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To cite this article: Matteo Cesari MD, PhD, Emanuele Marzetti, Marco Canevelli & Giovanni Guaraldi (2016): Geriatric syndromes: How to treat, Virulence, DOI: [10.1080/21505594.2016.1219445](https://doi.org/10.1080/21505594.2016.1219445)

To link to this article: <http://dx.doi.org/10.1080/21505594.2016.1219445>



Accepted author version posted online: 11 Aug 2016.  
Published online: 11 Aug 2016.



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REVIEW

## Geriatric syndromes: How to treat

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### ABSTRACT

The survival of HIV-infected persons has been increasing over the last years, thanks to the implementation of more effective pharmacological and non-pharmacological interventions. Nevertheless, HIV-infected persons are often “biologically” older than their “chronological” age due to multiple clinical, social, and behavioral conditions of risk. The detection in this population of specific biological features and syndromic conditions typical of advanced age has made the HIV infection an interesting research model of accelerated and accentuated aging. Given such commonalities, it is possible that “biologically aged” HIV-positive persons might benefit from models of adapted and integrated care developed over the years by geriatricians for the management of their frail and complex patients.

In this article, possible strategies to face the increasingly prevalent geriatric syndromes in HIV-infected persons are discussed. In particular, it is explained the importance of shifting from the traditional disease-oriented approach into models of care facilitating a multidisciplinary management of frailty.

### ARTICLE HISTORY

Received 25 March 2016

Revised 26 July 2016

Accepted 27 July 2016

### KEYWORDS

elderly; frailty; geriatrics; HIV; integrated care; prevention

## Global aging and changing scenarios

The demographic changes occurring worldwide are exposing the current models of healthcare to the risk of collapsing.<sup>1</sup> Patients that are today usually seen in clinical services are indeed very different from those for whom the same services were designed decades ago. Nowadays, the daily clinical routine is mostly absorbed by the assessment and treatment of patients characterized by older age, more comorbidities and syndromes, and higher consumption of medications.<sup>2</sup>

This transition is evident across most medical disciplines, including infectious disease medicine (IDM). Indeed, with the widespread implementation of highly active antiretroviral therapy (HAART), the survival of HIV-infected persons has been substantially extended, approaching that of the general population in high-income countries.<sup>3</sup> At the same time, specific pathophysiological features brought about by HIV infection have led to considering it a model of accelerated and accentuated aging,<sup>4</sup> and a condition of possible use for developing strategies against age-related conditions.<sup>5</sup> Indeed, HIV-positive patients can often be considered “old and frail” under a biological viewpoint, although still “young”

if the obsolete chronological age criterion is used as reference.

It is not far from reality saying that multiple disciplines sharing this same problem are today looking with increasing interest to the background and specificities of geriatric medicine. This is not surprising because the historical background of geriatricians has always been centered on the management of frail and complex elders. In this context, geriatric medicine has been contributing over the years with the development of specific strategies and methodologies (although not always correctly interpreted and applied).<sup>6</sup>

It is noteworthy that the nosographic entities at the basis of traditional medicine tend to lose their meaning and relevance with advancing age. The simultaneous presence of multiple and interacting clinical and subclinical conditions in the older individual leads to heterogeneous phenotypic manifestations, which are often not attributable to any of the single conditions the person suffers from. In such a scenario, the concept of “stand-alone” diseases (all individually targetable with specific interventions) is therefore not applicable in contemporary medicine. Indeed, by focusing the medical attention

on individual diagnoses and treating each of them according to standard protocols and guidelines, the overall picture of the patient would be ineluctably lost, easily resulting in over-diagnosis and/or over-treatment.

A related problem is the lack of randomized controlled trials recruiting participants with the characteristics and complexities of the average patient attending clinical services. This means doubting and arguing the appropriateness of standard protocols and decisional algorithms traditionally used in medicine.<sup>7</sup> This issue may potentially drive toward the opposite condition of over-diagnosis and over-treatment, which is “ageism” and preclusion from therapeutic options.

In the present article, we discuss the possible treatment strategies that can be adopted to face the increasingly prevalent geriatric syndromes in clinical settings. In the first section, the need of reshaping the models of care is linked to the geriatric condition of frailty. Frailty is often described as a syndrome and for this reason included in the present document. However, we believe that frailty is something more than that and could represent the umbrella under which conducting the clinical care of geriatric conditions and syndromes. In the second part of the article, we show how frequently major geriatric syndromes occur in HIV-positive patients, and suggest possible *ad hoc* solutions developed by geriatricians over the years.

