HIV & Aging
The frailty

Thierry Pepersack, MD, PhD
Oncogeriatric unit
Institut Jules Bordet
Université Libre de Bruxelles (U.L.B.)
An Epidemic in Evolution: The Need for New Models of HIV Care in the Chronic Disease Era

Chu et al. Journal of Urban Health: Bulletin of the New York Academy of Medicine, Vol. 88, No. 3
What concepts can we share with you?

- Frailty
- Comorbidity
- Potentially inappropriate prescription
- The « geriatric syndrome »
- A new era in medicine
- Compression of morbidity
- Comprehensive assessment & Prevention
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1+2+3 rule

1+2+3 rule

1. Normal aging
2. Chronic diseases
3. Risk factors

Threshold
Disability

Definition(s) frailty

“It is a little like the classic definition of pornography:

- experts may disagree on exactly what it is
- but most people know frailty when they see it”
Definition(s) (frailty)

- There is *no consensus* on the best way to define and identify frailty systematically.
- Frailty is *not really a disease* but rather a combination of the natural aging process and a variety of medical problems and risk factors.

- **Two conceptual models:**
  - the *phenotype model* (Fried)
  - The *cumulative deficit model* (Rockwood)

1. The **Phenotype** model

A. **Characteristics of Frailty**

- Shrinking: Weight loss (unintentional)
- Sarcopenia (loss of muscle mass)
- Weakness
- Poor endurance; Exhaustion
- Slowness
- Low activity

**Cardiovascular Health Study**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Frailty</td>
<td>2469</td>
<td>260</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2480</td>
<td>474</td>
</tr>
<tr>
<td>Frail</td>
<td>368</td>
<td>130</td>
</tr>
</tbody>
</table>

1. The Phenotype model
1. The Phenotype model

Dynamics of frailty

Stable
(Mortality)

51.5% (4.2%)

Robust

40.1%

11.9%

Intermediate

4.2%

58.3% (4.9%)

57.6%

FU 54 m: 57.6% (424) : ≥1 transition

Fried criteria

n=754 (community-dwelling)

24.9%

23.0%

Fragile

63.9% (13.19)
HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls.

Fried’s criteria

Frailty appears to affect HIV-infected patients at a younger age than uninfected individuals.

AGEhIV Cohort Study Group AIDS 2016, 30:241–250
2. The **cumulative deficit model**

- views frailty as a state of *vulnerability*, rather than a syndrome.
- frailty arises from the **cumulative effects of nonspecific age-related health deficits** and does not have a unique pathophysiology but rather is related to the aging process.
- As people accumulate health deficits and *homeostatic mechanisms begin to fail*, those who are frail exhibit excessive changes in health in response to even minor further insults.

2. The **cumulative** deficit model

- describes the overall health state of an individual and therefore serves as an *integrative marker* of *biologic aging*, as opposed to *chronological age*
## Frailty Index (n/70)

### Appendix 1: List of variables used by the Canadian Study of Health and Aging to construct the 70-item CSHA Frailty Index

