

Frail and pre-frail phenotype is associated with pain in older HIV-infected patients

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Abstract

As HIV-infected patients grow older, some accumulate multiple health problems earlier than the noninfected ones in particular frailty phenotypes. Patients with frailty phenotype are at higher risk of adverse outcomes (worsening mobility, disability, hospitalization, and death within three years).

Our study aimed to evaluate prevalence of frailty in elderly HIV-infected patients and to assess whether frailty is associated with HIV and geriatric factors, comorbidities, and precariousness in a French cohort of older HIV infected.

This 18-month cross-sectional multicenter study carried in 2013 to 2014 had involved 502 HIV-infected patients aged 50 years and older, cared in 18 HIV-dedicated hospital medical units, located in South of France.

Prevalence of frailty was 6.3% and of pre-frailty 57.2%. Low physical activity and weakness were the main frailty markers, respectively 49.4% and 19.9%. In univariate models, precariousness, duration of HIV antiretroviral treatment >15 years, 2 comorbidities or more, risk of depression, activities of daily living disability, and presence of pain were significantly associated with frail and pre-frail phenotype. Multivariate logistic regression analyses showed that only pain was significantly different between frail and pre frail phenotype versus non frail phenotype (odds ratio = 1.2; $P = .002$).

Our study is the first showing a significant association between pain and frailty phenotype in older patients infected by HIV. As frailty phenotype could be potentially reversible, a better understanding of the underlying determinant is warranted. Further studies are needed to confirm these first findings.

Abbreviations: ADL = activities of daily living, BMI = body mass index, EPICES = Evaluation of Precarity and Inequalities in Health Examination Centers score, GDS = Geriatric Depression Scale, HIV = human immunodeficiency virus, PHIV = people living with HIV, VAS = visual analogic scale.

Keywords: frailty phenotype, geriatric assessment, HIV-aging, pain, precariousness

1. Introduction

The increasing life-span of people living with HIV (PHIV) presents new challenges related to aging.^[1] As PHIV grow older,

some experience multimorbidity, polypharmacy, altered physical function earlier than the noninfected ones.^[2–5]

These problems are not totally explained by age, severity of the HIV disease or duration, or toxicity of antiretroviral drugs. Literature suggests that frailty phenotype could be a marker of this variability between PHIV.^[6] Using data from the Cardiovascular Health Study, Fried et al identified 5 frailty markers: nutrition, weakness, slowness, energy, and physical activity.^[7] They reported that older persons with at least 3 of the 5 frailty markers have a significantly increased risk of suffering from adverse outcomes such as falls, worsening mobility, disability, hospitalization, and death within 3 years. Moreover, the presence of at least one of these markers confers an increased risk of adverse outcomes.^[7,8] Since 2001, in various context and population, such as cancer, cardiovascular diseases and osteoporosis, the Fried phenotype has demonstrated its capacity to predict adverse outcomes.^[9] Desquilbet et al first has shown that HIV infection was associated with an earlier occurrence of a phenotype related to frailty.^[3]

VISAGE is a French multidisciplinary study group focusing on elderly PHIV.^[10,11] Our study “VISAGE-3” aimed to evaluate prevalence of frailty in elderly PHIV and to assess whether frailty is associated with HIV and geriatric factors, comorbidities, and deprivation in a French cohort of older PHIV.

2. Methods

2.1. Study design

This 18-month cross-sectional observational multicenter study carried in 2013 to 2014 involved PHIV aged 50 years and older,

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cared in 18 HIV-dedicated hospital medical units, located in south of France. All patients provided a written consent for their participation to the study. Patients unable to answer a questionnaire or unable to do walking tests were excluded from the study.

Age, sex, body mass index (BMI), HIV data, socioeconomics and behavior factors, geriatric assessment, comorbidities, and frailty markers were collected by questionnaires and measures.

2.2. HIV data

Duration on HIV, CDC stage, last and nadir CD4 cell count, undetectable last viral load, and start of antiretroviral therapy (>15 years) were collected.

