

# Clinical implications of aging with HIV infection: perspectives and the future medical care agenda

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The increasing number of aging HIV-infected (HIV+) persons comprises a unique population at risk for illnesses and syndromes traditionally associated with the elderly. As a result, similar to the current need for primary care providers to manage chronic noninfectious comorbidities among aging persons with well controlled HIV infection, HIV clinical care will need to routinely involve geriatric medicine in a new HIV-geriatric discipline. The objective of this article is to provide a conceptual framework in which HIV and geriatric management considerations for healthcare professionals caring for HIV+ persons are integrated. The provision of contemporary HIV clinical care extends well beyond the achievement of HIV virologic suppression and antiretroviral therapy management and includes a need for careful characterization of geriatric syndromes based upon functional capacity and extent of disability. Screening for geriatric syndromes is both a multidisciplinary and multidimensional process, designed to evaluate an older person's functional ability, physical health, cognition, overall mental health, and socio-environmental circumstances. Although routine incorporation of geriatric assessment into clinical trials involving HIV+ persons is feasible, a current challenge is the availability of a consensus clinical definition of frailty or vulnerability. To maximize the efficiency, value, and convenience of outpatient care visits for older HIV+ persons, these visits should include encounters with multiple providers, including primary care clinicians, social workers, and geriatricians. Challenges may exist in the routine provision of these assessments to older HIV+ persons, but clearly such cross-disciplinary collaboration will not only markedly enhance the care of aging HIV+ persons but may also constitute a model of successful healthcare management that can be applied to all aging persons with changing healthcare needs.

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## Introduction

The United States Centres for Disease Control and Prevention estimate that over half of HIV-infected (HIV+) persons in the United States are now over the age of 50 years; similar demographic shifts exist in other nations where the timely use of potent combination antiretroviral therapy (ART) has resulted in marked extensions in survival. As a result, aging HIV+ persons comprise a unique population at risk for illnesses and

syndromes traditionally associated with the elderly. HIV+ elderly persons are no longer exceptional, but rather a growing demographic within both the global HIV+ population and among the larger group of elderly persons in clinical care. The implications for HIV+ patients and their medical providers are becoming clear: HIV care will intersect routinely with geriatric medicine [1]. This overlap in traditionally distinct clinical disciplines is not exclusively the result of advancing age among HIV+ persons but also reflects the acknowledgment that the

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emergence and prominence of traditionally age-related illnesses among ART-treated HIV+ persons at younger-than-expected ages involves pathophysiologic processes that are diverse and characteristic of both HIV infection and aging; these include chronic elevations in levels of systemic inflammation and immune activation (despite virologic suppression for HIV+ persons), gut microbial translocation, and host genetics. Other contributing factors among HIV+ persons include effects of ART drugs and inherent enrichment in competing risks for specific age-related illnesses.

The objective of this article is to provide a conceptual framework that joins HIV and geriatric clinical care management considerations for healthcare professionals caring for HIV+ persons.

Similar geriatric-focused clinical care paradigms have been configured within other medical specialties, including 'orthogeriatrics' [2], 'cardiogeriatrics' [3], or 'oncogeriatrics' [4].

### Changing paradigms in HIV management

Aging involves an extremely complex set of processes and the characterization of evolving health status; as a pathologic condition, aging requires considerations other than chronological age-based clinical data and must include careful characterization of geriatric syndromes based upon functional capacity and extent of disability.

These facts have necessitated that the provision of contemporary HIV clinical care extend well beyond efforts focused on HIV virologic suppression and ART management and include chronic comorbid disease management, preventive care, increasing polypharmacy, and other patient-specific and population-specific factors.

In recent years, initial clinical care recommendations for HIV+ persons have focused upon achieving the stepwise goals outlined in the 'Clinical Cascade' of HIV care; these span HIV infection diagnosis, linkage to care, immediate ART initiation, viral suppression, and retention in care. Achievement of these goals necessarily includes optimization of the HIV care delivery environment, routine availability of HIV testing, availability of ART, and monitoring for viral suppression [5]. The case can be made that achievement of these vital initial goals represents merely the beginning of a much longer HIV care continuum for which structured treatment guidelines do not yet exist, particularly with regard to aging and age-related disability. Extension of existing HIV management paradigms are needed that go beyond maintenance of viral suppression and retention in clinical care to include routine screening, preemption, and treatment of age-related illnesses, systematic assessments of functional status and disability, and the overarching goals of optimization of quality of life (QoL) and extending survival [6,7].

