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Médecine et maladies infectieuses

Médecine et maladies infectieuses xxx (2019) xxx–xxx

Original article

HIV-infected patients aged above 75 years

Patients de plus de 75 ans vivant avec le VIH

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Received 6 September 2017; received in revised form 28 February 2018; accepted 1st April 2019

Abstract

Background. – Little data is available on HIV-infected patients aged over 75 years.

Methods. – A descriptive study of HIV-infected patients aged over 75 years was conducted in six hospitals of the Pays de la Loire region, France. Socio-demographic, immuno-virological, and therapeutic characteristics were collected via an electronic medical record software (Nadis®). To assess frailty, a simplified geriatric assessment was conducted during an HIV routine visit.

Results. – Among the 3965 patients followed in the six centers, 65 (1.6%) were aged over 75 years. From January to May 2016, 51 patients were included in the study: median age 78.7 years, male patients 74.5%, homosexual transmission 41.2%, living at home 98% and single in 54.5% of cases, median duration of HIV infection 18.8 years, median CD4 nadir 181 cells/mm^3; CDC stage C 36.4%. All patients were on antiretroviral therapy and 98% of them had an HIV RNA < 50 c/mL; 82% of patients had at least one comorbidity and 58% at least two comorbidities. Eleven of 51 patients (21.6%) were diagnosed as at risk of frailty and 2/51 (3.9%) were considered frail. Cognitive disorders were diagnosed in 60.8%, depression in 35.3%, malnutrition in 25.5%, and vitamin D deficiency in 45.9%.

Conclusions. – HIV-infected patients aged above 75 years are well-managed, but the prevalence of geriatric comorbidities is high.

Keywords: HIV; Aging; Geriatric assessment

Résumé

Introduction. – Peu de données sont disponibles sur les PVVIH □ 75 ans.

Méthodes. – Étude descriptive transversale des PVVIH ≥ 75 ans dans les six centres hospitaliers des Pays de la Loire. Les caractéristiques épidémiologiques, immuno-virologiques et thérapeutiques de cette population ont été recueillies via un logiciel de dossier médical informatisé et une évaluation gériatrique standardisée simplifiée a été réalisée en parallèle pour évaluer la vulnérabilité de ces patients.

Résultats. – Parmi la file active des six services, 65/3965 patients (1,64 %) avaient □ 75 ans. Parmi ces 65 patients, 51 ont eu une consultation pendant la période d'étude et ont été inclus (âge médian 78,7 ans ; 74,5 % d'hommes ; 41,2 % infectés par contamination homosexuelle ; 98 % vivant à domicile et célibataire dans 57 % des cas ; durée médiane de l'infection à VIH : 18,8 ans ; nadir de CD4 médian 181/mm^3). Tous les patients étaient sous TARV et 98 % avaient une charge virale indétectable (< 50 copies/mL) ; 82 % des patients avaient au moins une

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https://doi.org/10.1016/j.medmal.2019.04.001
0399-077X/

comorbidité et 58 % au moins deux. Selon une évaluation gériatrique simplifiée : 21,6 % apparaissaient en voie de fragilité et 3,9 % comme fragiles ; 60,8 % avaient des troubles cognitifs, 35,3 % présentaient une dépression, 25,5 % une dénutrition, 45,9 % un déficit en vitamine D. **Conclusion**

Les PVVIH ≥ 75 ans sont bien suivis et contrôlés pour l'infection à VIH mais la prévalence de comorbidités gériatriques est importante.

Mots clés : VIH ; Vieillissement ; Évaluation gériatrique

1. Introduction

New antiretroviral therapies (ART) are associated with better quality of life and with a significantly reduced morbidity and fatality in treated patients. HIV infection is therefore now considered a chronic disease, with a life expectancy close to that of the general population. The aging of HIV-infected individuals raises many pathophysiological, clinical, therapeutic, and management questions as the frequency of comorbidities and co-prescriptions as well as the potential increased frailty are factors that are yet to be assessed [1]. In France in 2011, 41% of HIV-infected patients were aged above 50 years [2].

