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MAJOR ARTICLE

One-year frailty transitions among persons living with HIV aged 70 years or more on antiretroviral treatment

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Background: People living with HIV (PLWH) are aging. Frailty is an age-related condition predictive of hospitalization and mortality. Here, we assessed the frequency and factors associated with frailty transitions at one-year follow-up in elderly PLWH.

Method: 508 PLWH aged 70 years or older, on antiretroviral treatment, were included in the French multicenter SEPTAVIH study in 2019-2020. Participants were classified as robust, prefrail or frail according to Fried frailty phenotype, at baseline and at one year. Logistic regression models were used to evaluate socioeconomic or medical factors associated with

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transition between frailty states. Models were adjusted for gender, age at baseline, education, and period of HIV diagnosis (before versus after 1996).

**Results:** 17 PLWH died during the one-year follow-up. Of the remaining 491 PLWH, aged 73 years in median, frailty status worsened for 18% of participants and improved for 14% at one year. Advanced age, baseline CD4+ T-cell count below 350 cells/mm³ and type 2 diabetes were associated with transition from prefrailty to frailty: adjusted odds ratio (aOR) 1.10 per a one-year positive difference [95% confidence interval (CI): 1.01; 1.20], 3.05 [1.14; 8.18] and 2.63 [1.05; 6.57], respectively. Being female was associated with more frequent improvement from prefrailty to robustness, aOR 2.50 [1.09; 5.55].

**Conclusions:** Preventing frailty in elderly PLWH is a long-term problem, beginning with the early diagnosis of HIV infection and the management of comorbidities.

**Article’s main points:**
- People with HIV aged 70 years or older can progress rapidly towards higher or lower stages of frailty within a year.
- Preventing frailty is a lifelong issue that begins with early HIV diagnosis and the management of comorbidities.

**INTRODUCTION**

Worldwide, people living with HIV (PLWH) are aging (1). In France, nearly 20% of PLWH (33,000 individuals) will be aged 70 years and older by 2030 (2).

Frailty is an age-related condition characterized by increased vulnerability to stressors. During an acute minor event (introduction of a new drug, benign infection…), a frail organism may endure a more severe, longer-lasting, and less reversible functional impairment than a non-frail organism (3). Fried et al. proposed a clinical screening tool for individuals above 65 years, that classifies individuals as robust, prefrail or frail according to their level of functional impairment (4). These phenotypes are predictive of adverse health outcomes (falls, hospitalizations, institutionalizations, death) with a higher risk of negative events associated with a higher level of frailty. Frailty is a dynamic process (5). Functional decline is commonly observed over time, but recovery may be possible with targeted interventions, such as physical exercise programs and interventions to reduce falls (6).

Most studies assessing frailty in PLWH evaluated populations with a median age between 40 and 60 years (7,8). The French ANRS SEPTAVIH study provided the first data on prevalence and factors associated with frailty in PLWH aged 70 years and more on antiretroviral therapy (ART) (9). Advanced age, low socioeconomic status and multimorbidity were associated with frailty.
Identifying factors associated with frailty worsening or improvement in older PLWH is fundamental to implement and evaluate preventive strategies of functional decline in this population. Here, we assessed the frequency and factors associated with frailty transitions over one year in PLWH aged 70 years or older on ART included in the ANRS SEPTAVIH study.

MATERIALS AND METHODS

Data source

The ANRS EP66 SEPTAVIH cohort study was conducted in sixteen university hospitals in France (Clinicaltrials.gov NCT03958786). 508 individuals aged 70 years or older, infected with HIV-1, on ART for at least twelve months, covered by French national health insurance, were enrolled from May 2019 to February 2020. Individuals under legal protection or with a life expectancy below six months were not eligible. Outpatient visits were scheduled at baseline and at twelve months. At baseline, sociodemographic factors, date of HIV diagnosis, history of clinical AIDS, comorbidities and standard HIV and geriatric biomarkers were collected. Socioeconomic precarity was assessed by an EPICES score (Assessment of precariousness and health inequalities in health examination centers) ≥ 30.17. At baseline and at twelve months, each participant was assessed for Fried frailty phenotype, level of autonomy (Activity of Daily Living Scale and Instrumental Activity of Daily Living Scale), and cognitive and psychiatric conditions (Montreal Cognitive Assessment Scale, Center for Epidemiologic Studies Depression Scale). Hospitals collected data on incident deaths during the study period.