Of note, some tertiary-level multidisciplinary clinics do exist, sometimes called 'HIV metabolic clinics' or 'HIV aging clinics', in which patients are evaluated by clinicians from multiple specialties and in which ART choices are undertaken with consideration of comorbidities that are present. These sites of care delivery may provide models for the development of approaches to comprehensive care provision for older HIV+ persons.

### The transition from chronic non-AIDS comorbidities to geriatric syndromes among HIV-infected persons

Persons with effectively treated HIV infection experience heightened risk for multiple noninfectious chronic comorbidities (NICMs) with advancing age. The excess presence of diabetes mellitus, cardiovascular disease, osteoporosis, chronic kidney disease, and chronic obstructive pulmonary disease among aging HIV+ persons may in part reflect greater prevalence of traditional lifestyle-related risks among HIV+ persons compared with the general population. NICMs are diverse and span different organ physiological systems, are in general age-related and have been observed to exist simultaneously as complex multimorbidities [8] at younger ages when compared with HIV-uninfected persons. Guidelines [9] that include standardized screening algorithms have been developed to detect clinical and subclinical chronic comorbidities among aging HIV+ persons.

However, the assessment of NICMs and multimorbidities alone does not reflect the complexity of aging as a health condition. Two people with the exact same comorbid conditions can have very different functional aging trajectories. In the general population of older adults, geriatric syndromes and measures of physical function are more predictive of self-reported health and mortality than diagnoses of chronic diseases or multimorbidities alone [10,11].

The majority of existing guidelines, however, remain organ system-based and do not include formal assessment for geriatric conditions. Recently, Italian guidelines for HIV care have been modified to include a section dedicated to 'The management of aging and frail HIV patients' in which geriatric screening including assessments for frailty and comprehensive geriatric assessment (CGA) are recommended [12].

Geriatric syndromes occur when the accumulated effects of coexisting impairments in multiple organ systems render an older person vulnerable to situational challenges. In addition, it is possible that biological dysregulation affecting fundamental mechanisms of homeostasis in different organ systems as well as anatomical integrity simultaneously exist and converge; a defining feature of geriatric syndromes is that multiple risk factors may summarily contribute to the emergence of frailty. Geriatric syndromes, such as delirium, falls, incontinence, and

frailty, are highly prevalent, in some cohorts affecting up to 30–50% of HIV+ patients over age 50 years. These conditions are multifactorial and associated with substantial morbidity and poor outcomes [13].

A debate has existed as to whether HIV infection constitutes a state of accentuated or accelerated aging [14]. Clinically, the observed increased prevalence of frailty and geriatric syndromes among HIV+ compared with uninfected persons supports an assertion that HIV infection specifically impacts risk for geriatric syndromes. To explain this association, several HIV-specific contributing factors have been proposed; these include chronic inflammation, immune dysregulation, long-term ART toxicity, neurocognitive impairment, and high rates of socio-behavioral risk factors. Lastly, the peripheral lipotrophy characteristic of many HIV+ persons with ART treatment histories that include thymidine-analog reverse transcriptase inhibitors has, for many affected persons, evolved into a sarcopenic/obesity phenotype associated traditionally with advanced age [15].

The transition from routine screening, preemption and treatment of multiple chronic comorbidities to the routine undertaking of assessment for geriatric syndromes among aging HIV+ persons necessitates both a structural and a cultural change in standard patient assessment. Screening for geriatric syndromes is both a multidisciplinary and multidimensional process, designed to evaluate an older person's functional ability, physical health, cognition, overall mental health, and socio-environmental circumstances. It differs from standard medical evaluation in that inclusion of nonmedical domains and assessments of functional capacity and QoL are essential and even central. The roles of interdisciplinary team members (e.g., nurses, social workers, pharmacists, psychologists, and occupational therapists in particular) are vital; it is these persons who most often administer screening tools and identify specific patient limitations that require more detailed evaluation. Furthermore, the identification and assessment of chronic comorbidities and multimorbidity does not conclude the clinical evaluation but rather comprises a starting point from which assessment of impairment can commence. Focuses include not only dysfunction and structural abnormalities in specific body systems (e.g., musculoskeletal, cardiovascular, and others), and their impact upon functional capacity, but also overall physical and mental functioning (ambulation, verbal ability, vision, and others) and the resultant extent of overall disability. Clearly, the goal of prevention becomes not merely the avoidance of mortality, but rather optimizing disability-free survival among aging persons. Patient education and involvement are essential to ensure that care plans are customized to the individual. The preexistence of a healthy ongoing patient–physician relationship, usually established during routine HIV care, provides an excellent starting point for successful geriatric care management.

