

HIV and Ageing Challenges and Goals

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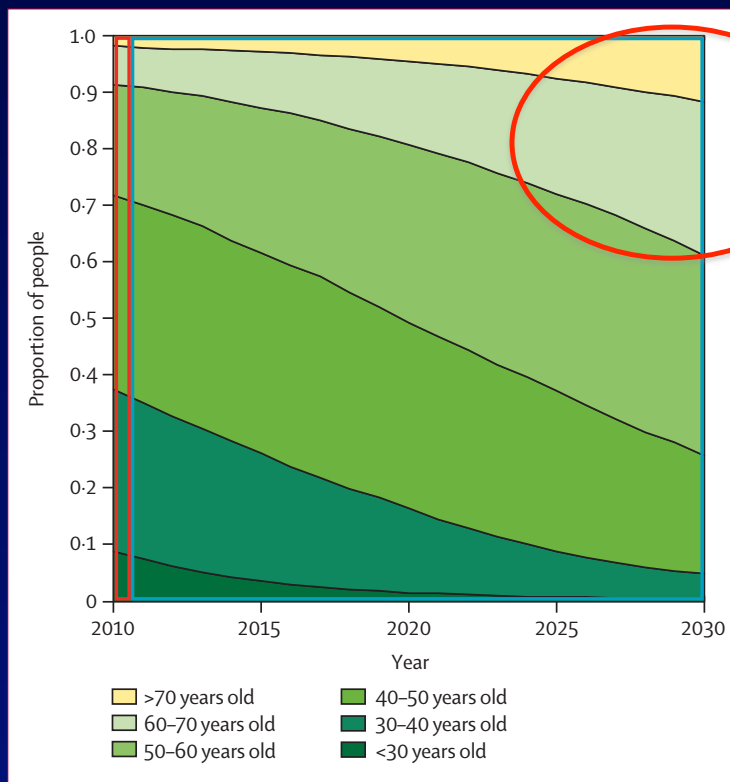
Conflict of Interest Disclosure

- **Speaker's bureau: Merck, ViiV, Gilead**

Outline

- Risks of late presentation: greater immunosuppression; multimorbidity; frailty and cognition
- Promoting healthspan: cognitive reserve; resilience
- Successful aging

Tsunami: projected age distribution of PLWH by 2030



2010- 30% older than 50 and 8% older than 60

2015- 50% older than 50

2030- 75% older than 50 (2.5x increase) and 40% older than 60 (5x increase)

Caveat

- Current epidemiologic modelling for PLWH is based on a variable mix of:
 - PLWH who survived the pre-HAART and early HAART eras
 - recently infected persons with radically different cART history and associated immuno-virologic profile
- Projections and clinical course of the latter is emerging

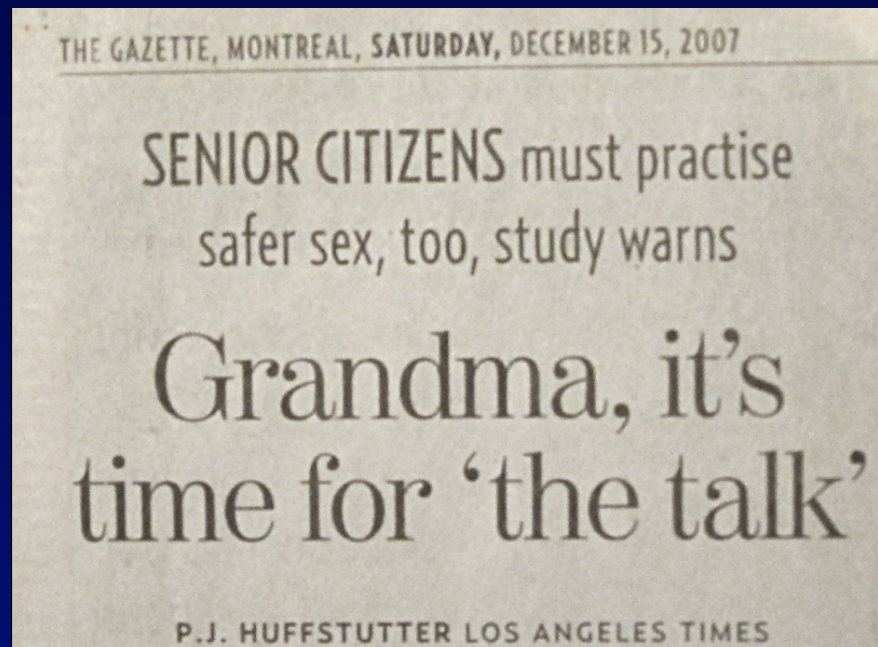
Realities of older PLWH

- **Late diagnosis:** HIV not considered, increased risk of heterosexual transmission (less condom use, age-related female genitalia changes, little blue pill et al)
- **Greater immunosuppression:** lower nadir CD4; more often symptomatic at presentation
- **Impaired immune recovery:** slower and more often incomplete (but more consistent cART adherence)
- **Multi-morbidity** including geriatric syndromes and under-diagnosed mental health disorders: related risks of polypharmacy and *polydoctory*
- **Lifestyle and social challenges:** stigmatization, isolation (family, friends), financial, unprepared community services

