

SPECIAL ARTICLE

THE MANAGEMENT OF GERIATRIC AND FRAIL HIV PATIENTS. A 2017 UPDATE FROM THE ITALIAN GUIDELINES FOR THE USE OF ANTIRETROVIRAL AGENTS AND THE DIAGNOSTIC-CLINICAL MANAGEMENT OF HIV-1 INFECTED PERSONS

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Abstract: *Objective:* This article deals with the attempt to join HIV and geriatric care management in the 2017 edition of the Italian guidelines for the use of antiretrovirals and the diagnostic-clinical management of HIV-1 infected persons. *Methods:* The outlined recommendations are based on evidence from randomized clinical trials and observational studies published in peer-reviewed journals and/or presented at international scientific conferences in recent years. The principles of starting antiretroviral therapy in elderly patients and the viro-immunological goals are the same as in the general HIV population. However, there are some specificities to consider, related to the host as well as the therapy itself. HIV care in elderly patients must shift from a combined AntiRetroviral Therapy specific approach to a more comprehensive management, and from a disease-based model (list of co-morbidities) to a multi-morbidity and frailty standpoint. The implementation of a geriatric approach, based on the Comprehensive Geriatric Assessment, is essential and consists of a broader evaluation of health status. This multidimensional and multidisciplinary evaluation is focused on the development of a tailored intervention plan. Polypharmacy is a frequent condition in the older population and an independent risk factor for negative health-related outcomes. This can be overcome with a multidisciplinary and cooperative approach involving HIV specialists, geriatricians and primary care physicians. *Conclusion:* The inclusion of geriatric care becomes necessary due to the novel needs of an evolving patient population. It is important to underline that the HIV specialist will continue to lead multidimensional interventions and optimize quality of care for HIV-positive people.

Keywords: Comprehensive geriatric assessment, frailty, HIV, guidelines.

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Background

In the context of the global ageing epidemic, HIV infection is not an exception, but rather a paradigm of this relatively new phenomenon. The greying of people living with HIV is – everywhere – part of the HIV landscape (1), arising from two phenomena: the general effectiveness of antiretroviral therapy and the increasing mean age of HIV acquisition (2).

Future projections of the evolving demographics clearly indicate that HIV care will intersect with geriatric medicine (3). This is not merely the result of an age shift. In fact, antiretroviral drugs, patients and, consequently, the disease itself have changed and continue to evolve:

1. Antiretroviral treatment has changed. Drug potency,

genetic barriers as well as short- and long-term toxicities have been the determinants of HIV-therapy success/failure during the early Highly Active AntiRetroviral Therapy (HAART) era. Antiretroviral regimens have become more effective and less toxic. Thus, in HIV-negative people aware of their HIV risk, the probability of morbidity and mortality might be lower in the future. This is due to early detection through the efficient continuum of care resting on wise networking strategies.

2. Patients have changed. HIV-infected people have experienced a dramatic improvement in life expectancy during the modern combined antiretroviral therapy (cART) era, particularly those who initiated therapy at earlier stages of the disease (4). Several recent cohort studies have suggested that the life expectancy of HIV-infected individuals may soon

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approach that of the general population (5). At the same time, an increasing number of people is seroconverting HIV at an older age because of a lower perception of sexual risk in the elderly (6). The net result is that nowadays HIV-people display a heterogeneous clinical presentation with a substantially increased risk for comorbidities in the former group (i.e., 'HIV-aged people') compared to the latter (i.e., aged HIV-people) (2).

3. HIV disease itself is changing. A rapid progressive disease is evolving into a chronic condition with a substantial variation in the immunopathological driver of the disease. Immune-deficiency is leaving the room for immune-activation.

Although there is now a broad consensus that immune-activation and inflammation persist in the majority of HIV-infected individuals maintaining long-term ART-mediated viral suppression (even in those that restore normal CD4+ T cell counts) (7), the degree to which inflammation is a direct cause of morbidity and mortality remains controversial.

In this context, in the current edition of the Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons (IHIVGL), the Italian Society of Infectious and Tropical Diseases, in collaboration with the Italian Ministry of Health, have included a chapter entitled: "Management of the ageing, geriatric and frail individuals with HIV". This could be interpreted as a momentous report, given that specific sections regarding the management of geriatric HIV patients do not exist in other European guidelines.

The objective of the present article is to introduce a first attempt to join HIV and geriatric care management for all the involved healthcare professionals (in particular, geriatricians and HIV-specialists) as well as for people living with HIV and their communities. Such effort reflects the emergence of a novel "Geriatric-HIV" clinical know-how similar to what has previously occurred in other medical specialities like orthogeriatrics (8), cardio-geriatrics (9), or onco-geriatrics (10).