Despite restoration of a good immunological status and a sustained virological control with treatments, HIV-infected individuals remain more vulnerable than the general population. They are at higher risk of non-infectious comorbidities related to aging such as cardiovascular diseases, high blood pressure, diabetes, renal insufficiency, osteoporosis, and cancer [3–5]. Over the past years, several studies assessed HIV-infected individuals aged above 50 years in terms of morbidity, fatality, and iatrogenic events. The 50-year threshold was selected based on epidemiological criteria (age pyramid of HIV-infected people) and not on clinical criteria. Yet, the geriatric population of developed countries usually refers to people aged above 75 years as, irrespective of comorbidities, frailty syndrome may be observed from this age onwards. Frailty is defined as a clinical syndrome indicative of a reduction in reserve physical capacities impairing the stress adaptation mechanisms. Little data is available on the geriatric HIV-infected population in western Europe. We aimed to better characterize HIV-infected individuals aged above 75 years and to assess their vulnerability to comprehend the complexity of the aging process and to adequately adapt their management.

2. Method

We performed an observational, epidemiological, multicenter, regional, and cross-sectional study in the six centers of the Regional coordination for the management of HIV (French acronym COREVIH) of the Pays de la Loire region (Angers, Laval, La Roche-sur-Yon, Le Mans, Nantes, Saint-Nazaire) from January to May 2016. The study protocol was approved by the advisory committee on research-related data processing in health (French acronym CCTIRS). The computerized management of data was approved by the French Data Protection Authority (French acronym CNIL). We aimed to describe the HIV-infected population aged above 75 years, to perform a geriatric evaluation of this population with a particular focus on comorbidities and iatrogenic events.

Included patients were aged 75 years and above and consulted as part of their usual HIV follow-up. They gave oral consent for study participation after having received an information letter during their consultation.

Data was anonymized and collected using Nadis® software. Nadis® is a standardized computerized medical record software for the follow-up of HIV-infected patients and/or patients infected with hepatitis B virus and/or hepatitis C virus in French hospitals. Clinical, biological, and therapeutic data is captured in this software. The following data was collected: age, sex, contamination mode, level of education, marital status, lifestyle habits (alcohol, tobacco), CDC stage, presence or absence of hepatitis coinfection (HCV and HBV), CD4 lymphocyte level, and HIV viral load at diagnosis, age at diagnosis, CD4 level, current viral load, CD4/CD8 ratio, cytomegalovirus serological status, number of antiretroviral treatment lines, current ART, history (diabetes, high blood pressure, cardiovascular diseases, neurovascular diseases, depression, cancer), body mass index (BMI), albumin level, vitamin D level.

Alongside data collected in Nadis®, a simplified geriatric evaluation was performed using a standardized questionnaire (used by the mobile geriatric team of Angers). The geriatric evaluation assessed eight health items among the following: cognition using a Three-Word Test [7], mood using the mini-Geriatric Depression Scale (GDS) [8], mobility using the ADTM scale (sitting-standing-changing position-walking), autonomy using the AGGIR grid (autonomy-gerontology-group-iso-resources) [9], pain using a Numeric Verbal Scale [10], nutrition with BMI measurement and albumin level [11], comorbidity burden by counting the number of drugs taken by the patient, environmental status using the socio-family evaluation. The geriatric evaluation was assessed out of 24 points; patients were considered "frail" with a score higher than 16 and "at risk of frailty" with a score between 8 and 16. Undernourishment was defined by an albumin level between 35–30 g/L or a BMI < 21, and severe undernourishment by an albumin level < 30 g/L or a BMI < 18. Vitamin D deficiency was defined as a vitamin D level < 10 ng/mL, and vitamin D insufficiency as a level between 10 and 30 ng/mL. Renal insufficiency was defined by a glomerular filtration rate estimate < 60 mL/min/1.73 m^2 with the MDRD formula.