### **Frailty: A mere syndrome or a cornerstone condition for remodeling healthcare services?**

A geriatric syndrome is a non-disease clinical condition of older persons characterized by multiple causes determining a unified manifestation. By definition, it encompasses a group of signs and symptoms variably occurring together and characterizing a particular abnormality. This implies that geriatric syndromes present a multifactorial and extremely heterogeneous background, grounding its roots in clinical, psychological, social, and environmental vulnerabilities.<sup>8</sup>

As previously argued, in a world experiencing the consequences of global aging (even in low-income countries), the traditional concept of advanced age to define the “older” individual is no longer effective. The current clinical reality calls for new paradigms that are able to offer more accurate and personalized care. Such a transition may be accomplished through the quantification of the homeostatic reserves of the organism in order to obtain an estimate of its “biological age.” This is the main reason why geriatric medicine started developing specific activities around the so-called “frailty” condition.

Frailty (defined as a condition of increased vulnerability due to the reduction of homeostatic reserves,

exposing the individual to higher risk of negative outcomes) is sometimes presented as a syndrome,<sup>9</sup> some others as a state of health determined by the age-related accumulation of deficits.<sup>10</sup> Such ambiguity largely depends on the operational definition adopted to frame it.<sup>11</sup> In fact, frailty is frequently described as a syndrome because associated with the widely diffused model proposed by Fried and colleagues.<sup>12</sup> The so-called frailty phenotype based on the assessment of 5 epidemiologically-derived criteria (i.e., poor muscle strength, slow gait speed, exhaustion, sedentary behavior, and involuntary weight loss) clearly describes frailty as a syndrome. However, the automatic translation of a condition with an instrument designed for measuring it should be cautious because highly arguable. In particular, by doing the equivalence between frailty and frailty phenotype, several aspects are neglected:

- 1) Frailty existed and was treated in geriatric medicine well before the development of the frailty phenotype from the Cardiovascular Health Study database;<sup>13</sup>
- 2) The instrument was designed with the properties of a screening tool;<sup>11</sup> and as such it is unable to adequately support the design of interventions against the underlying causes of frailty;
- 3) Many other instruments are available that similarly identify older persons at increased risk of negative health-related outcomes, sometimes even in an easier and more reproducible way;<sup>14,15</sup>
- 4) The detrimental consequences of frailty in the older individual frequently find their causes in domains beyond the physical dimension;<sup>16</sup> and
- 5) Adding the notion of frailty to a standard clinical assessment has very modest relevance if the information is not translated into a specific counteraction (obviously not doable on the basis of the result of a screening test).<sup>17</sup>

Differently, if frailty is more broadly considered a continuous parameter reflecting the “biological aging” of the individual, it might represent much more than a mere condition to be screened. It may indeed assert to the criterion for taking decisions of public health relevance.<sup>16</sup> In fact, if we disregard the concept of frailty as a syndrome and start looking at it as a point in the continuous process of aging, it will be possible to use it to replace the obsolete criterion of chronological age in clinical decisional algorithms. To put it differently, instead of talking of older persons in terms of years of life lived, we might focus the concept of aging on the clinical and biological features determining the vulnerability of the older individual. This reasoning might directly affect the allocation of resources, which would be used to cover different needs in a “biologically young”

person of 80 y of age (suitable for traditional medical paradigms and protocols) versus a “biologically old” individual of 50 (as frequently occurring among HIV-positive patients).

The incorporation of frailty assessment in clinical practice might take advantage of the large and increasing diffusion of the frailty concept across medical specialties. Frailty is no longer an exclusivity of geriatricians and gerontologists. Having multiple disciplines familiar with the term may allow its use as common denominator/shared language for facilitating interdisciplinary cross-talks and exchanges. This is really the direction to take to effectively deal with frailty.

