Clinical Epidemiology of Frailty in HIV Infection

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HIV and Aging

4 Similarities between HIV and aging at the biological level
  • T-lymphopenia, decreased cellular immunity
  • Replicative senescence of T-lymphocytes
  • È pro-inflammatory markers (IL-6, TNF-α, IFN-γ)

4 Similarities between HIV and aging at the clinical level
  • Sarcopenia, weight loss, wasting
  • Cognitive disorders, dementia
  • Rheumatologic disorders, decrease in bone mineral density
  • Frailty-like clinical presentation presaging disability and death
Frailty: A Brief Overview

**Definition**

“A central definition of frailty in geriatric medicine is that it is a clinical state of vulnerability to stressors, [...] resulting from aging-associated declines in resiliency and physiologic reserves and a progressive decline in the ability to maintain a stable homeostasis.” [1]

Frailty is a predictor of poor outcomes

- Falls
- Hospitalization
- Institutionalization
- Disability
- Mortality [2]

Frailty in HIV Infection: Why Is It Important?

4 Associated with adverse outcomes in non-HIV populations, and probably in HIV+

4 Associated with untreated HIV, but may persist even after HAART and viral suppression
  • Treatment may contribute to frailty development

4 May be treatable or preventable

4 Better understanding of mechanisms would inform treatment and studies of non-HIV frailty
Frailty: How Is It Recognized?

Definition of Frailty Phenotype: An individual is “frail” if ≥ 3 components of these 5 are present:

- Physical shrinking (unintentional weight loss)
- Weakness (grip strength)
- Exhaustion (self-reported)
- Slowness (time to walk 15 feet)
- Low physical activity level (weighted score of kcal/week)

Validated phenotype and medical syndrome [2]

Frailty in the MACS (1994-2005)

Definition of a frailty-related phenotype (FRP)

- The FRP definition was based on the frailty phenotype of Fried et al.

- Components of the frailty phenotype:

  - Physical shrinking (unintentional weight loss) - available
  - Weakness (grip strength) - not available *
  - Exhaustion (self-reported) - available
  - Slowness (time to walk 15 feet) - approximated (SF-36) *
  - Low physical activity level - approximated (SF-36)
    (a weighted score of kilocalories/week)

Exhaustion: During the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra effort)?

Slowness: Does your health now limit you in walking several blocks?

Low physical activity: Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?

* Grip strength and walking speed assessed directly in the MACS since 2006

Studies of a Frailty-Related Phenotype (FRP) in the Multicenter AIDS Cohort Study (MACS)

4 4954 MSM (HIV- as well as HIV+) followed semiannually since 1984
4 The FRP was present if ≥ 3 of the above 4 components were answered “yes” (#1 and #2) or “yes, limited a lot” (#3 and #4)
4 Covariates: Age, Education, Ethnicity, CD4 cell count, HIV RNA
4 Study population
   • MACS individuals enrolled before 1996
   • Seroconverter and seroprevalent men
   • ≥ 1 measurement of CD4 cell count between visit 21 and visit 41
4 Visits:
   • All HIV+ visits between visit 21 and visit 41
4 Final study population: N = 1045 (N person-visits = 12,916)
   • 98 men had no measurement of CD4 count
The image presents a logistic regression analysis of the Frailty-Related Phenotype (FRP) and duration of HIV infection during the Pre-HAART era. The graph illustrates the odds ratio [95% CI] to manifest the FRP as a function of the duration of HIV infection in years. The odds ratios and confidence intervals are as follows:

- 0 years: Ref
- 0-4 years: 3.4 [1.2-9.1]
- 4-8 years: 13.0 [6.6-25.4]
- 8-12 years: 14.7 [7.6-28.4]

The same FRP prevalence is observed between a 55-year old man infected < 4 years and a >65-year old uninfected man.

*Logistic regression models (GEE)
Relationship between CD4 T-cell count and Prevalence of Frailty-Related Phenotype (FRP), by Calendar Period

Effect of Age on Prevalence of Frailty-Related Phenotype (FRP) by CD4 T-Cell Count

Prognostic Effect of FRP on HAART Response
(AIDS-free at HAART Initiation)

% Alive without clinical AIDS

Logrank p-value < 0.01

Time since HAART initiation (years)

Desquilbet L et al, unpublished, not for citation
Impact of FRP in the 3 years before HAART initiation on subsequent clinical AIDS or death among 596 men enrolled in the MACS, using multivariate Cox models.

