ARTIGO DE CONSENSO

Gestão clínica de comorbilidades no envelhecimento da população que vive com VIH: uma revisão de peritos – Parte I

Clinical management of comorbidities in the aging population living with HIV: an expert review – Part I

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/ Resumo

Introdução: a melhoria da eficácia e segurança de novas terapêuticas antirretrovíricas permite que pessoas com infeção por VIH vivam mais e com melhor qualidade de vida. Em Portugal, como noutros países europeus, está a aumentar o número de pessoas com 50 ou mais anos de idade e infeção por VIH, e a maioria apresenta pelo menos uma comorbilidade. As últimas diretrizes internacionais reconhecem que este grupo precisa de tratamento e cuidados personalizados.
Objetivos: este primeiro manuscrito descreve a metodologia de painel de peritos seguida neste projeto e revê o estado da arte sobre a gestão clínica das comorbilidades no envelhecimento da população que vive com VIH.
Métodos: entre julho de 2017 e dezembro de 2018, realizaram-se vários painéis de peritos, num total de sete peritos de diferentes áreas clínicas e dois peritos em infeciologia. O projeto foi coordenado por um comité científico independente.
Resultados: apesar dos recentes avanços na prevenção, deteção precoce e tratamento de comorbilidades em pessoas mais envelhecidas com VIH, faltam recomendações específicas que incentivem o cuidado integrado destas pessoas.
Conclusões: a implementação de recomendações específicas e integradas permitirá que os adultos em envelhecimento e com infeção por VIH alcancem melhores resultados clínicos e melhor qualidade de vida.

Palavras-chave: Envelhecimento; vírus da imunodeficiência humana; comorbilidade

/ Abstract

Introduction: *improved efficacy and safety of novel antiretroviral therapies regimens allow people with HIV to live longer and with better quality of life. In Portugal, like in other European countries, the number of individuals aged 50 years and older that have HIV infection is increasing and the majority present at least one comorbidity. The latest international guidelines recognize that older people with HIV need personalized treatment and care.*
Aims: *this first manuscript describes the expert panel discussion methodology followed for this project and reviews the state of art on clinical management of comorbidities in the aging population living with HIV.*
Methods: *between July 2017 and December 2018, several expert panel discussions were coordinated with medical specialists, in a total of seven experts from different areas of clinical practice and two infectious diseases specialists. The project was supervised by an independent scientific committee.*
Results: *despite the latest advances on prevention, early detection and treatment of older people with HIV in a multimorbidity setting, specific insights that foster an integrated comprehensive care are still missing. Conclusions: implementation of specific and integrated guidances will allow for older adults with HIV to achieve better health outcomes and quality of life.*

Keywords: *Aging; human immunodeficiency virus; comorbidity*

/ Introduction

The aging phenomena in adults living with the human immunodeficiency virus (HIV) is recognized as a process featuring some specificities, with underlying accelerated (premature) and accentuated effects, increased immunosenescence and chronic inflammation conditions occurring at a younger age.[1] Current guidelines recommend that antiretroviral treatment (ART) should be initiated in all HIV positive individuals.[2,3] Because of the improved efficacy and safety of novel ART regimens, people with HIV live longer and with better quality of life, which naturally increases the number of older persons with the infection.[4] An econometric analysis conducted in Portugal revealed that, in 2037, adults with HIV infection aged 50 years and older will significantly increase up to 80%.[5] In Portugal, 15.4% of the people living with HIV were 50 years or older in 2018.[6] Additionally, 28% of the new cases were aged 50 years or older at the date of diagnosis, and this proportion is still increasing.[6]

Due to changes stemming from a natural aging process, the number of pathologies and unhealthy conditions rise and, consequently, people with HIV need greater medical support and more treatments. Up until now, various studies demonstrated that non-infectious comorbidities (mainly diabetes *mellitus*, cardiovascular diseases, chronic kidney disease, hypertension, osteoporosis and non-AIDS related cancers) are more common in people with HIV than in the general population.[7] Both simultaneous and premature presence of more than two non-infectious comorbidities (polypathology) are frequent and have been associated with disease severity (e.g., lower $CD4^+$ T count) and prolonged ART exposure.[8–10] Individuals with longer history of HIV infection show higher prevalence of multiple comorbidities and concomitant treatments.[11] Therefore, aging people with HIV show an increased risk of multiple morbidity, compared to those diagnosed with the infection later in life.[10]