All participants gave written informed consent. The study design was approved by the ethics committee, CPP Ile-de-France XI (ref ID-RCB: 2018-A03100–55).

Frailty evaluation

The five components of Fried frailty score were collected by patient self-report or physical examination by a physician, as follows:

1. Shrinking: weight loss ≥ 5% of body weight or ≥4.5 kilograms in the previous year.
2. Exhaustion: self-reported by two questions from the Center for Epidemiologic Studies Depression Scale (“I felt that everything I did was an effort”, “I could not get going”).
3. Physical activity level: self-reported using the IPAQ questionnaire.
4. Slowness: measured in a 4-meter walking test, adjusted for gender and height.
5. Weakness: identified as low grip strength of the dominant arm, adjusted for gender and body mass index.
The participants who suffered no impairment in any of these criteria were classified as robust. Otherwise, the participants were classified as prefrail if they had one or two functional impairments, and frail if they had three or more functional impairments according to Fried definition. We defined transitions between frailty states at twelve-month follow-up as an improvement in functional status (from frailty to prefrailty or robustness, from prefrailty to robustness), worsening of functional status (from robustness to prefrailty or frailty, from prefrailty to frailty) or stability of Fried frailty phenotype.

We determined the Fried phenotype for each participant at baseline and at twelve months. If one or more of the five criteria were missing for a given patient, the Fried score was considered as missing.

**Missing data handling**

Missing data for Fried score were handled by multiple imputation by chained equations (mice R package) under the missing-at-random assumption, meaning that the probability that a value is missing depends only on the observed values (10). Incomplete Fried scores at baseline and at twelve-months visit and missing Fried scores for lost to follow-up participants were completed in the same model. We used the highest prevalence of missingness among the five components of Fried score at baseline or twelve-months to determine the number of datasets to impute (11). Twenty-two datasets were imputed. The variables used in the imputation model are reported in supplementary Table 1. Missing criteria for Fried score were imputed by predictive mean matching, then Fried score was calculated for each participant. The analyses described below were done separately for each imputed datasets, then pooled according to Rubin’s rules (12).

**Statistical analyses**

Participants who died during the one-year follow-up were not included in the analysis of frailty transitions. We compared the sociodemographic and medical characteristics of participants with a complete Fried score and participants with an incomplete or missing Fried score, at baseline and at twelve-months. Categorical variables were compared using Chi-square or Fisher test. Continuous variables were compared using Kruskal-Wallis test.

We calculated the mean frequency of robust, prefrail and frail participants at baseline and at twelve-months over the twenty-two imputations.

Logistic regression models were used to evaluate factors associated with frailty transition at twelve-months, according to Fried frailty phenotype at baseline. We considered the following outcomes: 1) deterioration of robust PLWH towards prefrailty or frailty versus stability of robustness over one year, 2) improvement of prefrail PLWH towards robustness versus stability of prefrailty over one year, 3) deterioration of prefrail PLWH towards frailty versus stability of prefrailty over one year and 4) improvement of frail PLWH towards prefrailty or robustness versus stability of frailty over one year.
To study factors associated with frailty transitions in robust and prefrail participants, models were adjusted for potential confounders according to the literature: gender, age at baseline, level of education (college degree versus below) and period of HIV infection diagnosis (before versus after the 15th of July, 1996, right after the 11th International Conference on AIDS in Vancouver that approved the use of protease inhibitors in combined antiretroviral therapy) (13–15). Age as a continuous variable respected the linearity hypothesis with the logit of dependent variables. We excluded any collinearity between the variables introduced into the multivariable models by analyzing the cross-tabulated data for the dichotomous variables and assessing the variance inflation factor (16). Considering the small size of the frail population at baseline, we only performed univariable analysis to study factors associated with improvement in this group.

Analyses were performed using SAS (9.3 version) and R (4.2.1. version).

RESULTS

Characteristics at baseline

491 participants were included in the analysis, of whom 49 were lost-to-follow-up during the first year (Figure 1). 94.3% of participants had an undetectable viral load at baseline. The median age at enrolment was 73 years [95%CI: 71.6; 77.0]. 81.5% of participants were men. Most participants were born in Western Europe (81.0%) and did not suffer from socio-economic precarity (65.8%). 40.7% of participants had a college degree. The median known duration of HIV infection was 22.7 years [15.5; 28.1]. 37.6% of PLWH were aged between 30 and 50 years at the time of HIV diagnosis and 10.8% were diagnosed after the age of 65. 47.5% of PLWH had been diagnosed before the widespread use of protease inhibitors in 1996. A clinical AIDS stage was reported in 27.7% of the study population, of whom 53% were diagnosed for HIV infection before 1996. Most PLWH were autonomous at baseline in their activities of daily living (ADL score ≥ 5 in 99.0% of cases and IADL score ≥ 6 in 91.4% of cases).