As aging HIV+ persons are at risk for diminished QoL [16], often at chronologic ages during which they would not typically be considered geriatric, pursuing a structured evaluation, the so-called comprehensive geriatric assessment (CGA), in such persons may be indicated. Again, as aging-related syndromes are increasingly common among nonchronologically elderly HIV+ adults, a more appropriate nomenclature for the diagnostic and treatment process may be comprehensive HIV assessment (CHA).

Conceptually, CGA (or CHA) involves several domains of care that are shared by several providers in the assessment team. The overall care rendered by CGA teams can be divided into six steps:

- (1) Data gathering
- (2) Discussion among team members
- (3) Development of a treatment plan
- (4) Implementation of the treatment plan
- (5) Monitoring response to treatment
- (6) Revising the treatment plan

Each of these steps is essential to optimize the likelihood of achieving maximal clinical and functional benefits. So far, the CHA approach has rarely been applied in a structured fashion to HIV+ persons, but the increasing recognition of multimorbidity, frailty, and disability among older HIV+ patients warrants its more routine application. Consequently, systematic assembly and training of necessary collaborative clinical team members will be needed to achieve routine implementation of CHA for aging HIV+ adults.

### **Clinical and research end points to be used in HIV-geriatric medicine**

Current clinical trials are unlikely to inform or enhance the treatment of older HIV+ patients; outcome measures that are of primary importance to this patient group have been included in only a minority of studies. As a scientific and care-giving community, investigative efforts are direly needed to inform the delivery of evidence-based, customized care to our rapidly growing population of older HIV+ persons. The choice of appropriate investigative clinical endpoints is important to assess the benefit of interventions including, but not limited to, ART therapy. The standard HIV research endpoints of virologic suppression and CD4<sup>+</sup> improvements may not be the most important with which to evaluate the risk/benefit ratio of even ART clinical trials involving older HIV+ persons. Competing non-HIV risks for death and morbidity, and greater risk for acute and chronic antiretroviral-related toxicity, must be considered.

Although the inclusion of geriatric assessments has been incorporated into many clinical trials involving cancer treatment [17], challenges remain in using such assessments as criteria for interventional stratification or

**Table 1. Issues in clinical trial design for older patients with HIV.**

RCTs remain gold standard when possible
Clinical trials should preferably integrate whole age range, including fit and frail older individuals
Trials of treatment strategy comparing different strategies (e.g., different ARV strategies or drug classes or therapy vs. best supportive care) should be encouraged
Randomized phase II or even single-arm phase II trials in specific subsets of older patients can provide insight into range of efficacy and toxicity in older populations but ideally should be confirmed in large phase III trials, which might be hard to perform for various reasons (e.g., insufficient interest from sponsors/investors, difficulty in finding sufficient numbers of patients)
Not all questions can be answered with randomized trials, and large observational cohort studies or registries in the community can provide further insight for frail population with less selection bias (preferably in parallel with or linked to RCTs)
Comparable/uniform geriatric assessment should be integrated into future clinical trials involving older HIV-infected persons
Regulatory authorities should require evaluation of efficacy and safety of new drugs in older and frail patients as well as in younger patients

RCT, randomized clinical trial.

randomization, in part because of the lack of standardization of definitions of frailty and disability.

Table 1 lists factors enumerated in recent recommendations involving Clinical Trial Design for Older Patients with HIV, incorporating recommendations recently issued by oncogeriatric medicine providers [18]. In general, interventional clinical trials have tended to use eligibility criteria that result in exclusion of older patients, creating a selection bias. A US National Institutes of Health team concluded that decreasing physical function and comorbidity-based eligibility restrictions can dramatically increase accrual of elderly persons into clinical trials [19].

Nevertheless, some advances have been made in recent years in identifying clinical and research endpoints in geriatric research. In addition to the traditional 'hard' clinical endpoints of mortality and hospitalization rates, other outcomes that include QoL, preservation of functional capacity, and independence have been added.