Cohort studies from the United States and European countries appraised comprehensively the profile of aging individuals living with HIV.[12–16] Overall, those analyses concur with the hypothesis that there is an additive risk factor for persons with HIV, besides traditional factors in general population, for comorbidities development and aging.[12–15] The Dutch ATHENA cohort study projected that more than half of the people with HIV infection will be receiving co-medications by 2030.[16] Therefore, due to the complex profile of the population living with HIV, health systems need to provide an integrated and comprehensive care, in terms of prevention, early detection and treatment, specifically for adults older than 50 years.[17]

According to data collected from the Directorate-General of Health (DGS) in Portugal, 59,913 persons with HIV infection have been diagnosed in the country between 1983 and 2018, but there are progressively fewer new HIV cases in last years.[6,18,19] Several strategies were defined as priorities to accomplish this milestone,[16] in addition to the UNAIDS ambitious goals established for prevention, diagnostic and treatment of HIV for 2020 and 2030.[19] The Aging Positive Study assessed the non-AIDS-related comorbidities in Portuguese people with HIV-1 aged 50 years and older.[20] This multicenter, cross-sectional study included 401 adults with a mean age of 59 years and having, at least, one comorbid condition (90%). Hypercholesterolemia, arterial hypertension and chronic depression/anxiety were the most common comorbidities and almost half of the people with HIV were under treatment with lipid-lowering drugs. While age and duration of HIV infection were positively correlated with the presence of comorbidities, traditional factors intrinsically related with the aging process might also play an important role in this process.[20]

Albeit national and international guidelines were recently revised, there is still a gap in care regarding the aging population living with HIV.[2,3] Great attention has been paid to drug interactions and simplification of ART regimens but focus on how to prescribe in the elderly must be consolidated. For instance, clinicians should be educated on how to assess and manage older age-related syndromes, with regard to multiple comorbidities and polypharmacy, especially in those receiving two or more drugs for different conditions at the same time.[21–24] This manuscript Part I belongs to a set of two expert review articles and describes the expert panel discussion methodology followed for this work. In addition, we review the current state of art to provide further insights on clinical management of most relevant comorbidities in people aged 50 years and older living with HIV, within the Portuguese health care setting. The Part II of this manuscript will include the key points on prevention, diagnosis and treatment considerations of most relevant comorbidities in the Portuguese population living with HIV, to improve their management.

/ Methods

Expert group meetings

This project was conducted between July 2017 and December 2018 and followed the methodology for an expert panel discussion.[25] In summary, the discussion process behind the expert panel discussion is described in Fig. 1.

First, a three-member scientific committee of HIV medical specialists was formed to design and supervise the project. This scientific committee was responsible also for identifying, at the inception phase of the project, the most relevant comorbidities and aspects that affect the Portuguese population with HIV in clinical practice. In addition, two infectious diseases specialists were involved in the revision of the document and moderation of the expert meeting, according to their key role as group coordinators. In a first attempt to define the project strategy and main goals of the expert document, a preparatory meeting was conducted. Clinical specialists were selected considering areas of those comorbidities that are more frequently associated with the