These guidelines are addressing clinical needs of older adults living with HIV, in the geriatric age definition, over 65 years (according to geriatric age definition) or rather any age but only if they meet frailty criteria.

To conceptualize the age-related increase of vulnerability, the term "frailty" has been commonly used in the medical literature over the past two decades. Frailty is defined as a condition caused by the reduction of homeostatic reserves exposing the individual to higher risk of negative outcomes (11).

Frailty can be considered either as a specific syndrome (12) or as state with degrees of risk for adverse outcomes (13). It might represent much more than a mere condition to be screened for but rather an interval parameter reflecting the "biological age" of the individual. The argument further is that this could replace the obsolete criterion of chronological age in clinical decision algorithms.

In HIV setting, frailty has been operationalized both with a frailty phenotype and frailty index tools. The frailty phenotype

(FP) is based on a predefined set of five criteria exploring the presence/absence of signs or symptoms (involuntary weight loss, exhaustion, slow gait speed, poor handgrip strength, and sedentary behavior). The number of criteria (a six-level ordinal variable ranging from 0 to 5) is categorized as a three-level variable depicting robustness (meets none of the criteria), pre-frailty (meets one or two criteria) and frailty (meets three or more criteria) (14).

The only frailty index tool validated in HIV cohorts comprises 37 health variables that are routinely collected at each visit (15). Each variable included in the FI is coded with a value of 1 when a deficit is present, and 0 when it is absent. Missing values are removed from both the numerator and the denominator of the FI (16). $FI > 0.3$ has been used to identify frail individuals.

Frailty as well as falls, urinary incontinence, polypharmacy and delirium describe the so called geriatric syndromes which are multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges (17), posing some special clinical considerations. First, for a given geriatric syndrome, multiple risk factors and multiple organ systems are often involved. Second, diagnostic strategies to identify the underlying causes can sometimes be ineffective, burdensome, dangerous, and costly. Finally, therapeutic management of the clinical manifestations can be helpful even in the absence of a firm diagnosis or clarification of the underlying causes (18).

Geriatric syndromes are more predictive of self-reported health and mortality than diagnoses of chronic diseases or MM alone (19, 20). The majority of existing guidelines, however, remain organ system-based and do not include formal assessment for geriatric conditions (21).

Methods

The recommendations issued in IHIVGL are based on evidence from randomized clinical trials and observational studies published in peer-reviewed journals and/or presented at international scientific conferences in recent years. Controlled studies were critically evaluated, in particular by analysing their design, power, sample representativeness, primary and secondary objectives, duration of follow-up, criteria of superiority, non-inferiority and equivalence, methodology, and analytical approach. Information from safety reports drafted by regulatory authorities (FDA - Food and Drug Administration, EMA - European Medicines Agency, AIFA - Italian Medicines Agency) was also considered.

Following governance directions, the IHIVGL expert panel (subdivided into working groups) established a work-plan and drafted a preliminary text after a progressive assessment of electronic contents. Later, in a plenary session, agreements on the contents and degrees of recommendation were reached.

The experts declared their conflicts of interest specifically indicating every potential association (i.e., financial interests,

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research grants, participation in advisory boards, commissioned lectures at sponsored events) with companies involved in the production of antiretroviral drugs and/or diagnostic materials and/or tools for the monitoring of therapy and disease, over the last five years. LM, CM, JM, IF and MC, co-authors of this paper, are not members of the IHIVGL panel, but helped in the critical revision of the manuscript.

The present text complies with the aims in the methodological introduction to the full text of the Italian Guidelines for the use of antiretroviral drugs and the diagnostic-clinical management of people with HIV-1 infection. The present article should not be considered exhaustive compared to the full text version of the Guidelines (11) available at the website: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2696_allegato.pdf.

Ageing, geriatric and frail patients

The principles of starting antiretroviral therapy in elderly patients and the viro-immunological goals are the same as in the general HIV population. However, there are some specificities to consider, related to the host as well as the therapy itself.

In particular, polypharmacy, defined as the concomitant use of five drugs or more, is a very frequent condition in the older population and an independent risk factor of negative health-related outcomes (e.g., hospitalization, institutionalization, functional impairment, malnutrition and adverse drug events) (30, 31). Moreover, age-associated physiological changes altering pharmacokinetics (i.e., decreased GI transit, increased fat-to-lean body ratio, reduced hepatic metabolism and renal elimination) (32) and pharmacodynamics may result in increased sensitivity to medications and a higher risk for adverse side effects.