Patterns of missing data for multiple imputation

At baseline, there were no missing data for sociodemographic factors, HIV infection factors and comorbidities. 388 (79.0%) and 324 (66.0%) participants had a complete Fried score at baseline and at the twelve-months visit, respectively. The most frequent missing criterion was self-reported exhaustion, both at baseline (10.8%) and at the twelve-months visit (22.8%, half of which came from participants lost-to-follow-up) (supplementary Figure 1). Comparison of the baseline characteristics of participants with incomplete and complete Fried score are shown in supplementary Tables 2, 3, 4 and 5. No statistically significant differences were observed between these two groups with regards to socioeconomic and medical factors at baseline. Participants lost to follow-up (n = 49) had more often a baseline MOCA score below 26 (p = 0.03), but the distribution of Fried frailty phenotypes was similar to that of participants not lost to
follow-up. Participants with an incomplete Fried score at one-year, including PLWH lost to follow-up, were older (p < 0.01), more often had a baseline CD4+ T-cell count < 350/mm³ (p < 0.01) and a MOCA score below 26 (p < 0.01) than participants with a complete Fried score. Age, CD4+ T-cell count and MOCA score were included in the imputation model.

Frailty prevalence

Prevalences of prefrailty and frailty at baseline and twelve-months remained stable (Figure 2).

Characteristics of participants according to the Fried Frailty phenotype at baseline

At baseline, prefrail and frail PLWH were significantly older and more often precarious than robust PLWH (Table 1) and had more frequent depressive symptoms and cognitive impairment. Frail PLWH were significantly more likely to have been born in sub-Saharan Africa and to have hypertension or type 2 diabetes than robust PLWH. They also had more frequently a BMI<22 kg/m², the threshold of underweight in a geriatric population. The most frequent criteria associated with prefrailty or frailty were low grip strength and exhaustion, followed by slow gait (Figure 3).

Transitions between frailty states

68% of participants kept the same phenotype at one year, while 18% saw their functional status deteriorate and 14% improve.

Among the robust PLWH at baseline, 43% worsened to prefrailty, and 1% worsened directly to frailty (Figure 4). This progression was mainly related to a deterioration of grip strength (from 0% at baseline to 38.5% at M12) and self-reported exhaustion (from 0% at baseline to 31.4% at M12) (supplementary Table 6). Sociodemographic and HIV infection factors were not associated with the transition from robustness to prefrailty or frailty (Table 2). Robust PLWH with a history of hypertension were surprisingly more likely to remain robust at twelve-months than robust PLWH without a history of hypertension.

75% of the prefrail PLWH at baseline remained prefrail at twelve months, 14% reversed to robustness and 11% worsened to frailty. Of the prefrail at enrolment who became frail at twelve-months, 79.3% already had a poor hand grip at baseline (supplementary Table 6). The Fried score increased due to low physical activity (from 8.6% at baseline to 62.1% at M12), weight loss (from 2.9% at baseline to 31.4% at M12), self-reported exhaustion (from 34.3% at baseline to 72.4% at M12) and decline in walking speed (from 45.7% at baseline to 74.3% at M12). A positive difference of one year of age, a CD4+ T-cell count below 350 cells/mm³ and type 2 diabetes were significantly associated with worsening to frailty, in both crude and multivariable analysis considering gender, age at baseline, college education level and period of HIV diagnosis (aOR1.10 [1.01; 1.20], 3.05 [1.14; 8.18] and 2.63 [1.05; 6.57], respectively).
14% of prefrail PLWH at baseline recovered to robustness at twelve-months. They improved mainly in hand grip (from 66.7% at baseline to 0% at M12) and exhaustion (from 27.1% at baseline to 0% at M12), they also improved in physical activity (from 9.1% to 0% at M12) (supplementary Table 7). Men had a lower risk of improvement, in crude analysis and after adjustment for age at baseline, education and period of HIV diagnosis (aOR: 0.40 [0.18; 0.92]).