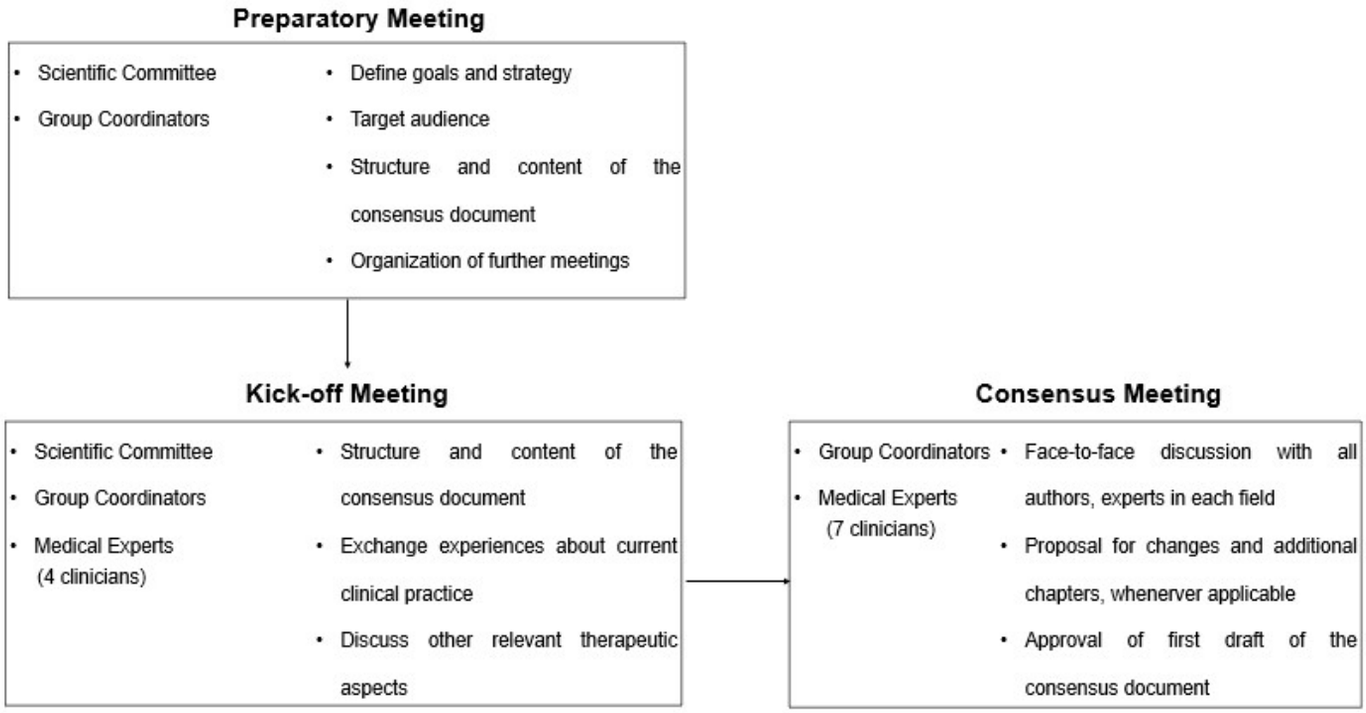

Figure 1: Flowchart for consensus development meetings.

aging process, those that are most frequently reported in the population living with HIV and those of interest in the Portuguese population.

After this first step, four medical experts in different clinical areas (i.e., cardiology, nephrology, endocrinology and neurology) were selected, based on their publication records, academic interests, current practice and clinical experience. Those experts were invited to participate in the kick-off meeting of the project, to discuss the most relevant diseases affecting the population with HIV that should be appraised in the expert document. Additionally, three medical experts in urology, oncology and psychiatry were suggested for invitation, accounting for a total of seven experts from different institutions across the country. The methodology for the elaboration of the expert document is described next.

Expert recommendations document

All experts were invited to conduct a literature review with focus on each clinical area, according to evidence-based data and current experience in clinical practice. The document described a comprehensive care plan embracing the most common comorbidities of the Portuguese population living with HIV and those that can interfere with patient management, regarding previously mentioned clinical areas. A non-systematic review was conducted in October 2017 to identify both original research and review articles that addressed epidemiology, risk factors and impact of HIV infection in comorbid persons. Transversal questions and recommendations in daily clinical practice were focused on screening, diagnosis, treatment and referral criteria. Publications were manually selected according to all relevant key words and terms and, then, considered for this expert review if written in English and/or Portuguese, indexed in MEDLINE/PubMed, without date limits. After the first drafting of the document, its content and structure were discussed face-to-face with all authors, during the expert meeting, moderated by infectious diseases specialists (group coordinators). The document passed through three revision cycles, including all authors, infectious diseases specialists and, finally, the Scientific Committee of the project.

/ Results

The key points on prevention, diagnosis and treatment considerations of most relevant comorbidities in the Portuguese population living with HIV were described in an expert recommendations document. The main conclusions and insights for each clinical area and related comorbid conditions will be presented in Part II of this manuscript.

