HIV & frailty

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MODENA E REGGIO EMILIA

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Reflections in Internal Medicine

The geriatric management of frailty as paradigm of "The end of the disease era"

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- The traditional paradigm of stand-alone disease medicine has become out-of-date
- Several medical specialties have started looking with interest at some geriatric concepts (and frailty is a paradigmatic example) in order to better face the increased complexity of their patients
- The diffusion of geriatric concepts is frequently accompanied by misinterpretations and underestimation of the geriatrician's role
- The comprehensive geriatric assessment is meaningless if conducted in the absence of an integrated care model and without the geriatrician's expertise at managing the complexity of frail elders

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JAMDA

journal homepage: www.jamda.com

Special Article

Frailty Consensus: A Call to Action

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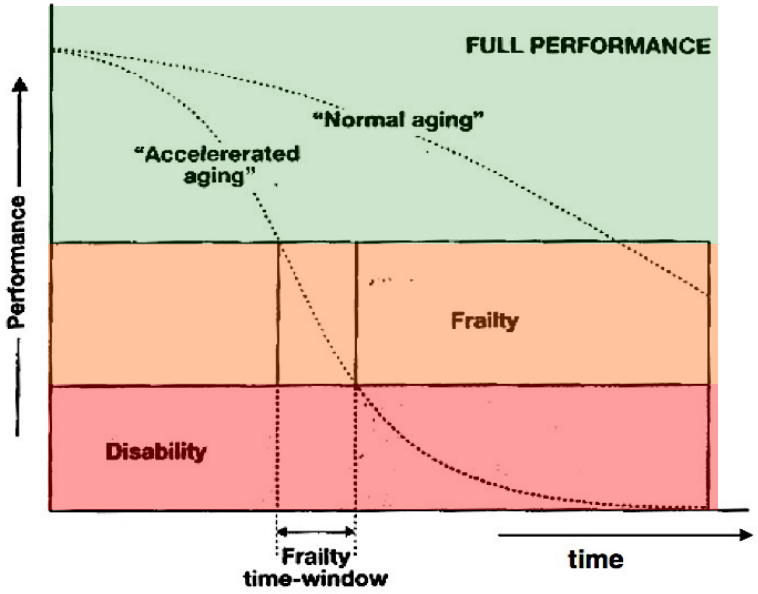
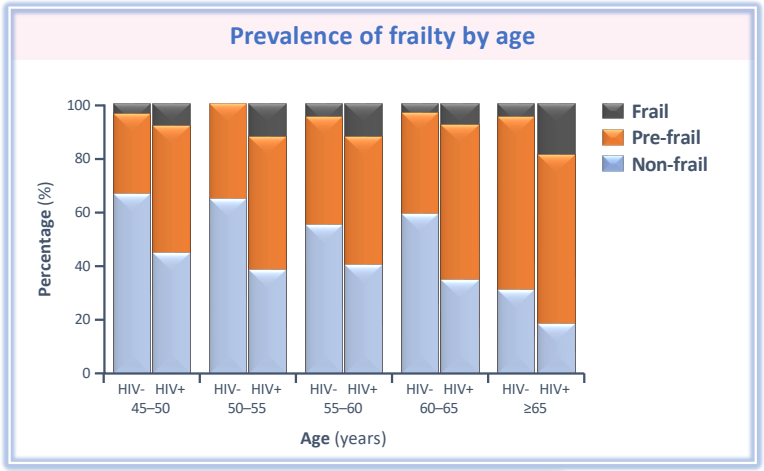
"…A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death…"

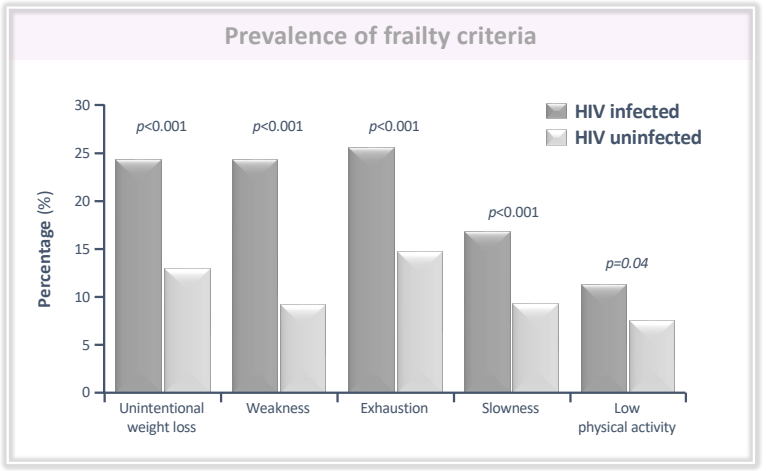


Is the accumulation of deficit exposing the individual to higher risk of negative outcomes

It conceptualize the age-related increase of vulnerability and it is considered to be a measure of **biological age** of the individual

PLHIV ARE FRAILER THAN HIV-UNINFECTED PERSONS





HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls

Katherine W. Kooij[a], Ferdinand W.N.M. Wit[a,b], Judith Schouten[a,c], Marc van der Valk[b], Mieke H. Godfried[b], Ineke G. Stolte[b,d], Maria Prins[b,d], Julian Falutz[e], Peter Reiss[a,b,f], on behalf of the AGE$_{h}$IV Cohort Study Group

HIV infection was independently associated with prefrailty/frailty in middle-aged HIV-infected patients compared with HIV-uninfected controls

PLHIV: people living with HIV

outline

1. How to measure aging
2. How to depict aging trajectories
3. How to modify aging trajectories

Why there are so many frailty definitions

Translational potential of frailty assessment tools in humans and mouse models

- ✓ Frailty phenotype
- ✓ Frailty index, examples of clinical signs
- ✓ Frailty index, examples of laboratory measures

X Clinical frailty scale
X Tilburg Frailty indicator
X Groningen Frailty indicator
X Edmonton Frail Scale
X FRAIL scale

