Giovanni Guaraldi · Julian Falutz
Chiara Mussi · Ana Rita Silva
Editors

Managing the Older Adult Patient with HIV

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Editor Biographies

Giovanni Guaraldi, **MD**, is Assistant Professor of Infectious Disease at University of Modena and Reggio Emilia, Italy, where he also completed his medical training. Dr Guaraldi undertook his residency at Liverpool School of Tropical Medicine, UK, and Jackson Memorial Hospital, USA.

Dr Guaraldi was awarded the Dean's Delegate Cooperation for development projects of Modena University. He has extensive experience in HIV in resource-limited countries and has coordinated the European, Africa, Caribbean, Pacific project CoBaSys (Community-Based System in HIV treatment) focused on antiretroviral access programs in sub-Saharan African countries.

In 2002 Dr Guaraldi started a liver and kidney transplant program for people with HIV at the multivisceral transplant center at Policlinico of Modena, Italy. Since the center opened, he has personally cared for approximately 80 patients with HIV who have received solid organ transplantation. Dr Guaraldi has led the Modena HIV Metabolic Clinic (MHMC) since 2000. This referral center cares for more than 4000 patients and offers a multidisciplinary team consisting of infectious disease physicians, nutritionists, occupational therapists, psychologists, cardiologists, nephrologists, endocrinologists, and plastic surgeons for the diagnosis and treatment of noninfectious comorbidities.

Dr Guaraldi has been the principal investigator in several studies generated by the MHMC, mainly focused on frailty and HIV-associated comorbidities. He has extensive experience in scientific publication, with more than 260

peer-reviewed papers, he is coeditor of *Journal of Antimicrobial Chemotherapy* and serves as reviewer for the major HIV journals and as a consultant for EMA. He supervises PhD students in the Experimental Medicine PhD course at Modena University.

Dr Guaraldi is a panel member of the European AIDS Clinical Society guidelines on prevention and management of HIV-associated comorbidities and has published widely on clinical aspects of HIV treatment and care.

Julian Falutz MD, **FRCP(C)**, is Assistant Professor of Medicine at McGill University and Associate Physician at the Montreal General Hospital Site of the McGill University Hospital Centre (MUHC), Canada. He is the director of the Comprehensive HIV and Aging Initiative in the Chronic Viral Illness Service and a Senior Physician in the Division of Geriatrics at the MUHC.

Dr Falutz attended McGill University School of Medicine, where he completed his residency in General Internal Medicine and received subspecialty training in both internal medicine and geriatrics. He has been actively involved in the clinical care of both HIV and geriatric patients at the MUHC for over 25 years. He is active as a clinical teacher at the undergraduate and graduate levels and was the director of the HIV elective program at the MUHC for 20 years.

His research in HIV has focused on the interaction of immunodeficiency, nutrition, and metabolic complications. He has initiated and participated in numerous studies on the management of HIV-related complications. He was the coprincipal investigator for the pivotal multinational studies investigating a novel growth hormone-releasing factor for the treatment of abdominal obesity in patients with HIV. The investigated drug has since been approved for use in both the USA and Canada. He is the Canadian coordinator for the REPRIEVE study, a multinational study of statins to prevent cardiovascular disease in low-risk treated HIV patients. He has initiated a program for the evaluation of patients aging with HIV and plays an active role in emerging studies evaluating frailty and comorbidities in patients aging with HIV.

Chiara Mussi, **MD**, **PhD**, is a Doctor in Medicine within the Modena HIV Metabolic Clinic at the University of Modena and Reggio Emilia, Italy. Dr Mussi earned her medical degree from the University of Modena and Reggio Emilia in 1995, and her graduation thesis centered on orthostatic hypotension in the elderly. In 1999 Dr Mussi specialized in geriatrics, and in 2004 she gained her PhD in biology and pathophysiology of aging, where her main research topic was cardiovascular autonomic changes in older patients. In 2008 she obtained a research grant from the University of Modena and Reggio Emilia to research syncope in the elderly. Dr Mussi has been a researcher and Chair of Geriatrics at the University of Modena and Reggio Emilia since 2009. She also works as an MD at the New S Agostino-Estense Civil Hospital in Baggiovara, Modena.

Dr Mussi has authored more than 100 peer-reviewed papers published in international and national journals, is an expert in multidimensional geriatric evaluation and geriatric syndromes, and has been a consultant in the Multidisciplinary Expert Working Group dedicated to HIV aging population issues since 2013 (sponsored by ViiV Healthcare).

Ana Rita Silva, **MD**, is an infectious disease specialist in the Department of Infectious Diseases at the Hospital Beatriz Ângelo, Portugal. She works within the infectious disease ward and is a consultant at the outpatient clinic. Dr Silva is currently undertaking her PhD in Clinical and Experimental Medicine at the University of Modena and Reggio Emilia, Italy, where Dr Giovanni Guaraldi and Dr Emília Valadas are her tutors.

Dr Silva attended the Coimbra School of Medicine (Faculdade de Medicina da Universidade de Coimbra) in Portugal and started her residency in Infectious Diseases in 2008. In 2009, after attending a 3-month internship at the Clinica Metabolica, Dr Silva helped to create the Metabolic Consult at the Hospital de Joaquim Urbano, Portugal. Since 2009 she has been involved in several projects in the area of HIV and aging, both in Portugal and with Dr Guaraldi in Italy, and has published several papers in this field. Dr Silva

has also collaborated in the formation of residents and has participated as a lecturer in several courses, community actions, and congresses.

In 2013 she was awarded the certification in travel medicine by the International Society of Travel Medicine (ISTM) after taking the Certificate of Knowledge Examination. Throughout her career, Dr Silva has participated both as principal and coinvestigator in several studies on HIV and HIV/hepatitis C coinfection.

Contributor Biographies

Thomas Brothers is a medical student at Dalhousie University in Halifax, Nova Scotia, Canada.

Marta Calvo, **MD**, **PhD**, is the Spanish Medical Affairs manager for HIV and hepatitis at Gilead Sciences, Spain. She trained in medicine at the Universidad Autónoma de Madrid, Spain, and completed her residency in Internal Medicine at Hospital de Móstoles, Madrid, Spain, in 2006. Her academic training also includes a master's degree in AIDS, doctorate degree in medicine, and master's degree in design and analysis of clinical research from the Universidad de Barcelona, Spain.

Dr Calvo was responsible for a start-up hospital, Fundación Vicente Ferrer Hospital de Bathalapallí, dedicated to the care of patients with HIV/AIDS in rural India. She served as infectious disease specialist and medical scientist at the Infectious Disease Unit, Hospital Clínico de Barcelona-IDIBAPS, Spain, from 2007 to 2011, where she was also subinvestigator for several clinical trials. She has also completed a fellowship at the Infectious Disease Unit, University Hospital of Bonn, Germany, and served as an internist at the Emergency Department, Hospital de Fuenlabrada, Spain.

Dr Calvo has published over 20 peer-reviewed papers in international journals, written several book chapters, and spoken at numerous conferences, including the International AIDS Conference. She is fluent in Spanish, English, German, and Catalán.

André Fragoso Gomes, **MD**, is currently undertaking his residency in Infectious Diseases at the Department of Infectious Diseases of Hospital Garcia de Orta, Portugal, which he started in 2011. Dr Fragoso Gomes attended the Lisbon School of Medicine (Faculdade de Ciências Médicas, Universidade Nova de Lisboa).

Dr Fragoso Gomes has been actively involved in clinical care of patients with HIV at the Hospital Garcia de Orta, both within the wards and the outpatient clinic. He is particularly interested in metabolic disorders and other complications of HIV infection, especially the comorbidities that arise as patients age. Dr Fragoso Gomes worked at the Modena HIV Metabolic Clinic, Italy, for 3 months, where he develop his skills within the field and actively participated in ongoing clinical studies.

Esteban Martínez, **MD**, **PhD**, is an Associate Professor of Medicine at the University of Barcelona and Senior Consultant in Infectious Diseases at the Hospital Clínic in Barcelona, Spain. Since 1996, he has devoted his time to outpatient care and the clinical research of HIV infection, and, in 2001, he took up a teaching role in infectious diseases at the University of Barcelona.

Dr Martínez was born in León, Spain, in 1963. He studied at the School of Medicine in Valladolid, Spain, from 1980 to 1986, and specialized in Internal Medicine at Hospital de la Santa Creu i Sant Pau in Barcelona, Spain, from 1988 to 1992. In 1996 he achieved his PhD in neurological infections from the Autonomous University of Barcelona. His fields of interest span opportunistic infections, simplification of antiretroviral therapy, incidence and causes of death in HIV-infected persons receiving antiretroviral therapy, toxicity of antiretrovirals, and noninfectious complications in HIV-infected patients.

Dr Martínez is a member of the Scientific Board of the International Workshop on Adverse Drug Reactions and Co-morbidities in HIV and was the coauthor of the Spanish Guidelines on Antiretroviral Therapy from 2001, Spanish Guidelines for Metabolic Complications in HIV-Infected

Patients since 2003, Spanish Guidelines for Kidney (2010) and Bone (2013) Complications in HIV-Infected Patients, and Guidelines for the Prevention and Management of Non-infectious Co-morbidities in HIV (European AIDS Clinical Society) from 2007.

He is a member of Grupo de Estudio de SIDA (GESIDA), Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), and European AIDS Clinical Society (EACS). He was elected as Regional (South Europe) Representative for EACS in 2012 for a 4-year period and has been a founding member of the International Symposium on Psychiatry and HIV (http://www.psiquiatria-vih.com/), held annually in Barcelona since 2007.

Dr Martínez has authored more than 200 papers and has led nine doctoral students. He has served as a reviewer for Dirección General de Investigación Científica y Técnica (Government of Spain), Agence Nationale de Recherche sur le Sida (France), UK Medical Research Council, South African Medical Research Council, Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazil), University of New South Wales, and University of Dublin. He has also served as a regular reviewer for major journals on medicine infectious diseases, chemotherapy, HIV/AIDS, endocrinology, bone, kidney, and circulation. He is an editorial board member of *AIDS Research and Therapy*, *HIV Medicine*, and *Journal of Acquired Immune Deficiency Syndromes*.

Preface

The 'graying' of the human immunodeficiency virus (HIV) epidemic is an established fact. Regardless of this evolving epidemiological context, no guidelines currently exist to offer a comprehensive view of the management of older patients with HIV.

This concise compendium addresses this gap by describing the aging trajectories of patients with HIV, by describing clinically meaningful end points, including comorbidities, multimorbidity, frailty, geriatric syndromes, and disability. Specific attention is given to the management of antiretroviral drugs in the context of polypharmacy in this special population.

In the context of the older patient with HIV, the model of HIV care is changing, and new strategies are needed to address the unmet healthcare needs of the aging patients. Best practices are presented together with the awareness that patient empowerment will remain at the core of innovative care models.

The authors of this book are infectious disease physicians and geriatricians, who are involved in the daily care of patients with HIV. We hope that this book will help not only doctors, but also allied care providers, including nurses, occupational therapists, social workers, psychologists, pharmacists,

community leaders, families, and especially patients to better understand this changing paradigm and prepare for the future.

Ana Rita Silva
Chiara Mussi
Julian Falutz
Giovanni Guaraldi

Abbreviations

AADL	Advanced activities of daily living
AADL-CDI	Advanced activities of daily living cognitive disability index
AADL-DI	Advanced activities of daily living disability index
AADL-PDI	Advanced activities of daily living physical disability index
ABC	Abacavir
ACC	American College of Cardiology
ADEs	Adverse drug events
ADL	Activities of daily living
AHA	American Heart Association
AIDS	Acquired immunodeficiency syndrome
AIN	Anal intraepithelial neoplasia
ALT	Alanine transaminase
AMPS	Assessment of motor and process skills
ANI	Asymptomatic neurocognitive impairment
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate transaminase
AZT	Azidothymidine
BI	Barthel index
BMD	Bone mineral density
BMI	Body mass index
BNCS	Brief Neurocognitive Screen
BUP	Bupropion
CAM	Confusion Assessment Method

cART	Combination antiretroviral therapy
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	Cytomegalovirus
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
DDI	Drug–drug interactions
DSM-IIIR	Diagnostic and Statistical Manual for Mental Disorders Third Edition Revised
DXA	Dual-energy X-ray absorptiometry
E/C/F/TAF	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
EACS	European AIDS Clinical Society
eGFR	Estimated glomerular filtration rate
EI	Entry inhibitor
EMA	European Medicine Agency
ENDS	Electronic nicotine delivery systems
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FRAX	Fracture risk assessment tool
FVC	Forced vital capacity
GALT	Gut-associated lymphatic tissue
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transphosphatase
HAART	Highly active antiretroviral therapy
HAD	HIV-associated dementia
HANA	HIV-associated non-AIDS
HAND	HIV-associated neurocognitive disorders
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus

HIVAN	HIV-associated nephropathy
HIV-VL	HIV-viral load
HLA	Human leukocyte antigen
HPV	Human papilloma virus
HR	Hazard ratio
HRM	High-risk morphology
IADL	Instrumental activities of daily living
ICKD	Immune complex kidney disease
IDU	Injecting drug users
IHDS	The International HIV Dementia Scale
IL	Interleukin
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
IRP	Immune risk phenotype
KS	Kaposi's sarcoma
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LGBT	Lesbian, gay, bisexual, or transgender
LPS	Lipopolysaccharide
MCI	Mild cognitive impairment
MDRD	Modification of Diet in Renal Disease
MHMC	Modena HIV Metabolic Clinic
MM	Multimorbidity
MNA	Mini Nutritional Assessment
MND	Mild neurocognitive disorder
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
MVC	Maraviroc
NHL	Non-Hodgkin lymphoma
NICM	Noninfectious comorbidities
NK	Natural killer
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRT	Nicotine replacement therapy
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
OTC	Over-the-counter
PI	Protease inhibitor

PLWHA	People living with HIV or AIDS
PPI	Proton pump inhibitor
PYFU	Person-years of follow-up
QOL	Quality of life
RDA	Recommended daily allowance
SCA	Successful cognitive aging
SGA	Subjective Global Assessment
STF	Single-tablet formulations
STR	Single-tablet regimen
T2DM	Type II diabetes mellitus
TDF	Tenofovir disoproxil fumarate
TMIG	Tokyo Metropolitan Institute of Gerontology Index
TNA	Total number of activities
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
VACS	Veterans Administration Cohort Study
VAR	Varenicline

Chapter 1
Introduction

Julian Falutz

Over 30 million people are infected with human immunodeficiency virus (HIV) today, more than 30 years after HIV/acquired immunodeficiency syndrome (AIDS) was first described [1]. AIDS describes a set of usually fatal infectious and malignant diseases that occur in previously healthy individuals and are due to a progressively severe acquired immunodeficiency state. This state is due to infection with HIV, a unique retrovirus. Following exposure (via perinatal, bloodborne, or sexual vectors) to HIV, most people, overall, remain relatively well during a clinically latent phase that lasts on average 10 years. Most infected people may not be aware of being seropositive unless specifically tested for HIV. During the initial 15 year period of the epidemic antiretroviral therapy (ART) was unavailable. Most patients died of poor response to appropriate therapy of often concurrently occurring infectious and malignant complications, usually within 2–3 years of the initial AIDS complication [2]. However, during this period important advances were made and a deep

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understanding of HIV biology and the pathogenesis of AIDS occurred. This led to the progressive development of effective antiretroviral (ARV) drugs by the mid-1990s. These drugs, when used in specific combinations, referred to as highly active anti-retroviral therapy (HAART), transformed AIDS into a mostly manageable chronic disease. As a result few effectively treated patients still develop traditional AIDS-related complications [3].

Since the widespread introduction of HAART in the mid-1990s the survival of treated patients has increased significantly [4]. This has impacted on the mean age of the infected population. Currently, about 50 % of infected persons in high-income countries are older than 50 years of age [5], with similar proportionate increases noted in non-industrialized countries. The age of 50 years has been used in HIV infection as a transition point separating older from younger patients, while recognizing that there is no specific biologic rationale for this precise age to represent older patients. Its use likely stems from the fact that during the first decade of the epidemic only a small minority (<10 %) of affected patients in industrialized countries were older than 50 years of age [6], a proportion that has progressively increased to 50 % at present [7].

Effective HIV risk prevention and education programs have significantly reduced new infection rates since HIV was identified as the etiologic agent of AIDS. However, new infections clearly still occur. The term 'long-term survivors' refers to patients infected early in the epidemic who either did not develop AIDS or survived those complications to benefit from the initial HAART regimens. Their improved survival is the main explanation for the overall increasing age of the majority of currently infected persons [5]. However, the age at the time of HIV seroconversion has also increased [8]. Older persons are at particular risk of exposure to HIV and other sexually transmitted infections for various reasons. Health care workers infrequently discuss sexual issues, including HIV, with older patients [9]; this is associated with a perception of low personal HIV risk among older persons. Also, the relative

predominance of HIV transmission by the known vectors differs by age. In most industrialized countries, among young adults, HIV is most often transmitted either between men having sex with men (MSM) or by injecting drug users (IDU), and less often heterosexually. Among older adults, HIV is more often transmitted heterosexually. This is partially related to several factors including, increased divorce rates and longevity, maintaining an active functional status (including sexual activity [10]), the availability of effective drugs for erectile dysfunction, and the known infrequent use of condoms between non-monogamous partners [11]. As well, while the public messages geared towards HIV prevention among younger adults are generally very effective, these messages carry less personal relevance among older adults.

The characterization of the life-cycle of HIV and the pathogenesis of the resulting immunodeficiency were well described by the late 1980s [12]. This facilitated the development of various ARV drugs that interfere with HIV replication by acting at multiple points in the life-cycle of HIV [13]. Since the licensing of the first ARV drug, azidothymidine (AZT) in 1987, drugs belonging to different classes have been produced and more than 30 now exist. Currently available ARVs have minimal toxicity, which has improved adherence compared to that associated with the large number of drugs that were required to be taken in the late 1990s with the first generation of HAART. Several drugs are now co-formulated allowing for daily use of a single pill [14], which also improves adherence. These regimens are available to more people worldwide by way of innovative collaborative programs involving the treating, research, government, and industry partners along with public organizations and the various affected communities. Current treatment guidelines do not specifically address the issue of treating older patients as there is no consensus that specific HAART regimens are better tolerated or more effective in older patients.

Aging as a biologic process occurs in most species and can be defined at the population, individual, organ or system,

tissue, or cellular level. In sum it can be viewed as a multidimensional process involving progressive impairment of specific physical, psychological, and social functions acting under environmental and genetic control, whereby an organism's ability to maintain optimal activity becomes impaired in the absence of specific disease entities and is primarily related to the dimension of time.

This book will address in practical terms the multiple interrelated issues facing patients aging with HIV, including the changing clinical landscape and evolving aging-related comorbidities, and the similarities and differences in typical geriatric syndromes that many of these patients are increasingly developing. Information necessary to maintain functional independence and prevention of complications related to aging and HIV will be addressed. The hope of both clients and care providers is that aging gracefully with HIV will become a reality rather than a dream.

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Chapter 2
Pathophysiology of HIV/AIDS

Julian Falutz

Key Points

- Inflammaging describes the increase in inflammation-driven chronic illnesses that exist in older adults.
- In seropositive patients the effects of chronic immune activation and chronic inflammation contribute to incomplete CD4 recovery and limit overall immune reconstitution.
- Human immunodeficiency virus (HIV) positive older patients are generally less likely to attain the same degree of post-HAART immune recovery than younger patients, regardless of better adherence to drug therapy.
- Chronic stimulation of the immune system occurs by various on-going elements including life-long exposure to environmental antigenic stressors, persistence

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of non-curable infections (eg, cytomegalovirus [CMV] and herpes viruses), and increase in age-related gastrointestinal microbial translocation.
- Chronic immune activation contributes to development of accelerated age-related immunosenescence, typically observed in patients with HIV.

2.1 Immunodeficiency, Immune Activation, and Chronic Inflammation

HIV infection causes progressive immunodeficiency by specifically targeting CD4+ cells of the monocyte/macrophage lineage. This leads to both functional impairment and destruction of target cells [1]. Untreated seropositive patients develop a profound CD4 cytopenia (normal CD4 count in uninfected adults is >600–800 cells/μL) and dysregulation of both cellular and humoral immunity, resulting in disruption of immune homeostasis parameters. The serum HIV viral load (HIV-VL) is often increased to very high levels, up to several million copies per mL in some untreated patients. All currently available highly active antiretroviral therapy (HAART) regimens effectively reduce HIV viral replication to below the level of detection of currently available assays (<40 copies/mL) within several months of starting therapy. This results in a variable and slowly progressive immune recovery (defined as the return of the absolute number of CD4+ T cells towards, but rarely to, normal levels) but only limited immune reconstitution (the re-establishment of normal quantitative relationship between CD4 and CD8 T cells) [1]. However, the usual extent of immune recovery significantly reduces the risk of developing typical AIDS-related complications. Higher levels of CD4 recovery, particularly to levels >500 cells/mL, are associated with a lower risk of developing AIDS. This relationship informs the clinical scenarios faced by aging patients with HIV.

Older patients with HIV are more likely to present with significant immunosuppression or AIDS-related complications.

This is most likely due to the clinical reality that HIV is considered less often in the differential diagnosis of common HIV-related symptoms. Older patients' baseline CD4 counts are also usually lower at the time of initial clinical presentation, due to both a delay in making a timely diagnosis of HIV and to the possible effect of accelerated age-related immunosenescence that may occur in patients with HIV [2].

Although the evidence remains controversial, after beginning HAART older patients are generally less likely to attain the same degree of post-HAART immune recovery than younger patients, and their plateau CD4 counts are also lower [3]. This may be related to their starting HAART at lower CD4 levels. As a result, they remain at higher risk of developing AIDS-related complications. The survival of older patients after developing AIDS is also less than that of younger patients [4]. However, after starting HAART, older patients achieve an undetectable HIV-VL as often as younger patients [3]. Furthermore, they are more likely than younger patients to maintain an undetectable HIV-VL over time, and this is likely due to better adherence to drug therapy [5].

Persistent immune activation is a key feature in patients responding to HAART. This phenomenon refers to processes involving cell activation and proliferation, suggested by increased levels of inflammatory cytokines, monocytes, activated T cells, and coagulation parameters [6]. Patients with untreated HIV infection have laboratory evidence of an activated immune state even in the absence of concurrent infectious or malignant complications [1]. HAART reduces these increased activation markers, but rarely to pre-HIV infection levels [7].

Several factors predispose to persistent immune activation, including:

- low-level HIV replication [6], which occurs in treated patients with undetectable HIV-VL and is a strong stimulus to chronic immune activation;
- thymic dysfunction leading to impaired T cell maturation [8];
- co-infection with specific viruses such as hepatitis B and C, human papillomavirus (HPV), and CMV [6]; and
- microbial translocation.

Microbial translocation refers to the process by which intestinal microbial products enter the systemic circulation. Initial HIV infection affects the gut-associated lymphatic tissue (GALT) leading to epithelial injury and extensive CD4 T cell depletion. HAART does not completely reverse this injury and results in incomplete restoration of the initial severe histologic and immune disruption. Partial restoration of the GALT permits passage of biologically active products, including lipopolysaccharide (LPS), to the bloodstream, resulting in the activation of monocytes/macrophages, B and T cells, plus coagulation factors [9]. Microbial translocation also occurs to a lesser degree in normal aging [10], itself considered to represent a state of chronic immune activation, although to a much more limited extent than that caused by HIV.

Chronic immune activation interacts with and predisposes to chronic inflammation. Chronic inflammation is also associated with increased levels of cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-1β, and acute phase reactants that act in a positive feedback manner to attract further immune system components. Physiologic aging is also accompanied by low-grade inflammation leading to a chronic increase in inflammatory mediators [11]. In the general population these factors may contribute to an increase in age-related diseases such as atherosclerosis, dementia, diabetes, cancer, and sarcopenia. This pro-inflammatory state may also occur if the normal mechanisms that turn off the otherwise effective immune response are defective or inefficient.

The term ‘inflammaging’ was coined almost 15 years ago to describe the tripartite interaction between the up-regulated inflammatory response, the subsequent low-grade chronic inflammation, and the increase in inflammation-driven chronic illnesses that exists in older adults [12]. This process incorporates neuro-endocrine activation via a chronically stimulated hypothalamic–pituitary–adrenal axis, so that glucocorticoid hypersecretion functions as the major counteractive response, but is associated with its own long-term toxicities [13]. A similar scenario may be active in treated HIV disease [14].

2.2 HIV and Immunosenescence

Chronic immune activation and the related state of chronic inflammation also contribute to the development of immunosenescence, a term describing the changes in immune parameters that occur in normal aging [15]. These have been studied mostly in persons older than 80 years of age who are more prone to infections, have decreased responses to routine vaccines, and are at increased risk of disorders in which chronic inflammation plays a pathogenic role [16]. Genetic signals affect immune parameters via an impact on diet, age-related thymic involution (resulting in decreased thymic hormones required for normal T cell maturation) [15], and rates of telomere shortening [17], which are themselves possibly modifiable by lifestyle factors. Immunosenescence affects multiple components of innate immunity including neutrophils, natural killer (NK) cells, monocytes/macrophages, dendritic cells, and impacts markers of cellular senescence on T cell and B cell lymphocytes [16–18].

Age-related changes in immune parameters are mostly related to chronic stimulation of the immune system by various factors. These include life-long exposure to environmental antigenic stresses, persistence of non-curable infections (CMV and herpes viruses), and increase in age-related gastrointestinal microbial translocation. These stimuli lead to:

1. expansion of the pool of terminally differentiated senescent memory CD28– T cells that release the pro-inflammatory cytokines IL-6 and TNF-α, further contributing to chronic inflammation [16, 17];
2. reduction of the pool of naïve T cells capable of responding to new antigenic stimuli [17]; and
3. an inverted T-helper/T-suppressor cell ratio (normally greater than 1.0–1.5).

The inverted T cell ratio was shown to predict short-term morbidity and mortality in the prospective Swedish OCTO and NONA studies of community-dwelling octogenarians and nonagenarians [19]. The inverted CD4/CD8 T cell ratio has been referred to as the immune risk phenotype (IRP), and has been associated with poor health-related outcomes [20].

Immune dysfunction changes that occur in response to untreated HIV infection, and to a lesser extent in patients on HAART, are similar to those that occur in normal aging. On this basis, treated HIV has been described as a state of accelerated immunosenescence [21]. Immune changes that occur to a variable degree in both untreated and treated patients with HIV include [22–24]:

- a low CD4/CD8 ratio;
- low numbers of naïve T cells;
- low T cell proliferation potential;
- expanded CD8+/CD28− numbers;
- reduced T cell repertoire;
- increased IL-6 production;
- reduced thymus function;
- reduced T cell telomere lengths;
- expanded CMV-specific CD8 T cells; and
- reduced vaccine responses.

These similarities between immunosenescence-related changes in people with HIV and older seronegative adults is further supported by the finding that young patients with HIV and severe immunosuppression have naïve T cell numbers comparable to healthy seronegative persons of more than 80 years of age [19]. Rates of telomere shortening in terminally differentiated CD8+/CD28− cells of young patients with HIV are also similar to those in healthy seronegative centenarians [25]. Levels of a known biomarker of aging, cyclin-dependent kinase inhibitor 2A (CDKN2A), a cell senescence mediator, are increased in treated younger patients, suggesting that increased biologic aging may occur in these patients [26].

Chronic CMV infection also contributes to immune dysfunction in both HIV and elderly patients. In very old people, being CMV seropositive contributes to expansion of the CD8+/CD28− T cell pool [27]. The overall T cell response to latent herpes virus infections in the elderly is important and represents up to 20 % of the total memory T cell compartment [28]. Patients with treated HIV disease and good immune recovery have a strong anti-CMV response [29]. Treated patients also have an inverse relationship between strong anti-CMV T cell responses and both lower total and naïve CD4+ T cell numbers [30]. Treated patients with HIV who are CMV negative have higher CD4+/CD8+ T cell ratios, are more likely to achieve normalization of their CD4+/CD8+ T cell ratios (>1.0) with HAART, and are less likely to have immunosenescence related markers [31]. Although CMV seropositivity in patients with treated HIV represents a latent infection, the anti-CMV drug, valganciclovir, may decrease CD8+ T cell activation markers in treated patients [32].

2.3 Evolving Clinical Profile

Regardless of the effects of chronic immune activation and chronic inflammation, which contribute to incomplete CD4 recovery and limit overall immune reconstitution [33], it is clear that AIDS-related morbidity and mortality in treated patients has declined dramatically since the introduction of HAART in the mid-1990s. Long-term survival has improved significantly in adherent patients with reliable access to ARVs, but remains overall at about two-thirds that of uninfected, age-matched controls [34]. However, the subset of patients on HAART who maintain an undetectable HIV-VL and CD4 count (>500 cells/mL) for over 5 years are predicted to likely achieve normal long-term survival [35]. The main predictor of the extent of immune recovery is the ‘nadir’ CD4 count, which refers to the lowest CD4 count a patient had prior to starting HAART. Nadir counts less than

200 CD4 cells/mL are associated with poor immune recovery [36]. As noted, this is relevant to understanding the clinical consequences of older patients' generally less robust response to effective HAART.

