Summary of Key Differences Between HAND Criteria and New Proposed Framework

	HAND: Existing Criteria	Cognitive Impairment in PLWH: Proposed New Framework
Definition	A cognitive disorder caused by the direct effect of HIV on the brain	Symptomatic cognitive impairment from any cause in a persons living with HIV
Proportion with asymptomatic impairment	Most	None
Diagnosis	Based on performance on cognitive tests compared to matched controls	Based on clinical history, including observer account where possible
Low cognitive test performance without symptoms	Termed ANI, which is part of HAND and hence labeled a cognitive disorder	Described as "low performance on cognitive tests," which is not part of cognitive impairment
Comorbidities	Divided into confounding (not HAND) and contributing	Comorbid factors specified alongside relative contribution of HIV brain disease

Nightingale S et al, *Clin Infect Dis 2021*

DECADIMENTO COGNITIVO NELLE PWH

MND NELLE PWH: PRIMI DATI EPIDEMIOLOGICI

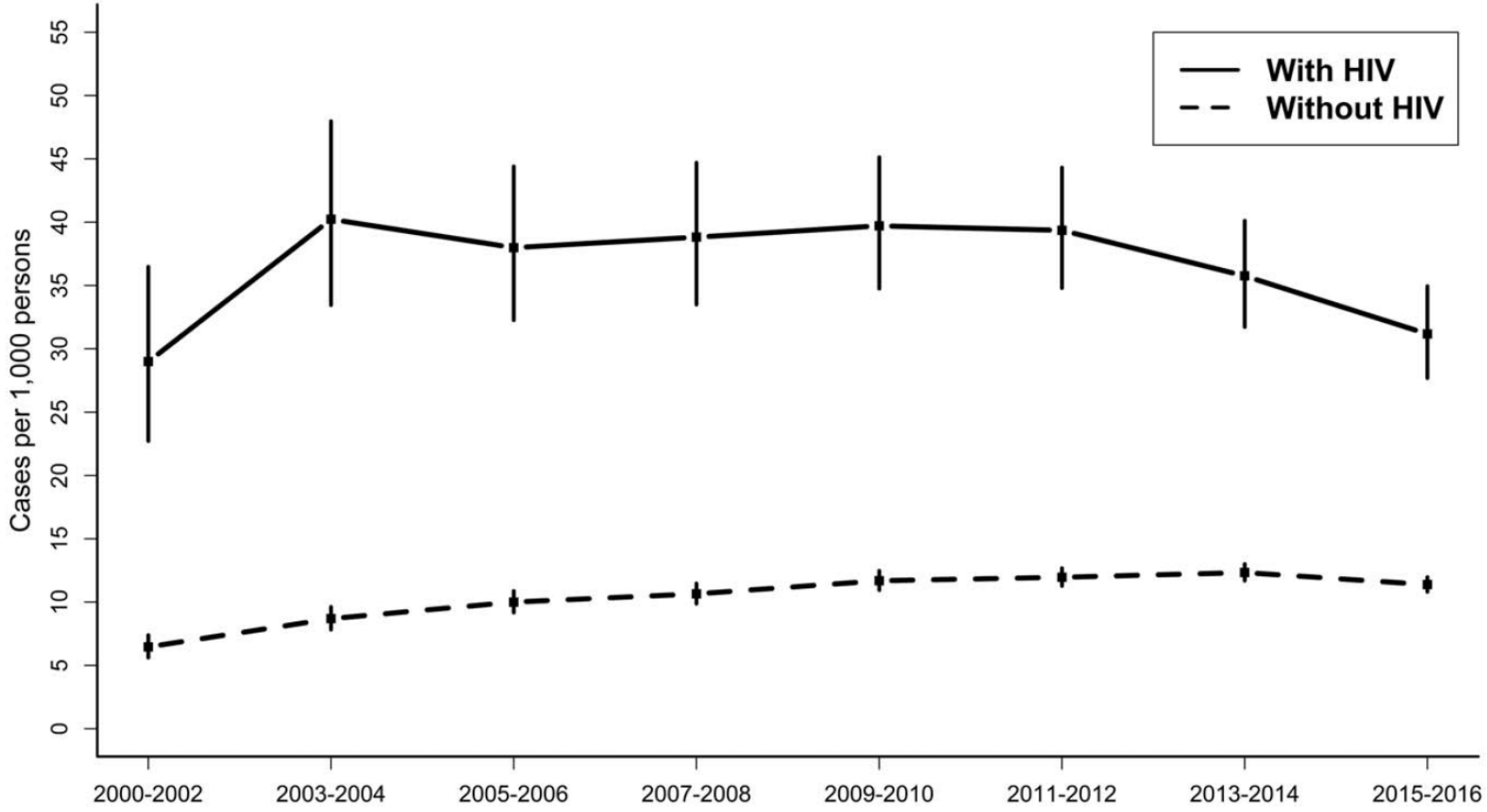
Comparison of dementia incidence and prevalence between individuals with and without HIV infection in primary care from 2000 to 2016