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Most frailty work in HIV/AIDS has been with the phenotype of with the frailty index

Frailty Phenotype

Risk prediction

Frailty Index

Trajectories of changes in the health status (Health transitions)

Approach to screening for Frailty

Older PLWH ≥ 50 years

At diagnosis and once a year in the follow-up

SCREENING FOR FRAILTY
walking speed or Short Physical Performance Battery (SPPB) or FRAIL Scale (FS)

NEGATIVE

Walk speed ≥ 1.2 m/s or SPPB 12 or FS 0 points

Usual follow-up

Diet and exercise recomendations

No

walk speed 0.8 - 1.2m/s or SPPB 10-11 or FS 1-2 points

> 1 geriatric syndromes:
falls, cognitive impairment, depression, polypharmacy, functional impairment

Yes

POSITIVE

Walk speed ≤ 0.8 m/s or SPPB ≤ 9 or FS 3-5 points

DIAGNOSE FRAILTY

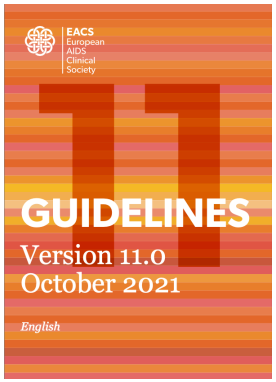
Physical Function, Frailty and Geriatric Syndromes Assessment integrated in the Comprehensive Geriatric Asessment (CGA)
by a health practitioner with specific training in frailty assessment

Care Plan integrated in the global approach

EACS European AIDS Clinical Society

Frail scale:
Simple questionnaire that quantify frailty risk based on 5 frailty components::

- Fatigue
- Resistance
- Ambulation
- Illness
- Loss of weight



Formal Frailty Assessment and Management

How to diagnose frailty		
	Frailty Phenotype	**Frailty Index**
Clinical definition	Clinical syndrome based on presence of specific signs and symptoms	Based on accumulation of deficits
How to assess	Assessed by five specific features: 1. self-reported weight loss (a) 2. self-reported exhaustion (b) 3. low levels of physical activity as measured by Minnesota Leisure physical activity questionnaire (c) 4. measured 4 m walk speed time (d) 5. measured grip strength (e)	A frailty index is calculated based on the number of health deficits out of > 30 assessed health deficits Health variables, including signs and symptoms of disease, laboratory measures, and self-reported data Data routinely collected in medical records can be included if they characterise age-related, acquired health deficits which cover a range of physiologic systems
How to interpret	Categorical variables Total score of 5 items: 0 deficits = fit 1-2 deficits = pre-frail 3 + deficits = frail	Continuous variables Index ranges from 0 to 1: ≤ 0.25 = fit 0.25 – 0.4 = frail > 0.4 = most frail
How to address frailty		
Promote Comprehensive Geriatric Assessment (CGA), aimed at personalising interventions according to benefits/priorities for a given person through a multidisciplinary diagnostic and treatment process, that identifies medical, psychosocial, and functional limitations aimed at maximising overall health with ageing and the improvement of quality of life		
Recommendations		

Differences at the basis of the two instruments

Frailty Phenotype

BIOLOGICAL SYNDROME

- ✓ Categorically defines the presence/absence of a condition of risk
- ✓ Such alert cannot generate immediate preventive or therapeutic interventions
- ✓ Specific conditions (such as disability or cognitive impairment) may affect the reliability or clinical utility.
- ✓ Ceiling effect
- ✓ Can be applied at the first patient visit

Frailty Index

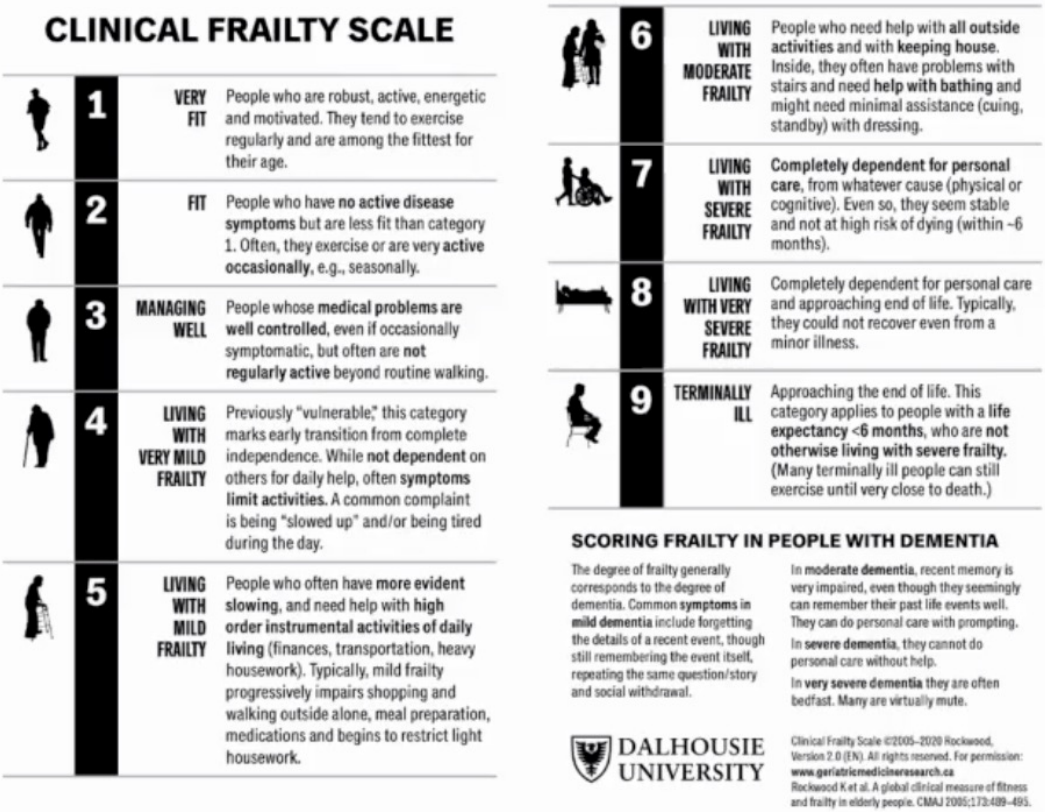
MULTIDIMENSIONAL RISK STATE

- ✓ Act as an objective marker of deficits accumulation
- ✓ it can only be generated after (or in parallel with) a comprehensive geriatric assessment.
- ✓ Can ascertain the effectiveness of any intervention
- ✓ Can describe the health status trajectories over time.
- ✓ Can be embedded into an electronic health record