<table>
<thead>
<tr>
<th>Causes</th>
<th>Causes</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in everyday activities</td>
<td>Mood problems</td>
<td>Seizures, partial complex</td>
</tr>
<tr>
<td>Head and neck problems</td>
<td>Feeling sad, blue, depressed</td>
<td>Seizures, generalized</td>
</tr>
<tr>
<td>Poor muscle tone in neck</td>
<td>History of depressed mood</td>
<td>Syncope or blackouts</td>
</tr>
<tr>
<td>Bradykinesia, facial</td>
<td>Tiredness all the time</td>
<td>Headache</td>
</tr>
<tr>
<td>Problems getting dressed</td>
<td>Depression (clinical impression)</td>
<td>Cerebrovascular problems</td>
</tr>
<tr>
<td>Problems with bathing</td>
<td>Sleep changes</td>
<td>History of stroke</td>
</tr>
<tr>
<td>Problems carrying out personal grooming</td>
<td>Restlessness</td>
<td>History of diabetes mellitus</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Memory changes</td>
<td>Arterial hypertension</td>
</tr>
<tr>
<td>Toileting problems</td>
<td>Short-term memory impairment</td>
<td>Peripheral pulses</td>
</tr>
<tr>
<td>Bulk difficulties</td>
<td>Long-term memory impairment</td>
<td>Cardiac problems</td>
</tr>
<tr>
<td>Rectal problems</td>
<td>Changes in general mental functioning</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>Onset of cognitive symptoms</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Problems cooking</td>
<td>Clouding or delirium</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Sucking problems</td>
<td>Paranoid features</td>
<td>Lung problems</td>
</tr>
<tr>
<td>Problems going out alone</td>
<td>History relevant to cognitive impairment or loss</td>
<td>Respiratory problems</td>
</tr>
<tr>
<td>Impaired mobility</td>
<td>Family history relevant to cognitive impairment or loss</td>
<td>History of thyroid disease</td>
</tr>
<tr>
<td>Musculoskeletal problems</td>
<td>Impaired vibration</td>
<td>Thyroid problems</td>
</tr>
<tr>
<td>Bradykinesia of the limbs</td>
<td>Tremor at rest</td>
<td>Skin problems</td>
</tr>
<tr>
<td>Poor muscle tone in limbs</td>
<td>Postural tremor</td>
<td>Malignant disease</td>
</tr>
<tr>
<td>Poor limb coordination</td>
<td>Intention tremor</td>
<td>Breast problems</td>
</tr>
<tr>
<td>Poor coordination, trunk</td>
<td>History of Parkinson’s disease</td>
<td>Abdominal problems</td>
</tr>
<tr>
<td>Poor standing posture</td>
<td>Family history of degenerative disease</td>
<td>Presence of snout reflex</td>
</tr>
<tr>
<td>Irregular gait pattern</td>
<td></td>
<td>Presence of the palomental reflex</td>
</tr>
<tr>
<td>Falls</td>
<td></td>
<td>Other medical history</td>
</tr>
</tbody>
</table>

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Rockwood K et al. CMAJ 2005;173:489-95
Frailty

- Using both models
- Frailty is associated with age-related deterioration in multiple systems, including:
  - immunosenescence and
  - chronic inflammation (« inflammaging »)


Measuring frailty in HIV+ individuals

- Veterans Aging Cohort Study (VACS) index = prognostic tool made up of both:
  - HIV-related factors:
    - Including CD4 count and viral load,
  - as well as:
    - hepatitis C coinfection, liver fibrosis (FIB-4), hemoglobin, estimated glomerular filtration rate (eGFR), race, and age.
    - + adding measures: inflammatory markers, D-dimer and soluble CD14

VASC index correlates with

- **mortality** in HIV-infected populations *more closely than measures of:*
  - age,
  - CD4 cell count, and
  - HIV RNA level alone.

- **fragility fractures**

- **Coronary heart disease-related mortality**


Factors associated with Frailty among HIV+ individuals on antiviral therapy

- Age
- HIV-related measures
- Longer time since diagnosis
- Lower current CD4 count
- Lower nadir CD4 count
- Low CD4/CD8 ratio
- Detectable viral load
- Longer duration of HAART
- Protease inhibitor-containing HAART regimen
- Comorbidities
- Hepatitis C coinfection
- Low BMI

- High BMI
- Lipodystrophy
- Diabetes
- Kidney disease
- Depressive symptoms
- Cognitive impairment
- Inflammation (IL6, D dimer, sCD14)
- Weak upper and lower extremities
- History of falls
- Social factors
- Lower education
- Current unemployment
- Low income in past year
Factors associated with Frailty among HIV+ individuals on antiviral therapy

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- **Comorbidities**
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What concepts can we share with you?

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- **Comorbidity**
- Potentially inappropriate prescription
- The « geriatric syndrome »
- A new aera in medicine?
- Compression of morbidity?
- Prevention
### What concepts can we share with you?

**Comorbidity**

<table>
<thead>
<tr>
<th>Olders</th>
<th>HIV-infected individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cancers</td>
<td>- Cancers</td>
</tr>
<tr>
<td>- Cardiovascular</td>
<td>- Cardiovascular</td>
</tr>
<tr>
<td>- Immune disorders</td>
<td>- Immune disorders</td>
</tr>
<tr>
<td>- Cognitive disorders</td>
<td>- Cognitive disorders</td>
</tr>
<tr>
<td>- Chronic inflammation</td>
<td>- Chronic inflammation</td>
</tr>
<tr>
<td>- Liver, renal, pulmonary diseases</td>
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*Is HIV infection an example of accelerated aging process?*
What concepts can we share with you?