We believe that the only possibility, probably the only feasible at this time, to manage the growing number of frail individuals is to remodel healthcare services in order to privilege and facilitate integrated and multidisciplinary models of care.<sup>18</sup> The design of the interventions around the patient’s needs and resources should thus be achieved on the basis of a coordinated and collegial discussion of the case in which the different specialists participate with their own expertise and background. Models of care based on a single-access point (e.g., case-manager<sup>19</sup>) and interdisciplinary exchanges formally nested in clinical services (e.g., orthogeriatric units<sup>20</sup>) have already shown their efficacy both for the patient (in terms of improved quality of life, prevention of negative health-related outcomes, and higher access to treatments)<sup>21,22</sup> and public health (in terms of reduction of healthcare expenditures).<sup>23</sup> Moreover, preliminary reports have started associating frailty to allocation of healthcare resources,<sup>24</sup> suggesting a higher profile for this concept in the near future.

### Management of geriatric syndromes

The concept of HIV infection as a model of pathological aging is reinforced by the fact that more than half of the HIV-infected population presents 2 or more geriatric syndromes.<sup>25</sup> The following paragraphs are not intended to be exhaustive. The aim is instead to show how frequent detrimental conditions affecting geriatric patients are found in HIV-positive persons. This population could therefore greatly benefit from the adapted and personalized models of care envisioned for older patients.

#### Falls

Falls (defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level) is a very common condition in older persons. Falls are particularly distressing for the individual, due to the consequent higher morbidity, loss of physical

function, and increased risk of death, as well as for health systems.

Hip fracture is the most feared fall-related injury. Such eventuality is particularly nurtured by the age-related reduction of bone mineral density. It is noteworthy that HIV infection and antiretroviral therapy have both been associated with significant bone loss, resulting in osteopenia and osteoporosis.<sup>26</sup>

In advanced age, falls have typically a multifactorial etiology, including age-related comorbidities, postural modifications, sensory impairment, musculoskeletal weakness, postural hypotension, medications, and environmental hazards.<sup>27</sup> The prevention of falls consequently requires the multidimensional assessment of a number of heterogeneous risk factors. It is also important to establish if the patient has a history of falls, because recurrent falls are a major cause of morbidity and mortality. Moreover, distinct interventions may be necessary for primary and secondary prevention. Indeed, once an older person falls, a “post-fall syndrome” may develop.<sup>28</sup> This condition is characterized by the patient’s fear of new events, leading the individual to unwittingly modify his/her posture and movements. Such postural modifications do nothing else than accentuating the risk of new events through altering the mechanics of movement. A vicious cycle may thus generate that accelerates the disabling cascade.

Gait and balance evaluation through standardized tests is a crucial step in primary and secondary fall prevention. Simply looking at how the patient walks or sit down/stand-up from a chair may already provide meaningful information about the risk profile.<sup>29</sup> Each comorbidity reported by the patient or detected during the clinical evaluation should be critically analyzed as a potential trigger of falls. Sensory deficits should be corrected whenever possible. Special attention should be paid to specific medications (e.g., long half-life benzodiazepines, anticonvulsants, anti-hypertensive drugs) potentially responsible for falls due to their pharmacodynamics and/or schedule of administration. Finally, a successful plan for reducing the risk of falls cannot ignore the elimination of eventual environmental hazards (both in the clinical facility and at the home).

#### Cognitive impairment and delirium

With the introduction of HAART, neurocognitive disorders in HIV-positive patients have been substantially reduced although still present. Obviously, HIV-associated neurocognitive disorders present a pathophysiological background completely different from those observed in older age.<sup>30,31</sup>

The mechanisms leading to the HIV-associated neurocognitive disorders are not yet completely clear. Surely, HIV plays a pivotal role in 1) permitting infected monocytes to pass the blood-brain barrier, 2) turning them into perivascular macrophages with parallel microglia activation, and 3) promoting the release of neurotoxic molecules. The consequence of such events is neuron demise via the direct actions of viral proteins, or indirectly via apoptosis triggered by the related inflammatory response.<sup>30</sup>

Alzheimer disease is traditionally believed to be the most common cause of dementia at older age. However, the categorization of different forms of dementia is quite a complex (and probably meaningless) exercise in advanced age. In fact, it cannot be ignored that 1) a clear pathophysiological mechanism for many types of dementia is not yet defined;<sup>32</sup> 2) the age-accumulation of subclinical and clinical deficits leads to a cloud of different causes (frequently overlapping and all potentially valid);<sup>7</sup> and 3) no specific treatment able to reverse the neurodegenerative process (whatever the etiology) is available to date.