Theou O, Walston J, Rockwood K . Frailty in Aging. op Gerontol Geriatr. Basel, Karger, 2015, vol 41, pp 66–73 .Cesari M et al Age and Ageing 2013; 0: 1–3

Frailty has stereotypical clinical manifestations which change as the degree of frailty increases

The Clinical Frailty Scale lets us grade the degree of frailty at baseline



CLINICAL FRAILTY SCALE

1	VERY FIT	People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
2	FIT	People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.
3	MANAGING WELL	People whose **medical problems are well controlled**, even if occasionally symptomatic, but often are **not regularly active** beyond routine walking.
4	LIVING WITH VERY MILD FRAILTY	Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up" and/or being tired during the day.
5	LIVING WITH MILD FRAILTY	People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
6	LIVING WITH MODERATE FRAILTY	People who need help with **all outside activities** and with **keeping house.** Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.
7	LIVING WITH SEVERE FRAILTY	**Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).
8	LIVING WITH VERY SEVERE FRAILTY	Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
9	TERMINALLY ILL	Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

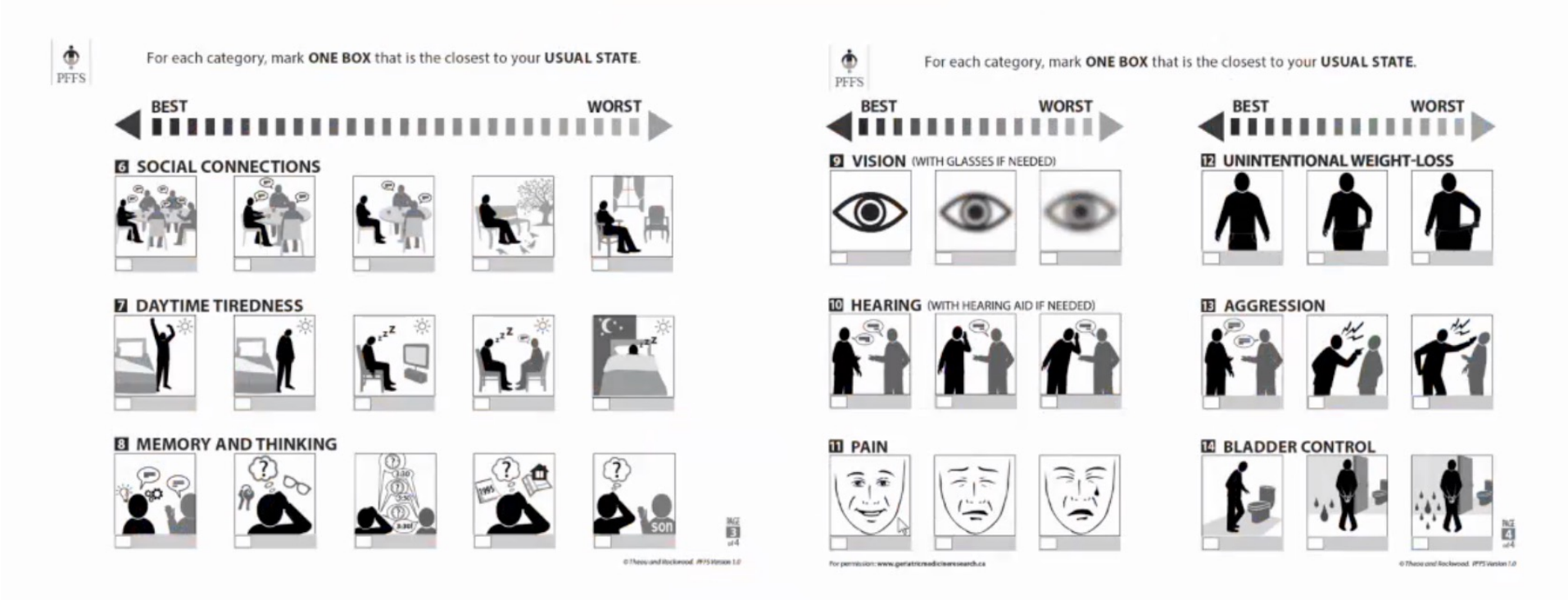
In **very severe dementia** they are often bedfast. Many are virtually mute.

DALHOUSIE UNIVERSITY

Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

https://www.dal.ca/sites/gmr.html

The Pictorial Fit Frail Scale allows a self assessment of Frailty which can be integrated in patient reported outcomes tools