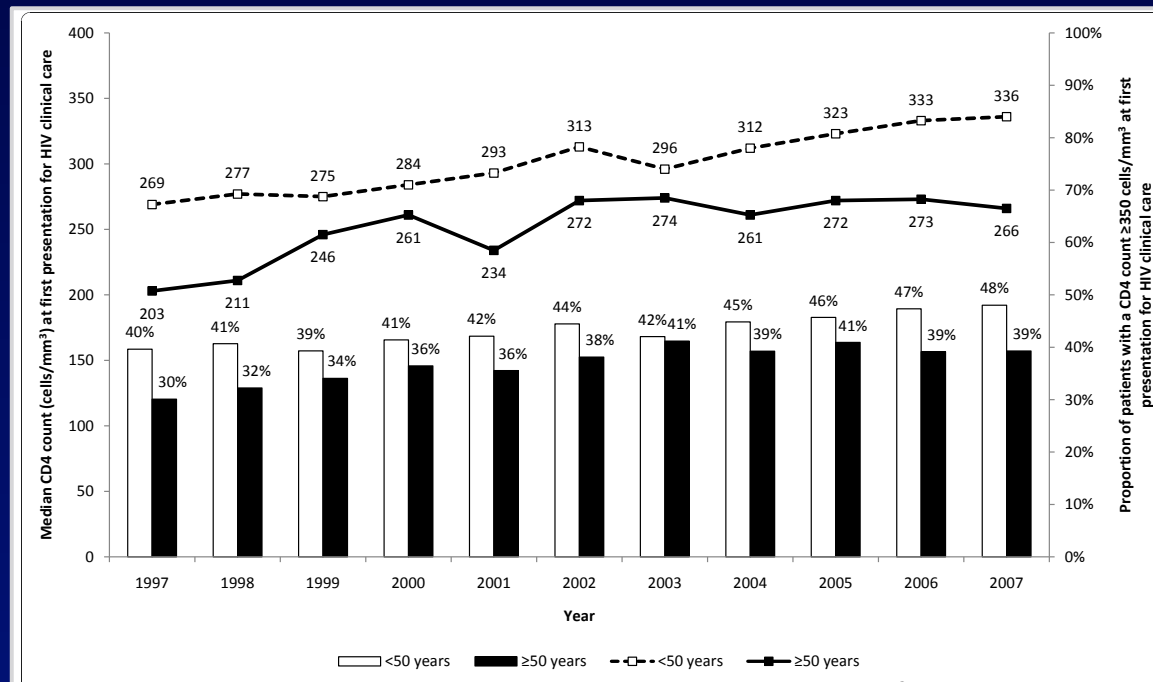
Late presentation of HIV (CD4<350): increased risk with older age and heterosexual transmission

	Coefficient \pm SE	Odds ratio (95% CI)	p-value
Intercept	21.6 \pm 56.6	—	—
Year of presentation for care	-0.011 \pm 0.028	1.0 (0.94-1.1)	0.69
Age (by 10 years older)	0.23 \pm 0.084	1.3 (1.1-1.5)	0.0069
Sex (0 = Female, 1 = Male)	0.35 \pm 0.11	2.0 (1.3-3.1)	0.0021
SSA ^a origin (0 = No, 1 = Yes)	0.61 \pm 0.14	3.4 (1.9-5.9)	<0.0001
Other ^a non belgian origin (0 = No, 1 = Yes)	0.31 \pm 0.16	1.9 (1.0-3.4)	0.044
Heterosexual ^b mode of acquisition (0 = No, 1 = Yes)	0.43 \pm 0.14	2.4 (1.4-4.1)	0.0024

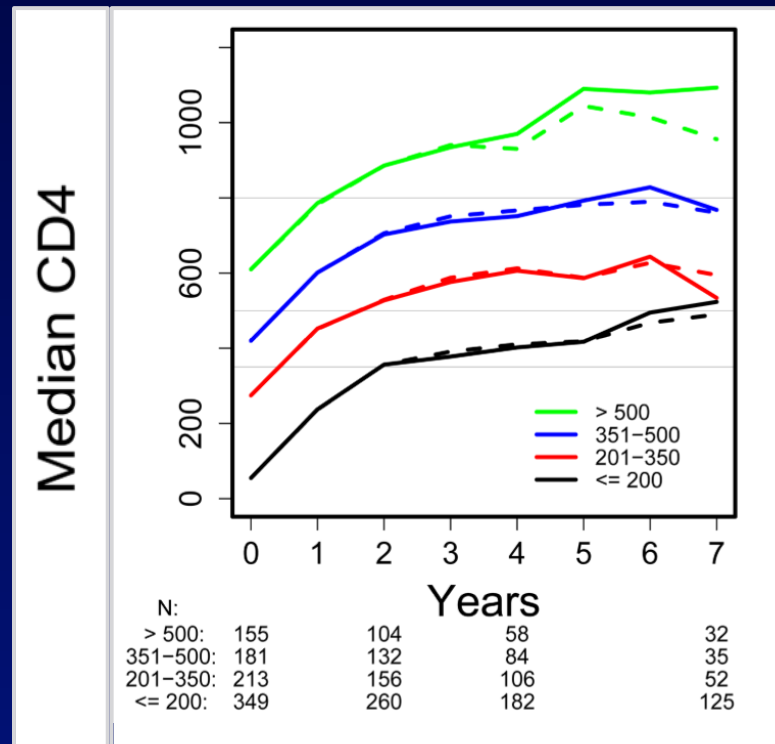
Modes of HIV transmission in the elderly