While the incidence of typical AIDS complications has decreased, complications continue to occur. However, the spectrum of clinical disorders has changed. These currently consist of generally common medical conditions and typically include [37]:

- cardiovascular disease;
- bone demineralization;
- metabolic disorders with associated body composition changes;
- distinct malignancies;
- certain hepato-renal diseases; and
- non-dementing cognitive dysfunction.

In treated HIV infection, ongoing low-grade HIV viremia and the resulting chronic immune response plays an important pathogenic role in the development of the major non-AIDS complications, including atherosclerosis, osteoporosis, neurocognitive decline, and the increasingly recognized geriatric frailty syndrome [38]. The clinical presentation and course, plus response to treatment of these conditions are broadly similar to that occurring in non-HIV infected persons. However, the risk of developing these complications is variable and appears to be related to a post-HAART plateau CD4 count <500 cells/mL [39]. This limited immune recovery is more likely to occur in older patients with HIV [40]. This helps to inform why aging patients with HIV with lower nadir and plateau CD4 cell counts will be faced not only with typical aging related comorbidities but may also have an increased risk of these complications occurring at a younger age. Evidence suggests that, at least for bone demineralization and cardiovascular disease, older (but not typical geriatric aged) patients do have an increased risk compared to younger patients with similar CD4 counts [41, 42].

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Chapter 3
HIV Associated Non-AIDS Conditions in Patients Aging with HIV

Giovanni Guaraldi, André Fragoso Gomes, and Ana Rita Silva

Key Points

- Despite effective highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV)-infected persons may have an excess of certain non-AIDS comorbidities that affect overall survival.
- These commonly include cardiovascular disease (CVD), type II diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD), osteopenia/osteoporosis, chronic kidney disease (CKD), HIV-associated neurocognitive disorders (HAND), and certain cancers.

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- The clinical spectrum of comorbidities in older patients with HIV is poorly understood and consequently their management remains based on the single-organ-dysfunction model versus a comprehensive aging-related approach.
- A better understanding of the interaction between aging, HIV, associated comorbidities, and concurrent antiretroviral (ARV) treatment is needed in order to improve the treatment of older individuals who are HIV positive.

3.1 HIV-Associated Non-AIDS Conditions Versus Comorbidities

With a reduction in AIDS-defining conditions and increase in life expectancy, age-related diseases are becoming more prevalent in the elderly HIV population. Such conditions include CVD, T2DM, COPD, osteopenia/osteoporosis, CKD, HAND, and certain cancers. HIV infection is an independent risk factor for these diseases, after adjustment for traditional risk factors [1]. The epidemiological overlap between HIV and age-associated conditions generated the concept of HIV-associated non-AIDS (HANA) conditions, often used interchangeably with the common term comorbidities. HANA describes the multifactorial contribution of risk factors in the pathogenesis of comorbidities and, at the same time, it underlines that the clinical presentation of comorbidities are an intrinsic component of the clinical spectrum of HIV disease in the HAART era.

It is assumed that the three pathogenetic pillars of HANA conditions are:

1. HIV disease;
2. ARV drug toxicity; and
3. host-related risk factors.

The proportion of each individual risk factor may vary in the different diseases, different host and environmental conditions, and in different time periods within the same individual. Particularly with age progression, it is expected that host-related risk factors will make an increased contribution in comparison to younger age. This is a major reason why environmental and lifestyle components become increasingly important with age.

In this book we will use terms HANA and comorbidities in an interchangeable manner. Nevertheless, HANA is the more accurate term when HIV is assumed to be an independent risk factor of the mentioned clinical condition, whereas comorbidities refers to the global risk burden of these diseases observed in older patients infected with HIV.

In the following section we present an overview of the key HANA conditions. The management principles of such diseases are addressed in Chap. 10.

3.1.1 Cardiovascular Disease

In a recent projection of mortality and burden of disease, the WHO predicts that the proportion of deaths worldwide due to non-communicable disease will rise from 59 % in 2002 to 69 % in 2030 [2]. HIV/AIDS and ischaemic heart disease are projected to be among the leading causes of disease in this time frame [2].

With regards to CVD in patients with HIV, a meta-analysis of papers published pre-2010 found that the relative risk of CVD was 1.6 for untreated and 2.0 for treated HIV infection compared to HIV uninfected patients [3]. These estimates were based on studies that often lacked information about traditional cardiovascular risk factors, and major channelling bias could not be ruled out [4–8].

Recent studies, including a large analysis from the Veterans Aging Cohort Study (VACS) found HIV infection to be associated with a 48 % increased risk of acute myocardial infarction [9].

The New York City HIV Surveillance Registry, in an observational study with nearly 1.2 million total person-years follow-up (PYFU), showed that while the proportion of deaths due to CVD rose between 2001 and 2012 from 7 to 13 %, the actual cardiovascular mortality rate for people with HIV decreased over time. Cardiovascular mortality in the general population declined as well, from 47 to 39 %. Overall, after adjusting for other factors including sex, race/ethnicity, and year, people with HIV had a 54 % higher CVD death rate than HIV-negative people. CVD mortality was significantly higher in people with HIV in all age groups through to 65 years of age. Among individuals aged over 65 years CVD mortality was similar or higher in uninfected individuals [10].

The etiology of CVD in patients infected with HIV reflects the complex interaction of factors associated with the aging of this population, the high prevalence of classic CVD risk factors such as smoking and cocaine use, the effects of HIV infection itself, and of antiretroviral therapy (ART) [11].

HIV infection itself, as well as its secondary impact on the destruction of gut permeability resulting in bacterial translocation, may lead to the development of accelerated atherosclerosis and decreased high density lipoprotein (HDL) levels [12]. This may be mediated through the actions of proinflammatory populations of T cells and activated monocytes to produce functional or structural vascular changes linked with the development and vulnerability of coronary plaques [13, 14].

A routine age-appropriate evaluation of CVD risk and the initiation of preventive measures should therefore be routinely considered in all patients at all disease stages [11].

Guidelines for screening of CVD in the setting of HIV infection are summarized in the literature and largely follow guidelines for individuals without HIV infection [15]. Most recently, both the Framingham risk score and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines have been shown to underestimate the risk of cardiovascular events [16]. Even by 2013 guidelines, statin therapy would not be recommended for the

majority (74 %) of patients with HIV and subclinical high-risk morphology (HRM) coronary plaque. Outcome studies are needed to determine the utility of new statin recommendations and the contribution of HRM coronary plaque to CVD events among patients infected with HIV [17].

The interruption of ART has been associated with an increased risk of cardiovascular events in untreated patients with HIV [18] as was demonstrated in the Strategies for Management of Antiretroviral Therapy (SMART) study. Patients in the SMART study who were randomized to the drug conservation arm (intermittent therapy guided by CD4 cell counts) had a 60 % increased risk of CVD over a mean of 16 months of follow-up compared with those in the viral suppression arm (continuous therapy) [18]. For this reason, HIV viral control remains the main priority in the clinical management of CVD in HIV-positive patients.

It is important to consider the CVD risk potential of individual drugs when selecting ART for a given patient. Although there is the possibility to use lipid lowering agents, drug interaction profiles must be considered. Thus, the use of ART agents with more favorable lipid profiles is particularly important as a form of both primary, and for patients with known CVD, secondary prevention of CVD (with the goal to achieve low density lipoprotein [LDL] target levels).

In general, after initiation of ART there is an increase in total cholesterol, LDL-cholesterol, and triglycerides, with HDL-cholesterol often remaining low. These lipid changes occur to different degrees depending on the drug classes and individual ARV drugs used.

Although many studies were published evaluating HIV infection and CVD risk, few of them focused on the cardiotoxicity of this therapy in the elderly. Treatment with different protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) has been associated with several metabolic disorders, including dyslipidemia. PI regimens have been associated with increased triglycerides, total cholesterol, and LDL levels, and these metabolic disturbances vary by specific PI. In addition, NNRTIs may

increase total cholesterol and LDL levels, but will result in an increase in HDL levels, which theoretically may lower CVD risk. Like PIs, the lipid effects seen with NNRTIs vary by the individual drug used. Lipid abnormalities may be more dangerous in older patients because of overall increased CVD risk [19].

In summary, modulation of both traditional and non-traditional risks is necessary to prevent CVD in the aging HIV population. While we have learned much in regard to the unique pathophysiology and characteristics of plaque formation in HIV, significant challenges remain, including identifying particularly vulnerable patients and developing effective preventive strategies.

3.1.2 Diabetes and Insulin Resistance

At least 20 % of patients in the general population over the age of 65 years have T2DM, and this number is expected to grow rapidly in the coming decades, partly related to the concurrent obesity epidemic, which patients with HIV are also at risk of developing. Older individuals with diabetes have higher rates of premature death, functional disability, and coexisting illnesses, such as hypertension, coronary heart disease, renal disease, poor eyesight, and stroke [20].

The incidence of T2DM is reported to be as much as four times higher in patients infected with HIV compared to uninfected patients and increases with age [21, 22]. This occurs with an incidence of 5.7 and 14.1 cases, respectively, per 1000 PYFU, as demonstrated in the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) [22] and French cohorts [23].

Risk factors of T2DM in patients with HIV are summarized in Table 3.1 [24].

In patients without history of CVD, short-term gains in body mass index (BMI) 1 year following ART initiation were associated with increased risk of CVD and diabetes [25].

Table 3.1 Risk factors of Type II diabetes mellitus due to HIV disease or iatrogenic factors in patients with HIV [24]

Diabetes due to HIV disease	Diabetes as a result of iatrogenic factors
Risk factors (eg, advancing age, male gender, high BMI, certain ethnic backgrounds or culture) Autoimmune destruction Hepatitis C infection Endocrine abnormalities Inflammation caused by HIV Viral factors: • Viral burden • Lower CD4 count • Duration of viral infection	Exposure to ART: • Causes insulin resistance • Decreases insulin secretion • Elevates proinflammatory levels of CRP, TNF-α, and IL-6 • Fat distribution changes leading to lipodystrophy • Leads to β-cell lipotoxicity

ART antiretroviral therapy, *BMI* body mass index, *CRP* C-reactive protein, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-α

The pathogenesis of ARV treated HIV-associated diabetes involves the development of peripheral insulin resistance with insulin deficiency relative to hyperglucagonemia and a high BMI [26], systemic inflammation [27, 28], mitochondrial toxicity [22, 29], and restoration of immunological response in the case of type I diabetes.

In general, there is an increasing prevalence of obesity in the older population. Clinicians should encourage older patients with HIV infection to maintain a normal BMI, as obesity is a risk factor for development of the metabolic syndrome and hyperglycemia [30]. Complications such as foot ulcers, retinopathy, hypertension, and vascular disease can be prevented and should be actively screened for and treated as per usual guidelines. Renal function and the presence of proteinuria, as well as

microalbuminuria, should be carefully monitored, as both diabetes and HIV increase the risk of renal disease.

Patients with diabetes mellitus should have their hemoglobin A1c (HbA1c) level monitored every 6 months with a goal of <7 % [22] for younger patients. This may be increased to 8 % for frail older patients, especially if their life expectancy is less than 5 years, as they are at high risk for hypoglycemia, polypharmacy, or drug interactions [30]. However, HbA1c may not be accurate for assessing glycemia among patients with HIV infection on nucleoside reverse transcriptase inhibitor (NRTI)-based therapy, especially those with macrocytosis or those on abacavir therapy. Fructosamine may be an appropriate alternative for assessment of glycemia in this context [31].

If modification of lifestyle measures is not sufficient to control glucose levels oral antidiabetics should be started (Fig. 3.1) [32].

The impact of ART on diabetes has been extensively studied. In a large observational study from France, increased incidence of T2DM was associated with older age (hazard ratio [HR] = 3.63 for age ≥50 years), time-updated lipoatrophy, and with short-term exposure to indinavir and stavudine (first generation ARVs rarely used now) [32].

While use of PIs, NRTIs, and nucleotide reverse transcriptase inhibitors (NtRTIs) has been associated with increased risk for T2DM [33], and PIs have been shown to reduce glucose tolerance [34], the D:A:D [22] and Swiss Cohort Studies [33] have shown no association between NNRTI therapy and diabetes risk.

It is important to recall that the concomitant use of metformin and NRTIs may increase the risk of lactic acidosis, and is contraindicated in patients with renal or hepatic dysfunction. NRTI therapy should be stopped when lactate levels of 5 mmol/L are reached [35]. Recently, it has been shown that the co-administration of dolutegravir and metformin, although well tolerated, significantly increased metformin plasma exposure (with effects being dolutegravir dose dependent) [36].

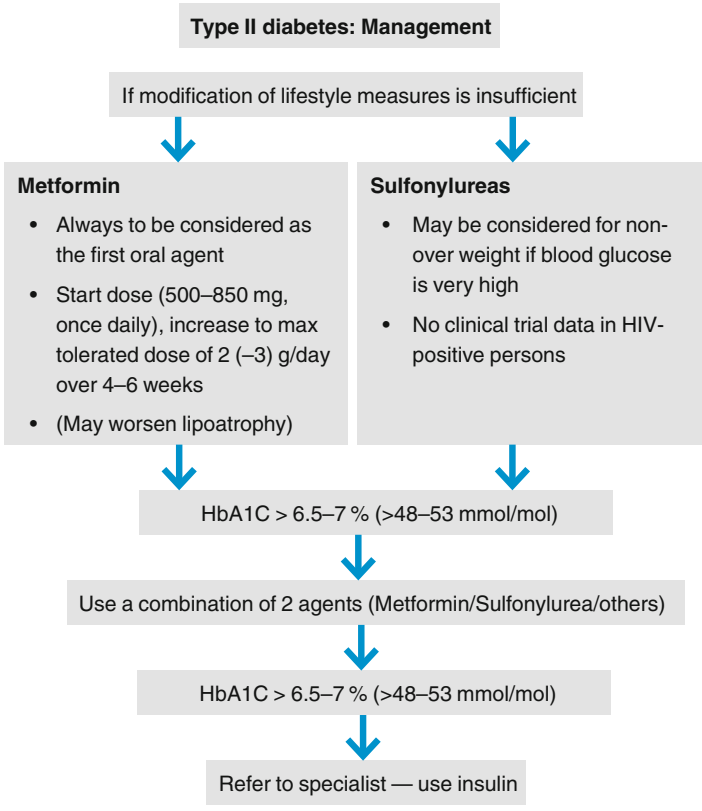

FIGURE 3.1 Management of type II diabetes according to European AIDS Clinical Society guidelines [32] (Adapted with permission from © European AIDS Clinical Society, authors own translation)

3.1.3 Bone Disorders

Osteoporosis is a disorder characterized by decreased bone density and deterioration of the skeletal microarchitecture, resulting in bone fragility [37].

According to the WHO criteria osteoporosis is defined as a bone mineral density T-score less than –2.5 and osteopenia is defined as between –1 and –2.5 standard deviations [38].

An increased prevalence of osteoporosis and osteopenia up to 60 % and 10–15 %, respectively, has been reported in both men and women infected with HIV, but the mechanism and consequences of these changes are not fully understood.

Classic risk factors for lower bone density include [31]:

- older age;
- female gender;
- hypogonadism;
- family history of hip fracture;
- low BMI ($\leq$19 kg/m^2);
- vitamin D deficiency;
- smoking;
- physical inactivity;
- history of low impact fracture;
- alcohol excess (>3 units/day); and
- steroid exposure (minimum prednisone 5 mg/day or equivalent for >3 months).

HIV specific risk factors include ART exposure and immunologic status. The proinflammatory state typically seen in patients with treated HIV infection and the direct HIV viral effects on bone formation and re-absorption are likely to play a role in these processes [39]. Low CD4 cell count has been associated with fracture risk, suggesting that chronic immune activation and persistent inflammation may play an important role in bone demineralization and fracture development.

Whether these factors are particularly relevant to older people infected with HIV who already experience a higher chronic inflammation burden and are at highest risk of fragility fractures is unknown [40].

Skeleton aging is a physiological phenomenon: bone mass peaks at around 25–30 years of age and declines gradually thereafter in both men and women [41, 42]. The amount of bone in older people is determined by the peak bone mass, together with the rate of bone loss with age [43].

Several studies have shown that menopause onset occurs at an earlier age in HIV-infected women, and this may represent a sign of accelerated senescence [44–48]. During the menopause there is an increase in bone turnover and a

decrease in bone formation within individual remodelling units, leading to rapid bone loss [49].

Given that the age-associated decline in bone mass accounts for the high rates of bone fractures experienced by older people, bone mass loss can be considered a surrogate of bone aging [40].

Screening and assessment of bone disease is thoroughly described in the European AIDS Clinical Society (EACS) [31] and Bone guidelines [50]. In the setting of the HIV population, an age of 50 years for males has been recommended for screening and assessment, while this value is higher in the general population [50]. Peri- and postmenopausal women with HIV should be screened as in the general population.

Treatment for osteoporosis should be initiated for patients with HIV infection using the same criteria as those stated in country/region-specific guidelines for the general population [31, 51]. Use of the fracture risk assessment tool (FRAX) score is recommended.

Secondary causes (as described in the recent Bone guidelines [50]) of low bone mineral density (BMD) should be evaluated [39, 51, 52]. Avoidance or discontinuation of medications associated with bone loss and fragility fracture (eg, anti-epileptic drugs, proton pump inhibitors, thiazolidinediones, and corticosteroids) should be considered if appropriate alternatives are available.

Given the higher prevalence of osteoporotic fractures in older persons, it is intuitive that these recommendations are particularly applicable to postmenopausal women, and men over 50 years of age with HIV infection.

Management strategies for patients at high risk of a fragility fracture include dietary and lifestyle changes (regular weight-bearing and muscle-strengthening exercise, avoidance of tobacco use and excessive alcohol intake, and prevention of falls). Pharmacological measures include calcium and vitamin D supplementation and alendronate or zoledronic acid.

Once osteoporosis therapy is started, dual-energy X-ray absorptiometry (DXA) should be repeated in 1–2 years to determine treatment effect and stability of BMD [53].

After more than a decade of investigation, no agreement exists as to the direct effects of HAART or their component drugs on bone cells in vivo, or their mechanisms of action on the skeleton. In fact, it is probably that all HAART

formulations may be inherently detrimental to the skeleton and that bone loss following HAART may be a recoupling of bone formation and re-absorption [54].

Osteomalacia is defined as softening of the bone caused by defective bone mineralization due to inadequate amounts of available calcium and/or phosphorous and can lead to bone pain, muscle weakness, low bone density, and fragility fracture. Among patients with HIV osteomalacia has been, albeit rarely, associated with tenofovir disoproxil fumarate (TDF) or efavirenz treatment, due to effects on phosphorus homeostasis and vitamin D metabolism, respectively [55–59]. Osteomalacia should be suspected in a patient with low BMD who has hypophosphatemia or phosphate wasting (fractional excretion of phosphorus >20–30 %), or severe vitamin D deficiency (generally a 25-hydroxy vitamin D <10 ng/mL [25 nmol/L], accompanied by increases in parathyroid hormone and alkaline phosphatase).

The differential diagnosis of osteomalacia and osteoporosis is relevant due to a different treatment approach. In patients with osteomalacia only vitamin D is recommended, and a rapid recovery of BMD within 1 year is expected. Alendronate treatment is contraindicated.

Osteonecrosis is defined as the infarct of the epiphyseal plate of long bones, resulting in acute bone pain. It is rare but the prevalence is increased in patients with HIV. Risk factors include low CD4 cell counts, glucocorticoid exposure, solid organ transplant, and intravenous drug use. Magnetic resonance imaging (MRI) is the best method to detect early osteonecrosis [31]. Osteonecrosis is not a disease of bone metabolism but rather the expression of a vascular disease affecting endothelial dysfunction of the bone.

3.1.4 Kidney Impairment

Both acute renal failure and CKD are more common in patients with HIV than in the general population [60–62]. They account for significant morbidity and mortality in 30 %

of individuals with HIV [63], with age being an important risk factor. Other risk factors include [64–66]:

- racial background (higher risk amongst black people);
- hypertension;
- diabetes;
- high viral load;
- CD4 < 200 cells/uL;
- co-infection with hepatitis C;
- nephrotoxicity from medications;
- male gender; and
- the use of tenofovir or ritonavir-boosted PIs.

Renal impairment in patients with HIV is multifactorial and individuals may suffer from renal damage related to the HIV infection itself; HIV-associated nephropathy (HIVAN) and immune complex kidney disease (ICKD), or related to ART exposure; renal tubular disease, interstitial nephritis, nephrolithiasis, and acute renal failure.

Nonspecific metabolic complications might also increase the risk of vascular CKD in patients on HAART. Given the benefits of HAART, fear of nephrotoxic effects is never a valid reason to withhold ART. Identification of patients with pre-existing CKD, who are at increased risk of renal damage, enables appropriate dose modification, close monitoring, and avoidance or cautious use of potentially nephrotoxic medications [67].

It is recommended to evaluate kidney function using urine dipstick and estimating glomerular filtration rate (GFR) in all HIV-positive patients at baseline [68] and when ART is initiated or changed [69, 70]. Re-evaluation should be carried out at least once a year for patients with stable kidney function and no risk factors, or at least every 6 months for patients with additional CKD risk. Evaluation every 1–3 months is recommended during the first year in patients initiating either a tenofovir-based regimen or drugs that influence creatinine secretion, including cobicistat, dolutegravir, and rilpivirine [69].

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is considered the most accurate and is

recommended in HIV-positive individuals [71–74]. While the Cockcroft-Gault equation is considered less accurate (than the CKD-EPI), it is the equation that is used for dosage adjustment of ARVs for patients with altered kidney function. The Modification of Diet in Renal Disease (MDRD) equation is also commonly used. Whichever equation is chosen it should be used consistently [69].

ARV drugs may need dose adjustment below the estimated GFR (eGFR) (50–60 mL/min) [75, 76] and can be made according to readily accessible dose adjustment tables [31, 77, 78]. Fixed-dose combinations are not recommended in renal insufficiency, depending on eGFR thresholds [79].

The recommendations shown in Table 3.2 summarize the treatments that should be avoided for different eGFR ranges, however, consultation of prescribing information for individual ARV agents is recommended.

The decision to switch combination antiretroviral therapy (cART) in patients with kidney disease is also dependent on eGFR and/or level of proteinuria (measured by the protein to creatinine ratio) regardless of patient age [80, 81].

Non-ARV drugs can also be nephrotoxic by direct injury or drug–drug interactions. To prevent or manage interactions an evidence-based information resource should be used (eg, www.hiv-druginteractions.org) [82].

3.1.5 Chronic Obstructive Pulmonary Disease

COPD is characterized by incompletely reversible chronic airflow limitation that is usually progressive and associated with chronic inflammatory processes [83].

COPD prevalence is increased among patients with HIV (between 6.8 and 21 %) [84, 85] and HIV infection is a risk independent of other contributing factors for COPD, including smoking, illicit drug use, and previous pulmonary opportunistic infections, which also have a high prevalence in this population [86].

Table 3.2 Recommendation of treatment avoidance for particular eGFR ranges

eGFR		
eGFR <70 mL/min	**eGFR <50 mL/min**	**eGFR <30 mL/min**
Avoid: • Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	Avoid: • Coformulated emtricitabine/ tenofovir/ efavirenz, lamivudine/ zidovudine; elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate • Coformulated abacavir/ lamivudine/ zidovudine	Avoid: • Emtricitabine/ tenofovir disoproxil fumarate

In observational studies, individuals with HIV and a viral load >200,000 copies/mL had a 3.4-fold increase in the odds of COPD compared with HIV-negative controls [87] and those with CD4 cell counts less than 100 cells/mL had a more rapid decline in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) than HIV uninfected patients [88].

Symptoms such as dyspnea, chronic cough, or sputum production, and exposition to risk factors should be considered for the clinical diagnosis of COPD. Spirometry is required to make the diagnosis. The presence of post-bronchodilator FEV_1/FVC <0.70 confirms COPD [83].

Lifestyle modifications, primarily smoking cessation, must be reinforced, and exposition to noxious substances should be avoided. Recently, Helleberg et al. [89] showed that treated individuals with HIV may lose more life years through smoking than through HIV [89].

Pneumococcal and influenza vaccination is recommended for patients with COPD as well as in older patients with and without HIV [83].

Current therapy of COPD in patients with HIV should follow the management guidelines for HIV-uninfected patients, as there is no specific data for the HIV-positive population [66, 83].

Ritonavir has been reported to increase systemic levels of inhaled or intranasal fluticasone [90]. Dexamethasone should not be used in combination with PIs, except as a single dose treatment [79]. Other potential interactions between ARV and other drugs should be monitored using easily available charts (eg, http://www.hiv-druginteractions.org) [79, 82, 91].

Due to the high smoking prevalence and aging of the HIV-infected population, a large proportion of these individuals would merit screening spirometry [84, 87, 92–101].

3.1.6 Cancer

As cancer incidence increases exponentially with advancing age, it is expected that the numbers of patients with concurrent malignancies will increase. Malignant disorders have always been linked to the HIV epidemic. Nevertheless, limited data are available evaluating the impact of HIV infection on cancer risk in older persons [102]. ARV therapy has led to a reduction in HIV/AIDS morbidity and mortality, changing the prevalence and types of cancers in the HIV population. Patients with HIV have a higher risk of both AIDS-defining and non-AIDS-defining cancers than the general population [103–106]. More than 2000 cases of AIDS-defining malignancies were diagnosed per year from 2001 to 2005 in the US accounting for 15–19 % of all US deaths in people living with HIV [107–109].

HIV infection itself predisposes to several neoplastic conditions, in particular those cancers associated with chronic viral infections, including Epstein-Barr virus (non-Hodgkin lymphoma [NHL]), human herpes virus 8 (Kaposi's sarcoma [KS]), hepatitis B and C viruses (hepatocellular carcinoma),

and human papillomavirus (cervical intraepithelial neoplasia [CIN] and anal intraepithelial neoplasia [AIN]) [110].

Some of the proposed mechanisms for the role of HIV infection in cancers associated with oncogenic human viruses (eg, NHL, CIN, AIN, and KS) are the immunosuppressive effect and interference with immune-mediated tumour surveillance. HIV-1, through the regulatory protein *tat*, may also have a direct promoting effect on KS lesions, but is not essential for their development.

Other cancers (eg, Burkitt's lymphoma and Epstein-Barr-virus-negative large-cell lymphoma) have an increased incidence in the HIV population, but not in immunosuppressed transplant patients, which may indicate either a direct role for HIV or other cofactors [111].

In a large prospective hospital cohort study conducted in France, the only predictive factor of Hodgkin's lymphoma, lung cancer, and liver cancer was current CD4 cell count. Current CD4 cell count and viral load, and absence of cART therapy were risk factors for KS and NHL. Cervical cancer was associated with both current CD4 cell count and absence of cART, and the risk of anal cancer increased with the time during which the CD4 count was less than 200 cells/μL and viral load greater than 100,000 copies/mL [110].

As the HIV infected population ages, while exhibiting persistent alterations of the immune system related to premature immunosenescence, an increasing number of malignancies can be expected over time [112].

At present, there are no specific data regarding whether the clinical presentation is altered in patients with HIV and whether management of cancer in aging patients with HIV should follow standard protocols. It may be reasonably assumed that what is known in the general population regarding a poor prognosis and higher multifactorial clinical risk also applies in particular to this vulnerable population.

The D:A:D study found that the cumulative use of any cART was associated with reduced AIDS defining cancers, with a protective effect occurring with both PI- and NNRTI-HAART. However, there was an increased risk of non-AIDS defining cancers, and the association with cART

appeared to be restricted to PI use (3 % higher risk per year). Biological mechanisms for the latter association, possibly indicative of an adverse effect of PI, merit further careful investigation [113]. These results favor an earlier diagnosis of HIV infection and an earlier treatment initiation in order to restore or maintain a higher CD4 cell count. In the START study, there was a 72 % relative reduction in serious AIDS-related events in the immediate-initiation group (largely due to reductions in rates of tuberculosis, Kaposi's sarcoma, and malignant lymphomas), whereas the 39 % relative reduction in serious non-AIDS-related events was largely due to non-AIDS-defining cancers [114]. In HIV clinical settings, cancer screening should take into account the particular cancer risk profile in a specific HIV population.

Guidelines developed for the general population may be appropriate for cancers of which the risk is similar between people with and without HIV infection, such as breast and prostate cancer. However, for other cancers, performance of screening interventions may warrant modified approaches, as suggested in some HIV guidelines [31, 79, 115].

The management of patients with HIV and cancer is frequently complicated by treatment-induced immunosuppression, comorbid diseases, drug interactions, and social issues (delayed presentation and/or limited financial resources). There is a need for a greater interdisciplinary approach between oncologists, HIV physicians, and palliative care doctors to ensure that people living with HIV and malignancies are suitably managed [116].

3.1.7 HIV-Associated Neurocognitive Disorders

HAND includes a spectrum of neurological disorders ranging from asymptomatic neurocognitive impairment (ANI), an intermediate form termed mild neurocognitive disorder (MND), and the most severe form, HIV-associated dementia (HAD) [117].