47% of the frail PLWH at baseline improved to prefrailty at twelve-months, mainly through an improvement in physical activity, with a prevalence of low physical activity of 21.7% at twelve-months compared to 73.9% at baseline, and through an improvement in self-reported exhaustion, with a prevalence of exhaustion of 26.0% at twelve-months compared to 78.3% at baseline (supplementary Table 7). None of the frail PLWH recovered to robustness. No sociodemographic or medical factors were associated with improvement at twelve-months.

We compared the crude odds-ratios of frailty transitions estimated with multiple imputation to those obtained with complete cases. Overall, crude odds-ratios were similar in both analyses (supplementary Table 8). The variance of the estimated regression coefficients was smaller in the pooled analysis of imputed datasets than in complete cases, due to the larger population size in the imputed data.

The 17 participants who died during the study period did not differ significantly from the other participants in terms of age at baseline, duration of known HIV infection, AIDS status, baseline CD4+ T-cell and multimorbidity. However, deceased participants were more frequently socio-economically disadvantaged than non-deceased participants (64.7% versus 34.2% respectively). The frequency of mortality was higher among frail participants at baseline than in robust participants (7.7 versus 1.7%, respectively, in supplementary Table 9).

DISCUSSION

The SEPTAVIH study provides original longitudinal data on frailty in PLWH aged 70 years and more. Over one year, stability of functional status was more frequent than deterioration or improvement. Direct transition from robustness to frailty was rare. No participants recovered from frailty to robustness. Advanced age, baseline CD4+ T-cell count below 350/mm³ and type 2 diabetes were associated with transition from prefrailty to frailty. Men recovered less often from frailty to prefrailty than women.

Deterioration of functional status was slightly more frequent than improvement. Lorenzo-López et al. found similar results in a one-year study of a population-based cohort aged 65 years and above (17). A longer follow-up of elderly PLWH will likely reveal a higher frequency of progression to frailty (19). Phenotype changes most often occurred between adjacent frailty states, suggesting a gradual process that enables the early detection of new functional impairment.
and the implementation of remediation strategies to limit or reverse the deterioration of functional status over time.

We found a relationship between immunological status, as measured by CD4 cell counts, and the onset of frailty in prefrail PLWH over one-year. The DUNEDIN and POLSENIOR cohorts, which included HIV-uninfected young adults and elderly respectively, also established an association between aging of the immune system and functional decline (20–22). Immunosenescence may occur with chronologic age or prematurely in PLWH (23). In PLWH, this accelerated immunosenescence may promote excessive frailty compared with HIV-uninfected people of the same age (24). Molina-Pinelo et al. suggested that low CD4+ T-cell count may be a marker of premature aging of the immune system in PLWH on ART (25). Our result is also consistent with the analysis of middle-aged men living with HIV in the MACS cohort, in which a low CD4+ T-cell count was strongly predictive of frailty over time (15).

Physiological knowledge gives insight on the association of type 2 diabetes with transition from prefrailty to frailty over one year. Yanase et al. suggested a positive feedback between type 2 diabetes and frailty (26). In this model, glucose-mediated cellular oxidative stress, mitochondrial dysfunction, chronic low-grade inflammation, and hormonal dysfunction would promote deterioration of muscle and nerve functions and loss of executive functions that are characteristics of frailty. Sarcopenia is the most important physical factor associated with frailty (27). Exercise training should be encouraged, particularly in diabetic PLWH, to prevent age-related physical decline (28). Association of hypertension with maintenance of robustness at twelve-months was unexpected (4). One year of follow-up may be too short to observe incident hypertension-related events such as stroke or heart failure that are risk factors for frailty (4,29).

We found no significant association between the period of HIV diagnosis (before versus after 1996) or the history of clinical AIDS and the progression to frailty. This contrasts with the results of the MACS cohort, in which an HIV diagnosis before 1996 or having AIDS were associated with frailty in middle-aged men (15). In the MACS cohort, PLWH may have suffered from an excess of morbidity linked to a suboptimal therapeutic management in the late 90s – early 2000s, compared to PLWH followed in a more recent period in SEPTAVIH. Besides, the limited sample or a selective survival effect in our study may explain these discrepancies.

We previously found that participants in the SEPTAVIH study were similar to PLWH of the same age followed in French hospitals at the same time in terms of country of birth, duration of known HIV infection, immunologic and virologic status (9). Thus, the findings of the SEPTAVIH study can probably be extrapolated to French PLWH of the same age on ART.