Functional status can be measured either subjectively through self-report or objectively through performance tests. The Short Physical Performance Battery (SPPB), an objective measure of lower extremity function, has been validated in the general population among persons 65 years of age and older as a predictor of disability, need for nursing home placement, and mortality [20]. The SPPB has been used investigatively to identify HIV+ persons at risk for adverse events. In multivariable models, HIV infection was independently associated with a 30% increased risk of reduced physical performance in a study that also demonstrated that HIV infection and reduced physical performance exert independent and joint effects on mortality [21].

Disability assessment begins with a review of two key domains of functional ability: activities of daily living (ADL) and instrumental activities of daily living (IADL). ADLs include self-care activities such as eating, dressing, bathing, transfers between bed and chair, using the toilet, and controlling bladder and bowel functions. IADL include activities needed to live independently (e.g., housework, meal preparation, taking medications, managing finances, and telephone use) [22]. Although review of ADL and IADL is routine among persons with obvious disabilities, these tools are underapplied among persons aged less than 75 years [23].

Newer tools to assess ADL and IADL involve information communication technologies (ICTs), such as smart phones, and allow immediate access to needed clinical and research information. Ecological momentary assessment (EMA) is a collection of methods for obtaining repeated real-time assessments of patients' behavior and experiences in their living environments. EMA techniques minimize recall bias, maximize accuracy, and allow clinicians and researchers to capture more dynamic views of patients daily lives, permitting improved insight into contextual factors and temporal processes [24]. EMA domains include physical activity, mood, stress level, social relationships, eating behaviors, and sleep quality. One small study involving 20 HIV+ patients aged more than 50 years documented that participants spent a remarkable amount of time at home, alone, and engaged in passive activities. Such data support the viability of EMA as a valuable tool to assess functional activities among older HIV+ adults [25].

### Model of care in HIV geriatrics

Recent systematic reviews and meta-analyses of studies conducted in the general population have evaluated and promoted the feasibility of undertaking routine geriatric assessments in both outpatient and inpatient settings and the impact of CGA on medical decision-making and outcomes (mortality and hospitalization) [26,27]. However, there may exist special considerations and/or challenges in the application of these assessments to HIV+ persons; vulnerabilities for disability and obstacles to care that are HIV-specific need to be taken into consideration (Table 2).

Social vulnerability has been shown to be a predictor of mortality and disability in elderly people [28]. HIV and aging stigma have been cited as important barriers to the uptake of HIV testing and acquisition of treatment services in numerous care settings, particularly in resource-limited countries, and have been associated with inequalities in social, economic, and political power [28].

Age-related stigma has been well described and includes multiple stereotypes characterizing older persons as needy, unhappy, senile, inactive, unable to learn new information, and less useful than their younger

**Table 2. Challenges to evaluation and parallel opportunities for care provision of older HIV-infected persons.**

	Challenges	Opportunities
The patient	HIV stigma Social vulnerability	Community empowerment HIV is still a high global health priority
The disease	High burden of chronic comorbid illnesses ART in the context of polypharmacy	Opportunity to assess and treat comorbidities in resource-limited settings Optimization of medication adherence and management
The care	Specialized HIV healthcare workers Low access to general practitioner resources	Opportunity for task shifting among occupational therapists High uptake of information communication technologies

counterparts [29]. HIV and aging stigma overlap in older HIV+ persons and may require interventions separate from those used for either individually. A small number of published studies exist regarding interventions designed to reduce stigma, the majority of which are based on cognitive-behavioral and social-cognitive models, employing such activities as information dissemination, empathy induction, counseling, and cognitive behavioral therapy [30]. The focus of these interventions is usually the affected person. A more comprehensive conceptualization of HIV/aging stigma and ascertainment is needed to develop stigma reduction programs at institutional and infrastructural levels. Based on principles of community organization and community building, new models for advocacy and social change in response to HIV/AIDS-related stigma are needed. Public participation and engagement of HIV+ persons at community and social levels would not only promote favorable responses to internalized stigma on the part of affected persons but could also provide powerful deterrents to stigmatizing impulses directed at the aging population in general.