/ Discussion

According to the World Health Organization (WHO), a successful and healthy aging can be achieved, despite having any comorbidity, as long as well-controlled.[26] Aging is also a multidimensional process and various authors have endeavored to define the criteria that establish if older persons are aging

well.[26–29] For instance, they should have equal access to basic needs, be empowered and able to make informed-based decisions, have both cognitive and physical functional capacities, be actively engaged in peers relationships and contribute to the society.[26–29] Vance *et al.* (2011) explored the concept of successful aging in people living with HIV, considering all factors interacting with this infectious disease, such as biological health, cognitive efficiency, mental health, productivity, life satisfaction, among others.[30]

Due to the increased complexity and rapid changes in ART development, current guidelines and recommendations are regularly revised to reflect those advances in clinical practice.[7] However, an unmet need for a personalized treatment in people with HIV persists, with focus on the patient, such as medical history, risk factors and comorbidities, as well as on the available therapies.[3,31] Clinicians should regularly review patients' tolerability and adherence to treatments, to reduce pill burden and the risk of drug-drug interactions, particularly in ART-experienced individuals under older therapies and with longer infection history.[2,3,31] The percentage of patients with $CD4^+$ T counts <350 cells/mm^3 increases with the age of diagnosis, affecting 63% of the adults aged 50 years and older.[4] Nonetheless, the elderly usually show higher adherence to ART, if not cognitively impaired.[32]

Latest international guidelines recognize that elderly people with HIV need special attention and management when prescribing ART, to avoid inappropriate medications.[3,33] Therefore, clinicians must be aware of lifestyle factors, long-term complications and treatment convenience for those patients, to improve their quality of life. In 2011, the American Academy of HIV Medicine (AAHIVM) and the American Geriatrics Society (AGS) were involved in a joint consensus document about strategies for physicians managing older HIV-positive persons, within areas most in need of clinical guidance regarding US practice.[34] In Europe, the AIDS Study Group (GESIDA) from Spain have recently worked on a consensus document about ART selection and management, considering evidence-based recommendations, with focus on special situations, including multimorbidity.[35]

In Portugal, national recommendations only highlight the need for early ART start in persons aged 50 or more years old.[2,36] Despite the absence of recommended actions, there is a tremendous effort to improve care for those individuals, resulting from integrated co-management strategies that involve interdisciplinary teams. Moreover, it is crucial to implement strategic education and self-management of patients, supported by a comprehensive chronic HIV-related care.[19] Last year, Cresswell and Levett (2017) described for the first time the challenges of current aging services for people with HIV at hospitals in UK.[24] Among a total of 102 clinics, only two had a specific HIV service for the elderly, but 68% of the respondent physicians supported the development of specific national guidance from the British HIV Association (BHIVA) for adults over 50 years.[24]

Aligning with this paradigm shift, Portuguese physicians that manage people with HIV infection also recognize the importance of following tailored recommendations and continuous care programs for the elderly. This way, national experts have worked together to develop specific guidances for older people living with HIV, published as an expert document, and made accessible to all clinicians and other health care professionals. The document covers the main domains of those people living with HIV and posits insights that should be proactively implemented when monitoring those individuals, in a multimorbidity setting. The discussion was coordinated with multiple medical specialists firstly aiming at prevention, diagnosis, early treatment and, in the long run, at avoiding polypharmacy and drug-drug interactions, according to their extensive experience in clinical practice.

In terms of prevention, common factors related with the endocrine and cardiovascular systems, oncology, urology and nephrology have been reviewed, as well as syndromic diagnosis for neurological and psychiatric conditions. Several screening and diagnostic tools, including questionnaires and scores, are proposed to be administered to patients for early detection of risk factors, easier diagnostic assessments and management. In general, all diseases stressed out in the document share both traditional risk factors and those stemming specifically from the HIV infection and ART side effects. Particularly, these specific factors can induce many comorbidities, such as diabetes *mellitus,* osteoporosis, erectile dysfunction, hypogonadism, some types of cancers, myocardial infarction, atherogenesis, hypertension, renal disease, impaired cognitive function (e.g., HIV associated neurocognitive disorder) and cerebrovascular disease. Besides, HIV-related stigma still profoundly affects these persons, increasing the practice of high-risk behaviors (e.g., unprotected sexual relations, use of illicit drugs).[21] Hence, a transversal psychiatric and psychosocial support might be required not only due to these problematics, but also due to the exacerbated effects of the aging process.