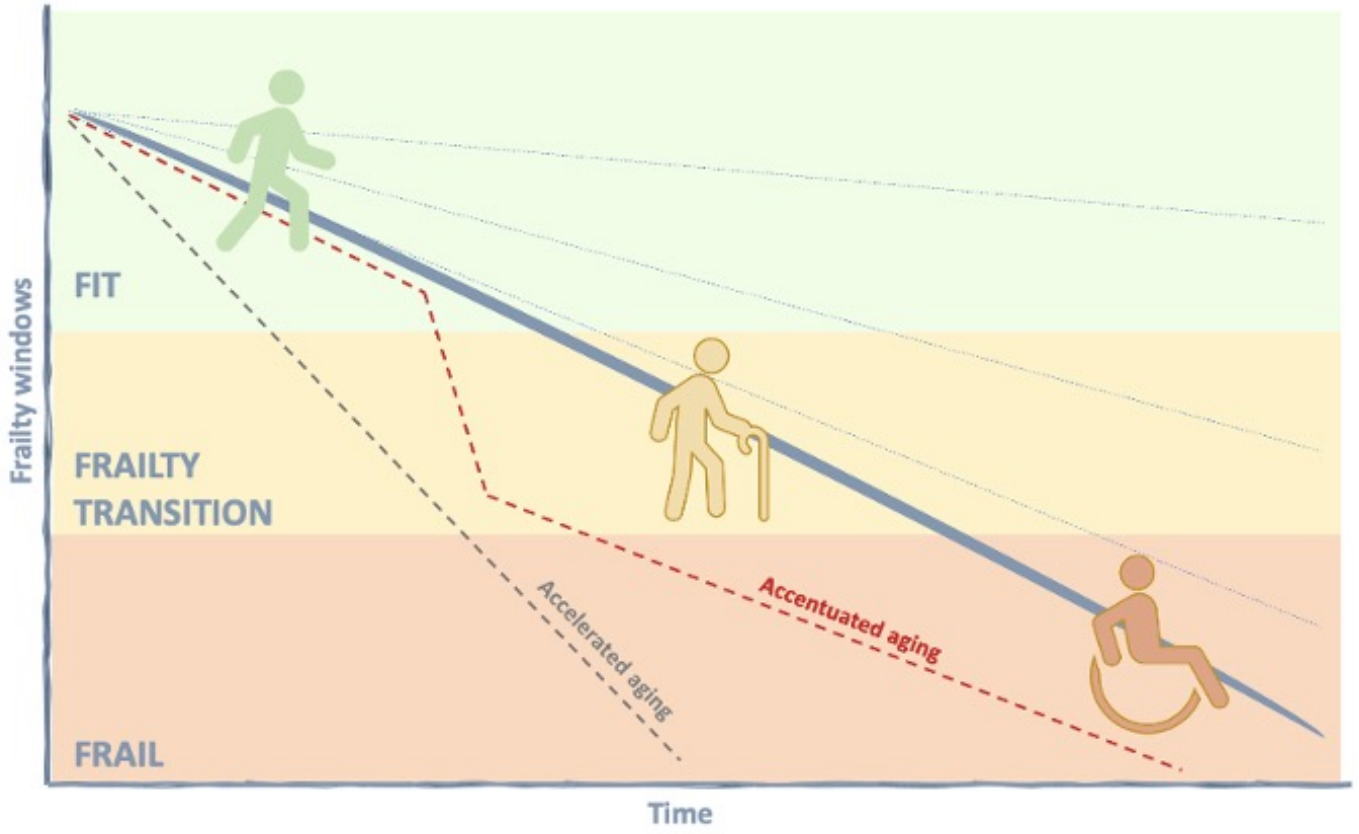


https://www.dal.ca/sites/gmr.html

outline

1. How to measure aging
2. How to depict aging trajectories
3. How to modify aging trajectories

Aging is a journey different from person to person and at a different speed at a different speed during life course



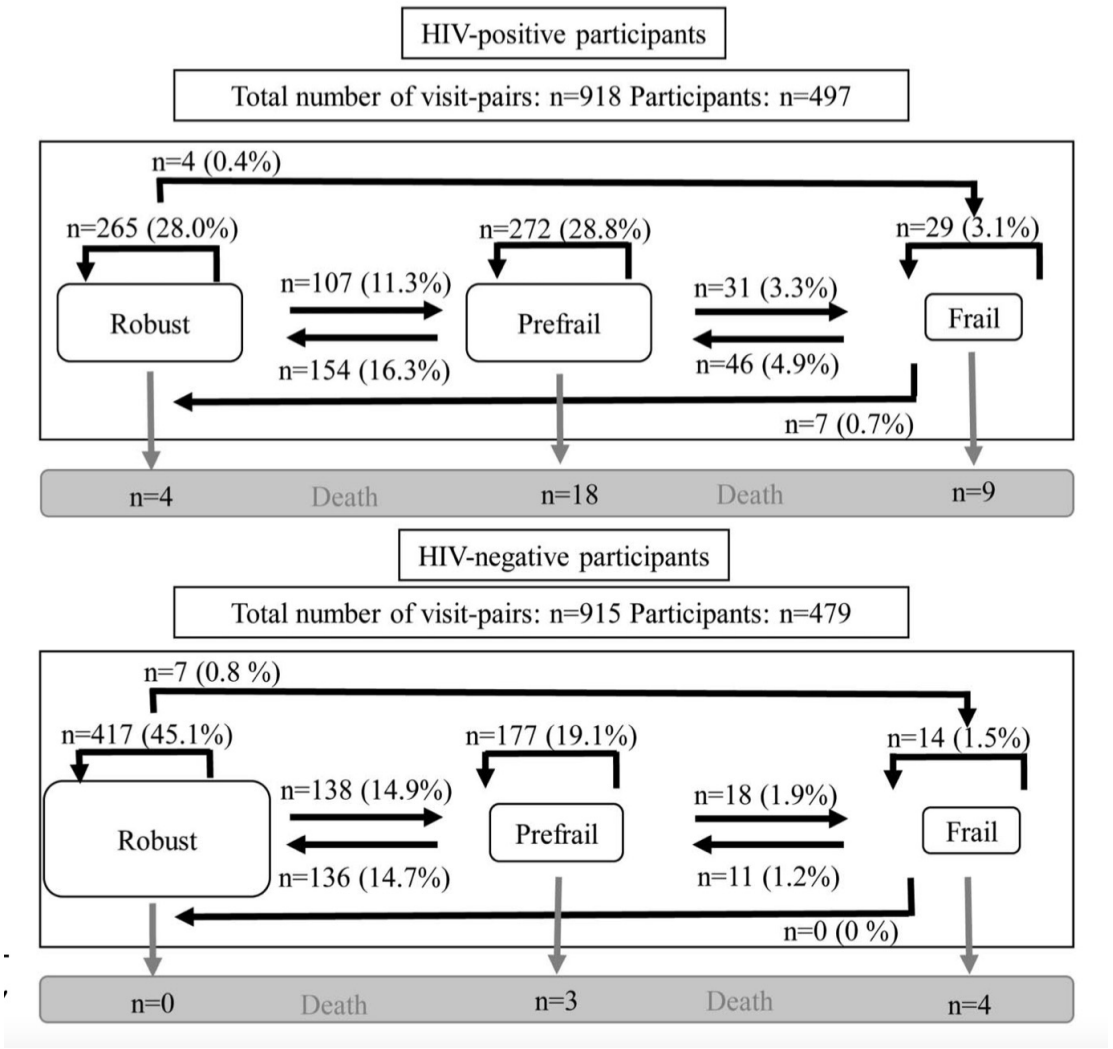
Frequency, Risk Factors, and Mediators of Frailty Transitions During Long-Term Follow-Up Among People With HIV and HIV-Negative AGE$_h$IV Cohort Participants