Characteristics of patients with or without frailty at the geriatric evaluation were compared using Fischer's exact test

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for qualitative variables and Wilcoxon–Mann–Whitney test for quantitative variables at a threshold of 5%.

3. Results

Sixty-five (1.6%) of the 3965 patients of the Pays de la Loire COREVIH were aged 75 years or above. Fifty-one of the 65 HIV-infected patients aged 75 years or above, followed up in the Pays de la Loire region, consulted and agreed to take part in the study. Epidemiological and immuno-virological characteristics of the studied population as well as ART distribution at the study visit are detailed in Table 1.

Of the 42 patients treated with a triple therapy, 14 (33%) were treated with a single-tablet triple therapy; 28 (67%) with a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) + one non-nucleoside reverse transcriptase inhibitor (NNRTI), nine (21%) with two NRTIs + one integrase inhibitor (II), four (10%) with a combination of two NRTIs + one boosted protease inhibitor (bPI) and one (2%) with a combination of one NNRTI + one II + one bPI. Overall, seven patients were treated with a two-drug combination therapy, including four patients with a combination with one NNRTI and one II, without any NRTI nor bPI. Two patients were treated with a four-drug combination therapy.

As for comorbidities: seven patients (13.7%) were managed for diabetes, 25 (49.0%) for high blood pressure, seven (13.7%) for cardiovascular disease, six (11.8%) had a history of stroke, 25.5% had renal insufficiency, 18 (35.3%) had a history of neoplasia. Vitamin D low level (25 OHD3 < 30 ng/mL) was observed in almost half of patients (insufficiency: 18.9%, deficiency [25 OHD3 < 10 ng/mL]: 27.0%).

Results of the simplified geriatric evaluation are detailed in Table 2 (all 51 patients were assessed using all tools): 84.3% of patients had a GIR score of 6 and 86.3% had an ADTM score of 5. The median number of different treatments per day were six. Three-quarters of patients were considered non-frail patients, 11 (21.6%) were at risk of frailty, and two (3.9%) were considered frail.

The comparison between the group of non-frail patients and the group of frail patients or patients at risk of frailty did not reveal any significant difference between both groups, neither in terms of immuno-virological parameters (Nadir CD4, CDC stage, current CD4, viral load, CD4/CD8 ratio, CMV serological status) nor in terms of treatment characteristics (age at treatment initiation, number of ART lines received, number of ARTs received). From an epidemiological standpoint, only female sex was significantly associated with frailty (53.8% in the frailty group or at risk of frailty versus 15.8% in the non-frailty group, $P = 0.0066$).

Table 1
Socio-demographic, immuno-virological, and therapeutic characteristics of HIV-infected patients aged 75 years and above.
Caractéristiques socio-démographiques, immuno-virologiques et thérapeutiques des PVVIH de 75 ans et plus.