2.3. Socioeconomic and behavior factors

Level of education, incomes and professional activity, smoking, alcohol and drugs consumption were collected. To assess deprivation, the French social validated EPICES (Evaluation of Precarity and Inequalities in Health Examination Centers) score was used.^[12] This score is calculated according to an algorithm based on the responses to 11-item questionnaire exploring socioeconomic individual deprivation. It varies from 0 (the least deprived) to 100 (the most deprived). A deprivation state is defined as a score ≥ 30 .^[13]

2.4. Comorbidities

Number and type of comorbidities were collected. Hepatitis C or B, cancers (acquired immune deficiency syndrome [AIDS] or not AIDS-related), cardiovascular diseases (atrial fibrillation, cardiac failure, coronary disease, ischemic cerebrovascular diseases), chronic kidney disease, chronic obstructive pulmonary disease, lipodystrophy, dyslipidemia, diabetes, hypertension, psychiatric, and osteoarthritis diseases were recorded from the medical chart.

2.5. Geriatric assessment

The functional status was assessed using 6 tasks of the Katz index of activities of daily living (ADL). Disability was defined as the need for assistance to complete at least one ADL.^[14] The 4-item Geriatric Depression Scale (mini GDS) was used to screen a risk of depression. A score of ≥ 1 indicated a risk of depression.^[15] Patients who had experienced ≥ 1 falls in the previous 6 months were considered to have a positive history of falls. Visual analogic scale (VAS, from 0 to 10) was used to assess pain.

2.6. Frailty markers

The 5 frailty markers adapted from the Fried phenotype were recorded: nutrition, energy, weakness, physical activity, and slowness.

- Nutritional status was assessed by the question: "In the last year, have you lost more than 4 kilograms unintentionally". An affirmative answer to the question indicated a positive marker of frailty for nutrition.^[7]
- Energy was assessed using a visual scale ranging from 0 (no energy) to 10 (full of energy). A score < 3 indicated a positive marker of frailty for energy.^[8]
- Weakness was assessed by the maximal value of 3 measurements of grip strength (in kilograms) in the dominant hand using a Jamar handheld dynamometer. The lowest quintile by

sex and BMI was considered a positive marker of frailty for weakness.^[7]

- Physical activity was assessed by a validated self-report question from the Canadian Study of Health and Aging Risk Factor Questionnaire.^[16] No exercise or a low level of exercise was considered a positive marker of frailty for physical activity.
- Slowness was assessed by gait speed (time to walk 4 m). Score under 0.8 m/s indicated positive marker for slowness.^[7,17]

Patients who had ≥ 3 markers were classified as frail, patients with 1 or 2 markers as pre-frail, and patients with no markers as not-frail.^[7]

2.7. Data analysis

Sample characteristics were detailed using mean/standard deviations for quantitative variables, and frequencies for qualitative variables. Two groups of individuals were constituted: "non-frail" (no marker of Fried phenotype); "frail and pre-frail" (≥ 1 marker). Comparisons between the 2 groups were performed using Student *t* tests for quantitative variables, and χ^2 or Fisher exact tests for frequencies. Multivariate analysis using logistic regression models was performed to determine variables potentially linked to frail profile, using a forward stepwise approach. Variables relevant to the models were selected on their clinical interest and/or a threshold *P* value $\leq .2$ during univariate analysis. Variables selected were age, sex, school diploma, deprivation, start of HIV therapy, comorbidities, depression, disability, and pain (*P* $< .20$). The final model expressed the odds ratios and 95% confidence intervals. All the tests were 2-sided. Statistical significance was defined as *P* $< .05$. The statistical analyses were performed using the SPSS version 17.0 software package (SPSS Inc, Chicago, IL).

2.8. Ethical statement

All the participants gave their written informed consent to participate. The study was promoted by the Clinical Research Department of Assistance Publique-Hôpitaux de Marseille (AP-HM) and approved by the French Consultative Committee for the Protection of Persons consenting to biomedical research (CCPP South Mediterranean Marseille I; registration number: 2011-A01679-32) and by the French Agency of Sanitary Security for Health Products (ANSM; registration number: B111670-40).

3. Results

A total of 509 PHIV were screened among whom 502 were included: 365 (72.7%) men and 137 (27.3%) women. The 7 patients excluded because of a lack of data were 5 men and 2 women.

Sixty percent of patients were between 50 and 59 years. HIV-infection lifetime was ≥ 25 years for one-fourth of the PHIV. Nadir CD4 count was < 200 cells/mm³ for almost half the PHIV and 438 (87.3%) had undetectable viral load. Almost one-fourth (23.7%) was at AIDS stage. Concerning the weight, on-third (34.4%) were overweight or obese (BMI ≥ 25). Tobacco consumption was high (61.5%). Almost half (49.0%) of PHIV had deprivation.