Eveline Verheij, MD,[a,b] Ferdinand W. Wit, MD, PhD,[a,b,c] Sebastiaan O. Verboeket, MD,[a,b] Maarten F. Schim van der Loeff, MD, PhD,[d,e] Jeannine F. Nellen, MD, PhD,[a] Peter Reiss, MD, PhD,[a,b,c] and Gregory D. Kirk, MD, PhD[f]

As frailty may be a dynamic state, authors evaluated the frequency of transitions between frailty states, and explored which factors were associated with transition toward frailty in this cohort.

In unadjusted analyses, HIV-positive status was associated with a >2-fold higher odds of transitioning to frailty.

Conclusion: PWH are at increased risk of transitioning to frailty, and thereby at increased risk of adverse health outcomes.



J Acquir Immune Defic Syndr 2021;86:110–118

Transitions in frailty phenotype states and its association with frailty index: A multi-state Markov model study

Jovana Milic[1], Stefano Renzetti[2], Sara Barbieri[1], Emanuele Aprile[3], Michela Belli[3], Maria Venuta[3], Marianna Menozzi[3], Antonella Santoro[3], Cristina Mussini[1,3], **Stefano Calza[2]**, Giovanni Guaraldi[1,3]

1Department of Surgical, Medical, Dental and Morphological Sciences, University of Modena and Reggio Emilia, Italy; 2Department of Molecular and Translational Medicine, University of Brescia, Italy; 3Department of Infectious Diseases, Azienda Ospedaliero-Universitaria, Policlinico of Modena, Modena, Italy

- Frailty phenotype (FP) and frailty index (FI) constructs have been applied in the HIV setting, identifying both the syndromic and the accumulation of deficit approach to aging.

Objective: We described longitudinal transitions of FP states in relation to FI at the Modena HIV Metabolic Clinic (MHMC), Italy.