Our study has certain limitations. First, we had no information on the time each participant spent in the categories of the Fried score before the study, whereas this duration may influence later patterns of frailty transition. Second, using multiple imputation requires the missing-at-random assumption. This hypothesis seems appropriate, since some observed variables (college
education level, CD4+ T-cell count and chronic cognitive disorders) were associated with missing data for Fried score. Third, we cannot exclude that part of the changes in frailty phenotypes were due to variability. This should be considered in future intervention trials, which must include a control arm. Nevertheless, in our study factors associated with worsening frailty phenotypes differed from those associated with improved phenotypes, suggesting that part of the transitions in frailty phenotypes were attributable to real change in health. Finally, we cannot exclude a possible impact of the Covid-19 pandemic on the frailty components of the Fried score. In particular, the level of physical activity and the feeling of exhaustion (secondary to isolation and possible depression) may have increased during this period. Of note however, all assessments at M12 were made after the end of the first lockdown period in France. Fatigue and level of physical activity measured according to the Fried score only concerned the 7 days preceding the medical visit at M12, and therefore did not coincide with the strict lockdown period for most participants. Among the 17 patients who died before M12 and were not included in the analysis of frailty transitions, only 2 died of Covid-19 during the study period.

CONCLUSION

The frailty state of PLWH aged 70 years or older can vary rapidly over the course of a year. Importantly, short-term improvement of functional capacities is possible, offering opportunity for prevention and rehabilitation strategies. Apart from constitutive risk factors such as advanced age and gender, our study highlights on modifiable risk factors, such as type 2 diabetes, for transition to frailty. Promoting early HIV diagnosis and high adherence to ART to maintain high levels of CD4 could be associated with less evolution to frail phenotypes. The long-term follow-up of SEPTAVIH participants will enable us to better identify frailty risk factors. Assessing frailty in elderly PLWH, for which the literature is scarce, is important to identify interventions levers specific to HIV infection.

NOTES

Data availability

Data not publicly available.

Acknowledgments

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P. Delobel (CHU Purpan, Toulouse), P. Leclercq (CHU de Grenoble), L. Slama (Hôtel Dieu, Paris).

Authors’ contributions: J.A. performed the statistical analysis and drafted the manuscript. D. A., A. M. and O. L. participated in the statistical analysis and drafting of the manuscript. L. M. and C.A. designed the study, coordinated assembly and organization of data, and supervised the statistical analysis, drafting and editing of the manuscript. All authors read, participated in editing the manuscript, and approved the final manuscript.

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Patient consent statement

The study was approved by national ethics committees in France (Comité de Protection des Personnes de Paris Ile-de-France XI). All participants provided written informed consent.

Conflicts of interest

All authors report no conflicts of interest.

References


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TABLES AND FIGURES:

Table 1. Participants’ characteristics according to their Fried frailty phenotype at baseline (n = 491).