In the case of HIV, the direct link between the viral infection and neurocognitive disorders lends support to pharmacological interventions potentially acting at the very bases of the infectious disease. For example, although evidence is still limited, antiretroviral drugs characterized by higher central nervous system penetration seem to provide some additional benefits in this context.<sup>33</sup> At the same time, it should not be underestimated the importance of multidomain interventions targeting exogenous risk factors. For example, interventions aimed at assuring social support to the patient, promoting healthier lifestyles, and tackling clinical conditions (e.g., sensory impairment, cardiovascular risk factors) potentially accentuating the cognitive decline and other commonly associated manifestations (e.g., behavioral and neuropsychiatric symptoms) might represent therapeutic commonalities between HIV-associated neurocognitive disorders and neurodegenerative disorders of advanced age.<sup>34</sup> As previously argued, also in this case, the definition of an optimal plan of intervention, which will have to necessarily be personalized according to the patient's characteristics, should imply a holistic approach and integrated care.

It is noteworthy that the cognitive impairment related to HIV infection combined with polypharmacy and reduced homeostatic reserves may expose the individual to a high risk of delirium. Delirium is indeed a frequent neurological complication of HIV infection, especially in critically ill patients.<sup>35</sup> Noticeably, the prevention of delirium passes through the (often non-pharmacological) management of risk factors. Amelioration of sensory

impairments, verification of patient's hydration, critical review of drugs prescriptions, and promotion of physical activity are only few of the habits that every clinician dealing with frail individuals should familiarize with.<sup>36</sup>

### **Sleep disorders**

Sleep disorders are frequently listed among the traditional geriatric syndromes.<sup>37</sup> They are also a common complaint in HIV patients.<sup>38</sup> Sleep disorders are a powerful risk factor for physical and cognitive decline, and able to enhancing the "pathological aging" of an individual (independently of the HIV infection).

The evidence around the nature of sleep disorders in HIV-positive patients is still limited, probably because the problem is underestimated.<sup>39</sup> Some reports suggest that concurrent psychiatric conditions (e.g., depression) may not completely explain sleep disorders in HIV patients, proposing that other factors (such as neuronal damage) may contribute to their pathogenesis.<sup>40</sup>

Again, in front of a geriatric syndrome (even when translated in a different field and with potentially diverse pathophysiological background), it is always important proceeding with a first multidimensional evaluation aimed at determining the underlying cause(s). The detection of the problem might lead to specific diagnostic procedures (e.g., polysomnographic exam) to guide in the choice of optimal therapeutic strategies. If sometimes non-pharmacological interventions (e.g., weight loss, physical activity, sleep hygiene recommendations) might be effective, some others special devices (e.g., oral appliances or positive airway pressure for sleep apneas), surgical interventions (e.g., nasal reconstruction, uvulopharyngopalatoplasty) or medications may be needed. In this latter case, physicians should cautiously prescribe the lowest effective dose, privilege molecules with shorter half-life, and follow the patient over time. The risk of polypharmacy and interactions among drugs is extremely high in HIV-positive patients, who are chronically exposed to multiple treatments as any frail and complex older adult.<sup>41</sup> A triage in the choice of interventions is thus needed and should be based on functional and pragmatic outcomes: quality of life and careful consideration of the altered homeostatic reserves are key factors for improving prescriptions and strategies.

### **Polypharmacy**

The exposure to polypharmacy, generally defined as the daily use of 5 or more medications, is an extremely common and clinically relevant condition in older persons as well as among HIV-positive patients. In a cornerstone study of geriatric literature, it was demonstrated that the

risk of adverse drug reactions is not related to age *per se*, but rather to the number of administered medications.<sup>42</sup> Surely, the aging process is associated with increasing “failure to thrive” of the homeostatic mechanisms, consequently rendering the person more vulnerable to the undesirable effects of drugs.<sup>43</sup> With advancing age, the metabolic capacities of kidneys and liver decline, exposing the individual to the risk of drug intoxication. Such a risk is also enhanced by the age-related changes in body composition, characterized by the inversion of the lean mass-fat mass ratio (even in the presence of a stable body mass). It is, for example, possible that a lipophilic medication administered after standardization for body mass or weight might be overdosed because the metabolically active tissues are reduced and the storage capacities increased. These crucial aspects to consider when treating an older person are equally important in HIV-positive patients. They might be even more important given the fact that this population is already (chronically) exposed to HAART agents in addition to those used to treat comorbidities.