1st presentation in >50 yo c/w >50:
-lower nadir CD4 count
-lower proportion with CD4 count ≥ 350



Lower nadir CD4 predicts lower “plateau” CD4 after effective cART: older PLWH at risk



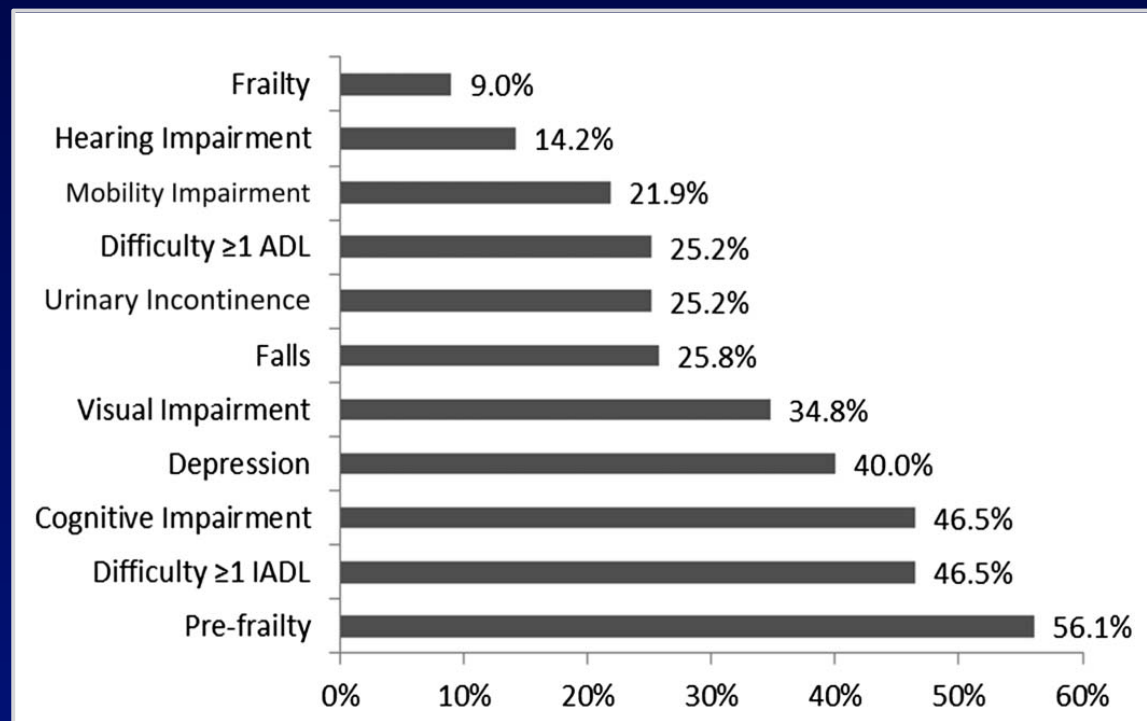
Lok JJ AIDS 2010

Non-AIDS co-morbidities are similar to those in the general older population but occur at a younger age