Conditions that increase vulnerability among older HIV+ persons include the high burden of non-AIDS chronic comorbidities and the consequent need for polypharmacy. Comprehensive diagnostic and treatment efforts focused upon multiple comorbidities has allowed for the development of highly specialized multidisciplinary clinics in high-income countries, focusing healthcare resources needed to treat older HIV+ persons [31]. Contemporarily, in resource-limited countries, HIV treatment centers often have been built as stand-alone programs, yet may be the only existing facilities capable of providing comprehensive care of older HIV+ persons with chronic comorbidities; hence, in the future, these entities may represent the best infrastructures in these countries in which to develop improved programs for care provision.

In the ART era, most HIV+ persons in care take five or more medications daily and are at risk of harm from polypharmacy, a risk that increases with advancing age and physiologic frailty [32]. Established risks of polypharmacy include decreased medication adherence and serious adverse drug events, including organ system injury, hospitalization, geriatric syndromes (falls, fractures, and cognitive decline), and mortality. Interventions addressing risks of polypharmacy among HIV+ persons

are in their infancy, and tools to identify systematically underprescribing and overprescribing are lacking. Nevertheless, considerable historical experience exists from the early HAART era regarding management of and adherence to complex first-generation HAART drug regimens. Ideally, lessons learned then are applicable to the management of contemporary HIV+ persons receiving treatment for multiple comorbidities and with potentially complex drug-drug interactions, including but not exclusive to ART.

The availability of easy to use mobile 'Apps' have greatly facilitated the ability to assess risk for drug interactions for both clinicians and patients. The process of medication reconciliation is often enhanced by the involvement of clinical pharmacists working in conjunction with other members of the HIV caregiving team. Such collaborations ideally include nonjudgmental awareness on the part of care providers that recreational substance use, particularly alcohol and marijuana, is common among HIV+ persons and can impact risks associated with polypharmacy, including risk for nonadherence and susceptibility to adverse drug reactions.

Robust evidence exists regarding the effectiveness of 'task-shifting' or 'task-sharing' ART management responsibilities between physicians and other healthcare providers, particularly in Africa [33]. For older HIV+ persons, task-shifting can also involve occupational and physical therapists, nutritionists/dietitians, and practitioners of physical medicine and rehabilitation, particularly in the assessment of age-related physical disability and triaging for geriatric consultation.

In the pre-HAART and early-HAART eras, HIV care provision was routinely provided at dedicated HIV clinics, with regular outpatient visits typically occurring every 3–4 months. More recently, the frequency of clinician visits deemed necessary has become more variable and is more often dictated by non-HIV care needs, particularly by comorbidities, physical frailty, and disability. It has become clear that to maximize the efficiency, value, and convenience of outpatient care visits for older HIV+ persons, these visits should include encounters with multiple providers who address diverse care needs, particularly for the subset of more vulnerable patients identified through frailty screening. Central to this paradigm shift in HIV care delivery is the centrality of

the primary care physician who, optimally, leads the diverse team of healthcare professionals and provides preventive and chronic care management throughout the stages of aging. Aspects of care requiring coordination include those facilitated by registries, information technology, health information exchanges, and other means to help ensure that patients receive care when and where they need it. Ideally, the assembled care team seeks to monitor and improve their own practices by utilizing evidence-based medicine and clinical decision support tools and by ensuring that patients and their families have the necessary education and support to participate actively in their care.

The incorporation of geriatric practices into HIV care, including defining the role of the geriatrician and ensuring collaboration with HIV primary care providers, can optimize clinical benefit and avoid excess patient risks due to lack of care coordination. Having the geriatric clinician present at the site of HIV and primary care delivery is optimal. Clearly, this model reflects needed changes in HIV care paradigms that are more complex than merely referring patients to consultants. This approach includes consideration of the changing physical, emotional, social, economic, and spiritual needs of aging HIV+ persons [34], as well as patient responses to illness, and the effect of the illness on the ability to meet self-care needs.

Achievement of such comprehensive coordinated care, capable of providing both primary and preventive care as well as specialized support for aging HIV+ persons, will require immense effort in terms of logistic coordination and diverse provider interaction. However, the successful accomplishment of such cross-disciplinary collaboration will not only markedly enhance the care of aging HIV+ persons but can also constitute a model of successful healthcare management that can be applied to all aging persons with care needs that increasingly involve geriatric considerations.

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### Conflicts of interest

There are no conflicts of interest.

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