Although the incidence and prevalence of HAD has been reduced in the era of HAART, the prevalence of HAND overall is actually increasing worldwide. The increased lifespan of

treated patients results in a chronic exposure of the brain to HIV-1 virions and viral proteins, leading to chronic inflammation, as well as a concomitant chronic inflammation involving the peripheral immune system, both contributing to the accumulation of neurological damage [118].

Cognitive disorder remains a frequent problem despite effective ART. Up to 50 % of patients with HIV will perform in an impaired range on neuropsychological testing batteries, however, only about a quarter of these patients will note symptoms and less than half are estimated to have HAD [119].

The etiology of HAND is multifactorial, and is associated with persistent systemic and central nervous system (CNS) inflammation (possibly related to HIV infection), aging, enhanced neuronal injury due to substance abuse, syphilis, and possibly with hepatitis C virus (HCV) infection, and ART [120].

Patients at particular risk are those with previous CNS disease, a low nadir of the CD4 cell count, detectable plasma viral load, and a low current CD4 cell count [119, 121]. Co-existing morbidities contribute to poor neuropsychological performance. These include diabetes, hypertension, HCV co-infection, medication toxicities, and psychoactive substance use disorders [122]. Among older individuals with HIV, one must also consider concurrent neurodegenerative disorders, principally Alzheimer's disease, and the cognitive impact of cerebrovascular disease [123].

HAND are classified under the following sections:

Asymptomatic Neurocognitive Impairment (ANI)

1. No evidence of pre-existing cause. Cognitive impairment must be attributable to HIV and no other etiology (eg, dementia, delirium).
2. The cognitive impairment does not interfere with activities of daily living.
3. Involves at least two cognitive areas (memory, attention, language, processing speed, sensory–perceptual, and motor skills) documented by performance of >1 standard deviation below the mean of standardized neuropsychological testing.

Mild Neurocognitive Disorder (MND)

1. No evidence of pre-existing cause. Cognitive impairment must be attributable to HIV and no other etiology (eg, dementia, delirium).
2. At least mild interference in >1 activities of daily living including mental acuity, inefficiency at work, homemaking, or social functioning.

HIV-Associated Dementia (HAD)

1. No evidence of another pre-existing cause for dementia (ie, CNS infections, CNS neoplasm, cerebrovascular disease).
2. Marked interference in activities of daily living.
3. Marked cognitive impairment involving at least two cognitive domains by performance of >2 standard deviations below the mean of standardized neuropsychological tests, especially in learning of new information, slowed information processing, and defective attention or concentration [124].

Multiple clinical tests have been used to evaluate neurocognitive function; however, there is no single and universal neuropsychological battery to specifically assess people with HIV. Evaluation of the different cognitive functions requires expert staff specialized in clinical neuropsychology that evaluates at least five of the following cognitive abilities:

- verbal/language;
- attention/working;
- memory;
- abstraction/executive functioning;
- learning/recall;
- speed of informational processing; and
- sensory–perceptual and motor skills.

Some screening instruments to assess HAND are available and can be performed in less than 10 min, namely the HIV Dementia Scale (HDS) [125], the International HIV Dementia Scale (IHDS) [126], or the Montreal Cognitive Assessment (MoCA) [127]. Other tests often used in conjunction with these include the Brief Neurocognitive Screen (BNCS) [128], screening battery of the HIV Neurobehavioral

Research Center (HNRC) [129], computed COGSTATE [130], or Neu Screening [131].

The diagnosis of HAND is confirmed by the clinical detection of cognitive impairment through neuropsychological testing and the evidence of neurocognitive impairment. Cognitive impairment must be attributable to HIV after excluding other causes that can justify the disorder [124]. Other conditions that can cause CNS complaints, such as thyroid disease, syphilis, B_{12} deficiency, substance use, and depression, should be screened for and treated.

The treatment of choice of HAND remains the use of HAART and better CNS penetrating ART should be considered, as accumulating data support that it better reduces HIV RNA levels in the cerebrospinal fluid (CSF) and leads to neurocognitive improvements [132]. However, HAART benefits for HIV cognitive disorders differ substantially between individuals [133]. Several studies have shown in recent years the persistence of asymptomatic or mild/moderate forms of HAND [119], leading to speculations that systemically effective HAART might fail to control CNS-HIV infection, and also that the type of ARV drug and its penetration may have a role in the development of HAND [124].

Recently, Underwood et al. [134] also conceptualized the possibility of an ART induced neurotoxicity (Fig. 3.2). So far there is clear evidence of neurotoxicity induced by efavirenz [126, 127, 135–142], however, more studies are needed to evaluate the long term toxicity of other ARVs.

The median survival of patients with HAD has improved considerably with the introduction of HAART [143], although, it remains a negative prognostic factor associated with mortality [144, 145]. Mild cognitive impairment is also associated with poorer adherence to treatment [146], higher rates of virological failure [141], difficulties in the development of everyday function [147], loss of employment [148], impairments in quality of life [149], and progression to dementia [150].

Avoiding cognitive impairment can be considered a measure of successful cognitive aging and an important clinical outcome among people aging with HIV. Successful cognitive aging (SCA) has been defined as aging without subjective or

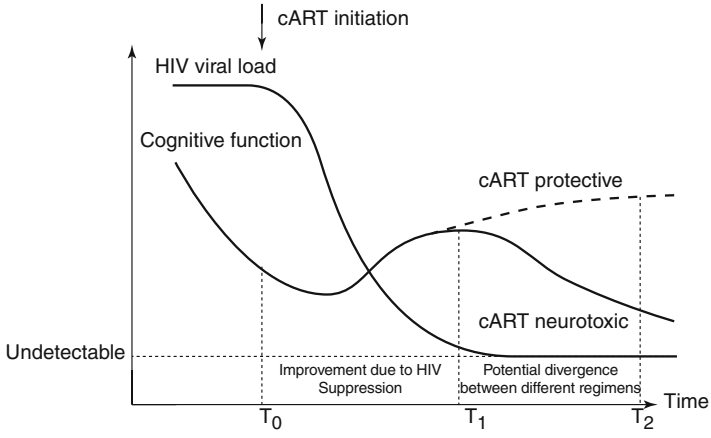

FIGURE 3.2 Dynamic cognitive function changes over time after injection of combination antiretroviral therapy [134]. cART, combination antiretroviral therapy (Reproduced with permission from © Wolters Kluwer Health Inc)

objective cognitive impairment, depressive symptoms, or functional impairment [151, 152].

Among people aging with HIV, SCA is associated with better mental quality of life [151], medication adherence, and capacity to interact with health professionals [152]. In studies that report SCA prevalence among middle aged and older adults with HIV estimates of SCA range between 19 % [151] and 32 % [152]. However, predictors of SCA are unknown, with one study identifying no relationship between odds of SCA and individual markers of HIV-disease severity, including current CD4 cell count and HIV RNA viral load, or with individual comorbidities, including diabetes or dyslipidemia [152].

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Chapter 4
Comorbid Conditions and Older Adults with HIV

Giovanni Guaraldi and Ana Rita Silva

Key Points

- Multimorbidity (MM) is an increasingly common age-related condition that has a higher prevalence amongst patients with human immunodeficiency virus (HIV) infection compared to the general population.
- MM describes the contemporary clinical complexity of HIV care.
- Whether MM describes an accelerated or accentuated aging process is matter of discussion, although some HIV variables depicting immune activation and chronic inflammation are associated with MM.
- The incidence of MM can be explored as an endpoint in clinical studies.

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As a consequence of the dramatic increase in life expectancy, observed both in industrialized and developing countries, people living with HIV (PLWH) are at an increased risk of both age-related conditions and HIV-associated non-AIDS conditions (HANA), which often may overlap.

The process of aging involves a continuum of changes in biological, functional, psychological, and social parameters depending on genetic factors and differences in organ function and reserves. Aging is often accompanied by chronic comorbid conditions frequently associated in a complex interaction between multimorbidity, disability, and frailty [1].

4.1 Multimorbidity

Multimorbidity is conceptualized as several serious health conditions that cannot be cured to a significant extent, occurring in an older person and engendering functional and/or cognitive disability [2]. Aging plus debilitating conditions interact to make morbidity and mortality worse than might otherwise seem apparent.

In the general population there is no consensus on the definition of MM or how to measure it. MM has been described as the simultaneous occurrence of several medical conditions in the same person [3]. Some clinicians would define MM as at least two or more conditions being present at the same time.

MM can be diagnosed by self-report, depending on the condition and clinical setting (cardiovascular disease [CVD], chronic obstructive lung disease, liver cirrhosis, osteoporosis [using fracture end point]), or by clinically determined prevalence (chronic kidney disease [CKD], anaemia, osteoporosis [using DEXA]), drug-tracing criteria (therapeutic drug monitoring, drug prescriptions), or by using administrative data set collecting diagnoses (ICD9-CM) [3–10].

4.1.1 Pathogenesis of Multimorbidity

The pathogenesis of MM is multifactorial, involving immune activation, chronic infection (including cytomegalovirus), immunosenescence, and chronic inflammation [4], the so called 'inflammaging' process. Persistent inflammation is likely to be a major driver of morbidity and mortality in treated HIV infection, and a better understanding of its underlying causes may help prioritize targets for interventions [5].

4.1.2 Epidemiology of Multimorbidity

Comorbidities are seen in patients of all ages; in a cross-sectional study by Barnett et al. [6] it was found that by the age of 50 years half of the study population had at least one MM and by the age of 65 years most had MM. Comorbidities within populations of HIV-positive individuals have also been considered and several studies assessing the prevalence of HANA conditions and MM have been carried out in EU and US cohorts [1].

There is an apparent significant difference in the prevalence of MM in different cohorts, with the limitation of epidemiological cross comparison data, which may reflect differences in risk factors and patient vulnerability (Fig. 4.1). Country specific data on the prevalence of MM in the age spectrum of HIV is needed to develop appropriate prevention strategies in the care of patients.

MM is increasingly becoming the norm rather than the exception among people infected with HIV. Patients with HIV are surviving long enough to experience HIV as a chronic disease, exposing them to a broad spectrum of comorbidities. Non-AIDS defining conditions including CKD, metabolic diseases, CVD, and malignancies have been observed as increasing in incidence in recent years [9–17].

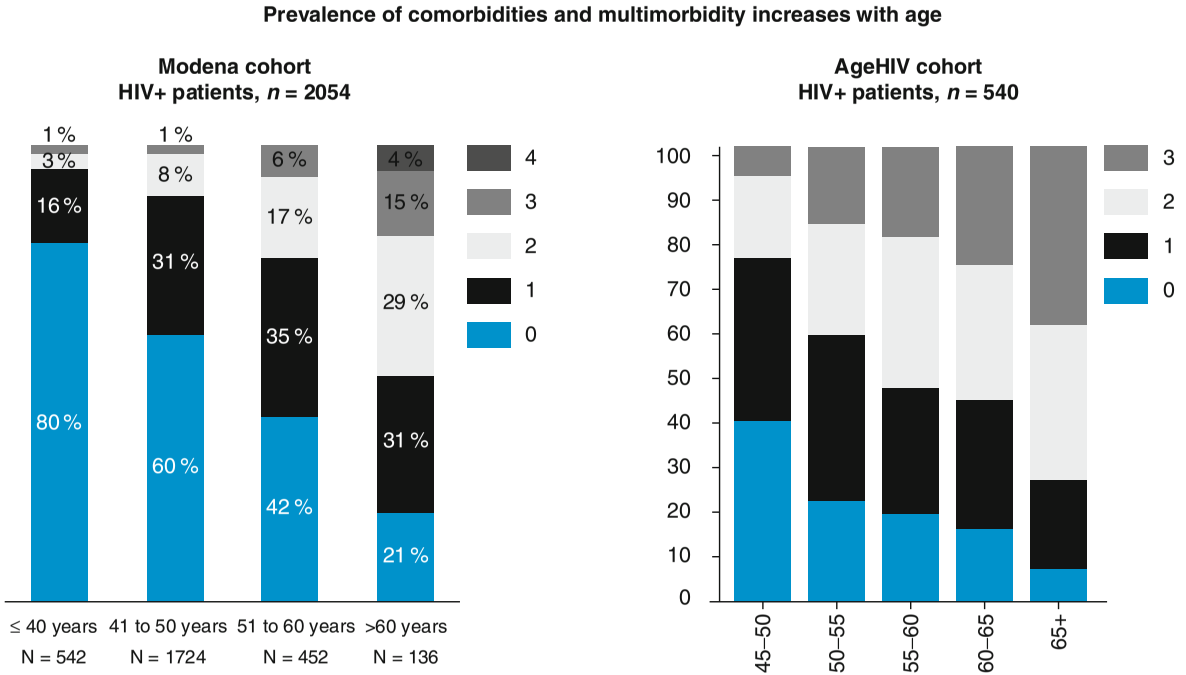

FIGURE 4.1 Comparison of the prevalence of comorbidity and multimorbidity in the Modena HIV Metabolic Clinic cohort [7] and the AgeHIV cohort [8] (Reproduced with permission from © Oxford University Press)

4.1.3 Methodological Issues in Multimorbidity

In addition to the careful description of the study population under consideration, other methodological issues should be taken into account when comparing prevalence and incidence of MM in PLWH and the general population. Firstly, the different distribution of age categories needs mathematical adjustments to compensate for differences in age group prevalence. Secondly, cohort studies cannot avoid a selection bias that may result in a distortion of the results of a study based on the way in which patients are sampled, and perhaps even more importantly, reverse causality often cannot be excluded [18]. Interestingly, this problem is quite similar to the 'survival bias' that complicates the interpretation of many studies on aging; the older patients, in an observational cohort, may represent the fittest population, while the vulnerable individuals may be under-represented because they have already died. The same mechanism can be true for MM, itself strictly associated with mortality [1].

As antiretroviral treatment (ART) regimens have become more effective and less toxic, and more patients initiate ART at earlier disease stages, it is possible that the risk of morbidity and mortality might be lower for older HIV-infected individuals in the future. On the contrary, most of the current older population of HIV-infected individuals survived the pre-ART and early-ART eras and may well be enriched for favorable host genetics and healthier lifestyles than the general population. Such a survival bias might result in a significant underestimation of the influence of HIV on morbidity and mortality in older populations. Uncertainty remains over whether inferences from recent cohort studies will accurately reflect a future HIV-infected population that is expected to be much older [5].

4.2 Accentuated Versus Accelerated Aging

The higher prevalence of comorbidities and MM in HIV cohorts when compared to HIV-negative controls does not resolve the question whether HIV is accelerating aging itself, through path-

ways and mechanisms common to the aging process [19, 20] or, alternatively, whether HIV may simply be an additional risk factor for a wide number of chronic conditions, thus accentuating the prevalence of disease at every age [19, 21].

In a schematic view, we may consider the model of aging and disease as a physiological process of progressive decline of clinical reserve. Organs and biologic systems have a clinical reserve that is progressively reduced in the physiological aging process.

Two 'pathological' aging patterns may identify an accentuated or an accelerated aging process.

- Accentuated aging identifies a trajectory pattern in which an initial pathological condition may abruptly cause reduced clinical reserve, which subsequently declines in a rate similar to that observed in a physiological aging pattern. In this context, MM occurs at the same ages but at a higher rate among HIV-infected participants than among HIV-uninfected comparators.
- Accelerated aging identifies a trajectory pattern in which a faster progression of clinical reserve is lost. Therefore, MM occurs earlier among HIV-infected participants compared with HIV-uninfected comparators and there are, for example, more cancer events. In this conceptualization, accelerated aging can be considered synonymous of 'premature aging'.

Given the great variability of the aging process, we may argue that in the clinical setting the aging trajectory is often a mixture of accentuated and accelerated aging occurring in the same individuals as the net result of competing adverse events and compensatory homeostatic processes (Fig. 4.2).

4.2.1 Does HIV Accelerate or Accentuate Aging?

A critical research question is whether HIV is accelerating aging through pathways and mechanisms common to the aging process [19, 20], or whether it is an additional risk factor for a wide number of chronic conditions and thus accentuates

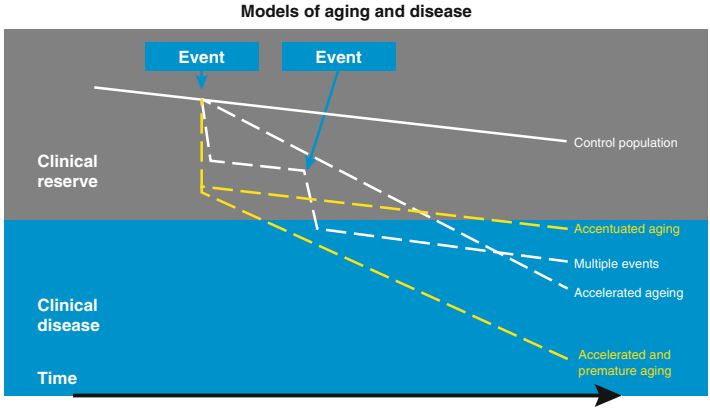

FIGURE 4.2 Models of aging and disease demonstrating that the aging trajectory is often a mixture of both accelerated and accentuated aging [22]

the prevalence of disease at every age [19, 21]. Although this may seem to be a semantic difference, it is critical to defining approaches that mitigate the sequelae of aging with HIV infection, and perhaps aging in uninfected persons.

To resolve this question, it will be important to account for differential exposure to risk factors (eg, smoking, alcohol abuse, and non-HIV sexually transmitted diseases) between HIV-infected and uninfected populations that are likely to result in residual confounding when assessing associations of HIV with increased risk of age-related illness. This is the reason why, more recently, some cohort studies are addressing the prevalence of MM in HIV-selected and HIV-negative control groups who share similar risk behaviours (Fig. 4.3).

Ultimately, it may be argued that an ideal match of HIV-positive and negative cohorts is not possible due to consideration of the expected social vulnerability that may be considered as the decisive reason why HIV-positive individuals acquired HIV infection.

Althoff et al. [24] evaluated almost 100,000 patients from the Veterans Administration database and analyzed prevalence and age of onset of myocardial infarction, CKD, and

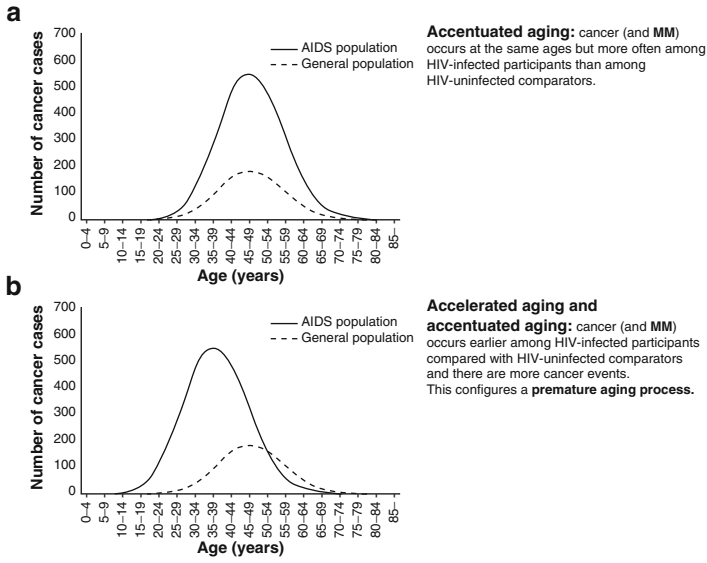

FIGURE 4.3 Hypothetical age-at-diagnosis distributions of cancer (and multimorbidity) in the AIDS and general populations (**a**) accentuated aging and (**b**) accelerated aging and accentuated aging [23] (Reproduced with permission from © The American College of Physicians)

non-AIDS defining cancers in both infected and uninfected veterans charts. The important findings were that all three diseases were seen more commonly in those patients infected with HIV, but the age of occurrence of these conditions did not significantly differ from the uninfected population. This is one of the largest studies looking at the question of 'accelerated' aging in the HIV-infected population and the conclusions do not appear to support the idea that HIV infection causes early aging.

In a clinical perspective the accentuated and accelerated dilemma may not necessarily be considered as an antagonistic interpretation of aging as a health condition but rather a two-sided perspective.

In order to begin to improve the overall health and quality of life of HIV-infected individuals with multiple

comorbidities, it is useful to recognize that this clinical phenotype is similar to that observed in older geriatric populations. Valuable lessons from geriatrics literature that are likely to be helpful for frail HIV-infected individuals include [5]:

- minimizing pill burden, overlapping toxicities, and drug interactions;
- avoiding destructive health-related behaviors; and
- focusing on interventions, such as moderate exercise, that holistically address overall function rather than specific disease states.

In contrast, if the goal is to identify targets for interventions to prevent MM and frailty in HIV-infected individuals, then understanding the specific diseases that are increased as well as the mechanisms that drive them is critical and specificity is important.

4.3 Aging Versus Aged

Current literature focusing on HIV in older populations is concentrated on studies comparing older HIV-positive populations with younger HIV-positive individuals, or comparing older HIV-positive individuals with older HIV-negative individuals [25–27]. Such comparative studies have highlighted the diversity of individuals aging with HIV, in terms of behavioral factors, social vulnerability, and ethno-racial differences, factors that may contribute to differences in patterns of aging [25]. Comparative studies within groups of older people with HIV may help to better understand relationships between age and other determinants of health, such as HIV treatment history, diagnosis, presentation of comorbidities, and HIV disease duration.

It has been suggested that effectively treated patients aging with long-standing HIV infection may have characteristically different health and care needs compared with those who seroconverted at older ages, but accurate data in this

evolving area is urgently needed [25, 28]. A recent study [29] hypothesized that longer HIV duration was an independent predictor of MM, and would be associated with higher risk of individual non-infectious comorbidities (NICM). Guaraldi et al. [29] compared prevalence for NICM and MM among three age- and sex-matched groups:

1. people aging with longer duration of HIV infection;
2. people with shorter duration of HIV infection who seroconverted at an older age; and
3. people without HIV.

Anthropometric, cardiovascular, and metabolic biomarkers between the HIV-positive groups were also compared. Patients in the Modena HIV Metabolic Clinic (MHMC) cohort with HIV duration in the longest quartile (≥20.6 years, 'HIV-aging') (n = 404, mean age 46.7 ± 6.2 years, 28.9 % women) were matched 1:1 to MHMC participants with HIV duration in the shortest quartile (<11.3 years, 'HIV-aged') and 1:6 to HIV-negative participants from the general population CINECA ARNO database (n = 2424) [29]. Analyses were performed among all participants and was also limited to middle-aged and older (>45 years) participants [29].

HIV-aging participants consistently exhibited the highest risk and HIV-aged had intermediate risk, though differences between HIV-positive groups were significant only for hypertension (36 vs 26 %, p = 0.001) [29]. Among HIV-positive participants aged 45 years and older, duration of HIV infection was independently associated with MM risk (p <0.001). HIV-aging participants had higher rates of lipoatrophy, lower body mass index, and higher rates of insulin resistance than in the HIV-aged participants, while HIV-aged participants had higher total cholesterol and low density lipoprotein [30]. These data support previous findings associating HIV infection with higher risk for age-related health problems, and further highlight heterogeneity in health status among people aging with HIV in relation to duration of HIV infection.

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Chapter 5
Frailty in HIV

Giovanni Guaraldi and Thomas Brothers

Key Points

- The clinical definition of frailty has evolved significantly in the last 15 years, such that it can be reliably recognized and quantified in a number of ways.
- Clinical details, including timeline of changes in cognition, mobility, and function are of particular importance in quantifying frailty in clinical settings.
- Frailty denotes vulnerability to poor health outcomes. Its presence should alert the clinician to opportunities to carefully weigh the risk/benefit ratio of health care interventions and to discuss prognosis.
- The frailty phenotype and frailty index instruments are appropriate clinical tools for use among people aging with human immunodeficiency virus (HIV) and are proven to be predictors of mortality and adverse health outcomes.

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- A frailty index can be used as an inclusion criteria for the selection of a vulnerable population to address specific antiretroviral (ARV) regimens/strategies or as clinical end point to design future ARV randomized clinical trials.

Health problems are generally accumulated as people age, but individuals of the same age can experience very different levels of health. The concept of frailty describes this heterogeneity in health status among people of the same chronological age [1]. Frailty is often evaluated in the setting of geriatric medicine, and the utility of frailty assessment has recently begun to be investigated in the context of HIV, with the first major study published in 2011 [2]. As chronic HIV infection is a multisystem illness, and individuals aging with HIV often have multiple comorbid medical and social factors influencing their health and care plan, frailty may be a useful concept. This will be especially so as the population of people living with HIV continues to age.

5.1 Defining Frailty

While age-related, non-AIDS comorbidities, and multimorbidity (MM) are increasingly recognized clinical issues related to people aging with HIV, frailty is an emerging marker of vulnerability among individuals aging with chronic HIV [3].

According to current views, frailty is defined as a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and deregulation of multiple physiological systems [1]. Individuals who are frail experience an extreme response to even relatively minor insults, due to impaired homeostatic responses [1].

Frailty exists on a continuum from fit or robust individuals to frail individuals. As individuals become more frail, vulnerability may become detectable by looking at various clinical, functional, and biological markers (Fig. 5.1). Understanding and detecting

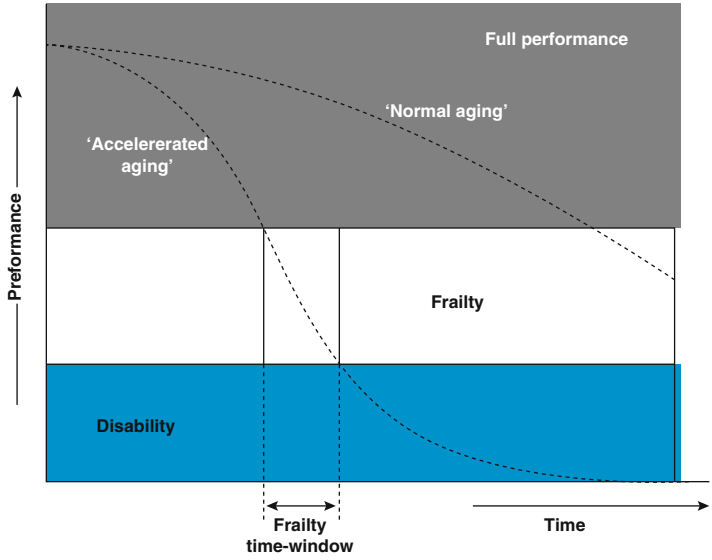

FIGURE 5.1 Normal and accelerated aging trajectories from full physiologic reserves to disability, across a frailty time window (Adapted from Fried et al. [4])

frailty at an early stage is important because frailty is a summary marker of overall vulnerability and is predictive of adverse health outcomes, including future clinical events, institutionalization, and mortality. Perhaps most importantly, increases in frailty severity can be prevented or delayed with intervention. Improvement in frailty status is also possible [1].

5.2 Measuring Frailty

There is currently no consensus on a single best operational definition of frailty, or best way to measure it [1]. Multiple frailty measurement instruments have been developed, which provide different strengths and limitations [5–7]. Two different conceptual models have emerged that inform most approaches to frailty: the phenotype model [4] and the cumulative deficit model [8].

The phenotype approach views frailty as a specific clinical syndrome arising from a cyclical process of chronic undernu-

trition, sarcopenia, and weakened strength and exercise tolerance, suggesting that the development of frailty is distinct from aging or other disease processes [9].

A frailty phenotype measurement instrument was proposed in 2001 to suggest that an individual is frail if they experience three or more of the following five symptoms: slowness, weight loss, impaired strength, exhaustion, and low physical activity/energy expenditure (Table 5.1). This approach has been widely studied and exhibits predictive validity for poor health outcomes across a wide range of illnesses and settings. In some clinical trials the 30 second Chair Stand Test [10] is used alternatively to the walking speed test, and other factors, such as cognitive impairment, have been suggested as further characteristics of a frailty phenotype [1]. While the frailty phenotype model calls for five specific measurements to be used, recent reviews have highlighted that the phenotype measurement instrument is commonly extensively modified across all published studies [11] and within the HIV literature [9]. The implications of these modifications are not fully understood, but affect the estimates of

Table 5.1 Frailty phenotype measurement and definition criteria

Item	Type of measurement	Criteria
Walking speed	Timed 15 ft (5 m) walk	Slowest 20 % by gender and height
Grip strength	Dynanometer	Weakest 20 % by gender and body mass index
Weight loss	Self-report	Lost 10 lbs (4.5 Kg) in the past year
Fatigue	Self-report: 'trouble getting going'	N/A
Activity level	Self-report: number of calories expended	Lowest 20 % Males: 383 kcals/week Females: 270 kcals/week

One or two positive results identify a pre-frail condition and three or more identify a frail phenotype [4] (Reproduced with permission from © Oxford University Press)

frailty prevalence and the relationship between the frailty phenotype and risk for adverse outcomes [11].