<table>
<thead>
<tr>
<th>Variables, n (%) or median [IQR]</th>
<th>Robust (n = 119)</th>
<th>Prefrail (n = 324)</th>
<th>p-value*</th>
<th>Frail (n = 48)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>93 (78.2)</td>
<td>267 (82.4)</td>
<td>0.33</td>
<td>40 (83.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.7 [71.0 ; 74.8]</td>
<td>73.9 [71.7 ; 77.2]</td>
<td>&lt;0.01</td>
<td>76.5 [73.3 ; 81.5]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI&lt;22 kg/m²</td>
<td>19 (16.0)</td>
<td>65 (20.1)</td>
<td>0.36</td>
<td>15 (31.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI&gt;30 kg/m²</td>
<td>11 (9.2)</td>
<td>44 (13.6)</td>
<td>0.24</td>
<td>8 (16.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>College education level</td>
<td>55 (46.2)</td>
<td>124 (38.3)</td>
<td>0.12</td>
<td>21 (43.8)</td>
<td>0.79</td>
</tr>
<tr>
<td>Deprived socioeconomic status a</td>
<td>27 (22.7)</td>
<td>111 (34.3)</td>
<td>0.03</td>
<td>30 (62.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Born in sub-Saharan Africa</td>
<td>15 (12.6)</td>
<td>46 (14.2)</td>
<td>0.71</td>
<td>14 (29.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of known HIV infection (years)</td>
<td>21.8 [15.8 ; 26.9]</td>
<td>22.7 [15.5 ; 27.7]</td>
<td>0.68</td>
<td>24.3 [14.6 ; 30.4]</td>
<td>0.45</td>
</tr>
<tr>
<td>HIV diagnosis before 1996</td>
<td>54 (45.4)</td>
<td>153 (47.2)</td>
<td>0.78</td>
<td>26 (54.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>History of clinical AIDS</td>
<td>30 (25.2)</td>
<td>87 (26.9)</td>
<td>0.69</td>
<td>19 (39.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseline CD4+ T-cell count &lt; 350/mm³</td>
<td>17 (14.3)</td>
<td>46 (14.2)</td>
<td>0.97</td>
<td>7 (14.6)</td>
<td>0.83</td>
</tr>
<tr>
<td>Multimorbidity (≥2 comorbidities)b</td>
<td>94 (79.0)</td>
<td>268 (82.7)</td>
<td>0.62</td>
<td>42 (87.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>Current smoker c</td>
<td>9 (7.6)</td>
<td>30 (9.3)</td>
<td>0.46</td>
<td>9 (18.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>High blood pressure d</td>
<td>72 (60.5)</td>
<td>216 (66.7)</td>
<td>0.25</td>
<td>39 (81.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Type 2 diabetes e</td>
<td>23 (19.3)</td>
<td>64 (19.8)</td>
<td>0.88</td>
<td>17 (35.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic kidney disease f</td>
<td>46 (38.7)</td>
<td>125 (38.6)</td>
<td>0.99</td>
<td>26 (54.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Depressive symptoms g</td>
<td>4 (3.4)</td>
<td>74 (22.8)</td>
<td>&lt;0.01</td>
<td>20 (41.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cognitive impairment h</td>
<td>50 (42.0)</td>
<td>199 (61.4)</td>
<td>&lt;0.01</td>
<td>34 (70.8)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The number of robust (n = 119), prefrail (n = 324) and frail (n = 48) participants was calculated as the mean prevalence of each phenotype in the twenty-two imputed datasets.

Data are presented as the mean frequency (percent) across the imputed datasets for categorical variables, and median [interquartile range] across the imputed datasets for continuous variables.

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Characteristics of prefrail and frail participants were compared respectively with characteristics of robust participants by univariable multinomial regression and pooled on imputed datasets according to Rubin’s rules.

*p-value for tests comparing prefrail PLWH to robust PLWH.

**p-value for tests comparing frail PLWH to robust PLWH.

a Assessed by an EPICE (Assessment of precariousness and health inequalities in health examination centers) score ≥ 30.17.

b High blood pressure, type 2 diabetes, angina/myocardial infarction, stroke and associated disorders, peripheral artery disease, dyslipidemia, chronic kidney disease, chronic respiratory disease, osteoporosis, cancer in medical record (except cervical cancer, non-Hodgkin lymphoma, Kaposi, and basal/spinoid skin cancers).

c At least one cigarette a day.

d Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg or previous diagnosis in medical record.

e Glycosylated hemoglobin > 7% or previous clinical diagnosis in medical record.

f Estimated filtration rate < 60 mL/min/1.73 m² (using the CKD-EPI equation) or diagnosis in medical record.

g CES-D (Center for Epidemiologic Studies – Depression Scale) score ≥17 for male and ≥ 23 for female (French standards).

h MOCA (Montreal Cognitive Assessment Scale) score < 26.

Table 2. Factors associated with the evolution of robust and prefrail participants at 12-months.