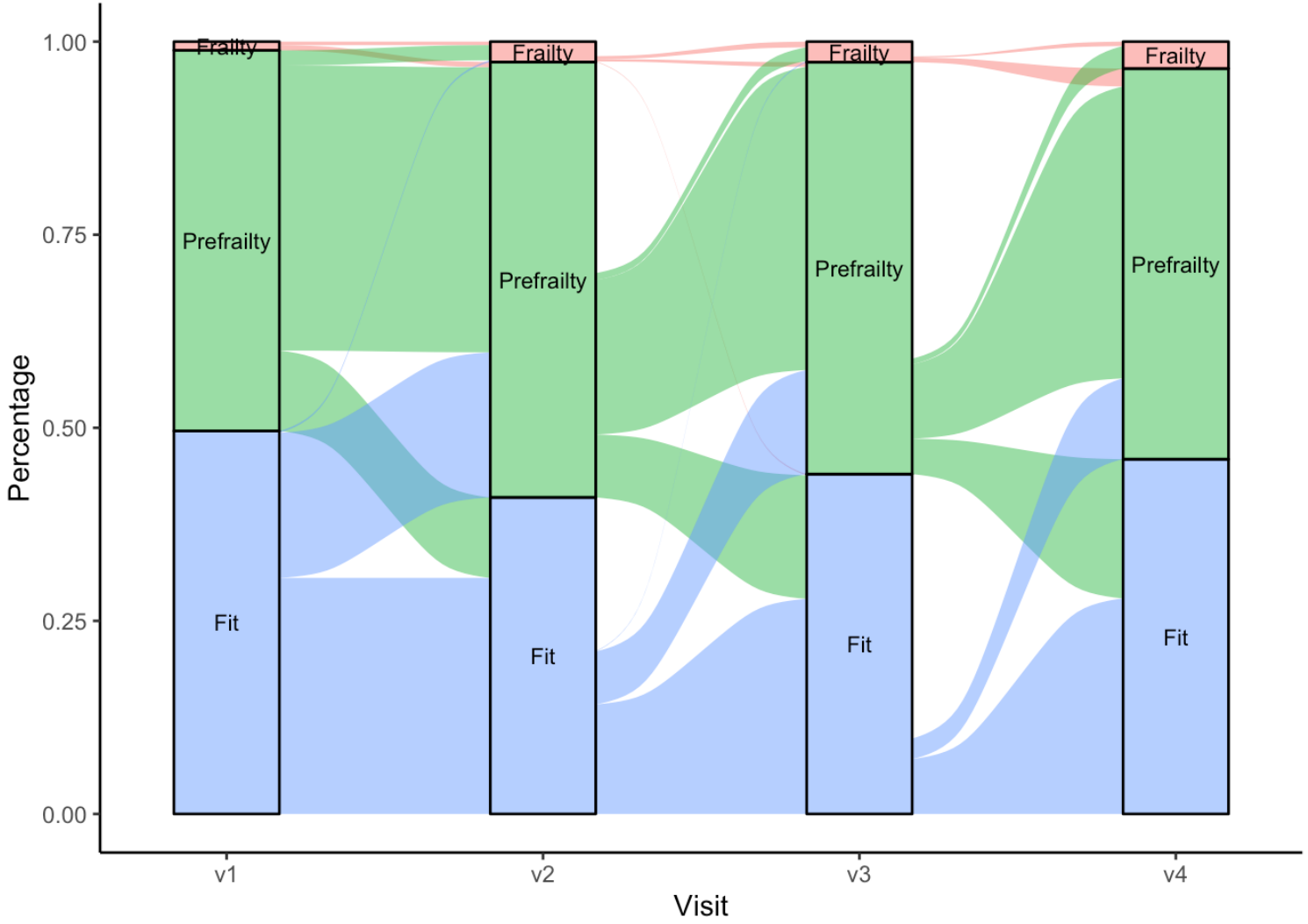
Methods

- PLWH with a minimum of two FP and FI measurements and maximum four visits were included.
- A continuous-time multi-state Markov model describes a process in which an individual moves through a series of states allowing joint analysis of care length, incidence of clinical outcomes and frailty progression or reversion.
- Next-state transition probabilities were estimated after adjusting for 37-item FI, age, sex, body mass index, CD4 nadir and HIV duration. The probabilities to switch from one state to another were modelled according to an exponential distribution for time-to-event data, which considers censored follow-up times.
- Time was measured in years and the events were the transitions between the states.

Results

Table 1	Total population (N=1325)
Frailty phenotype at the 1° visit Fit Pre-frailty Frailty	 657 (49.6%) 653 (49.3%) 15 (1.1%)
Frailty index at the first visit, median (Q1, Q3)	0.3 (0.2, 0.3)
Follow-up duration, years, median (Q1, Q3)	2.0 (1.4, 2.7)
Age at the first visit, median (Q1, Q3)	52.8 (48.7, 57.0)
Male sex, N (%)	986 (74.4%)
Multimorbidity at the first visit, N (%)	503 (38.0%)
Body mass index, kg/m2, median (Q1, Q3)	23.9 (21.7, 26.2)
Nadir CD4 cell count/µL, median (Q1, Q3)	207.0 (100.0, 306.0)
HIV duration, years, median (Q1, Q3)	22.5 (15.4, 27.8)

Results



Probability of state transition

Path	Estimates
1 – 1 Fit-fit	63.9%
1 – 2 Fit –prefrail	35.6%
1-3 Fit-frail	0.4%
2 – 1 Prefrail - Fit	30.1%
2 – 2 Prefrail-prefrail	68.6%
2 – 3 Prefrail-Frail	3.8%
3 – 2 Frail - prefrail	1.4%
3 – 3 Frail-Frail	20.3%

Table 2. The adjusted multi-state Markov model for frailty phenotype transition

Path	Estimates with 95%CI						
	Baseline	**Frailty index**	**Age**	**Male sex**	**Multi-morbidity**	**Nadir CD4**	**HIV duration>20 years**
1 - 1	-0.50 (-0.58, -0.44)	NA	NA	NA	NA	NA	NA (NA, NA)
1 - 2	0.50 (0.44, 0.58)	1.01 (0.99, 1.03)	1.0 (0.98, 1.02)	0.70 (0.5, 0.99)	**1.46 (1.06, 2.00)**	1.01 (0.91, 1.12)	1.097 (0.754, 1.597)
2 - 1	0.36 (0.31, 0.42)	**0.97 (0.95, 0.98)**	1 (0.98, 1.02)	1.05 (0.74, 1.50)	1.20 (0.87, 1.68)	1 (0.89, 1.12)	1.393 (0.926, 2.096)
2 - 2	-0.43 (-0.51, -0.36)	NA	NA	NA	NA	NA	NA (NA, NA)
2 - 3	0.07 (0.03, 0.14)	**1.05 (1.00, 1.11)**	0.96 (0.90, 1.02)	0.98 (0.37, 2.57)	0.39 (0.13, 1.19)	0.72 (0.51, 1.01)	0.233 (0.054, 1.007)
3 - 2	1.09 (0.52, 2.31)	1.01 (0.95, 1.07)	0.95 (0.89, 1.01)	1.15 (0.33, 3.99)	0.22 (0.05, 1.05)	0.71 (0.47, 1.07)	**0.15 (0.023, 0.974)**
3 - 3	-1.09 (-2.31, -0.52)	NA	NA	NA	NA	NA	NA (NA, NA)

Legend: 1 - fit; 2 - pre-frail; 3 – frail

Conclusion

- FP states and its subcategories are characterized by dynamic longitudinal transitions.
- **FI displays its bidirectional predictive nature.** Lower value predict reversibility of frailty transition while higher values predicted progression of frailty.
- Multimorbidity drives initial fit to prefrail state transition
- Shorter HIV duration (<20 years) predict frailty reversibility.
- **Both FP and FI should be used to monitor aging trajectories in PLWH.**

outline

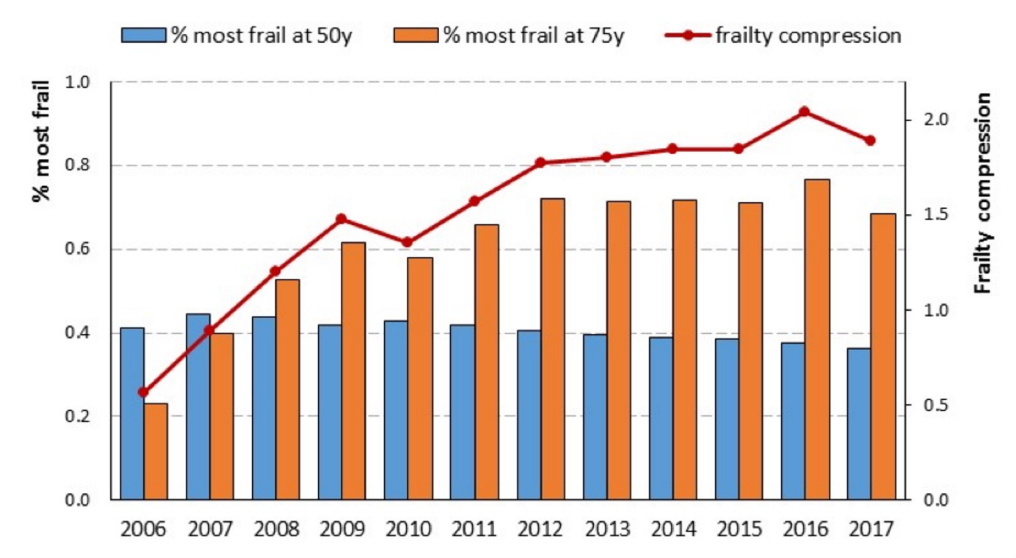
1. How to measure aging
2. How to depict aging trajectories
3. How to modify aging trajectories