The deficit accumulation model views frailty as a state, rather than a specific clinical syndrome. It suggests that frailty arises from the cumulative effects of relatively non-specific age-related health deficits. This model suggests that frailty does not have a unique pathophysiology, but rather is related to the aging process [12]. Under this model, frailty has been proposed to describe the overall health state of an individual, and therefore serve as an integrative marker of biologic aging [13].

A frailty measurement instrument using the deficit accumulation approach, the frailty index, was first proposed in 2001 [14]. A frailty index is measured by calculating the ratio of health deficits present within an individual out of a number of pre-specified health variables. The frailty index allows inclusion of any health variable, providing that a minimum of 30 deficits in total are included that cover multiple physiologic systems, and that each deficit is associated with adverse health outcomes and increases in prevalence with age [15, 16]. The frailty index approach has been widely studied across populations, with differing sets and numbers of variables included (from as few as 30 to as many as 100) and consistently found to predict survival, the risk of disease progression, the need for institutionalization, and the use of health care services [17]. The index value generally increases by approximately 0.03 points per year of life and there appears to be a reproducible proportion of deficits (approximately 0.7) beyond which survival is not possible [16].

Frailty indexes can be comprised of different variables in different settings; clinically, frailty indices can be calculated from electronic medical records [18] or from the information obtained in a comprehensive geriatric assessment [19].

One of the challenges of the frailty index, and other frailty measurement instruments that incorporate large amounts of information, is that feasibility might be reduced in some clinical settings due to the time required to gather this information. In such cases, another screening tool might also be needed, for example, the Clinical Frailty Scale, with which the assessor makes a judgment about the degree of a person's frailty based on clinical data, using a 9-point ordinal scale (Fig. 5.2) [8, 20].

Clinical Frailty Scale

1 **Very Fit** -People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** -People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, eg, seasonally.

3 **Managing Well** -People whose **medical problems are well controlled.** but are **not regularly active** beyond routine walking.

4 **Vulnerable** -While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being 'slowed up', and/or being tired during the day.

5 **Midly Frail** -These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** -People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal asistance (cuing, standby) with dressing.

7 **Severely Frail** -**Completely dependent for personal care,** from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within - 6 months).

8 **Very Severely Frail** -Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 **Terminally Ill**-Approaching the end of life. This category applies to people with **a life expectancy <6 months,** who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common symptoms in **mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well.They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

FIGURE 5.2 The clinical frailty scale [8, 20] (Reproduced with permission from © 2007–2009 Version 1.2. Geriatric Medicine Research, Dalhousie University, Halifax, Canada)

In this approach, the health professional considers information about cognition, mobility, function, and comorbidities, based on patient history and physical examination to assign a frailty level from one (very fit) to nine (terminally ill with a life expectancy <6 months). This method is simple to administer and effectively estimates important outcomes, such as survival and institutionalization. This makes the Clinical Frailty Index comparable to other methods (Table 5.2).

5.3 The Utility of Measuring Frailty

The ability to measure frailty is useful at a health care policy level as well as clinically; information about frailty helps program planners by identifying the range of services that might be required and the anticipated need for them. Clinically, frailty stratification can help to plan interventions focused on the goals of the patient and caregiver, or to predict a patient's risk of death or need for institutional care [8, 21]. A systematic review by Yourman et al. [22] of prognostic indices for mortality in older adults reported that more than a dozen non-disease specific indices can predict all cause mortality across a variety of clinical settings. However, all of the indices showed unexplained variation in the prediction of mortality. The authors concluded that even if an index cannot predict life expectancy certainly, it can improve accuracy in decision-making regarding clinical outcomes [22].

Four goals of frailty measurement were outlined in a recent review by Rockwood et al. [23]:

- risk stratification;
- to aid in diagnosis and care planning;
- understanding frailty (including its biology); and
- to serve as an outcome measure.

This perspective values the ability to grade frailty on a continuum of severity, rather than simply categorizing individuals as frail or not frail.

Frailty measurement is increasingly being incorporated into pre-operative assessment for older adults considering

Table 5.2 A comparison of three validated measures of frailty; Fried's Frailty Phenotype, the Clinical Frailty Scale, and the Frailty Index [16]

	Description and classification	Outcomes (HR and 95% CI for death and institutionalization, respectively)	Pros	Cons
Fried's frailty phenotype	Frail = ≥3 characteristics Pre-frail = ≥2 characteristics Robust = none	1.17 (1.13–1.20) 1.27 (1.19–1.35)	Four of the five items are objective (performance can be measured). Extensively validated to predict health outcomes. Correlation with physiologic markers of poor health outcomes including hemoglobin and pro-inflammatory markers.	Misclassification. Lack of consensus regarding nature and number of items. Does not stage degrees of frailty.
Clinical Frailty Scale	Classification on ordinal scale according to global clinical assessment	1.30 (1.27–1.33) 1.46 (1.39–1.53)	Clinically feasible.	Requires additional data on feasibility and validity in clinical settings.
Frailty index	Number of health deficits present/ number of possible health deficits	1.26 (1.24–1.29) 1.56 (1.48–1.65)	Precise measurement Reproducible across populations and disease states	Cumbersome to use in clinical setting.

CI confidence interval, *HR* hazard ratio

surgery [24–26], as well as identifying those who will fail to mount an adequate response to influenza and pneumococcal vaccination [27, 28].

Studies applying both models of frailty have identified associations between increasing severity of frailty and age-related deterioration in multiple systems, including immunosenescence and chronic inflammation [29, 30], which may be particularly relevant in people with treated HIV [31–35].

Frailty is strongly associated with comorbidity and disability, and is a sensitive indicator of changed medical care needs in patients with HIV infection [34], thus, frailty may represent an important marker for the inflammaging process for this patient population. Studies are needed to improve our understanding of the complex interrelationship between HIV infection, frailty, and comorbidity. Early studies [36, 37] suggest that frailty portends adverse outcomes in patients with HIV infection, however, these relationships are not yet well understood, including how frailty changes over time in individuals with HIV and which risk factors might be meaningfully modifiable. Understanding of such relationships would make the evaluation of frailty a useful clinical tool and a possible endpoint in clinical trial.

5.4 Frailty in the Context of HIV

Among individuals aging with HIV, frailty has been measured in order to identify individuals more vulnerable to adverse outcomes and to measure the effects of HIV disease progression and clinical interventions [12, 29, 38]. CD4 count and viral load are often uninformative (in terms of stratifying vulnerability) for many individuals on combination antiretroviral therapy (cART) and more holistic measures, like frailty, are beginning to prove useful. In this case, processes related to aging, environmental and social risk factors, and HIV disease and its treatment (Table 5.3) all contribute to vulnerability in multiple, interacting ways [9]. These factors influence the severity of frailty on an individual level, as they affect both the rate of insults faced as well as the integrity of intrinsic repair mechanisms [9].

Table 5.3 Summary of factors associated with frailty among HIV-positive individuals on antiretroviral therapy

Age
HIV-related measures
Longer time since diagnosis
Lower current CD4 count
Lower nadir CD count
Low CD4/CD8 ratio
Detectable viral load
Longer duration of HAART regimen
Comorbidities
Hepatitis C infection
Low BMI
High BMI
Lipodystrophy
Diabetes
Kidney disease
Depressive symptoms
Cognitive impairment
Inflammation
Weak upper and lower extremities
History of falls
Social factors
Lower education
Current unemployment
Low income in past year

Note that social factors and medical comorbidities are associated with frailty severity, along with markers of HIV disease severity and immune system dysfunction [3]. *BMI* body mass index, *HAART* highly active antiretroviral therapy, *HIV* human immunodeficiency virus (Reproduced with permission from © Oxford University Press)

Age-related chronic conditions have been associated with both immune activation (eg, soluble CD14 and CD163, CD16+ monocytes, HLA-DR+/CD38+ CD8+ T cells) and immune senescence markers (eg, terminally differentiated CD45RA+ CCR7− CD4+ T cells), as well as inflammatory circulating cytokines (eg, interleukin [IL]-6, tumor necrosis factor α [TNF-α]) [9, 36, 38, 39].

Frailty is associated with both CD4 count and viral load [40], yet relationships between frailty and markers of immune senescence and activation among HIV-positive individuals have not been established. Although the clinical spectrum of HIV disease differs whether individuals experience immune deficiency or immune activation, frailty might emerge in the context of both profiles. A hypothetical representation of the association between frailty, HIV-associated non-AIDS (HANA) conditions, and immune system dysregulation is depicted in Fig. 5.3.

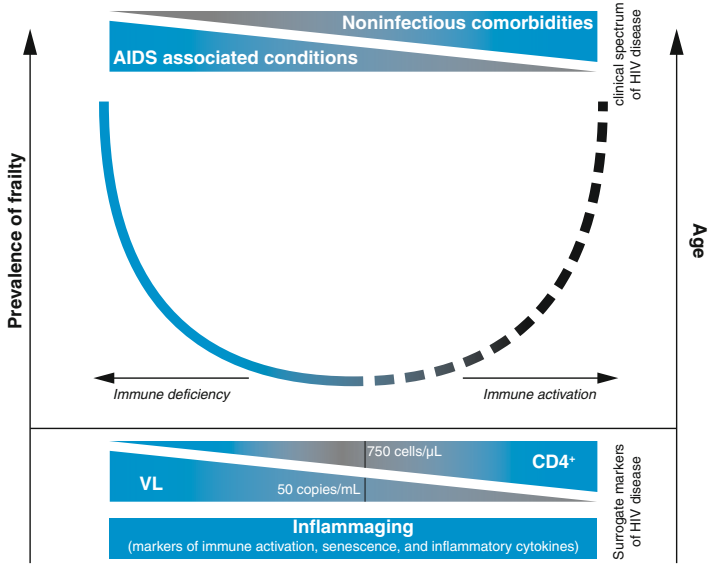

FIGURE 5.3 Hypothetical association between frailty prevalence, HIV-associated non-AIDS conditions, and immune system dysregulation [3] (Reproduced with permission from © Oxford University Press)

Causal pathways between these factors are not yet understood, in part because most studies investigating HANA or frailty in HIV have been cross-sectional. The potential for social vulnerability to contribute to frailty across the whole spectrum should also be recognized.

5.4.1 *Measuring Frailty in HIV-Positive Individuals*

Most published studies of frailty in HIV infection have used frailty scales composed of a limited number of specific health measures, following the frailty phenotype approach (Table 5.1). At present, only one study [41] has assessed frailty in people with HIV using the cumulative deficit/frailty index approach.

Table 5.4 illustrates the 37 non-HIV-related health variables included as items in the frailty index. Note that the frailty index approach calls for the inclusion of many non-specific health deficits, and so other health variables could be incorporated into a frailty index in other settings.

In a 10 year prospective analysis by Guaraldi et al. [41], participants in the Modena HIV Metabolic Clinic cohort were analyzed using the capacity of a deficit accumulation frailty index to predict MM. Thirty-seven routinely collected health variables were included in the frailty index. Predictors of survival were [41] (Fig. 5.4):

- frailty index (0.1 increment, adjusted hazard ratio [HR] 1.63, 95 % confidence interval [CI] 1.05–2.52);
- current CD4+ cell count (0.48, 0.32–0.72); and
- injection drug use (2.51, 1.16–5.44).

The study analysis included 2720 participants (mean age 46 ± 8; 32 % women), provided 9784 study visits, and over 8206 person-years follow-up (PYFU) (0.41/100 PYFU). In a Cox analysis to predict mortality rate, the frailty index was an independent predictor of survival after correction for age, gender, nadir, current CD4 count, and intravenous (IV) drug use [41].

Table 5.4 Non-HIV-related health variables included as items in the frailty index [41]

1	Lipoatrophy	**14**	High homocysteine	**27**	Proteinuria
2	Lipohypertrophy	**15**	Abnormal white blood cell counts	**28**	Elevated aspartate transaminase (AST)
3	Non-alcoholic fatty liver disease	**16**	Anemia	**29**	Elevated alanine transaminase (ALT)
4	Menopause or male hypogonadism	**17**	Hepatitis C co-infection	**30**	Abnormal alkaline phosphatase
5	High or low body mass index	**18**	Hepatitis B co-infection	**31**	Elevated gamma-glutamyl transphosphatase (GGT)
6	High waist circumference	**19**	Vitamin D insufficiency	**32**	Low platelets
7	High visceral adipose tissue	**20**	Polypharmacy	**33**	Abnormal potassium
8	Sarcopenia	**21**	Abnormal parathyroid hormone	**34**	Abnormal phosphorus
9	Insulin resistance	**22**	Elevated D-dimer	**35**	Abnormal thyroid stimulating hormone (TSH)
10	High total cholesterol	**23**	Elevated C-reactive protein	**36**	Elevated total bilirubin
11	High low density lipoprotein (LDL)	**24**	Sedentary lifestyle	**37**	Unemployment
12	Low high density lipoprotein (HDL)	**25**	Atherosclerosis		
13	High triglycerides	**26**	Hyponatremia		

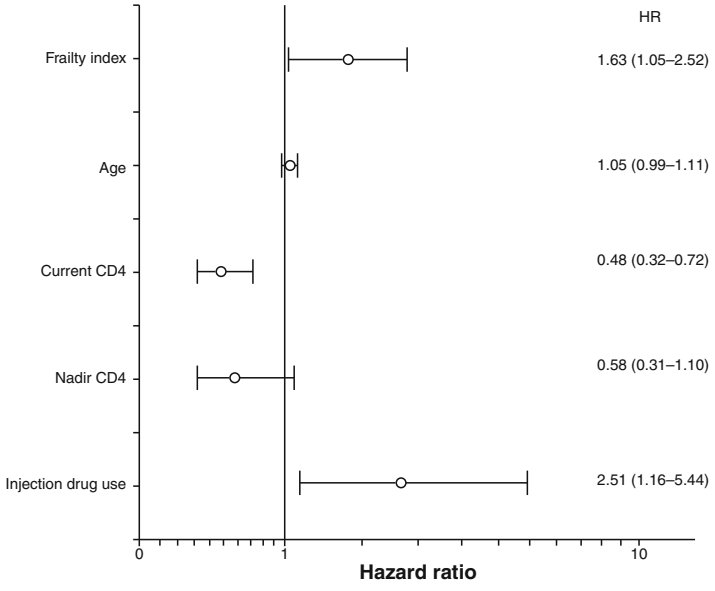

FIGURE 5.4 Predictors of survival in multivariate analysis [41]. *HR*, hazard ratio (Reproduced with permission from © Wolters Kluwer Health)

5.4.2 *The Veterans Aging Cohort Study Index*

The Veterans Aging Cohort Study (VACS) index, a measure of health status in individuals with treated HIV, has recently been proposed as a frailty measurement instrument [42–44].

The VACS index (Table 5.5) is a prognostic tool that incorporates traditional HIV disease-related factors, including current CD4+ T cell count and viral load, as well as hepatitis C virus co-infection, liver fibrosis, hemoglobin, renal function, race, and age. The VACS index is a measure of multisystem deterioration and vulnerability, and is associated with multiple adverse outcomes. As such, it could reasonably be considered a frailty measurement instrument. However, the VACS index differs from other frailty measures as it was designed specifically

Table 5.5 The Veterans Aging Cohort Study (VACS) index

Factor	Points
Age (years)	
<50	0
50–64	12
>65	27
CD4 cell count (cells/μL)	
>500	0
350–499	6
200–349	6
100–199	10
50–99	28
<50	29
HIV-1 RNA (copies/mL)	
<500	0
500–1×10^5	7
>1×10^5	14
Hemoglobin (g/dL)	
>14	0
12–13.9	10
10–11.9	22
<10	38
FIB-4	
<1.45	0
1.45–3.25	6
>3.25	25
eGFR (mL/min)	
>60	0
45–59.9	6
30–44.9	8
<30	26
Hepatitis C infection	5
Theoretical maximum index score	**164**

Reproduced with permission from © Wolters Kluwer Health, Inc
eGFR estimated glomerular filtration rate, *FIB-4* fibrosis-4

to predict mortality and includes chronological age [43]. Most frailty scales do not include chronological age, as they intend to describe biological age-related changes independent from age.

A study by Akgün [44] analyzed a modified version of the frailty phenotypes and the VACS index as predictors of hospitalization and mortality in HIV-infected and uninfected individuals. After adjustment for other covariates, the frailty phenotype was associated with hospitalization (HR 1.78; 95 % CI 1.48–2.13) and mortality (HR 1.75; 95 % CI 1.28–2.40). The VACS index was a better predictor of hospitalization and mortality than the frailty phenotype (area under receiver operating characteristic curve 0.584 and 0.565, respectively).

5.4.3 The Choice of Clinical Outcome in Studies That use Frailty as an Endpoint

Many studies of frailty measurement instruments in geriatric medicine consider mortality as the outcome of interest. Definitively, frailty (as an expression of a risk prediction measure), must be able to predict mortality after correction for chronological age. Nevertheless, clinicians may benefit from the capacity of a frailty measure to predict other health outcomes and transitions. In the context of HIV, in consideration of the relatively young age of patients with HIV, an appropriate outcome measure is the incidence of MM (Fig. 5.5).

In the Modena HIV Metabolic Clinic cohort, a 38-item frailty index was found to predict incident MM. Independent predictors of incident MM were the frailty index (incident rate ratio [IRR] 1.91, 1.62–2.26), age (1.06, 1.04–1.08), female gender (0.62, 0.44–0.86), current CD4 count (0.79, 0.66–0.93), and injection drug use (1.39, 1.04–1.86) (Fig. 5.6) [41].

Future research may investigate the association between MM, functional status, and frailty in people living with HIV as a new potential clinical marker. Researchers who study the aging process and geriatricians who care for older patients have already acquired considerable knowledge and

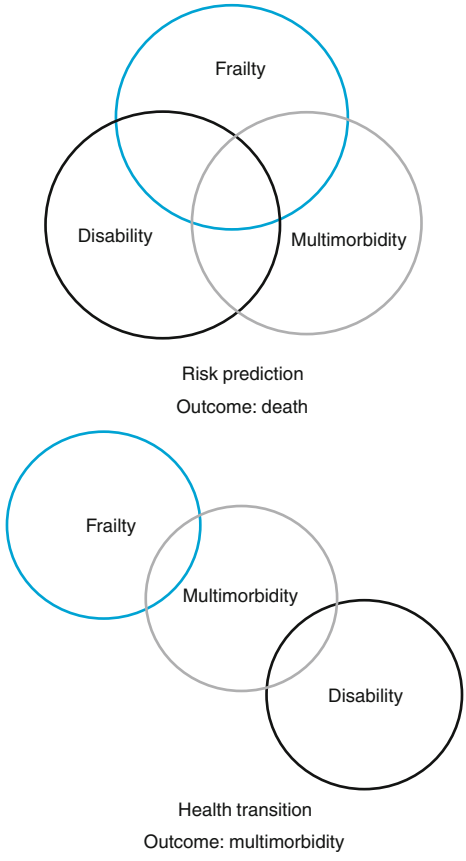

FIGURE 5.5 A theoretical model of the interplay of variables in the risk prediction of death or the heath transition of multimorbidity

experience on the mechanisms that lead to the aging phenotypes, frailty measurements and their consequences, and potential intervention strategies.

Further work is needed to determine the best approach to measure frailty in people aging with HIV, and the possibility to use a frailty index as an inclusion criteria for the selection of a vulnerable population to address specific ARV regimens/strategies or a clinical end point to design

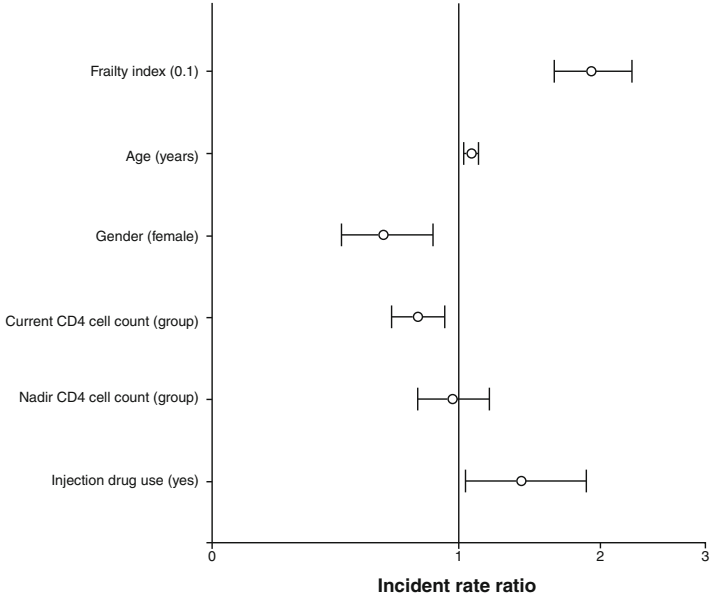

FIGURE 5.6 Predictors of incident multimorbidity in multivariate analysis. Points represent adjusted incident rate ratios, and whiskers 95 % confidence intervals [41] (Reproduced with permission from © Wolters Kluwer Health, Inc)

future ARV randomized clinical trials. While there is an expansive body of research on treating and preventing frailty in the geriatric medicine and gerontology literature [22, 45], these have not yet been evaluated among individuals aging with HIV.

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Chapter 6
Disability in HIV

Chiara Mussi

Key Points

- The definition of functional abilities is mandatory when an older patient has to be evaluated.
- Patients with human immunodeficiency virus (HIV) have one more reason for functional loss, represented by the HIV infection itself.
- In literature, a great number of scales are available, but in clinical practice the Activities and Instrumental Activities of Daily Living (ADL and IADL) indexes are widely used in the evaluation of elderly patients.
- In patients with HIV, Advanced Activities of Daily Living (AADL) and the Assessment of Motor and Process Skills (AMPS) can better define function and disability.

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6.1 Overview

In older patients, the maintenance of functional abilities is a fundamental component for a good quality of life. In addition to comorbidities and drug burden, older patients with HIV have one more reason for functional loss, represented by the HIV infection itself. For this reason it is really important to quantify objectively self-sufficiency in all HIV infected older patients, not only to quantify the loss of abilities, but also to build effective preventive programs to stop or slow down disability and to preserve quality of life.

6.2 Functional Impairment and Disability in Patients with HIV

While people with HIV are living longer as a result of the introduction of effective therapy, current evidence indicates that they are at a higher risk of early death and/or disability due to conditions not only related to the consequences of HIV/acquired immune deficiency syndrome (AIDS) but also to the use of antiretroviral therapy (ART). Promoting health and wellness through the use of sensitive assessments of disability is an important health promotion consideration, particularly as individuals with HIV are living longer and with greater risks for developing comorbid health conditions.

In literature, classical geriatric tools to evaluate disabilities are widely used [1]. The measure of activity and instrumental activities of daily living by means of the ADL (Katz index) and IADL (Lawton scale) indexes [2–4] is mandatory in the older population, regardless of the presence of HIV infection. Nevertheless, there is increasing evidence that such scales can show ceiling effects, decreased sensitivity, and decreased relevance in definite settings (eg, very fit older people with relatively mild physical and/or cognitive impairments) [5]. Moreover, a limitation of the instruments is the self-report or

surrogate report method of administration rather than a demonstration of the functional task. This may lead either to over-estimation or under-estimation of ability. In addition, the instrument may not be sensitive to small, incremental changes in function. To overcome these problems, the use of an objective measure of function, like the AMPS [6, 7], is recommended to obtain a more precise evaluation of skills in everyday life.

Verbraak and colleagues [8] found that patients who were defined to be 'fully recovered' (ie, asymptomatic) from a transient or not disabling ischemic stroke obtained AMPS ability measures that were below the norms of their healthy, age matched peers. While the participants in this study were able to perform ADL tasks independently, with very mild functional impairment, the AMPS ability measures accurately indicated that they were not performing at the same level as they used to (ie, the persons were less efficient and/or demonstrated mild effort to complete the tasks), and as a result supplemental intervention strategies were enhanced. Using a sensitive measure, greater opportunities were created for early identification of daily life challenges and the implementation of proactive intervention strategies to promote health and daily life function, and prevent future ADL decline and/or other adverse health outcomes. Given the chronic pattern of HIV, the higher risk of comorbidities leading to disability, and the wide age range, an assessment like the AMPS, although more complex than the anamnestic evaluation of ADL and IADL, has a great advantage because patients can choose tasks that are culturally and personally relevant, age appropriate, and of a suitable challenge.

Disability in older patients is often defined by basal ADL (such as clothing and bathing) and IADL (such as shopping and food preparation), nevertheless advanced ADL (AADL), such as hobbies and working, are very important to evaluate, since the preservation of advanced activities is important to help people maintain their self-identity. Patients with HIV in general, and especially those who develop dementia, need special support and person-centered intervention, which

includes understanding the patient's life history, individuality, and perspectives; this is the only way to deliver high-quality care [9]. Moreover, mild cognitive impairment (MCI) is defined as memory impairment without functional decline, nevertheless, the analysis of AADL can show mild changes, without determining overt disability.

6.3 Tools to Measure Disability

In literature there are many tools to quantify abilities in everyday life. The classical geriatric tools to quantify disability are the ADL (Katz index) (Table 6.1) [2, 3] and the IADL (Lawton scale) (Table 6.2) [4]. The ADL has been shown to be an effective tool for measuring baseline function and can provide data for functional comparisons with later assessment. Both the ADL and IADL indexes are widely used in research and in clinical practice. There is a gender difference in how the

Table 6.1 The activities of daily living index (Katz Index) [3]

Activities (Points 1 or 0)	Independence (1 point) No supervision, direction or personal assistance	Dependence (0 points) With supervision, direction, personal assistance or total care
Bathing points____	**(1 point)** Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	**(0 points)** Needs help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
Dressing points____	**(1 point)** Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	**(0 points)** Needs help with dressing self or needs to be completely dressed.

Table 6.1 (continued)

Activities (Points 1 or 0)	Independence (1 point) No supervision, direction or personal assistance	Dependence (0 points) With supervision, direction, personal assistance or total care
Toileting points____	**(1 point)** Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	**(0 points)** Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
Transferring points____	**(1 point)** Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	**(0 points)** Needs help in moving from bed to chair or requires a complete transfer.
Continence points____	**(1 point)** Exercises complete self control over urination and defecation.	**(0 points)** Is partially or totally incontinent of bowel or bladder.
Feeding points____	**(1 point)** Gets food from plate into mouth without help. Preparation of food may be done by another person.	**(0 points)** Needs partial or total help with feeding or requires parenteral feeding.
Total Points = ____ **6 = High** (patient independent). **0 = Low** (patient very dependent).		

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IADL scale is administered; women are scored on all eight areas of function, but, for men, the areas of food preparation, housekeeping, and laundering are excluded. However, in my opinion, this can be assessed on a case-by-case basis, dependent on whether the patient states that they carry out such tasks in their daily life. Patients are scored according to their

highest level of functioning in that category. A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women, and 0 through to 5 for men.

Although the reliability is still not completely defined, the Barthel Index (BI) has been recommended for the functional assessment of older people [10, 11] and is frequently used in the assessment of disability in older patients with HIV.

Table 6.2 The instrumental activities of daily living (Lawton) scale [4]

Category	Description	Points
A. Ability to use telephone	1. Operates telephone on own initiative; looks up and dials numbers	1
	2. Dials a few well-known numbers	1
	3. Answers telephone, but does not dial	1
	4. Does not use telephone at all	0
B. Shopping	1. Takes care of all shopping needs independently	1
	2. Shops independently for small purchases	0
	3. Needs to be accompanied on any shopping trip	0
	4. Completely unable to shop	0
C. Food preparation	1. Plans, prepares, and serves adequate meals independently	1
	2. Prepares adequate meals if supplied with ingredients	0
	3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet	0
	4. Needs to have meals prepared and served	0

Table 6.2 (continued)

Category	Description	Points
D. Housekeeping	1. Maintains house alone with occasional assistance (heavy work)	1
	2. Performs light daily tasks such as dishwashing, bed making	1
	3. Performs light daily tasks, but cannot maintain acceptable level of cleanliness	1
	4. Needs help with all home maintenance tasks	1
	5. Does not participate in any housekeeping tasks	0
E. Laundry	1. Does personal laundry completely	1
	2. Launders small items, rinses socks, stockings, etc.	1
	3. All laundry must be done by others	0
F. Mode of transportation	1. Travels independently on public transportation or drives own car	1
	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
	3. Travels on public transportation when assisted or accompanied by another	1
	4. Travel limited to taxi or automobile with assistance of another	0
	5. Does not travel at all	0

(continued)

Table 6.2 (continued)

Category	Description	Points
G. Responsibility for own medications	1. Is responsible for taking medication in correct dosages at correct time	1
	2. Takes responsibility if medication is prepared in advance in separate dosages	0
	3. Is not capable of dispensing own medication	0
H. Ability to handle finances	1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income	1
	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
	3. Incapable of handling money	0

Total Points = ____
Each criteria can be also graded:
Independent: 3 points
Any assistance needed: 2 points
Totally dependent: 1 point

The AMPS (Tables 6.3a and b) includes over 110 standardized ADL tasks that range from easy to hard and include personal care tasks (eg, grooming/hygiene, dressing), housekeeping tasks (eg, vacuuming, ironing, raking leaves), simple meal (eg, preparing coffee and toast, making simple sandwiches) and more complex meal preparation tasks (eg, preparing pasta, salad, and a beverage; baking a cake; preparing French toast). While patients can be able to perform ADL tasks independently, the AMPS ability measures accurately that they are not performing at the same level as they

Table 6.3 Skill categories and items in the assessment of a, motor skills and b, process skills

a. Motor skills

Body position
- Stabilizes
- Aligns
- Positions

Obtaining and holding objects
- Reaches
- Bends
- Grips
- Manipulates
- Coordinates

Moving self and objects
- Moves
- Lifts
- Walks
- Transports
- Calibrates
- Flows

Sustaining performance
- Endures
- Paces

b. Process skills

Sustaining performance
- Paces
- Attends
- Heads

Applying knowledge
- Chooses
- Uses
- Handles
- Inquires

Temporal organization
- Initiates
- Continues
- Sequences
- Terminates

Organizing space and objects
- Searches/locates
- Gathers
- Organizes
- Restores
- Navigates

Adapting performance
- Notices/responds
- Adjusts
- Accommodates
- Benefits

Adapted from Fisher and Jones [6, 7]

used to (ie, the persons were less efficient and/or demonstrated mild effort and/or clumsiness when completing the tasks), and as a result supplemental intervention strategies can be implemented to further enhance their everyday functional abilities. An AMPS evaluation consists of a series of steps, beginning with preparing for the AMPS interview [6, 7]. The initial step consists in identifying from the list of possible ADL tasks those that the patient knows

how to perform, are culturally relevant, can be achieved in the test environment, and present sufficient challenge to the patient. Then, the therapist chooses five ADL tasks, and from this shortened list, the patient chooses at least two ADL tasks to perform and decides which task to perform first. In the final step the patient is observed while performing ADL tasks and is scored on their performance according to standardized criteria [6, 7]. The performance of the patient on each ADL motor and ADL process skill is rated on a four-point ordinal scale:

4: The patient's observed performance is competent.
3: The patient's observed performance is questionable.
2: The patient's observed performance on an ADL skill item is ineffective.
1: The patient's performance is markedly deficient.