- Frailty
- Comorbidity
- **Potentially inappropriate prescription**
- The « geriatric syndrome »
- A new era in medicine?
- Compression of morbidity?
- Comprehensive assessment & Prevention
“Attention to the principles of geriatric prescribing is needed as this population ages in order to minimize complications from multiple medication use.”
A Pharmacist-Led Program to Evaluate and Reduce Polypharmacy and Potentially Inappropriate Prescribing in Older, HIV-Positive Patients
What concepts can we share with you?

- Frailty
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- **The « geriatric syndrome »**
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The « Geriatric syndromes»: Delirium, Falls, Incontinence, PIP….

- **Definition**
  - Prevalence increases with aging
  - Impact
    - Qol
    - Functional autonomy
  - Polyfactorial
    - Multiple diseases
    - Multiple risk factors
  - Manifestation of frailty
Geriatric Syndromes: Clinical, Research, and Policy Implications of a Core Geriatric Concept

Sharon K. Inouye, MD, MPH, Stephanie Studenski, MD, Mary E. Tinetti, MD, and George A. Kuchel, MD

The way we were...

1973

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<tr>
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<th>PATHOGENESIS</th>
<th>PRESENTING SYMPTOMS</th>
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</thead>
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<tr>
<td>Disease</td>
<td>Known</td>
<td>Known</td>
<td>Known, but variable in presentation</td>
</tr>
<tr>
<td>Syndrome 1</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Defined set of signs</td>
</tr>
<tr>
<td>Syndrome 2</td>
<td>Unknown</td>
<td>Known</td>
<td>Defined set of signs</td>
</tr>
<tr>
<td>Syndrome 3</td>
<td>Known</td>
<td>Unknown</td>
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Geriatric syndrome

Multiple aetiological factors → Interacting pathogenetic pathways → Unified manifestation

JAGS 2007;55:780-791
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**Geriatric syndrome**

Multiple aetiological factors → Interacting pathogenetic pathways → Unified manifestation

JAGS 2007;55:780–791

2017

The way we are...
The way you are managing HIV+ > 50yrs!

Geriatric Syndromes in Older HIV-Infected Adults

Meredith Greene, MD, MD, Kenneth E. Covinsky, MD, MPH, Victor Valcour, MD, PhD, Yinghui Miao, MD, MPH, Joy Madamba, BS, Harry Lampiris, MD, Irena Stijacic Cenzer, MA, Jeffrey Martin, MD, MPH, and Steven G. Deeks, MD
What concepts can we share with you?

*Geriatric syndromes*

**Olders >75 yrs**
- Cognitive
- Falls
- Malnutrition
- Potentially inappropriate prescription
- Social complexity
- Functional decline
- Falls and fractures
- Etc…

**HIV >50 yrs**
- Cognitive
- Falls
- Malnutrition
- Potentially inappropriate prescription
- Social complexity
- Functional decline
- Falls and fractures
- Etc…

*Curr Opin HIV AIDS. 2016 September; 11(5): 527–536. doi:10.1097/COH.0000000000000305*
HIV-infected adults age 50 and older who had an undetectable viral load on antiretroviral ART...
HIV-infected adults age 50 and older who had an undetectable viral load on antiretroviral ART.
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Development of new conceptual models

Development of new conceptual models

A. Traditional model:
   OK for conditions such as inborn errors of metabolism
B. **Concentric model**
More effective for cancer treatments by targeting multiple distinct oncogenic pathways
Development of new conceptual models

C. Interactive Concentric model
Reconcils the need for mechanistic research with the conditions’ multifactorial complexity by focusing on pathways associated with risk factor synergisms, thus offering a locus for the design of targeted interventions.
The perception that the disease model is “truth” rather than a previously useful model will be a barrier as well. Notwithstanding these barriers, medical care must evolve to meet the health care needs of patients in the 21st century.

Moving from standard care of ageing HIV-positive patients to care that incorporates key geriatric principles.
The boxes illustrate elements amongst HIV-positive patients that may further contribute to disease and condition in ageing. Within the circle ...
An Epidemic in Evolution: The Need for New Models of HIV Care in the Chronic Disease Era

Chu et al. Journal of Urban Health: Bulletin of the New York Academy of Medicine, Vol. 88, No. 3
What are the concepts we can share?