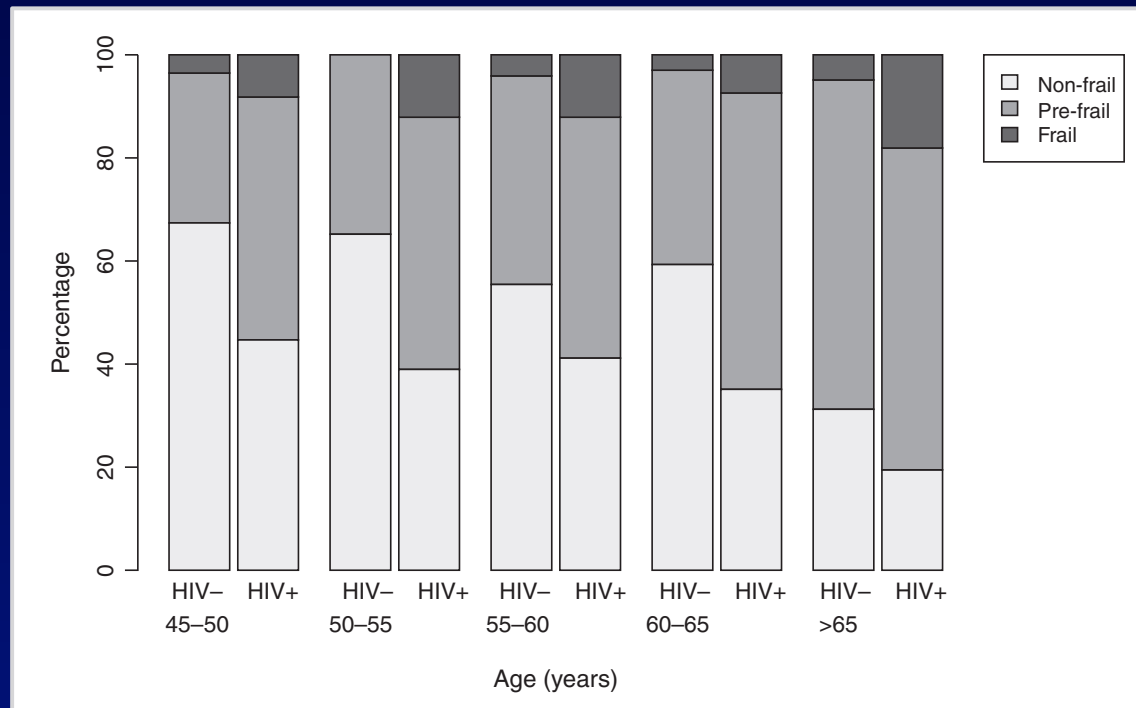
increased risk w low nadir (<200), poor CD4 recovery (CD5 < 500), CD4/CD8 <1.0

- Non-AIDS defining cancers
- Liver: viral hepatitis, NAFLD and ETOH-related
- Cardiovascular
- Metabolic (CVD, DLP, DM2, visceral adiposity, sarcopenia)
- Bone demineralization
- Renal
- JF ■ Neurocognitive decline

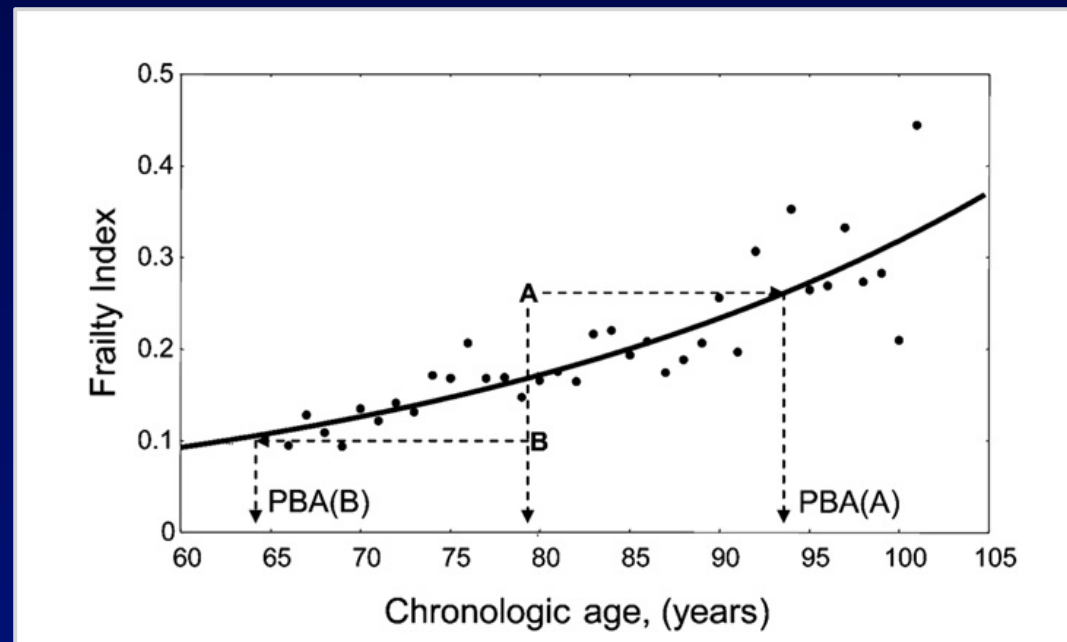
Also, high rates of geriatric syndromes in PLWH: UCSF SCOPE cohort



Increased prevalence of frailty (FP+) in PLWH c/w controls at all ages: AGEHIV Cohort



Change in biologic and chronologic age in the elderly is heterogenous: frailty may be a useful surrogate to operationalize this variability