The best way for tackling polypharmacy is to reduce inappropriate prescriptions. Specific guidelines and recommendations for “de-prescribing” are available in literature.<sup>44</sup>

In general, clinicians should carefully evaluate the list of drugs taken daily by older persons and HIV-positive patients. During the evaluation process, it is crucial that the physician is not driven at treating every single abnormality. Such an approach would easily conduct to overtreatment and risk of adverse drug reactions. The choice of a treatment should be judged on the basis of realistic and practical objectives, while maintaining a holistic vision of priorities.<sup>45</sup> By doing so, it is important to keep in mind that evidence for commonly used drugs is often derived from trials conducted in different (healthier) populations.<sup>46</sup> Moreover, in older persons and in HIV-positive patients, it is also important to explore social and economic issues potentially affecting the patient’s adherence and compliance to the therapeutic recommendations in order to reduce the risk of adverse drug reactions. For this reason, it is always wise to check the medications really taken by the patient at every clinical contact. Some evidence supports the benefits deriving from the adoption of computer-based prescribing systems.<sup>41</sup> Indeed, software applying specific algorithms for supporting the appropriateness of drugs prescription have shown to improve the healthcare provider’s behavior. Unfortunately, evidence about the beneficial effect of these systems on the patient’s outcomes is still very limited.

The clinician should also try to simplify as much as possible the drug prescriptions, both in terms of number

of medications and their daily schedule. In this context, the use of combined drugs might be helpful, but only if allowing adequate calibration of the single molecules according to the individual’s reserves. The general rule to follow in geriatric population and also applicable to frail HIV-positive patients is “Start low, go slow.”<sup>47</sup>

### **Mobility impairment and functional limitation**

Mobility is a basic function present in almost every living being. The incapacity to move has been related to negative health-related outcomes across species.<sup>48</sup> It is noteworthy that physical performance has repeatedly been considered as a marker of wellbeing. Its decline is closely related to the loss of the biological homeostasis of an organism as a whole. Thus, it is not surprising that individuals experiencing an accelerated and/or accentuated aging process are also characterized by impaired mobility.

Besides serving as an important marker to estimate the biological age of a person, mobility impairment also defines a major clinical outcome for older adults.<sup>49</sup> In fact, mobility disability is considered the first step of the disabling cascade, a condition to be prevented before the vicious circle of frailty-disability becomes more difficult to be halted.

The age-related impairment of the mechanisms devoted to mobility is multi-causal. Although the quantitative and qualitative decline of skeletal muscle (often referred to as “sarcopenia”) may represent the organ-specific impairment responsible for the loss of mobility with advancing age, it is indeed difficult to indicate one single cause for the syndromic manifestation of mobility impairment. For example, sensory deficits as well as environmental factors may easily explain the worsening of mobility.

A recent systematic review showed that mobility and motor function disability is highly prevalent (about 25%) among people living with HIV in sub-Saharan Africa.<sup>50</sup> HIV-positive patients receiving combination antiretroviral therapy frequently present specific body composition modifications (i.e., “lipodystrophy syndrome”), characterized by adipose tissue redistribution. Interestingly, central obesity has shown to be a strong predictor of frailty in community-dwelling older persons with HIV and to significantly impact physical performance measures.<sup>51</sup> Moreover, lipodystrophy is often accompanied by a reduction of bone quality,<sup>52</sup> which can further contribute to undermine the structure of the organism,<sup>53</sup> leading to a decline of function.

To date, the only intervention able to positively affect mobility impairment is physical exercise. The Lifestyle Interventions and Independence for Elders (LIFE) trial

has recently showed that a long-term structured physical activity is able to prevent mobility disability in older persons with physical function impairment.<sup>54</sup> Similar results have been reported in preliminary studies recruiting HIV-positive patients.<sup>55</sup> A physical activity program should always be proposed in parallel with nutritional counseling in order to meet the new (increased) energy demands and provide adequate protein intake to promote muscle growth and strengthening. It is indeed important to stress how lifestyle modifications are crucial and should be part of the HIV therapy.