	n (%)/median [IQR]
Age, median [IQR]	78.7 [76.2–81.6]
Men, *n* (%)	38 (74.5)
Transmission, *n* (%)	
Heterosexual	19 (37.3)
MSM-bisexual	21 (41.2)
Other	11 (21.6)
Age at diagnosis, median [IQR]	61.3 [55.4–66.7]
Type of accommodation, *n* (%)	
At home	50 (98.0)
Medicalized nursing home	1 (2.0)
Marital status, *n* (%)	
Living alone (single, widowed, separated)	29 (56.9)
In a relationship (civil covenant of solidarity, married, cohabiting partner)	22 (43.1)
Country of birth, *n* (%)	
France	42 (82.4)
Sub-Saharan Africa	4 (7.8)
Other	5 (9.8)
Hepatitis B and/or C coinfection, *n* (%)	4 (7.8)
Active smoking, *n* (%)	3 (5.9)
Daily alcohol consumption, *n* (%)	12 (23.5)
CDC stage C, *n* (%)	18 (35.3)
HIV 1, *n* (%)	51 (100.0)
Nadir CD4/mm^3, median [IQR]	181 [74–347]
Duration of HIV infection (years), median [IQR]	18.8 [12.5–21.9]
Most recent CD4/mm^3, median [IQR]	565 [441–697]
Last viral load < 50 copies/mL, *n* (%)	50 (98.0)
Duration of undetectable viral load (years), median [IQR]	3.4 [3.4–10.3]
CD4/CD8 ratio ≥ 1, *n* (%)	16 (31.4)
CD4 > 500/mm^3 and CD4/CD8 ratio ≥ 1	13 (25.5)
CMV+ status, *n* (%)	40 (78.4)
Age at ART initiation, median [IQR]	63.3 [57.8–68.9]
Number of treatment lines, median [IQR]	5 [3–7]
Number of antiretrovirals, median [IQR]	3 [1–3]
Number of antiretrovirals, *n* (%)	
2	7 (13.7)
3	42 (82.4)
≥ 4	2 (3.9)
Antiretrovirals at the last visit, *n* (%)	
2 NRTIs + 1 NNRTI	28 (54.9)
2 NRTIs + 1 II	9 (17.7)
2 NRTIs + 1 bPI	4 (7.8)
Treatment regimen without NRTI and without bPI	4 (7.8)

NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; II: integrase inhibitor; bPI: boosted protease inhibitor.

4. Discussion

This is one of the first study to specifically assess geriatric HIV-infected patients, i.e. patients aged 75 years and above. Our study sample may be considered representative as all HIV centers of the Pays de la Loire region participated in the study and as 78.5% of the 65 HIV-infected patients aged 75 years or above in the Pays de la Loire were included over a five-month period. The proportion of HIV-infected individuals aged above 75 years in our study is comparable to the proportion we reported in the Dat'AIDS cohort assessing 43,552 patients followed up in France (1.6% and 1.5%, respectively) [12]. HIV-infected individuals aged 75 years and above seem to be adequately followed up. Overall, 100% of patients were receiving ART and 98.0% had an undetectable plasma viral load. By way of comparison,

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Table 2
Simplified geriatric evaluation of HIV-infected patients aged 75 years and above. *Évaluation gériatrique simplifiée des PVVIH de 75 ans et plus.*

	n (%)/median [IQR]
Cognition: 3-word test (/6)	
3-word test ≤ 5, *n* (%)	31 (60.8)
Mood: Mini-GDS (/4)	
Mini-GDS ≥ 1, *n* (%)	18 (35.3)
Mobility: ADTM (/5)	
ADTM < 5	7 (13.7)
Autonomy: AGGIR grid (/6)	
GIR, median [IQR]	6 [6]
Pain: NVS (/10)	
NVS 0–1, *n* (%)	27 (52.9)
NVS 2–4, *n* (%)	7 (13.7)
NVS ≥ 5, *n* (%)	17 (33.3)
Nutritional state	
Albumin level, median [IQR]	41.5 [39–45.3]
BMI, median [IQR]	23.8 [21.1–26.09]
Severe undernourishment, *n* (%)	2 (3.9)
Moderate undernourishment, *n* (%)	11 (21.6)
Number of different drugs taken: median [IQR]	6 [5–9]
1–2, *n* (%)	3 (5.9)
3–6, *n* (%)	25 (49.0)
> 6, *n* (%)	23 (45.1)
Social and family evaluation (/15)	
Absence of risk, *n* (%)	13 (25.5)
Mild risk, *n* (%)	33 (64.7)
Moderate to severe risk, *n* (%)	5 (9.8)
Frailty status, as assessed by the simplified geriatric evaluation (/24)	
Absence of frailty < 8, *n* (%)	38 (74.6)
At risk of frailty 8–16, *n* (%)	11 (21.6)
Frailty > 16, *n* (%)	2 (3.9)

Mini-GDS: Mini-Geriatric Depression Scale; ADTM: ADTM Scale (sitting-standing-changing position-walking); AGGIR: AGGIR grid (autonomy-gerontology-group-iso-resources); NVS: Numeric Verbal Scale; BMI: body mass index.

over the same period 94.0% of HIV-infected patients – all ages – in the Pays de la Loire region were receiving ART and 92.8% had an undetectable viral load [13].