The evaluation of more complex skills is of great importance in older patients with HIV, since their lifestyles are slightly different from those of HIV-negative older patients, moreover, the early aging processes that characterize older patients, with HIV tend to surprise patients when they are still working.

The Tokyo Metropolitan Institute of Gerontology (TMIG) index (Table 6.4) [12] is a multidimensional 13-item index of competence that was designed to measure the higher level competence that could not be adequately assessed by existing scales.

Assessment of AADL can be of interest in patients with HIV for establishing earlier stages of cognitive decline, since these activities demand high cognitive functioning and are more responsive to subtle changes. The AADL tool is based on the total number of activities (TNA) performed by a person and takes each subject as their own reference. It distinguishes a total Disability Index (AADL-DI), a Cognitive Disability Index (AADL-CDI), and a Physical Disability Index (AADL-PDI), with lower scores representing more independency. In a study by De Vriendt et al. [13] the AADL score demonstrated good performance in differentiating normal from mild cognitive decline.

Table 6.4 The Tokyo metropolitan institute of gerontology index of competence [12]

Subscales	Question
Instrumental self-maintenance	1) Can you use public transportation (bus or train) by yourself?
	2) Are you able to shop for daily necessities?
	3) Are you able to prepare meals by yourself?
	4) Are you able to pay bills?
	5) Can you handle your home banking?
Intellectual activity	6) Are you able to fill out forms for your pension?
	7) Do you read newspapers?
	8) Do you read books or magazines?
	9) Are you interested in news stories or programs dealing with health?
Social role	10) Do you visit the homes of friends?
	11) Are you sometimes called on for advice?
	12) Are you able to visit sick friends?
	13) Do you sometimes initiate conversation with young people?
The response to each item was 'yes' (able to do) or 'no' (unable to do)	

6.4 Conclusion

The evaluation of self-dependency is of paramount importance for clinicians that take care of older patients, particularly if they are HIV-positive. ADL and IADL, expressed also as the BI, are the most frequently used in clinical practice, but

the ceiling effects and the self-reported anamnestic rating can cause some problems in the definition of disability. For this reason the AADL, TMIG index, and AMPS are proposed to obtain a more precise evaluation of functional performance in older patients with HIV.

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Chapter 7
Geriatric Syndromes

Chiara Mussi

Key Points

- Geriatric syndromes are multifactorial health conditions occurring when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges.
- The identification, removal, or prevention of the multiple causes that determine the geriatric syndromes is mandatory to construct an appropriate prevention and/or intervention program.
- Falls and delirium are the most frequent and disabling geriatric syndromes in older patients with human immunodeficiency virus (HIV) and are associated with increased mortality, morbidity, and disability.

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7.1 Definition

Geriatric syndromes are defined as multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges [1]. Geriatric syndromes, therefore, require special clinical considerations: firstly, for a given geriatric syndrome, multiple risk factors and multiple organ systems are often involved; secondly, 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 a thorough understanding of the underlying causes. Current studies support the presence of interaction between HIV and geriatric syndromes. Data also indicates that treatment of comorbidities and the early initiation of antiretroviral therapy (ART) may help to prevent the development of these conditions [2].

In this chapter we describe in detail two geriatric syndromes that are frequently found in both HIV-negative and HIV-positive older patients: falls and delirium. Other examples of common geriatric syndromes include malnutrition, loss of consciousness, pressure sores, and sleep disturbances.

7.2 Falls

7.2.1 Overview

Falls are defined as a sudden involuntary event, resulting in a person coming to rest on the ground or lower level from a higher level [3]. Falls are responsible for considerable morbidity, immobility, and mortality among older persons, leading to an increased risk of hospitalization and institutionalization, with prolonged recovery periods, and resulting in an increase in disability and health care costs [4]. Falls result from an interaction of multiple and diverse risk factors and situations.

This interaction is modified by age, disease, and by the environment. Proper management of this health problem has strong clinical and economic relevance. An appropriate assessment of the elderly at risk of falling and the implementation of an effective treatment plan after the event is an important principle of care [5]. Among the most serious consequences of a fall is a fracture, particularly hip fracture, which may lead to disability, poor quality of life (QOL), and death. Falls are a common geriatric syndrome in patients with HIV [6], therefore, careful attention should be given to the assessment and the intervention of this condition.

7.2.2 Causes of Falls

The recognition of the etiology of a fall, wherever possible, is important in order to prevent a repeat episode, the risk of which is increased after a first fall, and possibly a disabling fracture or injury such as a traumatic brain injury or minor concussive event. In older patients, falls are typically multifactorial; in an individual patient many predisposing and precipitating factors may coexist.

Causes of falls can be categorized into those with predisposing intrinsic conditions (due to the subject) (Table 7.1) and extrinsic conditions (due to the environment) (Table 7.2). Intrinsic causes can be divided into age-related physiological changes (Table 7.1a) and pathological predisposing conditions (Table 7.1b) [7]. Intrinsic predisposing conditions, with particular regards to neurological and psychiatric disease, occur with high prevalence in patients with HIV, making this population particularly vulnerable to falls.

7.2.3 Assessment

Older people with HIV who present for medical attention because of a fall, report recurrent falls in the past year, or demonstrate abnormalities of gait and/or balance should be offered a multifactorial falls risk assessment, preferably by a

health care professional with appropriate skills and experience. This assessment should be part of an individualized multifactorial intervention [8]. Multifactorial assessment should include:

- identification of fall history;
- assessment of gait, balance, and mobility;
- assessment of osteoporosis risk;
- assessment of the person's perceived functional ability and fear relating to falling;
- assessment of visual impairment;
- assessment of cognitive impairment and neurological examination;
- assessment of urinary incontinence;
- assessment of home hazards;
- cardiovascular examination; and
- medication review.

Table 7.1 Intrinsic predisposing conditions

a. Age-related physiologic changes

Sight:
- Reduction in visual acuity
- Reduction in ability to accommodate
- Reduction in discriminative capacity for colors
- Reduction in tolerance to glare
- Presbyopia and myopia

Hearing:
- Reduced perception of pure tones
- Reduced discrimination capability between sounds at different frequency and distance
- Reduced discrimination capability between contemporary voices in conversation

Musculoskeletal:
- Sarcopenia
- Reduced muscle strength
- Reduced range of movement

Central nervous system:
- Deficient tactile sensitivity, vibration sense, thermal sensitivity
- Increase in postural sway with instability
- Alterations in the integration of sensory inputs and motor responses causing increased time of reaction
- Alterations of balance

(continued)

Table 7.1 (continued)

b. Predisposing factors

Cardiovascular:
- Myocardial infarction
- Orthostatic hypotension
- Arrhythmias
- Valvular disease
- Flebopathy/venous insufficiency
- Syncope
- Dizziness

General medicine and endocrine:
- Hypoglycemia
- Hypokalemia
- Thyroid disease
- Hypo and hypernatremia
- Dehydration
- Hyperventilation
- Anemia

Musculoskeletal:
- Myopathies
- Degenerative joint disease
- Vertebral deformities
- Pathological fractures
- Sarcopenia

Neurological:
- Dementia
- Stroke
- Transient ischemic attack
- Parkinson's disease
- Carotid sinus hypersensitivity
- Vestibular system pathology
- Delirium
- Epilepsy
- Neuropathy

Gastrointestinal:
- Diarrhea
- Bleeding

Psychiatric:
- Depressive syndromes
- Anxiety syndromes
- Fear of falling

Genitourinary:
- Urinary incontinence
- Post-micturition hypotension

Iatrogenic:
- Drug side effects
- Polypharmacy and drug–drug interactions
- Immobilization

Adapted from Pasquetti et al. [7]

7.2.4 *Intervention*

All older people with recurrent falls or who are assessed as being at increased risk of falling should be considered for an individualized multifactorial intervention to identify and address future risk and individualized intervention aimed at promoting independence and improving physical and psychological function [8]. In successful multifactorial intervention programs specific components should be evaluated. Strength and balance should be assessed and in the case of balance and gait deficit a muscle-strengthening and

Table 7.2 Extrinsic risk factors

Extrinsic risk factors
• Obstacles
• Inadequate ambient lighting
• Inadequate footwear and clothing
• Uneven or slippery floors
• Presence of steps
• Lack of handrails
• Inadequate height of beds
• Inadequate chairs
• Inadequate bathroom
• Unfamiliar environment

Adapted from Pasquetti et al. [7]

balance program should be individually prescribed and monitored by an occupational therapist or appropriately trained professional.

Home hazard assessment and intervention should be carried out by health care professionals involved in the assessment and prevention of falls and should discuss what changes a person is willing to make to prevent falls (discussing vision assessment, referral, and medication review). Older people on medications, especially those on cardiovascular and psychotropic drugs, should have their medication reviewed, with specialist input if appropriate, and discontinued if possible to reduce their risk of falling.

To promote the participation of older people in falls prevention programs the following should be considered:

- In hospitalized patients home hazard assessment and intervention should be considered at the time of a discharge planning and be carried out within a timescale agreed by the patient or care giver. Home hazard follow-up evaluations are needed.

- Falls prevention programs should address potential barriers, such as low self-efficacy and fear of falling, and encourage activity change as negotiated with the participant.

Practitioners who are involved in developing falls prevention programs should ensure that such programs are flexible enough to accommodate the different needs and preferences of the participants and should promote the social value of such programs.

7.3 Delirium

7.3.1 Overview

Delirium is defined as a transient, usually reversible, sudden cause of cerebral dysfunction and manifests clinically with a wide range of neuropsychiatric abnormalities. It can occur at any age, but is more common in elderly patients. It affects 14–46 % of hospitalized older patients [9], 50 % of postoperative older patients [10], and occurs in up to 80 % of patients in the intensive care unit [11]. The point prevalence of delirium in hospitalized patients with acquired immunodeficiency syndrome (AIDS) is estimated to be between 30 and 40 % [12]. Delirium is independently associated with several adverse outcomes, including elevated in-patient costs, increased length of stay, long-term cognitive and functional decline, increased risk of institutionalization, higher mortality, as well as patient and care giver distress. The timely recognition of delirium can improve outcomes. However, 50–75 % of delirium is undetected or misdiagnosed in acute-care hospitals [13].

Delirium is the most common neuropsychiatric complication of hospitalized patients with HIV. In these patients, delirium presents with the same clinical features as in non-HIV-infected individuals. Typically, delirium is multifactorial in etiology and a complete evaluation to rule out all treatable and reversible medical conditions should be the first stage in the approach to a delirious patient with AIDS [12].

7.3.2 Diagnostic Criteria

The diagnosis of delirium is clinical and no specific laboratory test can be used. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) identifies the following diagnostic criteria [14]:

- Disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness.
- Change in cognition (ie, memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a pre-existing, established, or evolving dementia.
- The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.
- There is usually evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause.

7.3.3 Causes of Delirium

In immunocompromised patients with AIDS, delirium may be associated with opportunistic infection of the central nervous system (CNS) (eg, HIV, cytomegalovirus, toxoplasmic encephalitis) as well as systemic infection (eg, hypoxia associated with *Pneumocystis* pneumonia). However, in patients with satisfactory immunological control secondary to highly active antiretroviral therapy (HAART), delirium is more commonly associated with toxicity related to polypharmacy, HIV-related cerebrovascular disease, and psychoactive drug withdrawal or intoxication [15].

Patients with HIV/AIDS are also vulnerable to fluctuations in blood metabolites, particularly in cirrhotic patients

co-infected with hepatitis C virus (HCV), as well as sudden changes in hydration status.

7.3.4 Types of Delirium

Delirium subtypes have been defined based on the presence (hyperactive) or absence (hypoactive) of psychomotor agitation, perceptual disturbances, and/or changes in level of consciousness. Often both subtypes are present concurrently (mixed). The hypoactive form is the most difficult to detect, since the patient is confused, but calm, and does not call attention from nurses and/or physicians [16].

7.3.5 Assessment Instruments

Several screening tools have been evaluated to assess delirium. The Confusion Assessment Method (CAM) and 4 As test (4AT) in particular display high sensitivity and specificity, and allow for the characterization of delirium features.

The CAM [17] was originally developed by literature review and expert consensus, and was validated against the reference standard ratings of geropsychiatrists based on the DSM Third Edition Revised (DSM-IIIR) criteria. The CAM was designed to allow non-psychiatric clinicians to diagnose delirium quickly and accurately following brief formal cognitive testing (Table 7.3). CAM delirium diagnosis requires the presence of features 1 and 2 and either 3 or 4.

The 4AT is a new screening tool for delirium and is available at www.the4AT.com. It incorporates two simple cognitive screening items. This screening test shows the following advantages [18]:

- brevity (generally <2 min);
- no special training required;
- simple to administer (including in people with visual or hearing impairment);
- does not require physical responses;

- good for assessment of 'untestable' patients (those who cannot undergo cognitive testing or interview because of severe drowsiness or agitation); and
- incorporates general cognitive screening to avoid the need for separate tools for delirium and other causes of cognitive impairment.

7.3.6 Management

The goal of treatment is to identify the often multifactorial causes of the delirium and to stop, control, or reverse them. Components of delirium management include supportive therapy and pharmacologic management. Fluid and nutrition should be given carefully because the patient may be unwilling or physically unable to maintain a balanced intake; older patients may be unable to swallow safely (putting themselves at risk for aspiration). For the older patient suspected of having alcohol toxicity or alcohol withdrawal, therapy should include thiamine and careful use of benzodiazepines when indicated, usually in lower doses than in younger adults [19]. Reorientation techniques or memory cues such as a calendar, clocks, and family photos may be helpful. The environment should be stable, quiet, and well-lit. Delirium that causes injury to the patient or others should be treated with medications. The most common medications used are atypical short-acting neuroleptics. The careful use of benzodiazepines should be reserved for drug withdrawal states [20].

7.4 Conclusion

The detection of geriatric syndromes in older patients with HIV is of paramount importance, since the prompt recognition of the often multifactorial causes and the prompt initiation of preventive and therapeutic interventions is able to reduce mortality and, most importantly, disability in patients with HIV.

Table 7.3 The Confusion Assessment Method [17]

Feature 1	Acute onset and fluctuating course	This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: • Is there evidence of an acute change in mental status from the patient's baseline? • Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2	Inattention	This feature is shown by a positive response to the following question: • Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3	Disorganized thinking	This feature is shown by a positive response to the following question: • Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4	Altered level of consciousness	This feature is shown by any answer other than 'alert' to the following question: • Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

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Chapter 8
HIV Prevention and Screening in Older Adults

Ana Rita Silva

Key Points

- Older adults are the least likely of all age groups to practice safe sex [1, 2].
- Late-life changes in the reproductive tract and immune system may enhance their susceptibility to HIV acquisition [1].
- Physicians are less likely to recommend HIV testing to older patients [2–4].
- Asymptomatic older HIV-infected individuals are less likely to seek out testing and medical care [2, 5].
- Symptomatic older HIV-infected individuals are more likely to attribute symptoms to other illnesses or to aging [6].

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8.1 Age-Related Risk Factors

In the aging population, there are specific risk factors for acquiring HIV. These must be taken into account when designing HIV screening and counselling programs focused to overcome barriers to prevention and testing opportunities.

Several risk factors for HIV acquisition have been identified in the older population:

- Lack of knowledge:
  - As HIV risk factors were unknown before 1980, older adults may have a lack of knowledge regarding modes of transmission. Education on mode of transmission of HIV, sexually transmitted diseases, and risk perception are warranted [7].
- Risky behavior:
  - Many heterosexual and lesbian, gay, bisexual, or transgender (LGBT) adults remain sexually active [8] and they may maintain a certain lifestyle in older age. This includes unprotected sex [9], multiple sexual partners [10], and recreational drug use [11].
  - Reduced condom use may also be associated with other reasons. Older women starting a new sexual relationship, after many years of monogamy, may be embarrassed to talk about condom use. In men, the increasing prevalence of erectile dysfunction with age may make condom use even more challenging.
- Accessibility of erectile dysfunction medications:
  - The availability of medication to treat erectile dysfunction may also allow for increased sexual activity in older men [7], prolonging active sexual life and potential longer exposure to risk factors.
- Biological risk factors:
  - An identified biological risk factor is the vaginal thinning and dryness that occurs in women after menopause

that may increase transmission risk for HIV and other sexually transmitted infections [12]. Also, women who no longer worry about getting pregnant may be less likely to use a condom and to practice safe sex.

8.2 Barriers to Prevention

Providers must reduce barriers to effective prevention and detection of HIV in older adults, as they are more likely to present late, with greater associated mortality [13–15]. Barriers to prevention include:

- Aging stereotypes:
  - One of the main barriers for HIV diagnosis is aging stereotypes, mainly among health care providers. Talking to older patients about their sexual activity, asking questions regarding sexual orientation or knowledge of condom use and recreational drug habits are not yet a routine practice among most doctors, in part due to their own discomfort [16].
- HIV underdiagnosis:
  - Some HIV symptoms, such as asthenia, weight loss, or cognitive decline may mimic the normal aging process, further delaying the HIV diagnosis. This is particularly true in the menopause transition period in women.
  - Health care providers' failure to recommend HIV testing to older adults and their poor awareness of risks of contracting HIV are linked to low HIV testing rates. Most older adults learn of their HIV diagnosis while being hospitalized for other medical issues [17]. As a result, HIV infection is diagnosed at a later stage in older adults, and they are more likely to progress to AIDS [7].
- Discrimination and stigma:
  - Fear, discrimination, and stigma among minority races or ethnicities and older LGBT adults can also represent

an important reason for late diagnosis and treatment, as it may prevent them from seeking HIV care and disclosing their HIV status.

8.3 Screening and Counselling Opportunities

An effort must be made in order to educate both vulnerable populations and health care providers. Reviewing HIV prevention programs targeting older adults with HIV is mandatory. So far, most HIV awareness campaigns have been directed to specific groups, such as younger individuals and gay men, and excluding several other groups, in particular older women. Three major strategies can be implemented:

1. Universal HIV testing should be offered in an opt-out strategy. If it is found that the tested population has a HIV prevalence of ≥0.1 %, HIV screening in individuals between 55 and 75 years of age reaches conventional levels of cost-effectiveness. The cost-effectiveness of screening in patients between 55 and 75 years of age compares favorably to that of other interventions that are accepted as good uses of resources, particularly if providers implement screening with streamlined counselling and if the person being screened has a sexual partner at risk [18].
2. Indicator symptoms testing programs based on HIV symptoms (Table 8.1). HIV testing offered as a differential screening diagnosis process if signs of constitutional HIV symptoms or opportunistic diseases are present.
3. Counselling and testing. Accessible, confidential, and free HIV testing should be offered to any patient who is aware of a risk behavior for HIV. These services should also be provided at easily accessible locations where older adults participate in activities or reside (eg, older adult centres, retirement communities, nursing homes, or health fairs).
   - Clinical staff providing these services should be trained in HIV prevention for older adults.
   - Community leaders, health care professionals, policymakers, and researchers must develop appropriate prevention services that address the unique needs of older adults.

Table 8.1 Signs and symptoms of HIV infection [19]

General	Neurologic	Dermatologic
Fever	Meningitis	Erythematous maculopapular rash
Pharyngitis	Encephalitis	Mucocutaneous ulceration
Lymphadenopathy	Peripheral neuropathy	
Headache/retroorbital pain	Myelopathy	
Arthralgias/myalgias		
Lethargy/malaise		
Anorexia/weight loss		
Nausea/vomiting/diarrhea		

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Chapter 9
Multidimensional Geriatric Assessment in Older Patients with HIV

Giovanni Guaraldi and Julian Falutz

Key Points

- Models of care for aging patients with human immunodeficiency virus (HIV) are evolving.
- The one size fits all approach is inconsistent with current care needs.
- Interdisciplinary team-based models are needed.
- Models of care based on the proven Comprehensive Geriatric Care approach are increasingly employed.

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The success of highly active antiretroviral therapy (HAART) has significantly changed the pattern of HIV infection in developed countries, with the 'graying' of the HIV-infected population testament to its success.

Management of older patients is complicated by the likelihood of comorbidities requiring treatment, resultant problems with drug toxicity and interactions on polypharmacy, and changes in pharmacokinetics (potential for drug accumulation and toxicity) as hepatic and renal function often decline with age. This has provided new challenges relating to the care of older patients, particularly with regard to the management of comorbidities and antiretroviral (ARV) toxicity. This is being addressed through the refinement of existing antiretroviral therapy (ART), the development of new agents, and a growing focus on the need for a more holistic approach to care (involving the integration of accepted primary care principles into routine HIV care).

In the pre- and early-HAART era the provision of HIV care was standardized with outpatient visits performed in dedicated HIV clinics, with regular visits every 3–4 months. At present HIV patients require a more personalized approach to the frequency of visits and often a diversification to the type of health care providers.

The use of high efficacy and low toxicity ART is less likely to result in ARV switch compared to earlier treatment options (other than for drug simplification or patient convenience). As a result, knowledgeable and willing primary care providers will increasingly be central to the provision of routine assessments of patients with HIV on stable ART. On the other hand, patients with HIV, multimorbidity (MM), and age-related conditions will require HIV physicians to work in interdisciplinary teams with other specialists in a patient-centered model of care. This type of care has often been provided in tertiary referral level sites identified variously as 'HIV metabolic clinics' where the HIV-treating physician remains central to care, balancing the often competing demands of maintaining effective viral suppression while managing comorbidities, treatment side effects, and drug interactions.

Interestingly, this patient centered approach is conceptually close to the Comprehensive Geriatric Assessment (CGA) that is the standard approach to care in the geriatric context.

The term CGA is defined as a multidisciplinary diagnostic and treatment process that identifies medical, psychosocial, and functional limitations of a frail older person in order to develop a coordinated plan to maximize overall health with aging [1, 2]. The health care of an older adult extends beyond the traditional medical management of illness. It requires evaluation of multiple issues, including physical, cognitive, affective, social, financial, environmental, and spiritual components that influence an older adult's health. CGA is based on the premise that a systematic evaluation of frail older persons by a team of health professionals may identify a variety of treatable health problems and lead to better health outcomes. So far the CGA approach has rarely been used in a structured fashion in patients with HIV as in the geriatric context, but issues regarding multimorbidity, frailty, and disability are increasingly incorporated into the clinical assessment of older patients with HIV.

CGA programs to identify the health condition of patients with HIV include:

- age;
- medical comorbidities (such as heart failure, renal dysfunction, bone disorders, hepatic dysfunction, or cancer);
- psychosocial disorders (such as depression or isolation);
- specific geriatric conditions (such as dementia, falls, functional disability, or polypharmacy);
- previous or predicted high health care utilization; and
- consideration of change in living situation (eg, from independent living to assisted living, nursing home, or in-home caregivers).

Conceptually, CGA involves several processes of care that are shared over 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 the team;
3. development of a treatment plan;

4. implementation of the treatment plan;
5. monitoring response to the treatment plan; and
6. revising the treatment plan.

Each of these steps is essential if the process is to be successful at achieving maximal health and functional benefits.

Although the amount of potentially important information may seem overwhelming, formal assessment tools and shortcuts can reduce this burden on the clinician performing the initial CGA [3]. These questionnaires can be used to gather information about general history (eg, past medical history, medications, social history, review of systems), as well as gather information specific to CGA, such as:

- ability to perform functional tasks and need for assistance;
- fall history;
- sources of social support, particularly family or friends;
- depressive symptoms;
- vision or hearing difficulties; and
- whether the patient has specified a durable power of attorney.

Interdisciplinary team members (eg, nurses, social workers, occupational therapists, pharmacists, psychologists, etc) can administer screening tools to both save time and help the team to focus on specific limitations that need more detailed evaluation [4].

Further, education and involvement of the patient remains vital for the success of any treatment plan to ensure it meets the varying needs of individual patients. Moreover, a trusting patient–physician relationship established in HIV care may provide an excellent starting point for the management of these complex problems.

In the case of disability, the provision of care is seldom driven by HIV-related factors, while on the contrary geriatric syndromes (eg, cognitive decline, mobility, maintenance of independence, and polypharmacy), social support, and financial status are the major drivers of health care provision via home-based or supervised health setting (Fig. 9.1).

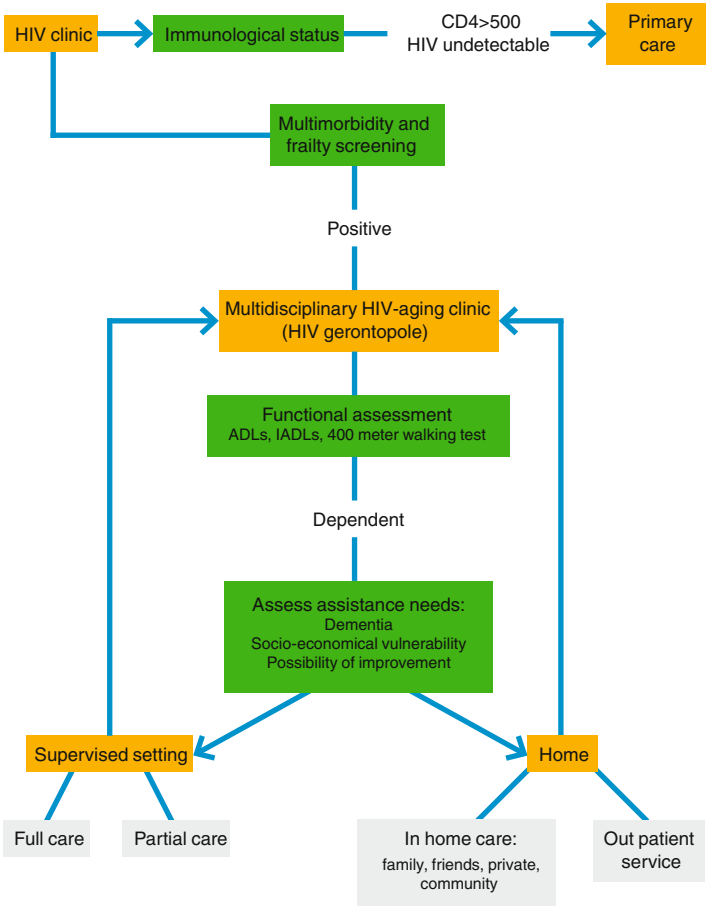

FIGURE 9.1 Summary of the proposed decision nodes for health care provision for patients with HIV

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Chapter 10
Antiretroviral Treatment in Older Patients

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Key Points

- Older and frail patients with human immunodeficiency virus (HIV) constitute a treatment challenge in terms of the cumulative effects of aging and antiretroviral therapy (ART).
- ART is recommended for patients >50 years of age, regardless of CD4 cell count, in consideration that the risk of non-AIDS-related complications may

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increase and the immunologic response to ART may be reduced in older patients with HIV.
- Recommended antiretroviral (ARV) drug choices for the elderly are the same as for the general population. However, due to age related comorbidities, specific drug toxicities should be considered when choosing drug regimens.
- Current guidelines do not recommend age or frailty as criteria for ARV switching. Three major issues frequently coexisting in this special population may indicate ARV switch: comorbidities, greater medication use and age-related changes in pharmacokinetics, and pharmacodynamics.