Consequently, drug-drug interactions in ageing patients with polypharmacy are unavoidable. Nevertheless, they can be curtailed and managed by adopting ad hoc strategies.

In elderly HIV infected patients, a broader evaluation of health status is clearly necessary as part of a multidimensional approach characterizing the Comprehensive Geriatric Assessment (CGA). This methodology is not limited to the evaluation of the individual's clinical conditions. Rather, it is focused on the development of tailored intervention plans. The geriatric approach is based on a multidimensional and multidisciplinary evaluation of the individual, to which every professional brings his/her own expertise and background in patient management. Consequently, functional capacity, fall risk, neurocognitive disorders and/or dementia, mood, polypharmacy, social support, and economic issues remain of special relevance in optimizing treatment goals according to personal needs (33, 34).

Table 1

Degree of recommendation and level of evidence

Degree of recommendation	
A	Highly recommended.
B	Moderately recommended.
C	Optional.
Level of evidence	
LEVEL I	The data are obtained from at least one controlled, randomized study with sufficient power or from a meta-analysis of controlled studies.
LEVEL II	The data are collated from non-randomized studies or from cohort observational studies.
LEVEL III	Recommendation based on case reviews or agreement among experts.

Table 2

Specificities of elderly HIV patients

	Recommendation (Strength of evidence)	Bibliographical references
Host-related		
Limited CD4+ T cell count recovering with ageing		
Superior virological response (due to higher treatment adherence) with ageing	[AII]	22, 23
Higher risk of progression compared to those below 50 years of age		
Higher risk of mortality related to non-AIDS conditions	[AII]	24, 25, 26
Higher risk of ART interruption due to toxicity	[AII]	27
Treatment-related		
The ART decisions should consider multi-morbidity and polypharmacy, as well as virological efficacy	[AII]	27, 28
When virological suppression is achieved, NRTI-sparing, boosted-free regimens or even a simplification in mono or dual therapy should be considered in multi-morbidity and/or polypharmacy conditions	[BII]	27
TAF should be preferred to TDF	[AI]	28, 29

Table 3
Specificities of the most common clinical conditions in elderly HIV patients

Actions	Recommendation (Strength of evidence)	Bibliographical references
Multi-morbidity, frailty, geriatric syndrome and disability are more prevalent in HIV patients compared to the general population, although the risk factors are similar.	[AII]	15, 35
Multi-morbidity is prevalent in older HIV patients, potentially serving as a risk assessment tool in the stratification of patient complexity.	[AII]	35
Frailty, independently of operationalization, recognizes HIV specific determinants such as CD4+ T cell count and HIV viral load.	[AII]	36, 37
Frailty assessments allow for a stratification of older HIV patients' vulnerability, enabling the identification of a target population that can benefit from specific health interventions such as diet and physical activity.	[BII]	37
A major biological correlate of frailty is skeletal muscle decline (or sarcopenia), a major risk factor for disability. Body composition assessment (in combination with physical performance evaluation) should be evaluated in patients with lipodystrophy.	[CII]	36
The high prevalence of geriatric syndromes (such as fall, delirium, visual and hearing impairment) and their association with health-related events justify their assessment in HIV patients above 50 years of age.	[AII]	36
The assessment of physical function is crucial to the evaluation of older persons and should be conducted using validated scales and indexes.	[CII]	37

Table 4
Evaluation and additional behaviours in the approach to elderly HIV patients

Actions	Recommendation (Strength of evidence)	Bibliographical references
Carefully assess social and family support, dependence on or abuse of substances and socio-cultural barriers (e.g., migration and social stigma).	[AI]	33
Maximize quality of life and the prevention of functional loss.	[AII]	38
Integrate individual clinical and geriatric care approach	[AII]	28
Perform periodic screening or depression and neurocognitive disorders.	[BII]	39
In case of neurocognitive impairment, consider the possibility of viral escape of HIV in the cerebrospinal fluid (CSF) and neuro-syphilis, thereby rendering a CSF assessment to be considered.	[AII]	31
Reinforce all the prevention principles of HIV and other sexually transmitted infections.	[AI]	30
Integrate skills and, wherever possible, resources across HIV/AIDS and geriatric care centres.	[AII]	40

Table 4 reports evidence about specific points to consider in the management of older HIV patients.

Discussion

The debate regarding accentuated or accelerated ageing processes affecting HIV patients is ongoing (41). Several factors have been proposed as detrimental contributors to the ageing process of HIV patients, including chronic inflammation, long-term ART drug toxicity, neurocognitive impairment, and a high prevalence of social and behavioural risk factors. Regardless of the causes, it is evident that HIV-positive persons are characterized by an older biological age

compared to the HIV-negative population. Moreover, because elderly HIV patients are generally excluded from clinical trials (42), there is limited information on the efficacy and safety of antiretroviral regimens in this particular population.