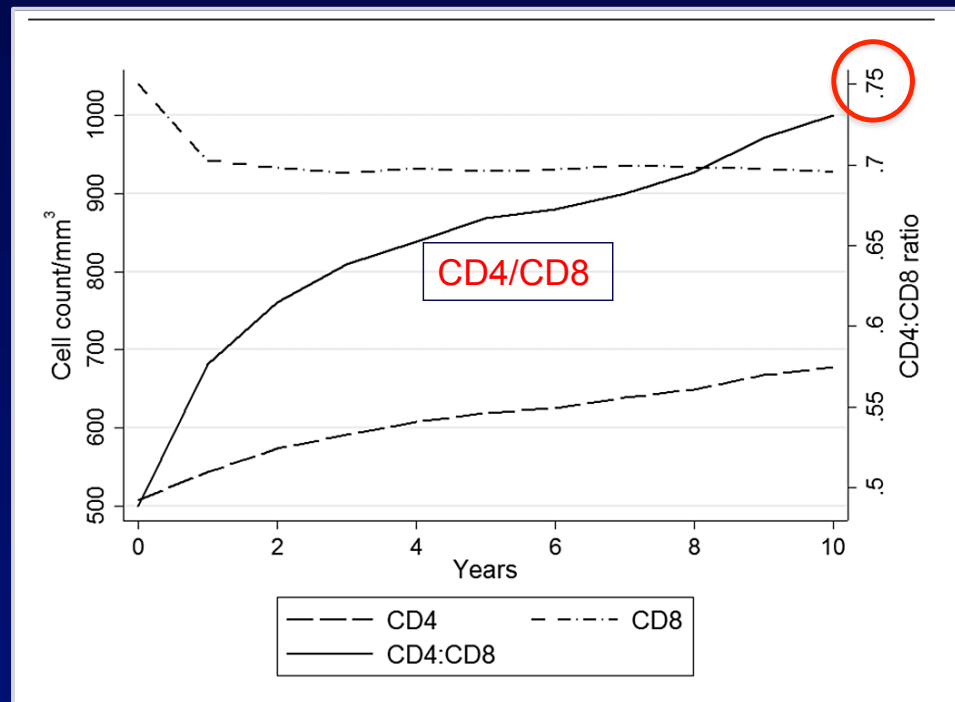


Physiologic aging (>80) is associated with changes in immune parameters and increased markers of chronic inflammation (immunosenescence):

- Expansion of terminally differentiated CD28-neg Tcells
- Reduction of naïve Tc pool (both CD4+ and CD8+)
- Associated with CMV seropositivity
- *Inverted CD4/CD8 ratio (<1.0)*

This profile (aka Immune Risk Profile-IRP):
predicts overall decreased survival in > 80 yo
healthy centenarians have normal CD4/CD8 ratio

**Most PLWH with durable viral suppression and CD4>350
do not achieve a normal CD4/CD8 ratio (>1.0)**



Trickey A et al. CID 2017

Pathobiology: does the changing co-morbidity profile in aging PLWH reflect *accelerated or accentuated* aging?

- Does HIV *accelerate* specific pathways and mechanisms common to an aging phenotype (no consensus on single definition of aging)?
- Is HIV an additional risk factor for development of chronic conditions *accentuating* prevalence of disease?

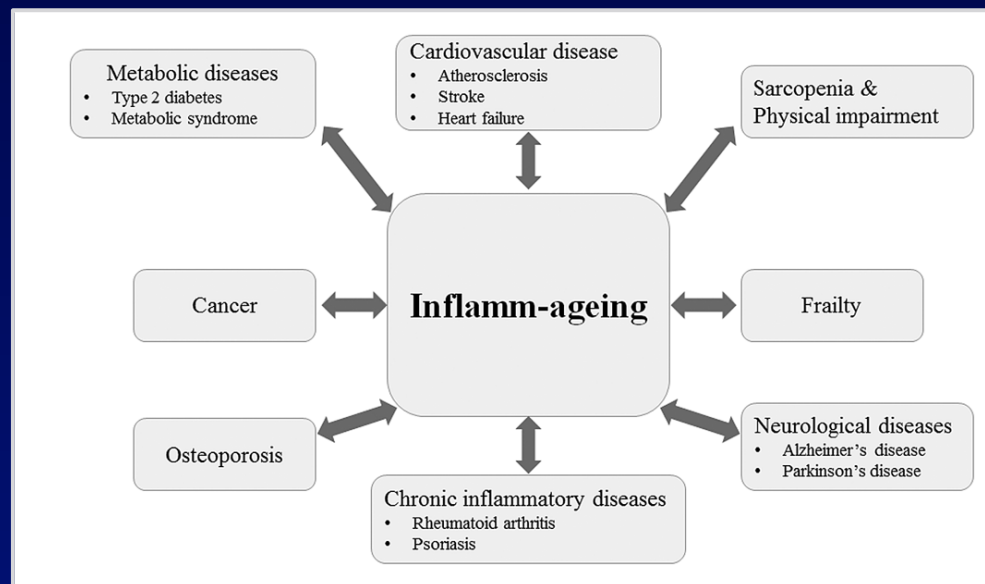
Evidence supporting *accelerated aging* phenotype in PLWH