Older and frail patients with HIV constitute a treatment challenge in terms of the cumulative effects of aging and ART. There are currently no specific treatment guidelines available that focus on the older population, mainly due to the limited information on the efficacy and safety of selected ARV regimens for older patients. Most recently, regulatory agencies such as the Food and Drug Administration (FDA) and European Medicine Agency (EMA) request age stratification (above or under 50 years of age) in the analysis of the results for registrational clinical trials. However, due to the exclusion of patients with comorbidities, the included elderly population may not be representative. Furthermore, 'frailty' as the phenotype of biological aging is not considered in the development of treatment guidelines.

HIV experts and primary care providers should work together to optimize the medical care of older and frail patients with HIV and complex comorbidities, in addition to preventing secondary transmission of HIV among older adults.

General issues regarding ARV toxicity (cardiovascular, renal, bone, polypharmacy, and drug–drug interactions),

although improved, are still a matter of concern when managing ARVs, particularly so in the elderly population.

10.1 When to Start Antiretroviral Therapy

Current Department of Health and Human Services guidelines [1] recommend starting ARV therapy in patients with HIV aged >50 years, regardless of CD4+ cell count. This is due to increased rates of progression of untreated HIV disease, immune senescence, comorbidities that are exacerbated by CD4+ cell loss, and inferior immune reconstitution after the initiation of therapy [2–12].

International Antiviral Society guidelines base their recommendations on the principle of 'treatment as prevention' and reinforce this level of recommendation in the elderly population [13]. European AIDS Clinical Society (EACS) guidelines, on the other hand, do mention age categories to suggest an intensified screening for comorbidities in the elderly population but do not suggest any age category for starting ARV in the adult population [14].

Several studies have documented that CD4 T cell recovery after starting ART is generally less robust in older patients than in younger patients [1, 11, 15–18]. This incomplete immune recovery occurs both in patients with CD4+ cell counts below and above 350 cells/mm^3 [11, 16–22]. These inferior clinical outcomes in older patients with HIV are not explained by poor virological results; older patients have an improved adherence to therapy [23, 24], more often achieve virological control of HIV replication, and subsequently develop virological breakthrough less often than younger patients [23, 25–28].

A systematic review and meta-analysis of 12 studies that included adherence data showed that older age was associated with a 27 % reduced risk of non-adherence to ART (relative risk 0.72; 95 % CI 0.64–0.82), including both short-term and long-term adherence [29].

10.2 What to Start

Recommended ARV drug choices for the elderly are the same as for the general population. However, in consideration of age-related comorbidities, specific drug toxicities should be taken into account when choosing drug regimens. Table 10.1 summarizes ART-associated common and/or severe adverse effects to be considered in the treatment of the elderly population at higher risk of comorbidities [30].

Particular attention should be paid to postmenopausal women or women entering menopause. Menopause is a physiological time frame where rapid hormonal, biochemical, anthropometric, and psychological changes occur, making women more vulnerable to ARV toxicities. The most relevant comorbidity in this category is osteoporosis.

Disentangling the effects of menopause in comorbidity onset requires well-designed studies with adequate numbers of HIV-infected and HIV-uninfected women. Future studies should follow women from premenopause through menopause, using both surveys and laboratory measurements for menopause diagnosis, and control for confounders related to normal aging processes, in order to inform optimal clinical management for menopausal women living with HIV.

Altogether, we may say that randomized clinical trials able to inform ARV choice in patients with comorbidities are still limited, but a changing landscape is appearing.

A study presented at the 2015 Conference on Retroviruses and Opportunistic Infections assessed the safety, tolerability, and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single-tablet regimen (STR) in treatment-naïve and treatment-experienced HIV-positive adult participants with estimated glomerular filtration rate (eGFR) between 30 and 69 mL/min, in which the median baseline age was 58 years [31]. Switching to E/C/F/TAF was associated with no change in actual GFR, reductions in proteinuria and markers of proximal renal tubular function, and improvements in hip and spine bone mineral density (BMD). Adverse

TABLE 10.1 Antiretroviral therapy-associated common and/or severe adverse effects

Adverse effect	Nucleoside reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)	Integrase strand transfer inhibitors (INSTIs)	Entry inhibitors (EIs)
Bone density effects	TDF: associated with greater loss of BMD than ZDV, d4T, and ABC. Osteomalacia reported in association with proximal renal tubulopathy.	Decreases in BMD observed in studies of regimens containing different NRTIs combined with NNRTIs, PIs, or INSTIs.			N/A

(continued)

Table 10.1 (continued)

Adverse effect	Nucleoside reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)	Integrase strand transfer inhibitors (INSTIs)	Entry inhibitors (EIs)
Cardiovascular disease	ABC and ddI: associated with an increased risk of MI in some, but not all, cohort studies. Absolute risk is greatest in patients with traditional CVD risk factors.	N/A	PIs: associated with MI and stroke in some cohort studies. Data on newer PIs (ATV, DRV, and TPV) are limited. SQV/r, ATV/r, and LPV/r: PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and co-administration with drugs that prolong PR interval. SQV/r: QT interval prolongation in patients in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG is recommended before SQV initiation and should be considered during therapy.	N/A	N/A

Diabetes mellitus/ insulin resistance	ZDV, d4T, and ddI	N/A	Reported for some PIs (IDV, LPV/r), but not all.	N/A	N/A
Dyslipidemia	d4T > ZDV >ABC: ↑LDL and TG	EFV: ↑TG, ↑LDL, ↑HDL	↑LDL, ↑TG, ↑HDL: all RTV-boosted PIs ↑TG; LPV/r = FPV/r and LPV/r >DRV/r and ATV/r.	EVG/ cobi/TDF/ FTC: ↑TG, ↑LDL, ↑HDL	N/A
Lipodystrophy	Lipoatrophy: thymidine analogs (d4T >ZDV). May be more likely when NRTIs combined with EFV than with a RTV-boosted PI.	Lipohypertophy: trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A

(continued)

Table 10.1 (continued)

Adverse effect	Nucleoside reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)	Integrase strand transfer inhibitors (INSTIs)	Entry inhibitors (EIs)
Nervous system/ psychiatric effects	Peripheral neuropathy (pain and/or paresthesia, lower extremities > upper extremities): d4T > ddI and ddC (can be irreversible). d4T: associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare).	EFV: somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased plasma EFV concentrations because of genetic factors or increased absorption with food. An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among younger patients and those with history of mental illness or substance abuse) was found in one retrospective analysis of several comparative trials.	N/A	All INSTIs: insomnia. RAL: depression and suicidal ideation (uncommon).	N/A

Renal effects/ urolithiasis	TDF: ↑SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis. Concurrent use with PI appears to increase risk.	N/A	ATV and LPV/r: associated with increased risk of chronic kidney disease in a large cohort study. IDV: ↑SCr, pyuria, hydronephrosis, or renal atrophy. IDV, ATV: stone, crystal formation; adequate hydration may reduce risk.	Cobi (a component of EVG/cobi/ TDF/ FTC) and DTG: can increase SCr by reducing tubular secretion of Cr without reducing renal glomerular function; however, assess for renal dysfunction, especially if SCr increased by >0.4 mg/dL.	N/A

Adapted from Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [30]
ABC abacavir, *ATV/r* atazanavir/ritonavir boosted, *BMD* bone mineral density, *Cr* creatinine, *CVD* cardiovascular disease, *Cobi* cobicistat, *d4T* stavudine, *ddC* zalcitabine, *ddI* didanosine, *DRV/r* darunavir/ritonavir boosted, *DTG* dolutegravir, *ECG* electrocardiogram, *EFV* efavirenz, *EVG* elvitegravir, *FPV/r* fosamprenavir/ritonavir boosted, *FTC* emtricitabine, *HDL* high-density lipoprotein, *IDV* indinavir, *LDL* low-density lipoprotein, *LPV/r* lopinavir/ritonavir boosted, *MI* myocardial infarction, *N/A* not applicable, *RAL* raltegravir, *RTV* ritonavir, *SCr* serum creatinine, *SQV/r* saquinavir/ritonavir boosted, *TDF* tenofovir, *TG* triglyceride, *TPV* tipranavir, *ZDV* zidovudine

events, grades, and frequencies were similar in patients with a baseline eGFR <50 and ≥50 mL/min. These 48-week data support the virological efficacy and renal and bone safety of once daily, single-tablet E/C/F/TAF therapy for patients with HIV and mild to moderate renal impairment (eGFR 30–69 mL/min). This particular drug combination has a 15-times lower concentration in serum than tenofovir, is 7-times more concentrated in the intracellular lymphocyte cytoplasm, appears to have a limited bone and kidney toxicity, and qualifies to be studied as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of the aging patient [32–34].

10.3 What to Change

Switching a successful ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. Before any treatment switch is implemented, it is critical to review the following:

- the patient's medical and full ARV history (including prior virologic responses);
- resistance test results;
- viral tropism (when maraviroc [MVC] is being considered);
- human leukocyte antigen (HLA) B*5701 status (when abacavir [ABC] is being considered);
- comorbidities;
- adherence history;
- concomitant medications and supplements (and their potential for drug interactions); and
- prior intolerances to any ARV drug.

Current guidelines do not recommend age or frailty as criteria for ARV switching. Nevertheless, three major issues frequently coexisting in this special population may suggest the need for an ARV switch, and are discussed in the following sections.

10.3.1 Comorbid Conditions

Bone, kidney, metabolic, and cardiovascular health impairment, for example, are more frequent in older adults with HIV and should be closely monitored in such patients. In the past 15 years, the availability of new and less toxic drugs have allowed a progressive switch from a reactive strategy, based on ARV switch in patients with clinical comorbidities, into a more aggressive pre-emptive strategy in which the switch is made to prevent the risk of functional decline of organ reserve. Table 10.2 summarizes switch strategies to cope with specific adverse event risk, providing a rationale for ARV choice [30].

10.3.2 Greater Medication Use

Polypharmacy in both the general older population and in patients with HIV infection is very common. Recent data from the Swiss HIV Cohort demonstrate that among patients 65 years of age and older, 14 % received medications from four or more classes of non-HIV medications, and lipid-lowering agents were the most commonly prescribed non-ART medication [35]. These data are consistent with findings from the Veteran's Administration Cohort Study (VACS), wherein among those 50 years of age and older, 55 % were on five or more daily medications [36]. These studies report prescription medication only and therefore likely underestimate the prevalence of polypharmacy.

Use of prescription and over the counter medication, herbal supplements, and even recreational drugs increase the possibility of complex and unpredictable drug–drug interactions (DDIs) [37–39]. Polypharmacy has also been associated with increased risk of adverse drug reactions, increased hospitalizations, poor adherence, falls, and fractures [40–45].

In this context, elevated pill burden and risk of severe DDIs appear to give an advantage to INSTI-highly active antiretroviral therapy (HAART) (regimen with particular

Table 10.2 Antiretroviral therapy-associated adverse events that can be managed with substitution of alternative antiretroviral agent

	Antiretroviral agent(s)/drug class		
Adverse event	**Switch from**	**Switch to**	**Comments**
Bone density effects	TDF	ABC	Declines in BMD have been observed with the start of most ART regimens. Modification of ART because of reduced BMD should be predicated on the clinical significance of the decline. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain.
Bone marrow suppression Anemia, leukopenia	ZDV	TDF or ABC	N/A

Central nervous system/neuropsychiatric side effects Dizziness, suicidal ideation, sleep disturbance, abnormal dreams, depression	EFV	Alternative NNRTI (RPV, ETR, NVP), a PI, or an INSTI	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV with an alternate ARV agent.
Dyslipidemia Hypertriglyceridemia (with or without elevated low-density LDL level)	RTV- or Cobi-boosted regimens or EFV	RAL, DTG, RPV, NVP, or unboosted ATV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improved TG and LDL levels have been seen following a switch from LPV/r to RTV-boosted and unboosted ATV.

(continued)

Table 10.2 (continued)

Adverse event	Antiretroviral agent(s)/drug class		Comments
	Switch from	Switch to	
Gastrointestinal effects Nausea, diarrhea	LPV/r	ATV/r, DRV/r, RAL, DTG, EVG/Cobi/TDF/FTC	GI intolerance is relatively common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient in nature, and do not warrant switching therapy. If GI adverse effects are persistent or intolerable, consider drug substitution.
	Other RTV-boosted regimens or EVG/Cobi/TDF/FTC	RAL, DTG, unboosted ATV, NNRTIs	In a trial of treatment-naïve patients, rates of diarrhea and nausea were similar for boosted EVG/Cobi/TDF/FTC and ATV/r plus TDF/FTC.

Adapted from Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [30]

ABC abacavir, *ART* antiretroviral therapy, *ARV* antiretroviral, *ATV* atazanavir, *ATV/r* atazanavir/ritonavir boosted, *BMD* bone mineral density, *CNS* central nervous system, *Cobi* cobicistat, *DRV/r* darunavir/ritonavir boosted, *DTG* dolutegravir, *EFV* efavirenz, *ETR* etravirine, *EVG* elvitegravir, *FPV/r* fosamprenavir/ritonavir boosted, *FTC* emtricitabine, *GI* gastrointestinal, *INSTI* integrase strand transfer inhibitors, *LDL* low-density lipoprotein, *LPV/r* lopinavir/ritonavir boosted, *N/A* not applicable, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NVP* nevirapine, *PI* protease inhibitor, *RAL* raltegravir, *RPV* rilpivirine, *RTV* ritonavir, *TDF* tenofovir, *TG* triglyceride, *ZDV* zidovudine

regards to fixed-dose combination and/or drugs with no ritonavir or cobicistat boosting). The new NNRTI, rilpivirine, appears to have limited DDIs. DDI occurs more commonly with boosted PI regimens.

10.3.3 Age-Related Changes in Pharmacokinetics and Pharmacodynamics

Pharmacokinetic (PK) changes associated with aging include a reduction in renal and hepatic clearance and an increase in volume of distribution of lipid soluble drugs (leading to a prolongation of elimination half-life). Pharmacodynamic (PD) changes involve altered (usually increased) sensitivity to several classes of drugs, such as anticoagulants, cardiovascular, and psychotropic drugs [46] (Table 10.3).

Aging is associated with a decrease in renal tubular secretion, glomerular filtration, and decreased functioning of the hepatic CYP450 [38, 48, 49]. A better understanding of the effects of aging on the clinical pharmacology of therapeutic agents would enhance the quality of prescribing.

In this context, the age-related changes in drug handling (PK) and response (PD) appear to provide advantages and disadvantages to the different ARV classes:

- Integrase inhibitor therapy offers the advantages of a favorable safety profile, good tolerability, and absence of significant DDIs.
- Fusion inhibitors have a null impact on PK and PD.
- NNRTIs and PIs may act as inducers or inhibitors of CYP metabolism and permeability glycoprotein transporters. NRTIs may enhance some metabolic toxicities, in particular interfering with mitochondrial function.

The general principles (mentioned above) that guide the choice for ART use in day-to-day management of ARV in older patients with HIV are summarized in Table 10.4.

Frailty has not been considered as a factor in choosing specific ARV regimens either in treatment-naïve or in treatment-experienced patients with HIV.

Table 10.3 Potential impact of age-related changes on pharmacokinetics

	PK parameter			
	Absorption (Ka, F)	**Distribution (Vd)**	**Metabolism (CL)**	**Excretion (CL)**
Age-related change affected PK parameter	↑ Gastric pH ↓ Gastric emptying ↓ Splanchnic blood flow ↓ Intestinal CYP3A4 ↓ Intestinal P-gp	↓ Albumin ↑ α-1-acid-glycoprotein ↑ Body fat composition ↓ Lean muscle and total body water ↓ Transport protein activity	↓ Albumin ↑ α-1-acid-glycoprotein ↓ Liver mass (↓ Vmax) ↓ Hepatic blood flow	↓ Renal function ↓Transport processes
PK impact	↓ F ↔ F, ↓ Ka ↔ F, ↓ Ka ↑ F ↑F	↑ Vd ↓ Vd ↑ Vd[a] ↑ Vd	↑ CL/F ↓ CL/F ↓ CL/F ↔ CL/F	↓ CL/F ↓ CL/F
Predicted overall PK effect	↓ F or ↑ F ↓ Ka	↑ Vd	↓ CL/F	↓ CL/F
Examples of potential HIV drugs affected	Atazanavir Rilpivirine Other PIs Maraviroc	NNRTI PIs Maraviroc	PIs NNRTIs Maraviroc INSTI	NRTI

Adapted from Schoen et al. [47]

CL/F apparent oral clearance, *F* bioavailability, *HIV* human immunodeficiency virus, *INSTI* integrase strand transfer inhibitor, *Ka* absorption constant, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *P-gp* permeability glycoprotein, *PI* protease inhibitor, *PK* pharmacokinetic, *Vd* volume of distribution

[a]An increase in Vd would be expected for lipophilic drugs, lipophilicity is assumed for hepatically metabolized medications

Table 10.4 Guiding principles for the choice of antiretroviral use in older patients with HIV

	NRTI	NNRTI	PI	INSTI	FI
1. **Comorbid conditions** eg, cardiovascular, hepatic, metabolic May be exacerbated by effects of HIV or treatment	×	✓ >×	× >✓	✓	✓ >×
2. **Greater medication use** Overlapping side effects or potential interactions with ARVs and concomitant medications	✓ >×	×	×	✓	✓
3. **Age-related changes in drug handling (PK) and response (PD)** Toxicity	×	×	×	✓	✓

FI fusion inhibitors, *HIV* human immunodeficiency virus, *INSTI* integrase strand transfer inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor. ✓ denotes the expected benefit, × denotes the expected disadvantages, ✓ >× denotes the benefits outweigh the disadvantages, and × >✓ denotes the disadvantages outweigh the benefits

10.3.4 Clinical Trials

A recent analysis from the Modena HIV Metabolic Clinic (MHMC) aimed to describe patterns of ARV use in relation to age, gender, and frailty (Figs. 10.1 and 10.2) [50]. In the retrospective review of data from 1240 participants with undetectable viral load and CD4 cell count ≥500 cells/μL (providing 5024 annual study visits) frailty was retrospectively quantified via 37-item frailty index, based on the cumulative deficits model. Frailty index variables excluded markers of HIV severity or immune depletion [50].

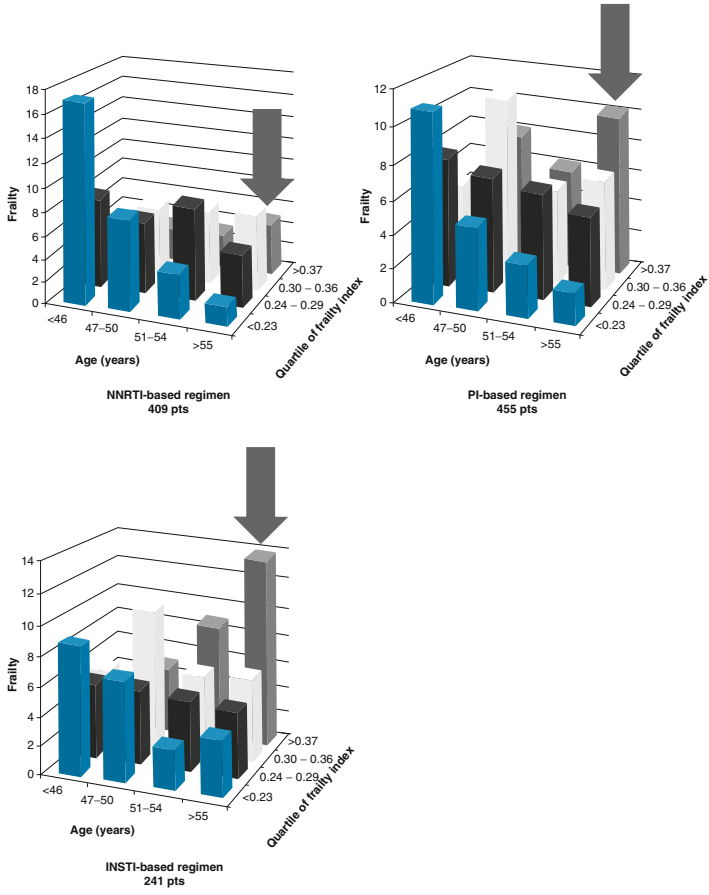

FIGURE 10.1 Age and frailty spectrum in different antiretroviral drug classes in patients currently exposed to treatment [50]

Regardless of the retrospective observational study design, which does not allow for any causative correlation, differences in ARV use were observed in relation to frailty and age. Patients on INSTI, NRTI-sparing regimens, or dual therapy

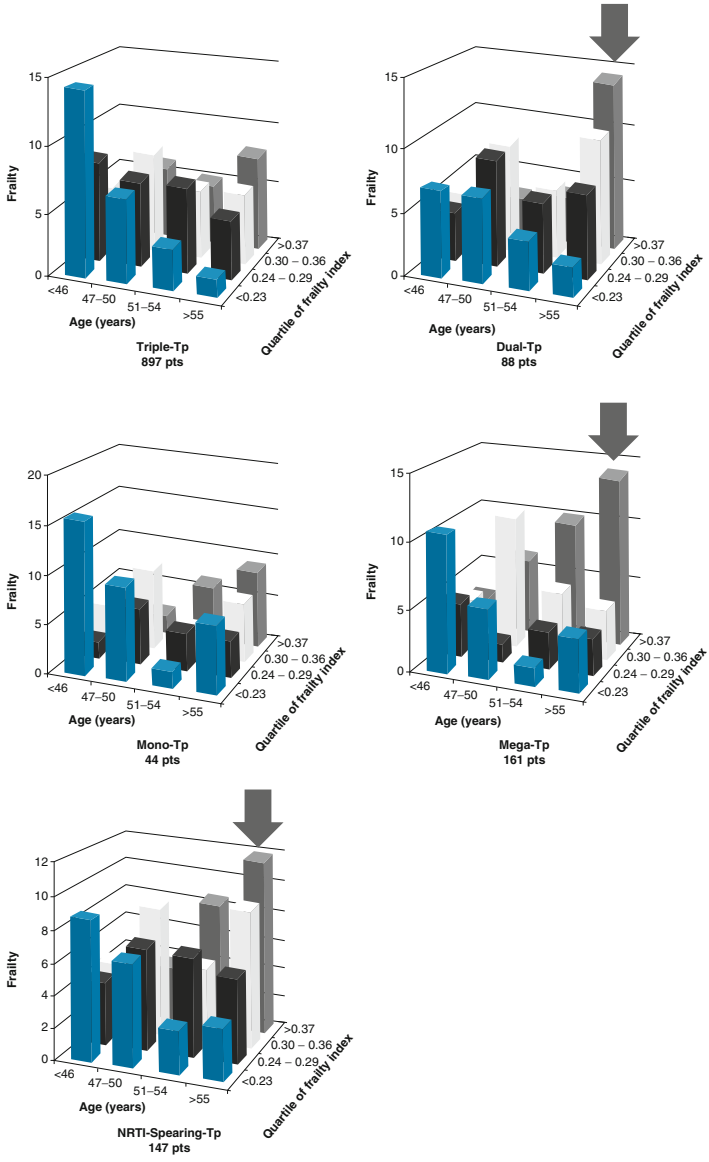

FIGURE 10.2 Age and frailty spectrum in different antiretroviral regimens in patients currently exposed to treatment [50]

were more likely to have a higher frailty index, independent of age. This may be the result of a clinical attitude towards ARV selection in frail patients, which could be the proof of principle for future randomized clinical trials, using the frailty index as a primary end point. Alternatively, the frailty index may be used as an inclusion criterion to stratify overall health of patients.

It is premature to state that INSTI regimens, NRTI-sparing regimens (usually dual therapy), and mono-PI therapy should be preferred in frail patients, nevertheless, in consideration of a progressive day-to-day use of these regimens in elderly and frail patients, the following sections summarize clinical studies using these treatment options.

Regardless of the small sample size in many of these studies the overall number of patients who have been enrolled in total is considerably high and it may be argued that a significant amount of clinical experience already exists with these regimens.

10.3.4.1 INSTI-Based Regimens

Integrase inhibitor (INI) therapy offers the advantages of a favorable safety profile, good tolerability, and absence of significant DDIs, in addition to high efficacy.

Messiaen et al. [51] conducted a review and meta-analysis of studies that used INIs in ARV-naïve and treatment-experienced patients with either virological failure or were switching while virologically suppressed. Combination treatment with INIs and dual NRTIs showed to be more beneficial for treatment-naïve patients compared to other currently used treatment strategies. In treatment-experienced patients with virological failure, use of INSTIs also proved to be beneficial. However, in patients with a history of therapy failure, switching a high genetic barrier drug towards an INI was not supported.

A summary of studies investigating INSTI therapy in treatment-naïve and treatment-experienced patients can be found in Tables 10.5 and 10.6, respectively.

Table 10.5 Dual therapy with INSTI based regimens in treatment-naïve patients

Author, name of trial/year/ published?	Design	Comparison	N	Follow-up (weeks)	Results
Cotte et al., No NUC No Boost/2013/No [52]	Phase II RCT, open label, single-arm	All patients received MRV + RAL + TDF/ FTC for 24 weeks. If HIV-RNA <50 copies/mL at week 20 and week 22 TDF/FTC was stopped at week 24 and pursued MRV-RAL until week 48.	10	48	HIV-RNA remained <50 copies/mL from week 8 to week 48 in all but one patient (who presented an unconfirmed 56 copies/mL blip at week 44). No SAE occurred during follow-up.
Cahn et al., PADDLE/2015 [53]	Phase IV RCT, open label, single arm	Analyse the antiviral efficacy, safety, and tolerability of 3TC + DTG as initial therapy among naïve HIV patients.	20	48	Ongoing

Adapted using data from Messiaen et al. [51]
3TC lamivudine, *DTG* dolutegravir, *FTC* emtricitabine, *HIV* human immunodeficiency virus, *MRV* maraviroc, *RAL* raltegravir, *RCT* randomized controlled trial, *RNA* ribonucleic acid, *SAE* serious adverse event, *TDF* tenofovir

Table 10.6 Dual therapy with INSTI-based regimens in treatment-experienced patients

Author, name of trial/year/ published?	Design	Comparison	N	Follow-up	Results
Reliquet et al.,/2014/Yes [54]	Retrospective, single-arm study	Patients with HIV-RNA <50 copies/mL for >6 months on an NVP-containing regimen switched to RAL+ NVP.	39	36 months	All patients with follow-up to month 24 (n=22) or month 36 (n=14) had HIV-1 RNA <50 copies/mL. No patient experienced grade 3 or 4 AEs. Median values of serum creatinine and lipids significantly improved after switch.
ROCnRAL/2013/ No [55]	Phase II RCT, single-arm study	Switch to MVC + RAL in supressed patients, with clinical lipodystrophy.	44	48 weeks	MVC/RAL dual therapy lacks virological robustness: Virological failure occurred in 5/44 patients. Emergence of resistance mutations to RAL occurred in 3/5 patients and switch from R5 to X4 tropic virus in 1/5 patients.

NCT01896921/ 2013/No [56]	Phase III interventional RCT	Switch patients on a stable ART regimen with a suppressed HIV-RNA <50 copies/mL for >1 year to MRV + RAL or DTG.	30	96 weeks	Ongoing
RALAM/2014/ No [57]	Phase III interventional RCT	Switch standard combination therapy in patients with prolonged virological suppression to RAL + 3TC.	75	24 weeks	Ongoing
Monteiro et al.,/2014/Yes [58]	Prospective cohort study	Virologically suppressed patients on PI or NRTI regimens, with problems of tolerability, safety concerns due to comorbidities, or risk of drug interactions for both PIs and NRTIs, were switched to ETR + RAL.	25	48 weeks	Efficacy (VL <50 copies/mL) was 84 % (95 % CI 65.3–93.6 %) by intent-to-treat analysis and 91.3 % (95 % CI 73.2–97.6 %) by per-protocol analysis. The CD4/CD8 ratio and plasma lipids improved.

(continued)

Table 10.6 (continued)

Author, name of trial/year/ published?	Design	Comparison	N	Follow-up	Results
Calin et al.,/2013/No [59]	Observational study	Virologically supressed patients, switched from a standard regimen to RAL + ETR. Main reasons for switch were metabolic toxicity/ lipodystrophy, renal impairment, or toxicity prevention.	91	12 months	Efficacy (VL <50 copies/mL) in per-protocol analysis, at 6 and 12 months respectively, was 98.2 % (55/56, 95 % CI 90.5–99.6) and 92.3 % (36/39, 95 % CI 79.6–97.3). Five virological failures occurred in a median (IQR) delay of 7 months [6–16].

Adapted using data from Messiaen et al. [51]
3TC lamivudine, *AE* adverse event, *ART* antiretroviral therapy, *CI* confidence interval, *DTG* dolutegravir, *ETR* etravirine, *HIV* human immunodeficiency virus, *IQR* interquartile range, *NRTI* nucleoside reverse transcriptase inhibitor, *NVP* nevirapine, *MVC* maraviroc, *PI* protease inhibitor, *RAL* raltegravir, *R5* R5-tropic, *RCT* randomized controlled trial, *RNA* ribonucleic acid, *VL* viral load, *X4* X4-tropic

10.3.4.2 NRTI-Sparing Regimens

One of the most important arguments in favor of the assessment of NRTI-sparing regimens has been a growing understanding of the long-term toxicity profile of the newer, relatively safe NRTIs in common use currently, such as tenofovir and abacavir. Newer drugs with high potency and often with a more favorable safety profile are becoming available, leading to an interest in NRTI-sparing regimens.