One of the strengths of our study was the screening for vulnerability in HIV-infected patients aged above 75 years, using a simplified standardized geriatric evaluation. The standardized geriatric evaluation assesses the frailty status of patients to prevent the risks of morbidity and mortality [14]. The concept of frailty is defined as a clinical state of vulnerability to external stimuli, resulting from an age-related weakening of physiological resources and of reactive capacity, with a progressive reduction in homeostasis level [15]. Frailty is associated with an increased risk of falls, hospitalization, living in a nursing home, disability, and fatality. Assessing frailty is helpful to understand the complexity of HIV-infected people's aging, and to adapt management [16]. We chose a simplified geriatric evaluation based on short tests (mini-GDS, Three-Word Test, etc.), known as screening tests, to allow for rapid evaluation at the follow-up visit. An evaluation based on longer tests, known as diagnostic tests, may have been more relevant but such tests could not be performed during standard visits. Overall, 21.6% of our patients were at risk of frailty and 3.9% were frail patients. These figures may be underestimated as some of the patients with the highest degree of frailty could not come to consultation during this period (hospitalization, transportation difficulties, etc.). Another study assessing frailty in a younger population of patients and using a different scale (VAS score) reported a frailty prevalence of 2% in virologically-controlled HIV-infected patients of a median age of 47.6 years (7.1% > 60 years) [17]. A case-control study of 520 HIV-infected individuals (mean age: 52 years; 10.8% > 65 years) reported a significantly higher incidence of frailty and pre-frailty in HIV-infected individuals (1.6% vs. 2.7% and 50.7% vs. 36.3%, respectively, $P < 0.001$) [18]. The authors of another study of female HIV-infected patients only, reported a frailty prevalence of 8%, using Fried's criteria [19]. In our study, frailty was significantly higher among women. This finding is concordant with data from the general population. We did not observe any relation between frailty and low CD4 nadir, unlike other authors who reported a correlation between low CD4 nadir and an increased risk of geriatric syndromes [20–22]. The adequate immunological restoration of HIV-infected individuals included in our study and the duration of undetectable viral load (median of more than 3 years), might have had a "compensatory" effect, thus avoiding the occurrence of frailty. We also did not observe any relation between the HIV infection duration and frailty, unlike findings from the pre-cART era [23]. Patients from our study had been living with HIV for a median of 18.8 years, but they were also receiving ART for a median of 15.4 years. The high immuno-virological efficacy of these treatments probably has a protective effect on some components of the frailty syndrome.

The high frequency (60.8%) of cognitive disorders, assessed by the three-word tests, was certainly overestimated as this score is not the most adequate with HIV-infected individuals. This test can nevertheless be used as a guiding test in studies of this type. Other studies already reported a high prevalence of cognitive disorders, although to a lower extent and in a younger HIV-infected population (50–60 years) [20]. Tests such as MOCA [24], TMT A-TMT B, or the clock-drawing test, would have probably been more adequate, but are time-consuming in routine practice. To confirm cognitive disorders and define their nature, all HIV-infected patients with a positive Three-Word Test, should undergo complete neurocognitive assessment or even brain imaging (CT scan or brain MRI). Screening for these cognitive disorders is crucial as they might be a risk factor for poor compliance with ART [25]. Most study patients maintained mobility and autonomy. The GIR test was sometimes difficult to administer during the consultation (when no caregiver or member of the multidisciplinary team was present) and results may have been overestimated. Greene et al. reported physical dependence in 10% of HIV-infected patients aged 65 years or above [20]. Sarcopenia screening, which was not performed in our study, also seems important [26]. The mini-GDS test contributed to detecting depression in 35.3% of included patients. Depression is probably underestimated and undertreated among HIV-infected individuals [27]. The prevalence of depression in the ambulatory general geriatric population is 15% to 30% [28]. The prevalence of undernourishment and vitamin D low

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levels in HIV-infected individuals (25.5% and 45.9%, respectively, in our study) is higher than in the general geriatric population living at home, with a prevalence of approximately 4% for undernourishment [11,29].