The prevalence of frailty and pre-frailty were 6.3% and 57.2%, respectively. Low physical activity and weakness were the main frailty markers, respectively, 49.4% and 19.9% (Table 1).

The 3 main comorbidities were: dyslipidemia (36.7%), lipodystrophy (30.3%), and hepatitis B or C (26.1%). More

Table 1
Baseline frailty's 5 markers.

	Total	Frail	Pre-frail
	502 (100%)	32 (6.3%)	291 (57.2%)
Low physical activity	248 (49.4%)	31 (96.9%)	215 (73.9%)
Weakness	100 (19.9%)	30 (93.8%)	70 (24.1%)
Nutrition/weight loss	66 (13.1%)	13 (40.6%)	53 (18.2%)
Poor energy	36 (7.2%)	16 (50.0%)	20 (6.9%)
Slowness	26 (5.2%)	10 (31.3%)	16 (5.5%)

than half (60.4%) had ≥ 2 or comorbidities and more than one-third had ≥ 3 or more comorbidities.

In univariate model, deprivation, start of antiretroviral therapy >15 years, ≥ 2 or more comorbidities, lipodystrophy, risk of depression, ADL disability, and presence of pain were significantly associated with frail and pre-frail phenotype (Table 2). Multivariate logistic regression analyses (67.1% of prediction; chi-square=26.954, df=10, $P=.003$; the -2 log likelihood=508.009, Cox and Snell R Square at 0.06) with age and variables $P < .20$ showed that only pain was significantly different between frail and pre-frail phenotype versus non-frail phenotype ($P=.002$) (Table 2).

4. Discussion

4.1. Main findings

In this study, two-thirds of PHIV had at least 1 frailty markers. All previous studies in HIV population, except the one performed by Kooij et al in 2016 had focused on presence of ≥ 3 markers.^[6,18] However, in her cohort, Fried has emphasized

that the pre-frail group (1 or 2 frailty markers) was also at risk for these outcomes (intermediate risk) and at risk for subsequent frailty. Then, assessing the presence of any frailty markers seems to be meaningful in PHIV, especially as all studies on the prevalence of the frailty phenotype demonstrate that it occurs about 10 years earlier than in the general population.^[13]

Using the phenotype approach, previous studies have shown that frailty phenotype is frequently associated in HIV infected patients with several comorbidities such as HCV co-infection, diabetes or kidney disease, cognitive impairment, depressive symptoms, with low socio-economic status (shorter formal education, unemployed, or with lower incomes) and HIV measures (current and nadir CD4 cell count, detectable HIV RNA viral load, duration on HAART therapy).^[19-28] These data are the basis of our starting hypothesis.

In the AGEHIV cohort, Kooij et al did not find any relationship between frailty and duration of VIH, nadir of CD4, last CD4 level, antiretroviral exposure as in our study, although their population was younger (mean age 52.8 years, one-third <50) and had low BMI.^[18] In our study, only presence of pain was significantly associated with the presence of any frailty markers.

In a previous study of our group, we found that >60% of PHIV used paracetamol regularly suggesting that pain is a major concern in this population.^[20,21] Recent literature questioned the role of pain in frailty phenotype.^[29,30] In a cross-sectional study including 252 community dwelling elderly, Coelho et al^[31] found that pain predicted 5.8% of the variance of frailty, 5.9% of the variance of physical frailty, 4.0% of the variance of psychological frailty, and intensity of pain was significantly associated with an increase of frailty. In a literature review, Nessighaoui et al, found 12 cross-sectional studies which directly examined the relationship between frailty and pain. Only one did not found a link between frailty and pain.^[32] This study used the frail index

Table 2
Associations of sociodemographic, HIV infection, number of comorbidities, health baseline characteristics with frailty and pre-frailty.