<table>
<thead>
<tr>
<th>Exposures at HAART initiation</th>
<th>AIDS-free at HAART (N=472)</th>
<th>AIDS at HAART (N=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aHR(^1) (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Education ≥ college</td>
<td>1.01 (0.64 - 1.62)</td>
<td>0.96</td>
</tr>
<tr>
<td>Ethnicity = White non Hispanic (vs others)</td>
<td>1.32 (0.65 - 2.68)</td>
<td>0.45</td>
</tr>
<tr>
<td>Age (per 10 years increase)</td>
<td>1.43 (1.03 - 1.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Nadir CD4+ T-cell count (per 100 cell/mm(^3) increase)(^3)</td>
<td>0.85 (0.72 – 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Maximum plasma viral load (per 1 log(_{10}) copies/ml increase)(^3)</td>
<td>2.08 (1.35 - 3.21)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Proportion of FRP visits before HAART (for a 25% increase)(^3)</td>
<td>1.35 (1.01 - 1.80)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

FRP, frailty-related phenotype; aHR, hazard ratios adjusted for variables listed in the table; CI, confidence interval; \(^1\) adjusted hazard ratios for AIDS/death; \(^2\) adjusted hazard ratios for death only; \(^3\) within the 3 years before HAART
Frailty-Related Phenotype (FRP) in the MACS- Summary

HIV-1 infection was associated with a >10-year earlier occurrence of a phenotype related to frailty (FRP) [1]

Non-linear association between CD4 cell count and FRP

Risk of FRP increased with decreasing CD4 cell count, especially when CD4 cell count < ~400/mm³ [2]

After adjusting for age and CD4 cell count, FRP prevalence decreased after the introduction of HAART, but has not further diminished with the establishment of HAART [2]

Older age, lower educational level, and clinical AIDS were independently associated with FRP among HIV+ men [1]

Proportion of visits with FRP prior to HAART initiation independently predicted the subsequent risk of AIDS or death, even after HIV suppression

True Frailty Phenotype is under investigation.

The Aging Phenotype and the Genesis of Geriatric Syndromes

### Aging Phenotypes
- Changes in Body Comp
- Discrepancy Energy Production/Utilization
- Homeostatic Dysregulation
- Neurodegeneration

### Disease Susceptibility
- Reduced Functional Reserve
- Reduced Healing Capacity
- Unstable Health
- Failure to Thrive

### Geriatric Syndromes
- Gait Disorders
- Falls
- Disability
- Sarcopenia
- Urinary Incontinence
- Sleep Disorders
- Cognitive Impairment
- Delirium
- Decubitus Ulcers

Ferrucci L. – Unpublished (do not cite)
FIG. 1. Changes from baseline in body weight and body composition in placebo- and testosterone-treated men

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<table>
<thead>
<tr>
<th>HIV-infected subjects, n = 259</th>
<th>Estimate (β)</th>
<th>$R^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (kg)</td>
<td>25.2079461</td>
<td>0.649</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Respiratory Quotient (CO₂ prod/O₂ consumption)</td>
<td>-654.23617</td>
<td>0.665</td>
<td>.004</td>
</tr>
<tr>
<td>Dietary carbohydrate (g)</td>
<td>.43184009</td>
<td>0.674</td>
<td>.027</td>
</tr>
<tr>
<td>CT VAT (cm²)</td>
<td>.68024196</td>
<td>0.689</td>
<td>.004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control subjects, n = 119</th>
<th>Estimate (β)</th>
<th>$R^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (kg)</td>
<td>22.6017946</td>
<td>0.722</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CT VAT (cm²)</td>
<td>.99145624</td>
<td>0.806</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total body fat (kg)</td>
<td>12.541516</td>
<td>0.812</td>
<td>.048</td>
</tr>
<tr>
<td>CT SAT (cm²)</td>
<td>-.6914458</td>
<td>0.818</td>
<td>.051</td>
</tr>
</tbody>
</table>

BMR= 108±1% Predicted (p<.0001)
BMR= 98±1% Predicted

Fitch et al, Metabolism: Clinical and Experimental 2009; 58:608-15
Reduction in aerobic capacity (VO2) in HIV-infected patients aged 30–80 years

Effros et al, 2008; CLIN INFECT DIS 47:542-553; from Oursler et al. [100]
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FRAILTY

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Ferrucci L. – Unpublished (do not cite)
Risk of Incident Diabetes Mellitus in the Multicenter AIDS Cohort Study (1999-2003)

4 fold increased risk of DM in HAART-treated men

* Adjusted for age and BMI at study entry

Brown et al, Arch Int Med, 2005
Insulin Sensitivity and Visceral Adipose Tissue in HIV-infected Patients with Lipodystrophy

Hadigan, Am J Phys Endo and Metabolism, 2006
PI-induced Changes in Adipocyte

↑ TNF-α, IL-6
↓ Adiponectin

↑ Lipolysis

↑ Free Fatty Acids

Impaired Insulin Signaling

Systemic Steatosis
# Homeostatic Systems Disrupted in HIV Infection

<table>
<thead>
<tr>
<th>System</th>
<th>Untreated</th>
<th>Treated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>X</td>
<td>X</td>
<td>“functional” homeostasis</td>
</tr>
<tr>
<td>Glucose</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>X</td>
<td>minimal</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Even if a system looks normal, need to know
- how hard it is working to maintain that appearance!
- if it can recover after a stress or injury
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Ferrucci L. – Unpublished (do not cite)
Additive Effect of Aging and HIV on Brain Function

Conclusions

4 Frailty appears to be measurable in HIV+ populations; impact may be serious
4 Longitudinal studies are needed to evaluate mechanisms, prognostic impact, treatment, and prevention of frailty, and the role of ART
  • Residual immune activation, chronic infections, aging itself
  • Further studies of normal homeostatic mechanisms and their perturbation by HIV and ART
4 Proper comparison groups will be critical for these studies
4 More studies are needed to assess aging phenotypes in HIV-infected people
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