A review by Acchra and Boyd [60] examined studies of NRTI-sparing regimens in adult patients with HIV (Tables 10.7, 10.8, and 10.9). They found that an NRTI-sparing strategy (with an INI and boosted PI) was supported in the treatment of experienced patients on a failing regimen. In naïve patients, or in those switching from virologically suppressive regimens, evidence was sparse and largely came from small exploratory trials or observational studies. In such cases caution should be exercised in choosing the right patient and new ARV regimen, in order to avoid virological failure. Another concern was the residual toxicity of the ritonavir boost in PI-containing NRTI-sparing regimens. Additional research is needed to understand the true potential of NRTI-sparing regimens and how to minimize adverse effects associated with ritonavir-boosting.

10.3.4.3 Mono-PI Therapy

The potential benefits from switching from a triple drug regimen to ritonavir-boosted PI (PI/r) monotherapy is currently a topic of some interest (Tables 10.10 and 10.11), as it allows reduction of NRTI-related toxicity (lipoatrophy, renal disease, BMD loss) and reduced cost versus dual or triple therapy, while retaining other classes as future treatment options. There is an increased risk of low level viremia with monotherapy, but this has been shown to be reversible with NRTI re-introduction. The emergence of PI resistance has been rare on PI/r monotherapy and re-introduction of NRTI remains possible in such cases.

Table 10.7 Studies with NRTI-sparing regimens in treatment-naïve patients

Author, name of the trial/year/published?	Design	Comparison	N	Follow-up (weeks)	Results
Mills et al., A4001078/2013/Yes [61]	RCT, phase IIb pilot	(i) MVC + ATV/r (ii) TDF + FTC + ATV/r	121	48	75 % in arm (i) and 84 % in arm (ii) had viral load <50 copies/mL
Reynes et al., PROGRESS/2013/ Yes [62]	RCT pilot study	(i) LPV/r + RAL (ii) LPV/r + TDF + FTC	(i) 101 (ii) 105	96	66.3 % in arm (i) and 68.6 % in arm (ii) responded by FDA-TLOVR
Kozal et al., SPARTAN/2012/Yes [63]	RCT pilot study	(i) ATV + RAL (ii) ATV/r + TDF + FTC	(i) 63 (ii) 31	24	74.6 % in arm (i) and 63.3 % in arm (ii) had VL <50 copies/mL
Taiwo et al., MIDAS/2013/Yes [64, 65]	Single-arm pilot	MVC + DRV/r	25	96	VL <50 copies/mL: 8.3 % and 10 % at week 48 and 96, respectively
Bedimo R et al., RADAR/2011/No [66]	RCT pilot	(i) RAL + DRV/r (ii) DRV/r + TDF + FTC	80	24	86 % in arm (i) and 87 % in arm (ii) had VL <50 copies/mL

Taiwo et al., ACTG5262/2011/Yes [67]	Single-arm pilot	DRV/r + RAL	112	48	26 % with VL >50 copies/mL, majority with low-level viremia (<200 copies/mL)
Riddler et al., ACTG5142/2008/Yes [68]	RCT	(i) EFV + NRTIs (ii) LPV/r + NRTIs (iii) LPV/r + EFV	(i) 250 (ii) 253 (iii) 250	96	89 %, 77 %, and 83 % had VL <50 copies/mL in arms (i), (ii) and (iii), respectively No difference in time to toxic effects At failure, resistance mutations more common in arm (iii)

Adapted from Achhra and Boyd [60]
ATV atazanavir, *ATV/r* atazanavir/ritonavir boosted, *DRV/r* darunavir/ritonavir boosted, *EFV* efavirenz, *FDA-TLOVR* Food and Drug Administration time to loss-of-virologic response algorithm, *FTC* emtricitabine, *LPV/r* lopinavir/ritonavir boosted, *MVC* maraviroc, *NRTIs* nucleoside reverse transcriptase inhibitors, *RAL* raltegravir, *RCT* randomized controlled trial, *TDF* tenofovir, *VL* viral load

Table 10.8 Studies with NRTI-sparing regimens in treatment-experienced patients

Author, name of the trial/year/published?	Design	Comparison	N	Follow-up (weeks)	Results
Boyd et al., SECONDLINE/2013/ Yes [69]	Phase-III/ IV RCT, non-inferiority	(i) LPV/r + RAL vs (ii) LPV/r + recycled NRTIs in those failing 1st line NNRTI-based ART	541 (271 vs 270)	48	Arm (i) non-inferior to arm (ii) for virological outcome No major differences in serious AEs Greater decline in BMD in arm (ii) [70]
Paton et al., EARNEST/2013/ No [71]	Phase-III/ IV RCT, non-inferiority	(i) LPV/r + RAL (ii) LPV/r monotherapy after endpoint induction with LPV/r + RAL (iii) LPV/r + recycled NRTIs (control) in those failing 1st line NNRTI-based ART	(i) 433 (ii) 418 (iii) 426	96	Arm (i) non-inferior to arm (iii) for a composite of virological and clinical Arm (ii) inferior to other arms for virological outcome and higher LPV/r resistance No differences in grade III/IV events

Tashima et al., OPTIONS/2013/No [72]	Phase-III/ IV RCT, non-inferiority	(i) NRTI-omitting optimized regimen (ii) NRTI-including optimized regimen in triple-class experienced failing patients	(i) 179 (ii) 181	48	Similar virological outcomes in both arms No differences in grade III/IV events Higher mortality in arm (ii)
Ruane et al., INROADS/2013/ No [73]	Single-arm exploratory phase-IIb trial	DRV/r + ETV in failing patients (78 %) or ART naïve patients with transmitted resistance (22 %)	54 (75 % completed the study).	48	100 % of ART naïve and 87 % of failing patients achieved virological success Two patients developed ETV mutations and none had DRV mutations

(continued)

Table 10.8 (continued)

Author, name of the trial/year/published?	Design	Comparison	N	Follow-up (weeks)	Results
Imaz et al.,/2011/Yes [74]	Observational	Salvage regimen of at least three active agents from DRV, ETV, RAL, and MVC, with or without NRTIs	122	48	78 % virologically suppressed (equal in both arms) Higher baseline viral load associated with worse outcomes
Nozza et al.,/2011/ Yes [75]	Observational	Salvage regimen of RAL + MVC + ETV	28	96	96 % virologically suppressed (<50 copies/mL)
Florence et al.,/2010/ Yes [76]	Observational	Salvage regimen of ETV + optimized regimen, 40 % without NRTIs	941	24	70 % and 90 % had VL <50 and 400 copies/mL, respectively

Adapted from Achhra and Boyd [60]
AEs adverse events, *ART* antiretroviral therapy, *BMD* bone mineral density, *ETV* etravirine, *DRV* darunavir, *DRV/r* darunavir/ritonavir boosted, *LPV/r* lopinavir/ritonavir boosted, *MVC* maraviroc, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *RAL* raltegravir, *RCT* randomized controlled trial, *VL* viral load

Table 10.9 Studies with NRTI-sparing regimens in treatment-experienced patients (virologically supressed on standard antiretroviral therapy)

Author, name of the trial/year/ published?	Design	Comparison	N	Follow-up (weeks)	Results
Monteiro et al.,/2014/Yes [58]	Observational	RAL + ETV	25	48	91 % virologically suppressed in per-protocol analysis Lipids improved
Ward et al.,/2013/ No [77]	Observational	Switching for toxicity concerns to a RAL + 1 or 2 agents, most commonly on RAL + ATV/r with or without ETV or MVC	62	168	92 % virologically suppressed 3 of 15 on dual therapy had to add third agent for low-level viremia
Calin et al.,/2013/ No [59]	Observational	Switching to RAL + ETV regimen	91	48	93 % had viral load <50 copies/mL 4 out of 5 with virological failures had past NNRTI mutations 3 patients had RAL mutations

(continued)

Table 10.9 (continued)

Author, name of the trial/year/ published?	Design	Comparison	N	Follow-up (weeks)	Results
Katlama et al., ROCnRAL/2013/ No [55]	Single-arm exploratory trial	R5-trophic suppressed patients switched to MVC + RAL	41	48	Failure in 11.4 % RAL mutations in 3 out of 5 patients who failed 1 out of 5 had R5 to X4 virus switch
Cotte et al., No Nuc No Boost/2013/No [51]	Single-arm exploratory trial	MVC + RAL	10	48	No virological failures (>50 copies/mL) No serious adverse events
Burgos et al.,/2012/ No [78]	Observational	Switching for toxicity concerns to a PI/r + 2nd agent, many with no NRTI	131	56	>90 % virologically suppressed
Ofotokun et al., KITE/2012/No [79]	Exploratory pilot trial	(i) LPV/r + RAL (ii) standard ART	60	48	92 % in arm (i) and 88 % in arm (ii) with viral load <50 copies/mL Higher triglycerides in arm (i) No difference in BMD or body composition

Carey et al., SPARTA/2012/Yes [80]	Pilot cross-over RCT	Patients receiving ATV/r randomized to: (i) ATV/r (300/100 mg, respectively once-daily) + RAL (800 mg once daily) (ii) ATV (300 mg twice-daily) + RAL (400 mg twice-daily)	25	76 % in follow-up for 48 weeks	Both agents pharmacologically compatible All patients remained virologically suppressed
Cordery et al., /2010/Yes [81]	Observational	RAL + ATV (unboosted)	20	72	Only 1 (5 %) failure
Allavena et al./2009/Yes [82]	Observational	Switching for toxicity concerns to a PI/r + RAL	29	48	100 % virologically suppressed
Fischl et al./2007/ Yes [83]	RCT, not fully powered	(i) LPV/r + EFV (ii) EFV + NRTIs	236	96	Arm (i): shorter time to failure or discontinuation Arm (i): greater increase in triglycerides

Adapted from Achhra and Boyd [60]

ART antiretroviral therapy, *ATV* atazanavir, *ATV/r* atazanavir/ritonavir boosted, *BMD* bone mineral density, *EFV* efavirenz, *ETV* etravirine, *LPV/r* lopinavir/ritonavir boosted, *MVC* maraviroc, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PI/r* protease inhibitor/ritonavir boosted, *R5* R5-tropic, *RAL* raltegravir, *RCT* randomized controlled trial, *X4X4*-tropic

Such a strategy can only be considered in stable, long-term virologically suppressed patients who have demonstrated good adherence to ART, have no history of PI failure, do not have chronic hepatitis B, do not have HIV-associated neurocognitive disorders, and who are able to tolerate low dose ritonavir [101].

The recent PIVOT study [99] (Table 10.11) randomized 587 UK patients, who already had an undetectable viral load on stable treatment, to either PI/r monotherapy or triple therapy. It included 4 years of follow-up. Approximately 80 % in the boosted PI monotherapy arm used darunavir/r (DRV/r), 14 % lopinavir/r (LPV/r), and 7 % another PI. Viral load rebounded much more frequently in the monotherapy group (35 %) compared to the triple therapy group (3.2 %). All rebounds on monotherapy re-suppressed either spontaneously or with NRTI re-introduction. The PI arm was non-inferior on the primary outcome of loss of future drug options. There were no significant differences in serious disease complications, adverse events, or neurocognitive function between the arms [99].

The PROTEA trial [93] (Table 10.11) randomized 273 patients with HIV-1 RNA <50 copies/mL for over 24 weeks on current ARVs. Patients were switched to DRV/r 800/100 mg once-daily, either as monotherapy or with two NRTIs. Monotherapy showed lower efficacy (86 %) versus triple ART at week 48 (95 %). However, this lower efficacy was seen mainly in patients with CD4 nadir levels below 200 cells/μL. There was no development of PI resistance [93].

The European AIDS Clinical Society guidelines state that PI/r monotherapy with either DRV/r or LPV/r, twice-daily, might represent an option in persons with intolerance to NRTIs or for treatment simplification in substance abusers with documented frequent interruption of combination ART. Such a strategy should only be applied to persons without a history of failure on prior PI-based therapy, who have had a HIV-viral load <50 copies/mL in at least the past 6 months, and who do not have chronic hepatitis B infection [14].

Table 10.10 Studies with mono-PI therapy in treatment-naïve patients

Study	Design	Comparison	N	Follow-up (weeks)	Results
MONARK study, 2009 [84, 85]	Pilot randomized trial	Safety and efficacy of LPV/r monotherapy compared to LPV/r-ZDV-3TC triple therapy for antiretroviral-naïve HIV-1 infected patients.	83 LPV/r arm; 53 LPV/r + ZDV + 3TC arm	96	VL <50 copies/mL in 47 % of monotherapy arm; 5 patients had major PI mutations, 13 patients had minor PI mutations; triple therapy arm was discontinued during the study by the high rate of abandonment.
IMANI-2 [86]	Phase II open label study	Safety, virologic response, and tolerability of LPV/r monotherapy in ARV naïve patients.	39	96	VL <75 copies/mL in 74 % of patients; no resistance mutations observed.

(continued)

Table 10.10 (continued)

Study	Design	Comparison	N	Follow-up (weeks)	Results
Cameron et al. [87]	Open-label, randomized study	Treatment with LPV/r plus 3TC/ZDV followed by LVP/r monotherapy versus a standard regimen of EFV plus 3TC/ZDV in ART naïve patients.	104 patients (LPV/r 400 mg/100 mg twice-daily + 3TC/ZDV150 mg/300 mg twice-daily), of which 92 patients were simplified to LPV/r monotherapy after HIV-RNA <50 copies/mL for 3 months. 51 patients (EFV 600 mg once-daily + 3TC/ZDV 150 mg/300 mg twice-daily).	96	VL <50 copies/mL in 48 % of the LPV/r monotherapy arm and 61 % in the EFV arm. Four patients in the monotherapy arm and one in the EFV arm developed new PI resistance mutations.

3TC lamivudine, *ART* antiretroviral therapy, *ARV* antiretroviral, *EFV* efavirenz, *HIV* human immunodeficiency virus, *LPV/r* lopinavir/ritonavir boosted, *PI* protease inhibitor, *RNA* ribonucleic acid, *VL* viral load, *ZDV* zidovudine

Table 10.11 Studies with mono-PI in treatment-experienced patients

Study	Design	Comparison	N	Follow-up (weeks)	Results
OK study [88]	Randomized, controlled, open-label, multicenter, pilot clinical trial	LPV/r monotherapy vs continuing LPV/r and two nucleosides in HIV-infected patients with suppressed HIV replication.	21 (LVP/r arm) 21 (LPV/r + 2 NRTIs arm)	48	VL <50 copies/mL in 81 % of the LPV monotherapy arm and 95 % in the triple therapy arm; no associated resistance mutations. Pulido et al. [14] described 67 % of the patients with LPV/r monotherapy with VL <50 copies/mL after 4 years. No major PI mutations were detected.
OK-04 study [89]	Randomized, open-label, noninferiority, multicenter clinical trial	LVP/r monotherapy vs continuing LPV/r and two nucleosides in HIV-infected patients with suppressed HIV replication.	100 (LPV/r arm) 98 (LVP/r + 2 NRTIs arm)	96	VL <50 copies/mL in 77 % of the monotherapy arm and 78 % of the triple therapy arm. PI major mutations in 2 % of patients in both arms.

(continued)

Table 10.11 (continued)

Study	Design	Comparison	N	Follow-up (weeks)	Results
KalMO study [90]	Open-label, randomized study	Feasibility of using LPV/r monotherapy in patients with undetectable VL.	30 (LPV/r monotherapy) 30 (PI or NNRTI + 2 NRTIs)	96	VL <80 copies/mL in 80 % of the monotherapy arm and 86.6 % in triple therapy arm. No PI mutations.
MONOI ANRS 136 study [91]	Prospective, open-label, non-inferiority, randomized trial	HIV-1 RNA suppression in patients receiving DRV/r monotherapy versus triple therapy containing DRV/r + two NRTIs. VL <400 copies/mL for ≥18 months and screening VL <50 copies/mL.	112 (monotherapy arm) 113 (triple therapy arm)	96	VL <50 copies/mL in 88 % of the DRV monotherapy arm and 84 % in the triple therapy arm. No associated DRV resistance mutations or accumulation of reverse transcriptase mutations.
MONET trial [92]	Randomized controlled, open-label phase IIIb trial	HIV-1 RNA suppression in patients receiving DRV/r monotherapy versus triple therapy containing DRV/r + 2 NRTIs. VL <50 copies/mL at inclusion.	127 (monotherapy arm) 129 (triple therapy arm)	144	By a strict ITT analysis (switches not considered failures), the percentage of patients with HIV-RNA <50 copies/mL was 84 % vs 83.5 %, in the DRV/r monotherapy and triple therapy arms. One patient in each arm showed genotypic PI mutations.

PROTEA trial [93]	Multicenter, randomized, open-label phase IIb study	HIV-1 RNA suppression in patients receiving DRV/r monotherapy versus triple therapy containing DRV/r + 2 NRTIs. VL <50 copies/mL at inclusion.	137 (monotherapy arm) 136 (triple therapy arm)	48	VL <50 copies/mL in 86.1 % of the DRV monotherapy arm and 94.9 % in the triple therapy arm. No development of PI resistance.
Santos et al. [94]	Single arm, prospective	Switch from triple therapy to DRV/r monotherapy. VL <50 copies/mL at inclusion.	95	48	VL <50 copies/mL in 81.1 % of patients. No mutations associated with DRV resistance.
Wilkin et al. [95]	Open-label, prospective, single-arm pilot trial	Evaluate the risk of virologic failure after switch to ATV/RTV in patients with undetectable VL.	34	48	VL <200 copies/mL in 88 %. No major mutations.
Karlström et al. [96]	Single-arm, single-center pilot trial	Investigate the feasibility of ATV/r monotherapy in HIV-1 infected patients with stable ART.	15	16–48	VL <20 copies/mL in 64.3 %. No PI mutations. The study was terminated according to protocol when 15 of the planned 30 patients had been recruited, because five cases of virologic failure had occurred.

(continued)

Table 10.11 (continued)

Study	Design	Comparison	N	Follow-up (weeks)	Results
ATARITMO trial [97]	Non-comparative 24-week pilot study	Evaluate the risk of virologic suppression and compartment penetration in PI monotherapy after simplification to ATV/RTV alone in patients with undetectable VL.	30	24	VL <50 copies/mL in 90 % of patients. 3/20 patients had elevated viral loads in CSF (HIV RNA >100 copies/mL), and 2/15 in semen, (despite viral suppression in plasma). Short term viral blips occurred in five patients (18 %); among those, four had a single viral load measurement >50 copies/mL, with only two patients (7 %) having a single blip >200 copies/mL.
MODAT study [98]	Multicenter, randomized, open-label, noninferiority trial	Virological efficacy of ATV/r monotherapy vs ATV/r + 2 NRTIs in HIV-1 treated individuals with HIV-RNA <50copies/mL.	51 (ATV/r monotherapy) 52 (ATV/r + 2 NRTIs)	48	VL <50 copies/mL in 73 % of the ATV/r arm and in 85 % of the ATV/r + 2 NRTIs arm. No mutation was observed in the ATV/r arm.

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PIVOT study [99]	Prospective, randomized, controlled, open-label, multicenter trial	Evaluate the loss of future drug options with PI monotherapy vs triple therapy.	291 (triple therapy) 296 (mono PI; 80 % DRV/r, 14 % LPV/r, 7 % other PI/r)	260	VL rebounded much more frequently in the monotherapy group compared to the triple therapy group (35 % vs 3.2 %). More patients lost treatment options on the PI/r vs the triple therapy arm (6 patients [2.1 %] vs 2 patients [0.7 %]).
Goelz et al. [100]	Prospective observational study	Virological outcome of LPV/r monotherapy in different situations of daily practice (13 % therapy-naïve, 41 % unfavorable side effects under NRTI, 19 % with need to simplify the regimen, and 27 % with failing regimens).	63	60	VL <50 copies/mL in 66 %. New PI resistance in one patient.

ATV atazanavir, *ATV/r* atazanavir/ritonavir boosted, *CSF* cerebrospinal fluid, *DRV* darunavir, *DRV*/r darunavir/ritonavir boosted, *HIV* human immunodeficiency virus, *ITT* intent to treat, *LPV* lopinavir, *LPV/r* lopinavir/ritonavir boosted, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor, *PI/r* protease inhibitor/ritonavir boosted, *RNA* ribonucleic acid, *RTV* ritonavir, *VL* viral load

10.4 Future Perspectives

The success of HAART has significantly changed the pattern of HIV infection in developed countries, with the 'graying' of the HIV-infected population as an important testament to its success. This has provided new challenges relating to the care of older patients, particularly with regard to the management of comorbidities and ART toxicity, which scientists and physicians are addressing through the refinement of existing ART, the development of new agents, and a growing focus on a more holistic approach to care (involving the integration of concepts from general medicine and geriatrics into HIV care).

It is evident that the management of ART in patients aging with HIV implies a detailed knowledge of patient health in both physical and psychological domains in order to tailor the most appropriate ARV regimen. Therefore, the choice of regimen goes beyond the goal of achieving HIV viral load below the limit of detection and contributes to the overall management of the health profile.

Future research should investigate the association between frailty and ARV choice in people living with HIV. In this context frailty may be useful either as inclusion criteria or as a clinical end point for randomized clinical trials comparing ARV treatment regimens in elderly patients with HIV. This knowledge and experience will likely be extremely useful in the care of older patients.

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Chapter 11
HIV, Aging, and Polypharmacy

Julian Falutz

Key Points

- Polypharmacy occurs commonly among older patients with human immunodeficiency virus (HIV).
- It is an independent and under-appreciated contributor to aging and drug-related complications.
- It requires regular and careful medication review.

Polypharmacy, commonly defined in the general population as taking five or more different medications on a daily basis [1], is an important but still poorly understood clinical problem in patients with HIV, particularly among those older than 50 years of age [2, 3]. This is not a new phenomenon in HIV disease, as patients have always needed to take multiple medications in order to remain stable. In the mid-1990s the first generation of highly active antiretroviral therapy

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(HAART) regimens included three different antiretrovirals (ARVs), each consisting of several tablets. All of these pills had to be taken three to four times daily, often according to strict dietary restrictions. These ARVs were taken in addition to the drugs patients often took either for primary or secondary prophylaxis of various opportunistic infections, as well as for symptomatic management of drug-related toxicities, or for the acute management of intercurrent complications.

It was demonstrated early in the HIV epidemic that polypharmacy increased the risk of poor adherence to HAART [4]. With the early HAART regimens, particularly the protease inhibitor (PI) based treatments, taking more than 95 % of the pills as prescribed was required in order to achieve undetectable HIV RNA levels. Suboptimal adherence to HAART predicts the development of drug resistance [5] as well as clinical progression and mortality [6]. In early clinical studies of antiretroviral therapy (ART) naïve patients, who were monitored and followed carefully, more than 80 % remained on their first HAART regimens at one year follow-up. In the 'real-world' experience of busy clinic-based care, often significantly less than two-thirds of patients were still taking their drugs as prescribed at 1 year of follow-up [7].

HAART has been greatly simplified over the past 10–15 years, and patients now are often able to take daily regimens. As well, several single-tablet regimens (STR) are available, each containing three distinct ARVs [8]. Currently available ARVs are better tolerated, have significantly less toxicity, and require fewer dietary restrictions, although some remain [9]. These drug regimens are also more forgiving in terms of strict adherence and 80–95 % adherence rates are increasingly associated with undetectable HIV viral loads. These changes in drug design and formulation allow for improved compliance and result in greater durability of response. Nevertheless, patients with HIV still have a greater prevalence of polypharmacy than age-matched controls [10, 11]. Furthermore, the prevalence of what has been termed excessive polypharmacy, the use of 10 or more medications, appears to be a particularly worrisome problem among older patients with HIV [10, 12].

The need to take multiple drugs in currently treated patients with HIV occurs for several reasons, including the increased prevalence of non-AIDS defining comorbidities, which often require medical therapy either for prevention or active therapy [13]. Treatments typically include drugs for cardiovascular disease, hypertension, gastrointestinal disorders, psychoactive disorders, non-HIV-related infections, non-AIDS-defining cancers, dyslipidemia, and type II diabetes. An important limitation in understanding the scope of the problem is that the manner in which the use of multiple medications is reported is inconsistent and therefore potentially confusing. In a study by Edelman et al. [3] the median number of drugs taken by all patients with HIV was between five and nine. Another study reported that between 15 and 75 % of treated patients with HIV in their 60s meet criteria for polypharmacy and that 14 % of patients older than 65 years of age were taking four or more non-ARV drugs, most of which were vitamins, supplements, or drugs for cardiovascular or neurologic disorders [14]. A further study focusing on older patients with HIV found that in a cohort, with a median age of 64 years, the median number of drugs patients were taking was 13, of which only four were ARVs [10]. In the general population older patients taking this many drugs have an increased risk of falls, impaired cognition, frailty, hospitalization, and mortality [1].

Non-medically prescribed drug use is very common and often under-reported or misrepresented in the general population, and is a particular problem in patients with HIV. In addition to over-the-counter (OTC) drugs, patients often take recreational drugs and alternative care-related drugs. A large discrepancy exists between what the patient is actually taking and what their provider believes they are taking [15]. Care centers following large numbers of injection drug users will experience an increased frequency of the use of pain medications and methadone. The anticipated increasing availability of potentially curative short-term regimens for hepatitis C co-infection will further add to the increased use of drugs [16]. All of these factors combine to increase the pill burden, overall cost, and the complications related to polypharmacy.

The consequences of polypharmacy in the general elderly population are well-known, and typically include poor adherence to necessary drugs, increased incidence of adverse drug events (ADEs), drug–drug interactions (DDI), and use of inappropriate medications. Fifteen percent of treated patients with HIV may take drugs with potential anticholinergic toxicity [10]. Patients with HIV may be particularly susceptible to the above noted complications because of increased rates of renal and hepatic dysfunction, ongoing systemic immune activation, and associated chronic inflammation as well as subclinical impaired organ function. It is therefore not surprising that several of these common age-related and polypharmacy-associated complications also occur in younger treated patients with HIV. These include frailty [17] and impaired cognition [18]. Medications have been shown to specifically contribute to increased risk of poor mobility and falls in HIV positive individuals [19, 20]. Although polypharmacy predisposes to frailty in older seronegative people [21], it is presently unknown whether polypharmacy independently contributes to the development of frailty and impaired cognition in patients with HIV. Although several studies have shown that overall adherence to medications is higher in older patients with HIV compared to younger patients, risk factors for poor adherence are also increased in older patients [22]. This is a particular problem in HIV patients with cognitive impairment, where it has been shown that adherence is decreased primarily in older patients who perform poorly on tests of executive function [22]. Although the incidence of HIV-associated dementia has significantly decreased with HAART, rates of mild cognitive impairment and asymptomatic cognitive decline are worryingly high and may be greater compared to appropriately selected control subjects [23]. Other risk factors for poor adherence and drug toxicity in older patients with HIV, as in the general population, include social isolation, substance abuse, and limited financial resources, which are increased in certain subgroups with HIV.

The large number of drugs taken by older treated patients with HIV increases the risk of important pharmacokinetic

interactions with ARVs, leading to important DDIs. Several examples highlight these negative interactions. Cardiovascular disease is the most common non-AIDS complication in treated patients, often requiring drug therapy. Interactions requiring dose adjustment and careful monitoring are required for patients with HIV taking antiarrthymics, several classes of antihypertensives, and warfarin, depending on the specific HAART components used [2]. Many treated patients with HIV develop dyslipidemia, and meet current criteria for use of statins. There is a recognized risk of statin-induced myopathy and rhabdomyolysis in patients on certain PI drugs that are potent inhibitors of CYP3-A4 and can thereby increase statin levels normally metabolized via cytochrome P450. Simvastatin and lovastatin are thus contraindicated in patients taking PIs, and only low doses of pravastatin, rosuvastatin, and atorvastatin are recommended, although higher doses are often prescribed to HIV-negative patients because of their improved efficacy. Atorvastatin may be used safely in usual doses along with the integrase inhibitor raltegravir [24]. It is unknown what interactions occur with higher doses of this statin or whether any interactions occur with the newest integrase inhibitor, dolutegravir. Proton pump inhibitors (PPIs), some of which are available OTC, are also frequently used by patients with HIV and may lower serum levels of the important PI, atazanavir, potentially leading to therapeutic failure and drug resistance [16]. Both PPIs and H2 blockers decrease absorption of rilpivirine, a recently introduced non-nucleoside reverse-transcriptase inhibitor (NNRTI) that is co-formulated in one of the currently available STR drugs. The risk of developing adrenal insufficiency and Cushing's syndrome with the concurrent use of inhaled or intranasal fluticasone and any ritonavir-boosted PIs is well described and must be avoided. Sleep disturbances and pain syndromes occur commonly in the elderly, and have also been described in patients with HIV [25, 26]. Patients are frequently treated with drugs associated with increased risk of DDI. Recently, the co-administration of opioids and benzodiazepines has been shown to increase mortality in treated patients with HIV [27].