Regarding polypharmacy and possible toxicities or interactions, this expert document followed the latest clinical recommendations published for management of people living with HIV,[2,3] in addition to informed options and expertise from the clinicians. We understand that the heterogeneity of needs and degree of dependency among people living with HIV are challenging and, fundamentally, changes must be addressed by an effective workforce of educated health care professionals. An individualized and holistic care for aging persons with HIV should be implemented in practice, accepting that different grades of burden exist, and other comorbidities might affect the patient's daily life more than a controlled HIV infection.[37] This way, it is possible to avoid or delay further complications and comorbidities in late life of individuals with HIV. The Portuguese medical experts also considered that referral to a specialist should occur whenever lifestyle and recommended pharmaceutical therapies are not enough to reach therapeutic goals, or whenever there are difficulties in diagnosis and other relevant comorbidities exist.

The most relevant aspects resulting from this expert panel discussion will be further detailed, including insights for each clinical area and related comorbid conditions, in the Part II of this manuscript.

Finally, a patient-centered care must be also an opportunity to cover the heterogenous requirements related with management of comorbidities. In a focus group conducted with US individuals with HIV and multiple comorbidities, managing polypharmacy, toxic interactions and side effects, as well as communication between different specialists were viewed as problematic.[38] However, people living with HIV prefer to primarily consult their infectious diseases specialist rather than other physicians, due to the need to disclosure highly sensitive data.[39] As part of the Veterans Aging Cohort Study (VACS), it was found that infectious diseases specialists are less comfortable to prescribe medicines for comorbidities and treat those diseases than general practitioners.[40] Another study found communication flaws between infectious diseases specialists and general practitioners, based on medical records from UK patients, in addition to contraindicated co-prescribing.[41] Therefore, an integrated care model, supported on training and experience of both HIV specialists and general medicine physicians, may improve the delivery and quality of care in aging persons living with HIV and complex comorbidities.

By understanding that both therapeutic and medical needs of people with HIV are becoming more complex nowadays, medical education and capability is of foremost importance, in order to provide the best treatment and management strategies. Ultimately, this document might become a cornerstone for adapting practices for those aging with HIV, considering the infectious disease and general practice/family medicine fields, while complementing current guidelines and recommendations.[2]

/ Conclusion

Anticipating that the proportion of older people living with HIV will rise within next years, further reviews of health care recommendations and policies should be encouraged by changes in real-world evidence and needs in clinical practice.

This manuscript Part I described how we have addressed this need for comorbidities with substantial impact in the clinical practice of Portuguese healthcare institutions where people with HIV are followed-up. Overall, we have reviewed the current evidence and clinical guidances to adequately approach the most relevant comorbidities of people with HIV in terms of prevention, diagnosis, and treatment. These insights will be provided in the Part II of this manuscript. We expect that with the implementation of integrated guidances in the decision-making process, physicians will become more qualified to provide older adults with HIV with greater quality of life and reduced negative health outcomes.

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/ Conflicts of interest

AH, FC and JF received fees from Merck Sharp & Dohme. NM received fees for lectures, advisory boards, travel grants or consultancy from Merck Sharp & Dohme, Abbvie, Gilead Sciences, Janssen-Cilag Farmacêutica and ViiV Healthcare. JM received advisor honoraria from Bial, Merck Sharp & Dohme and Zambon, as well as financial support to speak or attend meetings from Bial, Boston Scientific, GE Healthcare, Grunenthal, Medtronic, and Novartis. FM received financial support for consultancy services, meetings and teaching, research and publications from Abbvie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare. JSC received financial support from Merck Sharp & Dohme, Gilead and Janssen. RSC participated in advisory boards and lectures for Abbvie, Gilead Sciences, Janssen, Merck Sharp & Dohme and ViiV Healthcare. Other co-authors (AF, MB, NT and PF) have no conflicts of interest to disclose.

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