As the HIV-positive population grows, the healthcare needs to evolve, especially for the purpose of targeting chronic and disabling conditions more effectively. HIV care must therefore enrich the straightforward ART-specific approach with elements broadening older patients' assessment to capture their heterogeneity and complexity more accurately. Recommendations are provided to improve the so-called "HIV continuum of care", which defines the sequential steps that people living with HIV should go through from the initial

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diagnosis to the achievement of viral suppression. These actions include the optimization of the HIV care environment, an increase in HIV testing and care network, treatment coverage and monitoring of viral suppression (42). It is noteworthy that HIV care is a continuum going beyond the traditional goal of viral un-detectability. So far, no guidelines have included such new paradigms in HIV management.

The new section of the IHIVGL trying to introduce a new cultural paradigm in the management of elderly HIV patients based on the following shifts in clinical perspective:

1. from the assessment of single co-morbidities to the management of multi-morbidity
2. from the assessment of organ impairment to the evaluation of functional capacity
3. from age assessment to frailty evaluation.

Taken together, clinical evaluation is not a list of multiple organ impairments to be considered as a disease status, but rather a wider and more detailed image of health status described in functional capacities.

This change in health perspective is extremely important to adapt care models to the emerging needs of HIV-infected individuals characterized by a complex composition of multi-morbidity, frailty, geriatric syndromes and disability.

The geriatric approach, based on a CGA, establishes a multidimensional and multidisciplinary evaluation of the individual, to which every professional brings his/her own expertise and background in patient management. Therefore, the interdisciplinary team members (including nurses, social workers, pharmacists, psychologists, physical therapists) concur in the evaluation of ageing patients to objectivize their needs and resources to complete a multidimensional evaluation. This work is essential to identify frail patients and to develop tailored intervention plans, indicating priorities and setting goals. The objectives of the evaluation are also changing, shifting from a restricted focus on life expectancy (i.e., the estimated number of years to live) to a broader consideration of quality of life (e.g., expected life free from disability). From this perspective, the active empowerment of patients (through improved information and involvement) becomes crucial to the prevention of negative health-related events.

This multidimensional management can be integrated in "Total Patient Care" (TPC), which results in a more comprehensive patient approach, considering their physical, emotional, social, economic, and spiritual goals (43), as well as personal reactions to illness (including the ability to meet self-care needs). It implies the transition from a model based on a single referral care centre to a coordinated and multidisciplinary network providing primary and specialized support to people living with HIV.

Central to this paradigm shift is the recognition of the need for an active partnership with primary care physicians, who remain in charge of providing proactive, preventive, and chronic care management through all stages of life.

Primary care physicians could also be key players in the management of polypharmacy. This condition is common in elderly HIV patients. Consequently, these are at higher risk of drug-drug interactions between antiretroviral drugs and concomitant medications, which may compromise medication effectiveness and can be responsible for serious adverse drug events (including organ system injury, hospitalization, geriatric syndromes, and mortality). Interventions to address polypharmacy in the HIV setting are still missing and primary care physicians can help in this multidimensional approach to elderly patients, because they can share all clinical information across the entire healthcare system, using of registries, information technologies, and health information exchanges.

To conclude, it is also crucial to ensure that patients and their families receive proper education and support to actively participate in the planned care program. Patient risk factors may include social vulnerability, a predictor of mortality and disability in elderly people. In this context, HIV and Ageing stigma plays a crucial role and requires urgent action. HIV stigma is a well-known barrier for HIV testing and treatment in numerous settings, particularly in low-and-medium income countries, contingent on inequalities in social, economic, and political power (44). At the same time, many stereotypes (the so-called "Ageing Stigma") are typically associated to the older population (e.g., needy, unhappy, senile, inactive, useless to society, not receptive). Apparently, we are indeed in the presence of an augmented risk of stigmatization due to the overlap of two detrimental phenomena, the HIV and Ageing stigmas. This aspect also requires urgent consideration.

Finally, it is important to underline that the HIV specialist will continue to lead multidimensional interventions and optimize quality of care for HIV-positive people. The progress made over the years in the fight against HIV are not underestimated here. HIV care will remain an outstanding example of healthcare management. The inclusion of geriatric care becomes necessary due to the novel needs of an evolving patient population. The collaboration between HIV specialists, geriatricians and general practitioners will follow the already existing (and successful) paradigms developed in other interdisciplinary models of geriatric care, with an utmost respect for each and every stakeholder's expertise and background.

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