	Frail+pre-frail (1) n=323	No frail (2) n=179	(1+2) n=502	P*	OR (95% CI)	P**
Sex Male	228 (70.6%)	137 (77.0%)	365 (72.9%)	.14	0.96 (0.59; 1.57)	.89
Age, y	59.2 +/- 7.2	59.6 +/- 7.1	59.3 +/- 7.1	.60	0.99 (0.96; 1.02)	.63
BMI	24.3 +/- 4.4	24.0 +/- 3.0	24.2 +/- 4.0	.54		—
Professional activity	108 (35.4%)	73 (42.4%)	181 (37.9%)	.14	1.01 (0.62; 1.64)	.94
High school diploma	170 (56.3%)	101 (59.1%)	271 (57.3%)	.56		—
Alcohol	53 (16.6%)	23 (13.1%)	76 (15.4%)	.31		—
Tobacco	203 (63.4%)	101 (58.0%)	304 (61.5%)	.24		—
Drug use	76 (23.5%)	42 (23.5%)	118 (23.5%)	.92		—
Deprivation	164 (52.1%)	76 (43.4%)	240 (49.0%)	.067	0.95 (0.59; 1.51)	.83
HIV data:						
HIV-infection ≥ 25 y	75 (23.4%)	49 (28.3%)	124 (25.2%)	.23		—
Nadir CD4 <200 cells/mm ³	145 (48.5%)	75 (45.7%)	220 (47.5%)	.57		—
Last CD4 /mm ³ >350	283 (87.9%)	151 (86.3%)	434 (87.3%)	.61		—
Undetectable last viral load	281 (87.5%)	157 (88.2%)	438 (87.8%)	.83		—
Aids stage	77 (25.0%)	35 (21.3%)	112 (23.7%)	.43		—
ARV therapy >15 years	188 (62.5%)	85 (52.8%)	273 (59.1%)	.04	0.79 (0.51; 1.23)	.031
≥ 2 Comorbidities	209 (64.7%)	94 (52.5%)	303 (60.4%)	.008	0.78 (0.49; 1.23)	.30
Geriatric assessment:						
Risk of depression	141 (44.3%)	55 (30.9%)	196 (39.5%)	.003	0.72 (0.44; 1.16)	.18
Falls last past 6 mo	40 (12.4%)	15 (8.4%)	55 (11.0%)	.17	0.90 (0.44; 1.81)	.77
ADL disability	33 (10.4%)	6 (3.4%)	39 (7.8%)	.005	2.56 (0.94; 7.02)	.07
Pain score/10 (VAS)	2.4 +/- 2.7	1.4 +/- 2.1	2.1 +/- 2.6	<10-3	1.15 (1.05; 1.27)	.002

Data are represented as means \pm SD and n (%). Deprivation measured by EPICES Score. 95% = CI 95% confidence interval, ADL = activities of daily living, ARV = antiretroviral, BMI = body mass index, OR = odd ratio, VAS = visual analogue scale.

* P-value univariate analysis.

** P-value multivariate analysis.

instead of frailty phenotype which may explain different results because of a different assessment tool. Today no study has found this relationship in PHIV.

Frailty syndrome is usually considered a reversible condition, thus amenable of specific preventive interventions.^[33] Extensive literature focused on nutrition and physical activities.^[34,35] However, persistent pain in older adult population is very common and has multiple determinants. Pain may represent a relevant risk factor, easily accessible, as well as a potential target for interventions. Longitudinal studies are required to better understand the possible association between pain and frailty in PHIV.

4.2. Strengths and limitations

Our study presents several strengths. We used validated self-report and performance tests. We explored original domains such as deprivation, geriatric assessment and pain related to frailty which is a growing concern among PHIV. However, our study has potential limitations. We have selected patients for whom the frailty criteria were measurable, as described by Fried. This limit is inherent to the measurement tool. Nevertheless, excluding frail patients, especially those who were unable to answer a questionnaire or unable to do walking test, avoid to overestimate the prevalence of frailty. Our study was performed exclusively in the South of France. Although frailty prevalence is likely to vary across Europe, it is the first time that it is estimated on a regional scale in France and on PHIV. The lack of a reference group is explained by the preliminary nature of our report which is the starting point of a longitudinal study aiming to estimate the evolution of frailty over the years in this cohort.

5. Conclusion

Our study is the first to describe a link between pain and frailty in older HIV patients. It is a new additional marker of frailty in HIV patients. This observation should be confirmed by further studies. It would be interesting to have more practical frailty scores in order to perform them during routine medical examination. As reduced physical activity concerns half of our cohort, we could hypothesize that increasing physical activity by pain reduction could reverse the frail phenotype in most HIV patients.

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