- ***DNA methylation*** patterns suggest increased biologic age of about 5 years (*Gross, Mol Cell 2016*)
- ***Telomere length*** in PBMCs of PLWH at all disease stages are decreased and similar to those of controls about 40 years older (*Bestilny AIDS 2000*)
- ***Immune senescent cell markers*** in treated PLWH similar to patterns seen in HIV-negative controls decades older (*Appay Curr Opin HIV AIDS 2016*)

Chronic inflammation \cong idling motor (‘cost’ of idling too long







Aging associated chronic diseases regulated by chronic inflammation



Chronic disease and cognition in the elderly

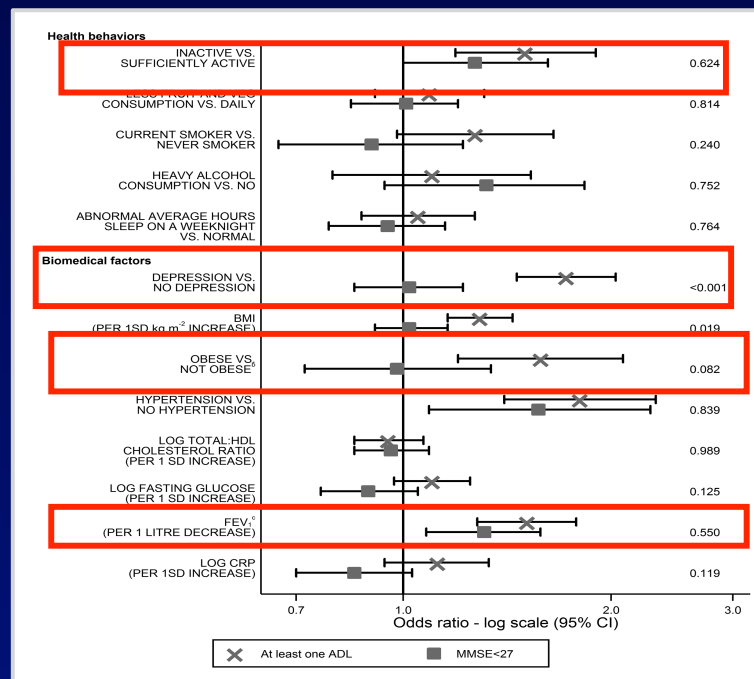
- **Common chronic diseases** are associated with cognitive decline in the middle-aged and older persons
- **Frailty** is associated with an increased risk of cognitive decline
- **White matter hyperintensities** (leukoariosis) increase risk of cognitive decline
- **Multimorbidity** leads to polypharmacy, often including drugs with high anti-cholinergic burden which are associated with cognitive decline

PLWH are more likely to take non-ARV meds with neurocognitive adverse effects: WIHS