Mobility impairment is usually considered to be the first stage of the disabling process. After losing the capacity to cover the necessary walking distance for maintaining independent life (traditionally estimated in 400 m<sup>56,57</sup>), the individual usually tends to develop additional disabilities: first in the accomplishment of instrumental activities of daily living (IADL), then in the execution of basic activities of daily living (ADL). The gradual loss of these capacities makes the clinical management increasingly challenging because of 1) the instauration of a detrimental vicious cycle, and 2) socio-economic barriers becoming more relevant and evident. For these reasons, the care of individuals with functional limitations requires a multidisciplinary team working in a dedicated network well nested in the territory. Actions aimed at treating disabilities and/or preventing further decline should foresee personnel dedicated to the identification of the underlying causes, the clinical management, and the close follow-up of the patient. Such strategy has shown to be particularly effective in the geriatric population when the members of the team (e.g., physician, nurse, physical therapist, social worker, etc.) work synergistically using shared information and closely monitoring the patient's clinical modifications.<sup>22</sup>

### How to incorporate geriatrics in the care of HIV patients

The increasing age of patients across multiple medical disciplines (not only in care settings for HIV) is challenging the sustainability of traditional healthcare systems. The old-fashioned models of care based on single diseases are no longer functional. In order to tackle the special needs brought by the “gray tsunami,” it is important to shift toward different paradigms based on syndromes, chronic conditions, multimorbid individuals, and person-tailored interventions.<sup>16</sup> Such mind setting is crucial for geriatric care and should be better nested in the training of healthcare professionals. In our “gray societies,” it is not anymore acceptable that the study of aging (and of its consequences) is only marginally included in the

education curricula and often used for only justifying nosographic conditions.<sup>6,58</sup>

In the specific field of HIV, geriatric care might be promoted by facilitating interdisciplinary exchanges between geriatricians and infectious disease specialists. As mentioned above, the development of structured collaborations mirroring previous successful experiences (e.g., orthogeriatric wards)<sup>59,60</sup> might represent a first promising (and not invasive) strategy. Surely, the special features of HIV-positive patients may require the design of *ad hoc* new tools for supporting the clinical assessment of this new frail population. In fact, the instruments used in geriatric medicine are based on scopes, criteria, and cut-points which are likely not applicable (or relevant) to HIV-positive patients. Nevertheless, geriatricians can provide the background and initial models for building up specific tools aimed at capturing the clinical complexity and peculiarities of the frail HIV-positive patients. For example, some studies conducted in HIV-positive patients have started using the Frailty Index developed by Rockwood and Mitniski<sup>61,62</sup> with the aim of measuring the individual's “biological age” and predicting negative outcomes.<sup>63</sup> Being based on arithmetic and not clinical assumptions, this instrument is more suitable than others for an immediate translation of the frailty concept from geriatrics to the IDM world given its quantitative nature. Differently, other instruments structured around specific socio-demographic, biological, and clinical features may require adaptations before being implemented in the new setting, but may still provide ground for thinking.<sup>64</sup>

### Conclusions

The growing prevalence and incidence of geriatric syndromes across medical disciplines is a sign of the socio-economic and cultural advances of our societies. At the same time, global aging is substantially modifying the scenarios where clinical practice is conducted. Clinical decisions are indeed extremely complex in biologically aged individuals and, as such, require multidisciplinary input. Healthcare systems are therefore called to abandon traditional paradigms in favor of new models of care in order to accommodate novel needs and demands. Such an endeavor may take advantage of the wealth of experience accrued by geriatricians over the last decades.<sup>6</sup>

The birth of clinical services convening healthcare professionals from multiple disciplines might be a promising venture to pursue, following the successful experience of other “mixed” clinical units. If medical specialties will continue to work in parallel without combining their expertise for the care of multimorbid and frail elders,

current healthcare systems will simply collapse. Such a revision is particularly urgent in those disciplines, like IDM, which increasingly face the management of geriatric syndromes in biologically aged individuals.

On the other hand, the transposition of the geriatric background to other disciplines is a difficult task to accomplish, especially because geriatric medicine does not typically operate under definitive rules. Older patients represent an extremely heterogeneous population, in which medical complexity is not determined by chronological age. The implementation of geriatric care in HIV clinics therefore requires the acceptance of new paradigms in the personalization of pharmacological and non-pharmacological interventions.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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