- People with HIV (PWH) on antiretroviral therapy (ART) and demographically similar people without HIV (PWoH), **all aged 50 years and older**, were identified from **Kaiser Permanente healthcare systems** in Northern California, Southern California, and Mid-Atlantic States.
- Dementia diagnoses were obtained from **electronic health records**. Incidence and prevalence of dementia, overalland by time period were calculated using Poisson regression. Rate ratios were used to compare dementia by HIV status with adjustment for sociodemographics, substance use, and clinical factors.
- The study included **13 296 PWH** and **155 354 PWoH** (at baseline: for both, mean age.54 years, 89% men; for PWH, 80% with HIV RNA <200 copies/ml).

Lam JO et al, *AIDS 2022*

Prevalence of dementia by HIV status: Kaiser Permanente, 2000–2016

Prevalence estimates were standardized to the overall age and sex distribution in the time period 2000–2002



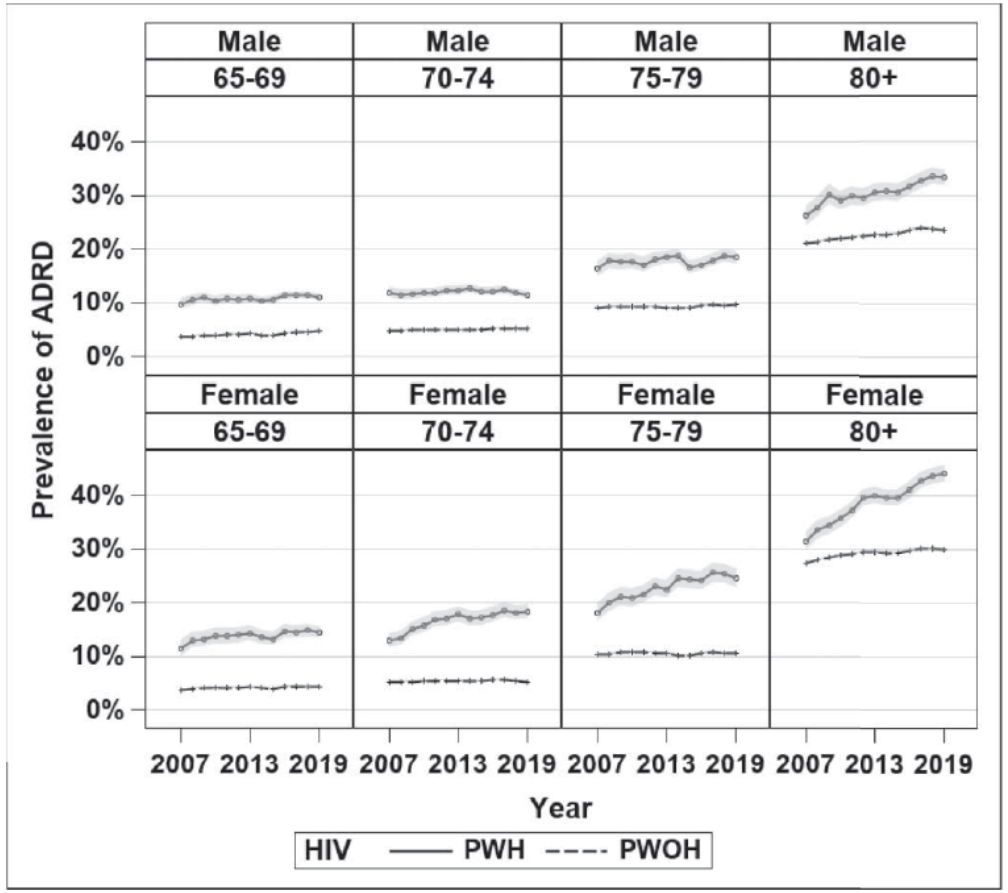
Lam JO et al, *AIDS 2022*

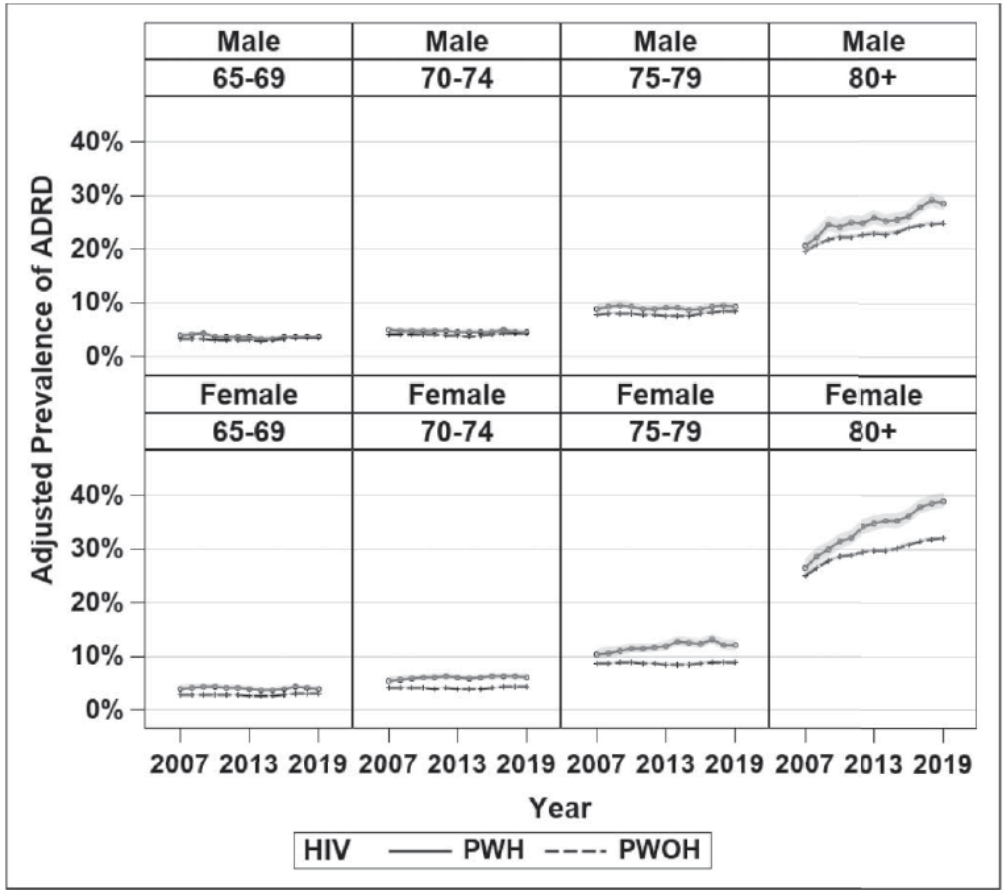
Dementias among older males and females in the U.S. Medicare system with and without HIV

- All PLWH **>65 years** (87216) and 5% PWoH (2.2 M) in Medicare (2007-2019)
- AD/ADRD cases were identified by ICD-9-CM/ICD-10-CM codes
- Both male and female PWH had a significantly higher overall prevalence of AD/ADRD across all years (**males with HIV**: **26.4%**, 95% CI 26.0-26.7%; **females with HIV: 39.4%**, 95% CI 38.9-40.0%) compared to PWOH (**males**: **22.9%**, 95% CI 22.8-23.0%; **females: 29.4%,** 95% CI 29.3-29.8%), with larger differences among females
- The gap between PWH and PWOH showed an increasing trend over time, was more prominent in females, and increased with age

Yu X et al, JAIDS 2023

Dementias among older males and females in the U.S. Medicare system with and without HIV