*Compression of morbidity*

- Frailty
- Comorbidity
- Potentially inappropriate prescription
- The « geriatric syndrome »
- A new aera in medicine
- *Compression of morbidity?*
- Comprehensive assessment & Prevention
This hypothesis holds that if the age at the onset of the first chronic infirmity can be postponed more rapidly than the age of death, then the lifetime illness burden may be compressed into a shorter period of time nearer to the age of death.
Compression of morbidity hypothesis

Detect frailty, prevention

Detect frailty before disability, propose prevention, compress morbidity!

Compression of morbidity hypothesis

REFERENCES


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*Comprehensive assessment*

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- A new aera in medicine?
- Compression of morbidity?
- Comprehensive assessment & Prevention
Comprehensive geriatric assessment

- «Comprehensive Geriatric Assessment»
  - medical
  - psycho-social
  - functional
  - Environnemental
  - Nutritional
- assessments
- Improves survival and autonomy

Stuck AE et al. Lancet 1993;342:1032-36
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- Comprehensive assessment & Prevention
Change our mind!

1973
The way we were...

2017
The way we are...

Thank you!

thierry.pepersack@bordet.be
What concepts can we share with you? **ALL !**

- Frailty
- Comorbidity
- Potentially inappropriate prescription
- The « geriatric syndrome »
- A new era in medicine?
- Compression of morbidity?
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**Why?**
The HIV-specific ‘Pillars of Aging’

Similarities Between HIV Disease and Normal Aging

- Syndromes
- Frailty phenotype associated with obesity
- Cardiovascular pathology–vascular stiffness/calcifications, diastolic dysfunction
- Multimorbidity and polypharmacy
- Bone loss and fragility fractures
- Prevalent chronic renal insufficiency
- Thymic involution—loss of naive T-cell production
- Immune senescent phenotype—accumulation of end-stage (short telomeres, CD28−) effector T cells with senescence-associated secretory phenotype
- Prevalent low-level inflammation
- Sarcopenia–muscle loss/fatty infiltration in muscle, reduced power and contractile force


Hypothetical age-at-diagnosis distributions of cancer in the AIDS and general populations

(A) **Accentuated**: cancer occurs at the same ages but **more often** among HIV-infected participants than among HIV-uninfected comparators.

(B) **Accelerated and accentuated**: cancer occurs **earlier** among HIV-infected participants compared with HIV-uninfected comparators and there are **more** cancer events.


Similarities Between HIV Disease and Normal Aging

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Differences Between HIV Disease and Normal Aging

- Increased substance abuse, smoking, mental health issues, and social isolation in HIV
- **HIV increases the risk of many cancers, but does not increase the risk of the two most, influenced by age—breast and prostate, cancer**
- HIV infection typically absent in aging—HIV replication not a source of immune activation or inflammation in aging
- Antiretroviral therapy confounds aging in the presence of HIV

Is HIV-infection a Model of Accelerated or Accentuated Aging?

Comparative risk of hypertension, diabetes mellitus, renal failure, cardiovascular disease, and fracture, by age, among HIV-infected participants versus control participants.

**there is an extra “hit” by HIV and/or ART—that is, accentuated aging**

Does HIV-infection accelerate or accentuated aging?

- The answer is probably *organ and disease/condition specific*.
  - For many processes, there appears to be a *pattern of accelerated aging*.
  - This is most clear in the immune system
    - where T-cell TL and CDKN2A expression, accumulation of CD28−CD8+ T cells, reduced naive T-cell generation, and evidence on ongoing immune activation strongly suggest *accelerated immune senescence*.

Does HIV accelerate or accentuate aging?

- The answer is probably *organ and disease/condition specific*.
  - the development of specific *geriatric syndromes* such as multimorbidity, frailty, and polypharmacy are hastened in those with HIV.
  - In specific end-organ diseases, it is less clear, but many illnesses appear to be accentuated rather than accelerated:
    - Cardiovascular disease, diabetes, and several other conditions are more prevalent at all ages in those with HIV, suggesting there is an extra “hit” by HIV and/or ART—that is, accentuated aging.