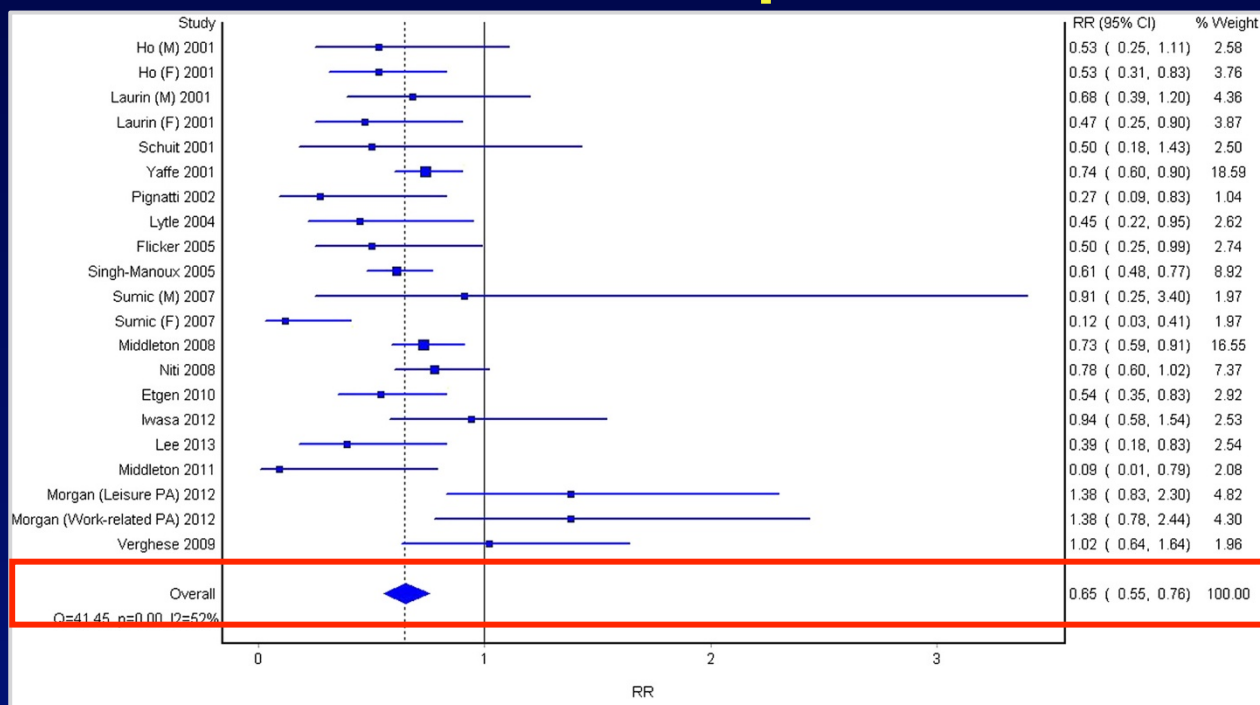
Medication Class	HIV Infected	HIV Uninfected	OR (95% CI)	P
	n visits (%)	n visits (%)		
Anticonvulsant	1274 (4.3)	450 (3.6)	0.96 (0.74 to 1.24)	0.74
Antianxiety 	3706 (12.4)	1047 (8.4)	1.41 (1.17 to 1.70)	0.0004
Anticholinergic	676 (2.3)	218 (1.7)	1.20 (0.86 to 1.67)	0.29
Antipsychotic	2074 (7.0)	903 (7.2)	0.93 (0.76 to 1.15)	0.52
Amphetamine	78 (0.3)	34 (0.3)	0.79 (0.28 to 2.20)	0.66
Opioid 	3420 (11.5)	1102 (8.8)	1.35 (1.15 to 1.60)	0.0003
Beta blocker	1004 (3.4)	304 (2.4)	1.29 (0.90 to 1.86)	0.17
Gastrointestinal	807 (2.7)	186 (1.5)	1.78 (1.27 to 2.50)	0.0009
Antihistamine 	2053 (6.9)	645 (5.2)	1.42 (1.17 to 1.73)	0.0004
Muscle relaxant	718 (2.4)	316 (2.5)	0.87 (0.66 to 1.16)	0.35
Antidepressant 	6231 (20.9)	1539 (12.3)	1.58 (1.35 to 1.85)	<0.0001

In the general population, modifiable risk factors at age 50 predict impaired physical function and cognitive decline 20 years later: Whitehall II Study

Modifiable risk factors:
 Physical exercise
 Depression
 Obesity
 FEV1 (tobacco)



Self-reported high physical activity is associated with lower risk of cognitive decline and prevalent dementia in older persons



Cognitive Reserve

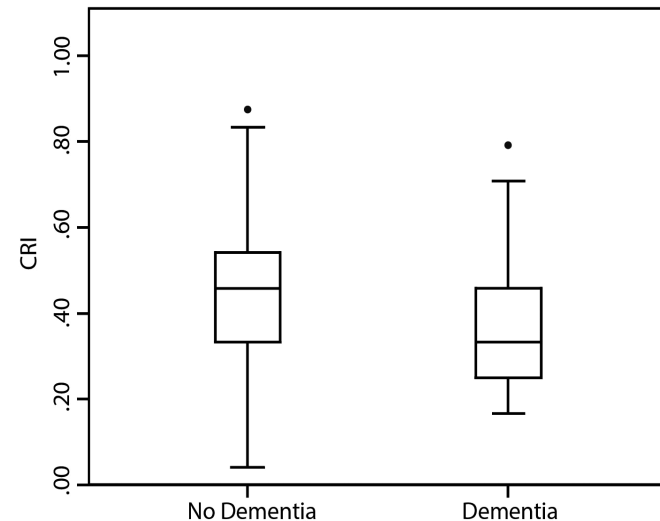
- Factor contributing to a weak association between neuropathologic evidence of dementia-related changes and clinical manifestations
- Initially felt to be linked to educational achievement (*sorry, but 3 PhD's doesn't always help*)
- Additional related factors include: occupational complexity, social participation, engagement in leisure activities
- May delay onset of clinical signs and symptoms ('compression of cognitive morbidity')
- Can be operationalized (no consensus)

Assessment of cognitive reserve (Cognitive Reserve Index) is associated with reduced dementia prevalence in the elderly