<table>
<thead>
<tr>
<th></th>
<th>Robust at M0</th>
<th>Worsening to prefrailty or frailty (n=52) vs. stability (n=66)</th>
<th>Prefrail at M0</th>
<th>Worsening to frailty (n=35) vs. stability (n=244)</th>
<th>Improvement to robustness (n=44) vs. stability (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR*</td>
<td>IC95%</td>
<td>p</td>
<td>OR**</td>
<td>IC95%</td>
</tr>
<tr>
<td>Crude OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.50</td>
<td>[0.20 ; 1.27]</td>
<td>0.15</td>
<td>0.81</td>
<td>[0.29 ; 3.23]</td>
</tr>
<tr>
<td>Age</td>
<td>0.97</td>
<td>[0.85 ; 1.10]</td>
<td>0.64</td>
<td>1.10</td>
<td>[1.01 ; 1.20]</td>
</tr>
<tr>
<td>College education</td>
<td>0.86</td>
<td>[0.39 ; 1.92]</td>
<td>0.71</td>
<td>0.95</td>
<td>[0.39 ; 2.29]</td>
</tr>
<tr>
<td>Socioeconomic deprivation ^a</td>
<td>1.40</td>
<td>[0.56 ; 3.49]</td>
<td>0.47</td>
<td>1.63</td>
<td>[0.71 ; 3.77]</td>
</tr>
<tr>
<td>Born in sub-Saharan Africa</td>
<td>0.68</td>
<td>[0.19 ; 2.43]</td>
<td>0.55</td>
<td>1.47</td>
<td>[0.51 ; 4.26]</td>
</tr>
<tr>
<td>HIV Diagnosis &lt; 1996</td>
<td>0.54</td>
<td>[0.24 ; 1.21]</td>
<td>0.14</td>
<td>1.21</td>
<td>[0.54 ; 2.71]</td>
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<tr>
<td>AIDS stage</td>
<td>0.57</td>
<td>[0.22 ; 1.48]</td>
<td>0.24</td>
<td>1.38</td>
<td>[0.57 ; 3.33]</td>
</tr>
<tr>
<td>Baseline CD4+ count &lt;350/mm³</td>
<td>1.18</td>
<td>[0.35 ; 3.98]</td>
<td>0.79</td>
<td>2.76</td>
<td>[1.05 ; 7.27]</td>
</tr>
<tr>
<td>Multimorbidity ^b</td>
<td>0.65</td>
<td>[0.26 ; 1.63]</td>
<td>0.36</td>
<td>1.34</td>
<td>[0.43 ; 4.17]</td>
</tr>
<tr>
<td>Hypertension ^c</td>
<td>0.44</td>
<td>[0.20 ; 0.99]</td>
<td>0.05</td>
<td>0.86</td>
<td>[0.36 ; 2.03]</td>
</tr>
<tr>
<td>Type 2 diabetes ^d</td>
<td>0.95</td>
<td>[0.36 ; 2.53]</td>
<td>0.92</td>
<td>2.44</td>
<td>[1.01 ; 5.91]</td>
</tr>
<tr>
<td>Chronic kidney disease ^e</td>
<td>0.60</td>
<td>[0.27 ; 1.36]</td>
<td>0.22</td>
<td>1.43</td>
<td>[0.64 ; 3.19]</td>
</tr>
</tbody>
</table>

Adjusted OR:

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR</th>
<th>Crude OR</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.56</td>
<td>[0.21 ; 1.44]</td>
<td>0.22</td>
<td>0.81</td>
<td>[0.28 ; 2.37]</td>
<td>0.70</td>
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<td>[0.18 ; 0.92]</td>
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<tr>
<td>Age</td>
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<td>[0.84 ; 1.10]</td>
<td>0.60</td>
<td>1.10</td>
<td>[1.01 ; 1.20]</td>
<td>0.03</td>
<td>0.93</td>
<td>[0.84 ; 1.03]</td>
<td>0.18</td>
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<tr>
<td>Variable</td>
<td>OR</td>
<td>IC95%</td>
<td>p-value</td>
<td>OR</td>
<td>IC95%</td>
<td>p-value</td>
<td></td>
<td></td>
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<tr>
<td>College education</td>
<td>0.83</td>
<td>[0.36 ; 1.91]</td>
<td>0.65</td>
<td>1.01</td>
<td>[0.39 ; 2.57]</td>
<td>0.98</td>
<td>1.55</td>
<td>[0.73 ; 3.28]</td>
<td>0.25</td>
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<tr>
<td>Socioeconomic deprivation ( ^a )</td>
<td>1.27</td>
<td>[0.49 ; 3.31]</td>
<td>0.61</td>
<td>1.51</td>
<td>[0.63 ; 3.61]</td>
<td>0.35</td>
<td>1.27</td>
<td>[0.56 ; 2.89]</td>
<td>0.56</td>
</tr>
<tr>
<td>Born in sub-Saharan Africa</td>
<td>0.58</td>
<td>[0.16 ; 2.16]</td>
<td>0.41</td>
<td>1.38</td>
<td>[0.55 ; 2.94]</td>
<td>0.58</td>
<td>1.45</td>
<td>[0.54 ; 3.87]</td>
<td>0.46</td>
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<td>0.56</td>
<td>[0.25 ; 1.35]</td>
<td>0.21</td>
<td>1.22</td>
<td>[0.53 ; 2.78]</td>
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<td>1.77</td>
<td>[0.84 ; 3.70]</td>
<td>0.13</td>
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<tr>
<td>AIDS stage</td>
<td>0.57</td>
<td>[0.21 ; 1.52]</td>
<td>0.26</td>
<td>1.33</td>
<td>[0.54 ; 3.29]</td>
<td>0.53</td>
<td>1.30</td>
<td>[0.60 ; 2.82]</td>
<td>0.51</td>
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<tr>
<td>Baseline CD4+ count &lt;350/mm(^3)</td>
<td>1.06</td>
<td>[0.30 ; 3.69]</td>
<td>0.93</td>
<td>3.05</td>
<td>[1.14 ; 8.18]</td>
<td>0.03</td>
<td>1.54</td>
<td>[0.54 ; 4.40]</td>
<td>0.41</td>
</tr>
<tr>
<td>Multimorbidity ( ^b )</td>
<td>0.69</td>
<td>[0.26 ; 1.82]</td>
<td>0.45</td>
<td>1.17</td>
<td>[0.37 ; 3.68]</td>
<td>0.79</td>
<td>0.96</td>
<td>[0.35 ; 2.67]</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension ( ^c )</td>
<td>0.45</td>
<td>[0.20 ; 1.02]</td>
<td>0.06</td>
<td>0.80</td>
<td>[0.33 ; 1.98]</td>
<td>0.63</td>
<td>1.07</td>
<td>[0.51 ; 2.26]</td>
<td>0.86</td>
</tr>
<tr>
<td>Type 2 diabetes ( ^d )</td>
<td>1.05</td>
<td>[0.38 ; 2.89]</td>
<td>0.92</td>
<td>2.63</td>
<td>[1.05 ; 6.57]</td>
<td>0.04</td>
<td>0.89</td>
<td>[0.32 ; 2.47]</td>
<td>0.82</td>
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<tr>
<td>Chronic kidney disease ( ^e )</td>
<td>0.53</td>
<td>[0.22 ; 1.26]</td>
<td>0.15</td>
<td>1.21</td>
<td>[0.53 ; 2.78]</td>
<td>0.65</td>
<td>0.76</td>
<td>[0.32 ; 1.80]</td>
<td>0.53</td>
</tr>
</tbody>
</table>

OR : odds ratio. IC95%: 95% confidence interval.
*reference for odds-ratio: robust PLWH at baseline that remained robust at twelve-months.
** reference for odds-ratio: prefrail PLWH at baseline that remained prefrail at twelve-months.
1 crude model.
2 each OR is adjusted for gender, age at baseline, college education level and period of HIV diagnosis (before vs. after 1996).
† Age is centered on 70 years old; odds-ratio is for a positive difference of one year of age.
aAssessed by an EPICE (Assessment of precariousness and health inequalities in health examination centers) score ≥ 30.17.
b High blood pressure, type 2 diabetes, angina/myocardial infarction, stroke and associated disorders, peripheral artery disease, dyslipidemia, chronic kidney disease, chronic respiratory disease, osteoporosis, cancer in medical record (except cervical cancer, non-Hodgkin lymphoma, Kaposi, and basal/spinoid skin cancers).
c Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg or previous diagnosis in medical record.
d Glycosylated hemoglobin > 7% or previous clinical diagnosis in medical record.
e Estimated filtration rate < 60 mL/min/1.73 m\(^2\) (using the CKD-EPI equation) or diagnosis in medical record.
FIGURE LEGENDS:

Figure 1. Flow-chart.

508 PLWH included at baseline

442 who completed the 12-months visit

491 PLWH analyzed

17 deaths

49 lost-to-follow-up

Figure 2. Prevalence of frailty according to Fried Frailty phenotype, at baseline and twelve-months visit (n = 491). Prevalences were calculated as the mean frequencies of Fried frailty phenotypes in the twenty-two imputed datasets.
Figure 3. Frequency of frailty criteria according to Fried Frailty Phenotype in prefrail and frail participants at baseline (M0) and at the twelve-months visit (M12). Prevalences were calculated as the mean frequencies for a given criterion in the twenty-two imputed datasets.
Figure 4. Evolution of Fried frailty phenotypes at 12-months according to the frailty status at baseline (n = 491). Number of robust (n = 119), Prefrail (n = 324) and frail (n = 48) participants were calculated as the mean prevalence of each phenotype in the twenty-two imputed datasets. We reported the mean frequencies of each type of frailty transition on the imputed datasets.