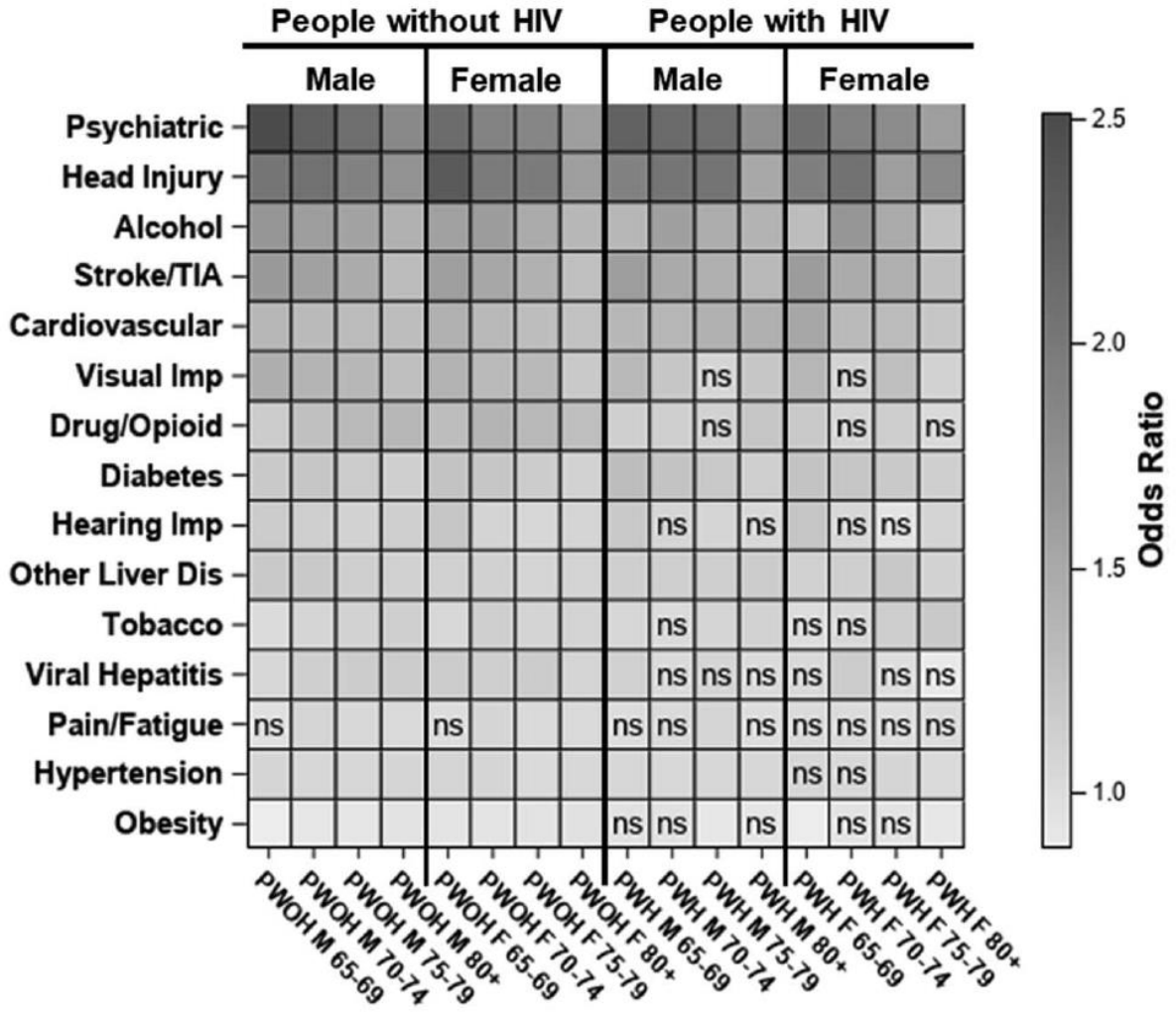




Adjusted for differential demographic and comorbidity characteristics

Yu X et al, JAIDS 2023

Association between comorbidities and AD/ADRD among PWH and PWOH by sex and age strata



Yu X et al, JAIDS 2023

Conclusions

- Aging is the primary risk factor for cognitive impairment in the general population.
- The introduction of ARV regimens with high CPE scores has reduced the prevalence of HIV-associated dementia in more recent years.
- There is some evidence, however, that shows an increased frequency of major cognitive disorders in PWH, and **this phenomenon is not only related to premature or neurocognitive accelerated aging**.
- **Many comorbidities contributing to cognitive decline** - such as cardiovascular disease, hypertension, diabetes mellitus, stroke, and depression - are more prevalent in PWH.
- This evidence underscores the need to introduce into clinical practice an approach that facilitates the **integration of screening, assessment, and management of cognitive impairment and comorbidities into the routine care of aging PWH.**

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