Variables Used to Create the Cognitive Reserve Index

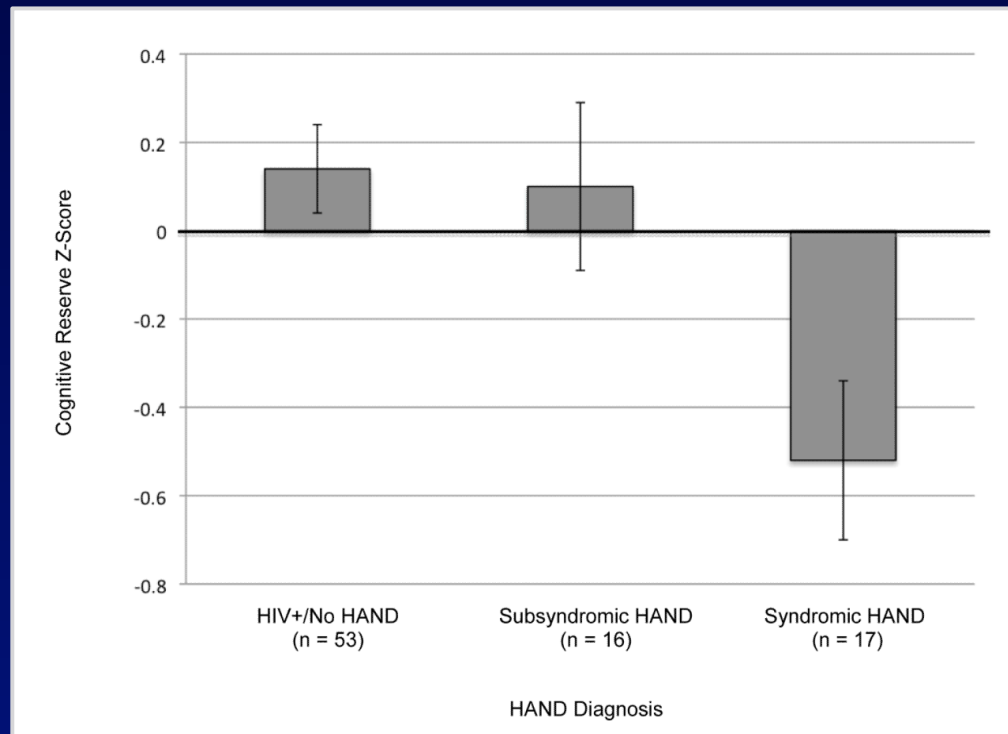
Components

- Education
- Socio-economic status
- Current physical activity
- Marital status
- Social participation
- Mental activities



PLWH with symptomatic HAND have lower cognitive reserve

Cognitive Reserve: composite mean z-scores: years of education; verbal IQ; highest occupation level.



Resilience

- Ability of a person to withstand or recover from functional decline after an acute or chronic health stressor
- Physical resilience focuses on maintenance or recovery of function after a biomedical challenge
- Reflects adaptive physiologic responses at the level of molecules, cells, and organs which support homeostasis
- Physical resilience is not the opposite of frailty

Variables associated with at least moderately high resilience in PLWH (50 yo, >20 yrs HIV+, nadir CD4-190)

Results

- Mean: moderately low
- 43% > moderate to high
- 37% moderately low-moderate
- 19% low

25 Item Resilience Scale*

- Perception of ageing
- Coping strategies
- QoL
- Depression & anxiety

Covariate	Multivariate regression		
	OR	95% CI	P value
Older age	-	-	-
Perception of ageing (EPSE)			
Cognitive self-concept	1.272	(1.105, 1.464)	.001
Subjective perception of time	-	-	-
Subjective perception of social relationships	1.182	(1.016, 1.375)	.030
Physical self-concept	-	-	-
Coping strategies (Brief COPE)			
Active coping	-	-	-
Substance use	-	-	-
Use of emotional support	-	-	-
Positive reframing	1.724	(1.159, 2.565)	.007
Planning	-	-	-
Humour	-	-	-
Acceptance	-	-	-
Self-blame ^a	-	-	-
Quality of life (NHP)			
HP Total ^a	-	-	-
Energy ^a	-	-	-
Emotional status (HADS)			
HADS Total ^a	0.874	(0.793, 0.963)	.007
HADS Anxiety ^a	-	-	-
HAD Depression ^a	-	-	-

*Heilemann J Nursing Measurement 2003

JF

Fumaz CR AIDS Care 2015

Is successful aging possible in PLWH?

Aging successfully with HIV *is possible*

No consensus on definition, WHO program evolving:
includes *at least* avoidance of disease and disability,
high cognitive and physical capacity, social engagement

Think beyond immuno-virologic control metrics

Aging successfully with HIV *is possible*

- Diagnose HIV early and treat rationally
- Assess and manage comorbidity risks proactively to avoid multimorbidity
- Minimize polypharmacy and review **all** Rx annually
- Recognize and manage risks for cognitive decline; encourage activities which contribute to cognitive reserve
- Assess functional status and adopt rehabilitation interventions to limit impairments

Aging successfully with HIV *is possible*

- Introduce *interdisciplinary* management principles: SW, OT, PT, pharmacist, dietician, peer and community support, geriatrician involvement
- **AI: Advocate + Initiate**: education and empowerment

New approach needed to manage aging PLWH

From One Syndrome to Many: Incorporating Geriatric Consultation Into HIV Care

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EDITORIAL

Geriatric-HIV medicine: A science in its infancy

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Virulence 2017

Thank you



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