Our study also confirms the high rate of polypharmacy in this geriatric population, with a median number of six drugs (including ART). Other studies had already reported similar data among HIV-infected individuals aged above 60 years [30,31]. The iatrogenic risk is major with some ARTs because of very frequent drug–drug interactions, mainly with ritonavir and some NNRTIs, and because of renal toxicity associated with some ARTs (TDF and boosted PI). The iatrogenic risk is also increased due to the high prevalence of undernourishment and renal insufficiency. Polypharmacy and the iatrogenic risk are challenging among this population of geriatric patients. Polypharmacy is also associated with a higher risk of non-compliance (and thus of resistance to ARTs), especially when more than five drugs are prescribed [32]. A re-evaluation of prescriptions focusing on geriatric needs is essential to ensure treatment adequacy, to adapt dosing regimens, and to limit potential drug–drug interactions.

Our study had several limitations: small sample size, screening scales preventing us from performing an accurate analysis of the various components of frailty, comparison difficulties with other studies of younger patients and using different tools. However, our study provided relevant epidemiological, clinical, and polypharmacy data. The various geriatric evaluation scales contribute to assessing the health of elderly HIV-infected individuals, to identify frailty risk factors, to guide treatment, to anticipate and prevent complications, but further studies are required to validate such scales for use in HIV-infected geriatric people. These evaluations could also help in implementing an individualized plan for care and assistance, especially as access to medical/social facilities for elderly HIV-infected people may be difficult because of institutional obstacles as highlighted by the French Directorate-General for Health [33].

5. Conclusion

Our study showed that HIV-infected individuals aged above 75 years are almost perfectly managed. We also underlined underdiagnosed and poorly treated frailty risk factors such as depression, cognitive disorders, undernourishment, low levels of vitamin D, and pain. We highlighted the importance of specific management for HIV-infected individuals aged above 75 years, with a collaboration between infectious disease specialists and geriatricians, which should be focused on geriatric syndromes (polypharmacy, undernourishment, deficiencies, depression, pain, etc.). Structuring management with dedicated geriatric/HIV consultations could help reevaluate prescriptions and lead to implementing a multidimensional approach based on varied and standardized scales to assess the complexity of geriatric HIV-infected people's health [34].

Contribution of authors

C. B, H. H, C. A, and F. R contributed to designing the study protocol, to collecting and analyzing data, and to writing the article.

S. S performed the statistical analysis, contributed to designing the study protocol, to collecting data, and to reviewing the article.

P. F, V. V, P. P, and C. M contributed to collecting data and to reviewing the article.

All authors approved the final version of the article.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgment

The authors would like to thank all patients who participated in the study, all members of the COREVIH Pays de la Loire team, and all members of the teams of the six participating hospitals: Angers (JM C, P F, V R, YM V, P A, S R), Laval (R V, H D), La Roche-sur-Yon (P P, M M, JL E, O B T G, S L, L L), Le Mans (H. H, N V, S B, L P, N C, N Q), Nantes (S S, M C, H H, C B, E B, C A, V R, N H, B B, P M, S B, F V, C B, B. G, J B, L K, D B, F R, M L, O G, O A, P P, M B), Saint-Nazaire (C M, C GC).

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Please cite this article in press as: Bernaud C, et al. HIV-infected patients aged above 75 years. Med Mal Infect (2019), https://doi.org/10.1016/j.medmal.2019.04.001