Open Forum Infectious Diseases

BRIEF REPORT

The Interplay Between Age and Frailty in People Living With HIV: Results From an 11-Year Follow-up Observational Study

Giovanni Guaraldi,[1] Davide De Francesco,[2] Jovana Milic,[1,3] Iacopo Franconi,[1] Cristina Mussini,[1] Julian Falutz,[4] and Matteo Cesari[5,6]



The frailty compression score increased from 0.56 to 1.89

Frailty Compression:

is the ratio of the proportion of frail individuals at the age of 75 and at the age of 50 years at any given year.

Predictors of FRAILTY COMPRESSION at multivariable analyses:

- male patients ($p=0.02$), age ($p<0.001$)
- nadir CD4+ T cell count ($p<0.001$)
- proportion of patients with HIV duration more than 20 years ($p=0.001$)

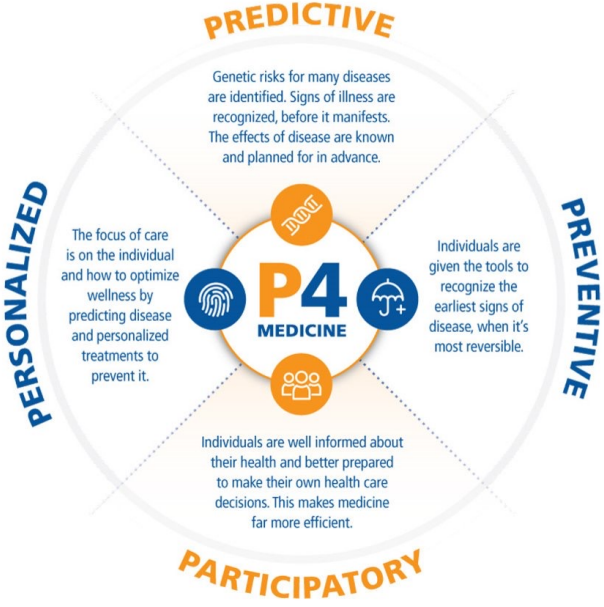
Risk/protective factors for frailty progression/reversal

	Risk factors associated with frailty progression	Protective factors associated with frailty reversal
Socio-demographic factors		
Older age		
Younger age		
Low aging satisfaction		
Older subjective age		
High aging satisfaction		
Younger subjective age		
Female sex		
Higher education		
Employment		
Antropometric variabels and lifestyles		
Smoking pack years		
Waist to hip ratio		
Combined exercise-nutrition intervention		

Risk/protective factors for frailty progression/reversal

	Risk factors associated with frailty progression	Protective factors associated with frailty reversal
HIV related variables		
Duration of ART exposure		
HIV virologic supression		
CD4 nadir >500		
Absence of AIDS diagnosis		
Cumulative exposure to zalcitabine (ddC)		
CD4 nadir		
Decreased inflammatory index		
HIV duration > 20 years		
Co-morbidities		
Burden of multimorbidity		
Cerebrovascular disease		
Depression		
Diabetes		
COPD		

Can we revert frailty in HIV?



Conditions	Mitigation interventions
Geriatric syndromes	
• Polypharmacy	Medication reconciliation at each visit Deprescribing
• Cognitive impairment	Early initiation of ART Screening for neurocognitive impairment according to guidelines
• Falls and fractures	Falls questionnaire Frailty screening Physical activity
• Sarcopenia	Screening and diagnosis of frailty with Frailty score and Frailty phenotype criteria Anaerobic physical activity three times a week Protein supplementation
• Malnutrition or overweight/obesity	Adequate daily caloric intake Nutritional counselling Physical activity

ART prescription in geriatric PLWH: WHAT TO FOCUS ON?

Efficacy	(?)
Impact on frailty/geriatric syndromes	(?)
Toxicity	(kidney)
Impact on Comorbidities	(CVD, CKD, OO, NCI)
DDI	(polypharmacy)
Pill burden	(polypharmacy)
PRO	(sleep)
Metabolic health	(Weight, Metabolic syndrome, Cardiac health, Diabetes, Insulin resistance, Lipids, NAFLD, bone, kidney)

Open Forum Infectious Diseases

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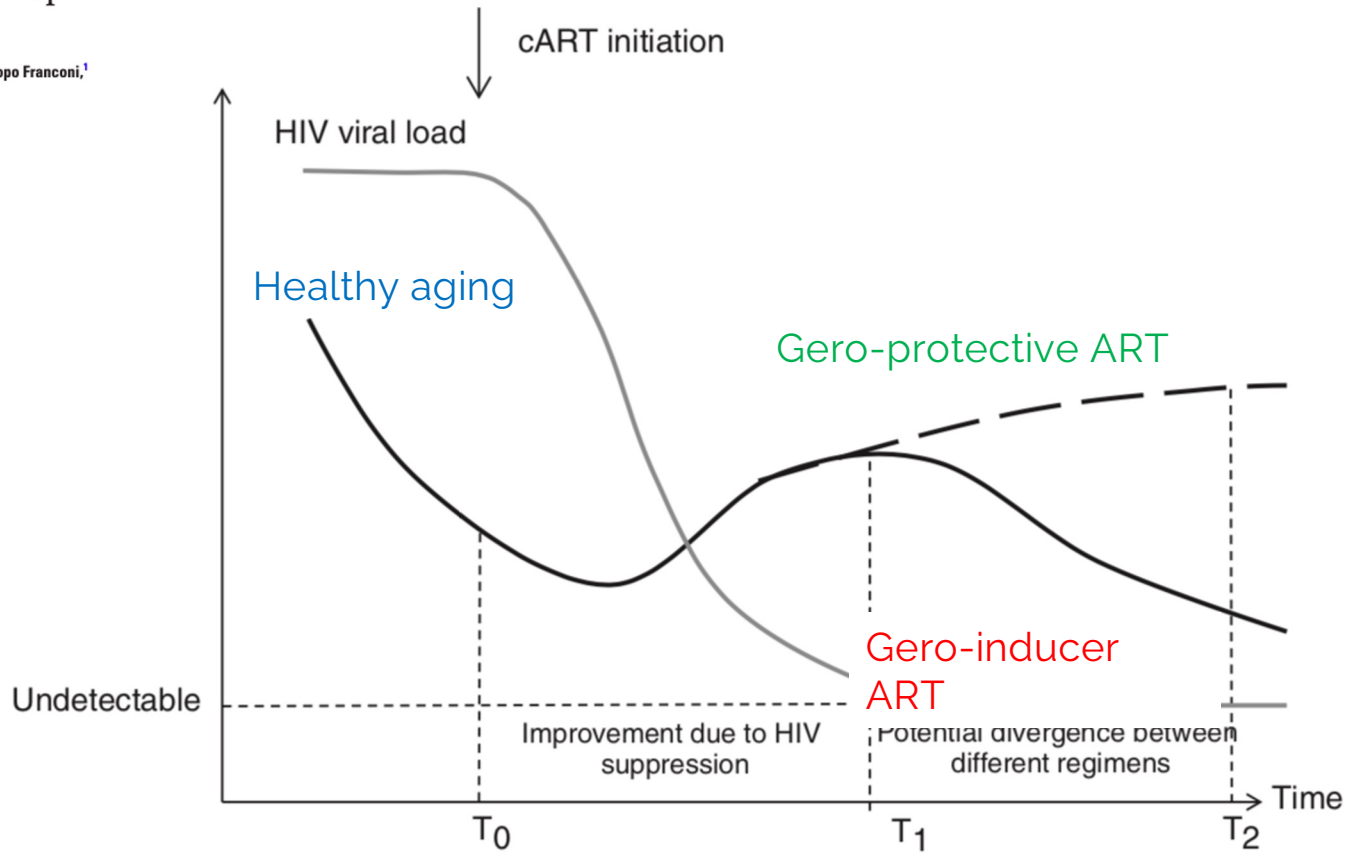
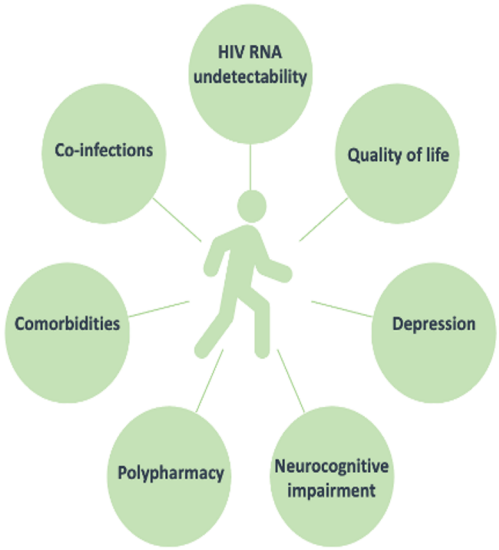
HIV remains a unique model of aging as a paradigm of the competing and opposite forces at the basis of the clinical transitions due to aging



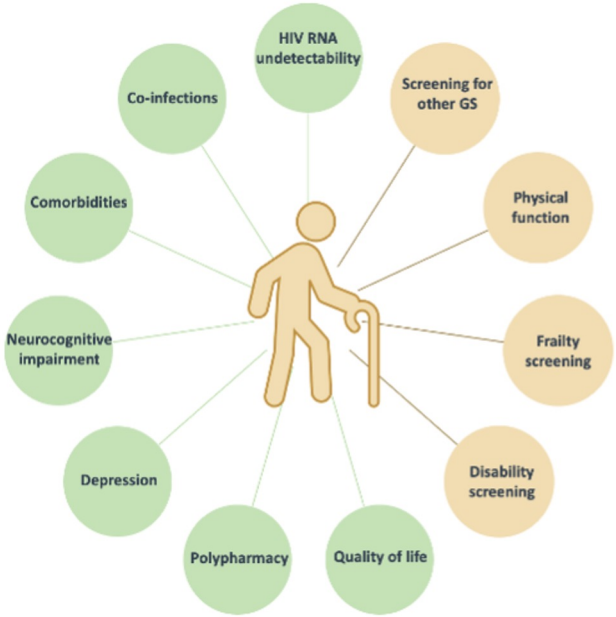
The patient centered HIV care models: what to screen, how to cope



Fit individual

Interventions

- Promote lifestyle interventions
- Introduce primary and secondary prevention
- Proactive ART switch
- Assess DDI
- Promote well-being
- Depression screening
- Fight stigma



Frail individual

Interventions

- Increase awareness and education
- Promote exercise and appropriate nutrition
- Assess inappropriate drug prescription
- Prevent falls
- Treat urinary incontinence
- Fight sarcopenia
- Avoid sedentary life

This «geriatric patient centered HIV model» implies a task shifting of HIV specialist into a health coach promoter

Conclusion

- Aging is a journey different from person to person and it is run at a different speed at a different speed during life course
- Both FP and FI should be used to monitor aging trajectories in PLWH
- Aging trajectories at a population level identify ART as a senomorphic intervention to postpone the onset of frailty
- P4 medicine is the new paradigm for «geriatric patient centered HIV model» which implies a task shifting of HIV specialist into a health coach promoter