One-third of treated patients with chronically suppressed HIV-viral load (HIV-VL) do not achieve immune recovery to more than 500 CD4+ cells. This occurs more frequently in older patients with HIV who remain at increased risk of both AIDS as well as non-AIDS-related complications compared to patients with more than 500 CD4+ cells. Some older patients with very low plateau CD4 counts may require primary prophylaxis of common opportunistic infections, such as *Pneumocystis* pneumonia and central nervous system toxoplasmosis. Low dose sulfamethoxazole is effective as the first-line drug for primary prophylaxis of these infections, which adds to the pill burden and risk of DDI, and thus requires careful monitoring (eg, in patients taking warfarin).

In summary, polypharmacy is very common in patients with HIV and is an essential component of comprehensive patient management. Polypharmacy independently contributes to morbidity and mortality and demands increased vigilance on the part of providers involved in the complex care of aging patients with HIV. It is highly recommended that all patients review their medications at every regular visit and have an annual medical reconciliation. This is best carried out by knowledgeable pharmacists, who are essential members of the HIV treating team.

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Chapter 12
Nutrition and Physical Exercise in Older Patients with HIV

Chiara Mussi

Key Points

- Both nutrition and physical exercise have a crucial role in determining the outcomes of patients infected with human immunodeficiency virus (HIV).
- Since malnutrition is considered a geriatric syndrome, the management approach must be multifactorial to succeed.
- There are many methods to describe malnutrition, but in patients with HIV the Mini Nutritional Assessment (MNA) and Subjective Global Assessment (SGA) are widely used.
- As far as intervention is concerned, WHO recommendations are the most commonly followed guidelines.

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- Sarcopenic obesity is an expression of malnutrition that is particularly frequent and characteristic of older patients with HIV.
- Physical exercise is important for everybody, but especially in patients with HIV:
  - enhances muscle strength and prevents sarcopenia;
  - improves outcomes of frequent non-HIV, age-related chronic conditions; and
  - reduces markers of chronic inflammation.
- Resistance exercises enhance strength and aerobic exercises improve outcomes.
- Mixed protocols are more complex, but more complete in terms of results.

12.1 Overview

Nutrition and physical exercise have a central and crucial role in influencing outcomes in older patients with HIV (Fig. 12.1) [1]. Emerging data shows that both nutrition and physical exercise can impact viral replication and the immune system in HIV. Optimal nutrition is an important adjunct in the clinical care of patients with HIV. Nutritional interventions may improve symptom management, the quality and span of life, support the effectiveness of medications, and improve the resistance of the patient to infections and other disease complications by altering immunity. Moreover, malnutrition can be considered a geriatric syndrome (for the definition, see Chapter 7), so the management has to be multifactorial.

The management of nutrition in older patients with HIV can be divided into assessment of risk of malnutrition (tools to define nutritional status) and intervention (asymptomatic and symptomatic phases of HIV infection).

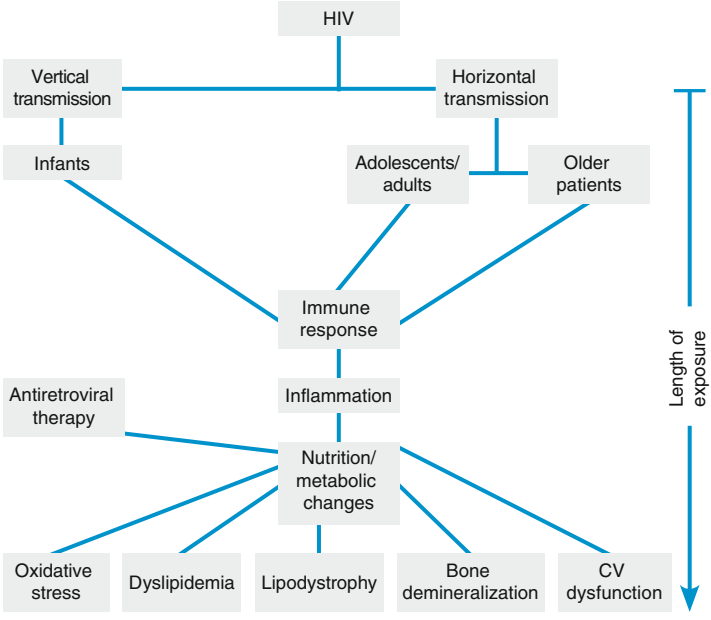


FIGURE 12.1 The central role of nutrition in the evolution of HIV [1]. *ART* antiretroviral therapy, *CV* cardiovascular (Reproduced with permission from © Dove Medical Press Ltd)

12.2 Assessment of Risk of Malnutrition

Screening for malnutrition at an early stage allows the intervention to be most successful. History, physical examination, and anthropometric measurements are essential parts of any nutritional evaluation. Incorporating biochemical measurements in the routine nutritional assessment provides an often-needed objective dimension, nevertheless, interpreting these measurements must take into consideration the normal biological changes seen with aging and the simultaneous presence of HIV infection.

12.2.1 Anthropometric Evaluation

The physical examination should determine general body habitus, body weight and height, and the presence of any sign of nutritional deficiency in the skin, hair, nail, eyes, mouth, or muscles. The body mass index (BMI) is a useful measurement for assessing nutritional status and can be calculated using the formula (BMI = weight (kg)/[height (m)]^2). The association between BMI and mortality in older adults follows a J-shaped curve, unlike the U-shaped curve relationship in younger adults. Data from several studies of individuals aged 60–90 years indicate the lowest mortality occurred at progressively increasing body weight, and higher mortality occurred with lower body weight [2]. BMI, however, may not be as informative in the elderly as it is at younger ages. There is little documentation relating BMI to direct measurements of body composition in the elderly, especially at very old ages or in non-Caucasian ethnic groups. In addition, stature often cannot be measured accurately in the elderly individuals because of increased prevalence of spinal curvatures, which is reported to be as high as 30 %. For such individuals, the estimation of stature from knee height is probably the best method for providing this information [3]. The anthropometric evaluation includes measurements of arm circumference, mid-arm muscle area, calf circumference, triceps skin-fold, and subscapular skin-fold thickness. Calf circumference has been recommended as a more sensitive measure of the loss of muscle mass in the elderly than arm circumference and mid-arm muscle area [4]. Skin-fold thickness is frequently used to assess body fat stores, nevertheless, the accuracy of this technique in nutritional evaluation is hampered by the unpredictable response of subcutaneous fat to undernutrition and the absence of a definite correlation between skin-fold thickness and total body fat in older men, especially in patients with HIV.

12.2.2 Biochemical Profile

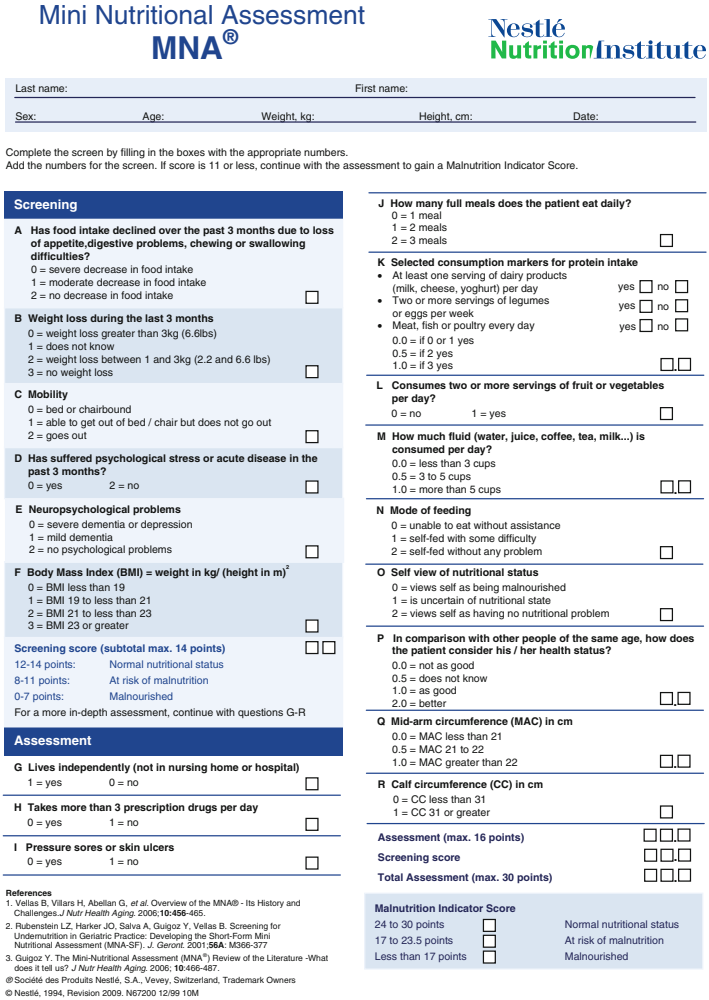
Serum albumin, total cholesterol, total lymphocyte count, and proteins with a shorter half-life than albumin (eg, prealbumin, retinol binding proteins, and leptin) are frequently used to assess malnutrition in older patients without HIV infection. However, specificity as markers of malnutrition in patients with HIV is lost.

Serum albumin level is the most frequently utilized biochemical marker for malnutrition in older patients. Albumin levels less than 3.5 mg/dL are strongly suggestive of malnutrition and levels less than 3.2 mg/dL are excellent predictors of mortality and morbidity in the elderly [5]. Nevertheless, in patients with HIV this biochemical parameter is not as useful as in non-infected older patients, since it does not consistently predict malnutrition outcomes. This suggests that albumin may measure end stage disease as well as malnutrition and should not be used as a proxy for nutritional status without further study of its association with validated measures [6].

12.2.3 Screening Tools

In literature there are many screening tools to evaluate malnutrition in elderly patients, but they are not validated in the HIV population. The two tests proposed are widely used in both older patients with and without HIV.

The Mini-Nutritional Assessment (MNA®) (Fig. 12.2) [7] evaluates the risk of malnutrition in elderly people. It is considered one of the most complete screening tools for malnutrition, since it involves anthropometric measurements, global assessment, dietary questionnaire, and a subjective assessment. It enables a patient to be categorized as normal (adequate nutrition), borderline (at risk of malnutrition), or malnourished. Ruiz et al. [8] suggest that the MNA® can be



Mini Nutritional Assessment
MNA®

Nestlé Nutrition Institute

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers.
Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite,digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3kg (6.6lbs)
1 = does not know
2 = weight loss between 1 and 3kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chairbound
1 = able to get out of bed / chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F Body Mass Index (BMI) = weight in kg/ (height in m)^2
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

Screening score (subtotal max. 14 points) ☐☐
12-14 points: Normal nutritional status
8-11 points: At risk of malnutrition
0-7 points: Malnourished
For a more in-depth assessment, continue with questions G-R

Assessment

G Lives independently (not in nursing home or hospital)
1 = yes 0 = no ☐

H Takes more than 3 prescription drugs per day
0 = yes 1 = no ☐

I Pressure sores or skin ulcers
0 = yes 1 = no ☐

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals ☐

K Selected consumption markers for protein intake
- At least one serving of dairy products (milk, cheese, yoghurt) per day yes ☐ no ☐
- Two or more servings of legumes or eggs per week yes ☐ no ☐
- Meat, fish or poultry every day yes ☐ no ☐

0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes ☐.☐

L Consumes two or more servings of fruit or vegetables per day?
0 = no 1 = yes ☐

M How much fluid (water, juice, coffee, tea, milk...) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups ☐.☐

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem ☐

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem ☐

P In comparison with other people of the same age, how does the patient consider his / her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better ☐.☐

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC greater than 22 ☐.☐

R Calf circumference (CC) in cm
0 = CC less than 31
1 = CC 31 or greater ☐

Assessment (max. 16 points) ☐☐.☐
Screening score ☐☐.☐
Total Assessment (max. 30 points) ☐☐.☐

Malnutrition Indicator Score

24 to 30 points	☐	Normal nutritional status
17 to 23.5 points	☐	At risk of malnutrition
Less than 17 points	☐	Malnourished

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For more information: www.mna-elderly.com

FIGURE 12.2 The mini-nutritional assessment [7] (Reproduced with permission from © Nestlé and ® société des Produits Nestlé)

used as a unique nutritional screening test that contains a combination of objective and subjective measures (including BMI, weight loss, dietary history, etc), since it is able to detect nutritional problems in elderly patients infected with HIV [8].

The SGA [9] does not use laboratory criteria but relies heavily on functional capacity and physical signs of malnutrition. Specifically, it combines information from the history of the patient (such as weight loss, dietary intake, functional status), physical examination (such as muscle and fat distribution, edema), and the clinician's judgement. As such, it is highly dependent on the screening clinician for accuracy. On initial validation, its ability to predict infection as a complication of malnutrition was compared to six other independent methods (including albumin and anthropometric measures). The SGA was found to be 82 % sensitive and 72 % specific, and out-performed all six methods [10]. Published literature demonstrates SGA as a valid tool for the nutritional diagnosis of hospitalized clinical and surgical patients, and point to a potential superiority of nutritional screening methods in the early detection of malnutrition [11].

12.3 Intervention

An effective intervention to prevent or cure malnutrition should be multifactorial, since malnutrition is considered a geriatric syndrome.

Mc Dermott et al. [12] described a customized nutrition intervention that produces changes in energy intake, maintenance of appropriate protein intake, and the reversal of unintentional weight loss over 5 to 15 months. Sustained improvements occurred across a socioeconomically diverse population, despite persistent disease- and medication-associated side effects. The intervention format consisted of weekly, customized, one-on-one counseling in a supportive environment, and an oral caloric supplement (480 kcal/day, with 30 g protein). Sessions were conducted with a nutritionist using an interactive, action-oriented learning approach. A strong nutrition

foundation that incorporated the concept of 'food as medicine' was accompanied by effective behavioral strategies, with problem solving and crisis management techniques defined by and specific to the needs of the patient. Twelve weekly sessions allowed sufficient time to introduce concepts, refine coping skills, and address a diverse array of issues bearing on nutritional status. Changing lifestyle habits requires commitment and substantial investment on the part of the individual and the medical team. By understanding the relationship of food choices, weight stability, and health status, the intervention fostered patient empowerment and provided an effective, sustainable treatment strategy for the reversal of HIV-associated wasting, regardless of adjunct therapies [12].

The effects of HIV infection on nutritional status and needs vary according to the stage of the disease. WHO recommendations are different for the two distinct phases of HIV infection: asymptomatic and symptomatic [13].

During the asymptomatic phase, energy requirements increase by 10 % over the level of energy intake recommended for healthy, non-HIV-infected people of the same age, sex, and physical activity level. For example, the energy requirements of a 35-year-old moderately active male with asymptomatic HIV are 3,152 kcal/day, compared with 2,865 kcal/day for a 35-year-old moderately active male who is not infected with HIV (2865 + 287 [10 %] = 3,152). The energy requirements of a 35-year-old moderately active female with asymptomatic HIV are 2,360 kcal/day, compared with 2,145 kcal/day for a 35-year-old moderately active female who is not infected with HIV (2,145 + 215 [10 %] = 2,360).

During the symptomatic phase, energy requirements of patients with HIV increase by 20–30 % over the level of energy intake recommended for healthy, non-HIV-infected people of the same age, sex, and physical activity level. The range in the requirement reflects the fact that people with more frequent and more severe symptoms need up to 30 % more energy. For example, the energy requirement of a 35-year-old moderately active male with HIV is 3,438 kcal/day (2,865 + 573 [20 %] = 3,438) during the early symptomatic

stage and 3,734 kcal/day (2,865 + 860 [30 %] = 3,725) during the late symptomatic stage. The energy requirement of a 35-year-old moderately active female with HIV is 3,438 kcal/day (2,145 + 429 [20 %] = 2,574) during the early symptomatic stage and 3,734 kcal/day (2,145 + 644 [30 %] = 2,789) during the late symptomatic stage.

Data are not sufficient to recommend an increase in protein or micronutrients for patients with HIV. The WHO recommends for people to get 12–15 % of energy from protein and take micronutrients at one recommended daily allowance (RDA). However, people with pre-existing or concurrent protein and micronutrient deficiencies may require higher intake. These recommendations are for all patients with HIV, whether they are taking antiretroviral (ARV) drugs or not [13].

Many years ago the Nutritional Pyramid was created to visually describe the nutritional needs of the general population. Since the introduction of the Nutritional Pyramid new models have been built; in 2007 the Modified MyPyramid for Older Adults was created by the Cardiovascular Nutrition Laboratory at Tufts University. The revised pyramid emphasized exercise, getting enough fluids, taking vitamins, and eating frozen or canned fruits and vegetables along with fresh. In 2011 the MyPlate for Older Adults (Fig. 12.3) was introduced and corresponds to the government's food group symbol, MyPlate.

12.4 Sarcopenic Obesity

The aging process is characterized by changes in the body composition, with a decrease in muscle mass and an increase in fat mass, particularly visceral fat. Sarcopenia is an important cause of frailty, disability, and loss of independence in older adults. Concurrently, there is an increased prevalence of obesity in the aging population. These age-related changes in the body composition determine a combination of excess weight and reduced muscle mass or strength, recently defined as sarcopenic obesity [15, 16].

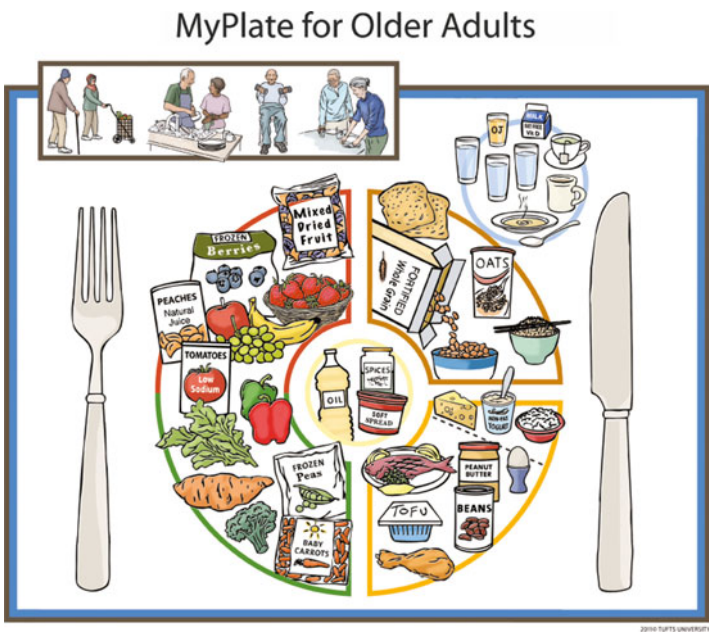

FIGURE 12.3 MyPlate for older adults places emphasis on the importance of physical exercise, foods that contain high levels of vitamins and minerals, a variety of fruits and vegetables, enriched or fortified whole grains, a range of protein, alternatives to salt (such as herbs and spices), and oils low in *trans* fat [14] (Reproduced with permission from © 2011 Tufts University)

Due to the loss of skeletal muscle, the basal metabolic rate declines [17]. There is also a decreased intensity and duration of physical activity as well as decreased postprandial energy expenditure due to a decreased fat oxidation, accounting for the decreased energy expenditure seen with aging.

Medical complications of obesity in the elderly are mainly concentrated around the metabolic syndrome (glucose intolerance, hypertension, dyslipidaemia, and cardiovascular disease). Elderly people who are obese are also likely to have functional limitations because of decreased muscle mass and strength, increase in joint dysfunction, disabilities of activities

of daily living, frailty, chronic pain, and impaired quality of life [18]. A study by Baumgartner [19] observed that men and women older than 60 years of age with sarcopenic obesity showed, respectively, an 8- and 11-fold higher risk of having three or more physical disabilities. More importantly, it was observed that the association with functional status impairment was stronger for sarcopenic obesity than for either obesity or sarcopenia alone. Obesity is an important risk for frailty either through increased levels of inflammatory markers or through sarcopenia. Sarcopenic obesity appears to be linked with the upregulation of tumor necrosis factor (TNF)-α, interleukin (IL)-6, leptin, and myostatin and the downregulation of adiponectin and IL-15 [20]. Multiple combined exercise and mild calorie restriction markedly attenuate the symptoms of sarcopenic obesity.

12.5 Physical Exercise

Regular exercise and physical activity are important to the physical and mental health of almost everyone, including older adults. Being physically active can help with staying independent, and regular physical activity over long periods of time can produce long-term health benefits. Hence, health experts say that older adults should be active every day to maintain their health. In addition, regular exercise and physical activity can reduce the risk of developing some diseases and disabilities that occur as people grow older. In some cases, exercise is an effective treatment for many chronic conditions. For example, studies show that people with arthritis, heart disease, or diabetes benefit from regular exercise. Exercise also helps people with high blood pressure, balance problems, or difficulty walking. In the United States, the Go4Life® is the National Institute on Aging's national campaign to help older people fit exercise and physical activity into daily life (www.nia.nih.gov/Go4Life). Patients and physicians can find practical guidelines to start or improve physical exercise [21]. Patients with HIV represent a specific

population that could benefit more than other groups from physical exercise, since exercise prevents sarcopenia and enhances muscle power, improves the outcomes in frequently associated non–HIV diseases (eg, diabetes and hypertension), and reduces chronic inflammation.

Many datasets indicate that individuals with HIV maintain a low level of chronic immune activation and inflammation even in the presence of effective antiretroviral therapy (ART). This residual immune activation seems to be associated with accelerated or accentuated aging and an increased incidence of non-AIDS-defining illnesses. Several published studies suggest that physical activity is a beneficial non-pharmacological intervention to reduce chronic inflammation: increasing evidence suggests that the introduction of regular physical exercise in the clinical management of individuals with HIV may have a significant positive impact in reducing some of the long-term complications of both infection and ART (Fig. 12.4) [22].

In older individuals with HIV infection, as well as those with other chronic diseases, it is important to improve muscle mass to preserve muscle tropism and functional status. Sakkas et al. [23] conducted a randomized double-blind, placebo-controlled study to evaluate the effect of creatine supplementation on muscle size, strength, and function in individuals with HIV. All subjects underwent three times-weekly supervised resistance exercise beginning at week 2 until week 14, while continuing on the assigned study medication. It was found that after 14 weeks, 1-repetition maximum strength increased in all muscle groups and that the magnitude of this increase was not greater with creatine supplementation. It was concluded that progressive resistance training is important in preventing and reversing muscle weakness and the administration of creatine may have a beneficial aesthetic impact but does not improve physical functional capacity. This last result is important, since in elderly patients with HIV renal function is not always preserved, so the use of protein surplus is not safe. Nevertheless, research has indicated that increased dietary protein intake (up to 1.6 g protein/kg/day) may enhance the hypertrophic response

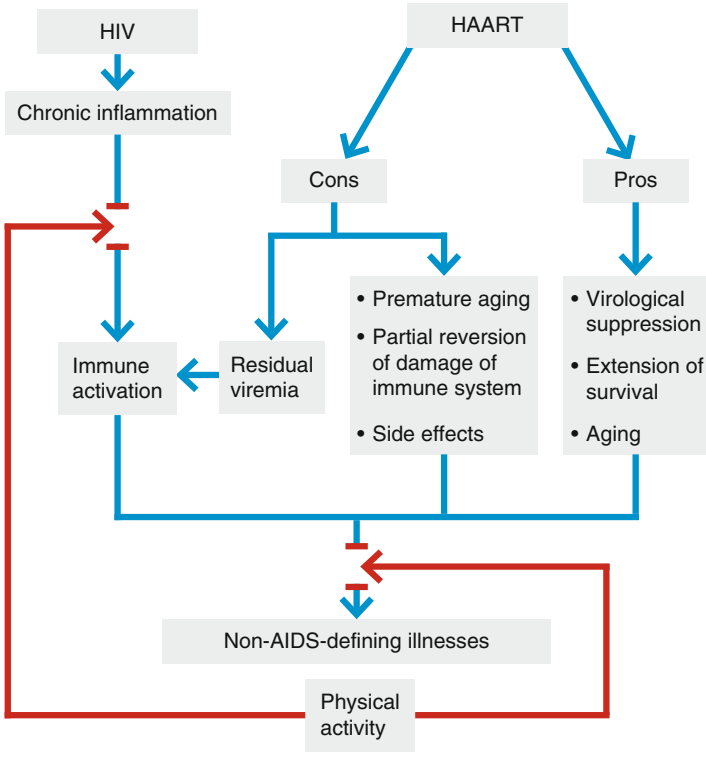

FIGURE 12.4 Potential benefits of physical activity on chronic HIV infection. *HAART* highly active antiretroviral therapy (Adapted from d'Ettorre et al. [22])

to resistance exercise [24]. It has also been demonstrated that in very old men and women the use of a protein-calorie supplement was associated with greater strength and muscle mass gains than the use of placebo.

Moderate physical activity can improve many immune parameters, reduce the risk of acute infection, and combat metabolic abnormalities. As people with HIV age, alternative therapies such as nutrition and physical activity may complement medical management.

12.5.1 Resistance Training

Despite the significant benefits associated with highly active antiretroviral therapy (HAART), HIV infection and its therapy have been associated with the development of several metabolic complications: increased central adiposity, peripheral lipoatrophy, peripheral insulin resistance, diabetes, dyslipidemia and hypertriglyceridemia, osteoporosis, and osteopenia [25]. These complications may predispose patients to a premature risk of metabolic and cardiovascular diseases. In addition, aging predisposes patients to the same biological effects, and one could expect that aging could act as a potentiator of those HIV infection- and HAART-related alterations. On the other hand, resistance training improves many of those alterations [26].

Souza et al. [27] demonstrated that a substantial strength increase related to all exercises in every patient who completed the proposed training program (progressive resistance exercises) regardless of their age, gender, baseline HIV infection stage, or the presence of any HIV/AIDS-associated morbidity.

A regular resistance exercise program has been shown to improve lean body mass and strength in patients with HIV; such exercise reduces serum triglyceride levels with and without anabolic therapies. Promoting regular fitness may minimize muscle wasting and normalize blood lipids without requiring the addition of pharmacologic therapies to patients already receiving complicated medical regimens.

12.5.2 Aerobic Training

In a recent Cochrane review, O'Brien et al. [28] demonstrated that aerobic exercise appeared to be safe and beneficial for adults living with HIV, nevertheless, these findings were limited by small sample sizes and large withdrawal rates considered in the meta-analysis.

In a study by Smith et al. [29] it was concluded that 12 weeks supervised aerobic exercise training safely decreases fatigue, weight, BMI, subcutaneous fat, and abdominal girth (central fat) in individuals with HIV-1 infection, while it did not appear to have an effect on dyspnea.

12.5.3 Mixed Protocols

Yahiaoui et al. [30] demonstrated good results with a combined protocol consisting of a mix of endurance and resistance exercises three times per week for at least 6 weeks to improve cardiovascular, metabolic, and muscle function. Stretching, before and after exercising, is also recommended to prevent injuries [30].

12.6 Conclusion

Extensive literature demonstrates that nutrition and physical exercise are probably the most important non-pharmacologic strategies to improve outcomes in older patients with HIV. The multifactorial nature of malnutrition and the complexity of interventions underline the importance of the multidimensional geriatric evaluation and effective interdisciplinary team work.

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Chapter 13
Smoking Cessation in Patients with HIV

Marta Calvo and Esteban Martínez

Key Points

- The number of life years lost due to tobacco consumption is twice as much as the number lost due to human immunodeficiency virus (HIV).
- People living with HIV or AIDS (PLWHA) who are smokers usually perceive that HIV infection impacts more on their health than other factors (including smoking) and are sensitive to the advice of HIV physicians.
- HIV physicians, nurses, and counselors should systematically encourage patients who smoke to quit.
- Several drugs have shown significant efficacy for nicotine dependence, but they should be prescribed in combination with health advice.

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- Checking for possible drug interactions with antiretroviral therapy (ART) is mandatory before prescribing anti-smoking drugs.

Tobacco consumption contributes critically to the development of serious non-AIDS-defining events [1]. The impact smoking has on developing cancer outweighs that of HIV-related factors [2], not only due to its high prevalence amongst PLWHA, but also due to its cumulative and synergistic role on a range of pathogenic pathways shared by tobacco smoking and HIV infection [3]. At present, we know that the number of life years lost due to tobacco consumption is twice as many as the number lost due to HIV [4].

PLWHA who also smoke register at the contemplation or preparation stage on the Prochaska's motivation to quit scale at twice the rate of uninfected smokers [5], consume an average of 20 cigarettes per day, and experience a medium level of nicotine dependence [6] (according to the Fagerström Test for Nicotine Dependence). Two to three out of four PLWHA smokers have tried to quit smoking [7], most of them immediately after HIV diagnosis [8]. Their expected success rate without anti-smoking therapy is low (3–8 %) [9]. The success rate of different anti-smoking strategies among PLWHA ranges from 10 to 42 % [10, 11].

Several benefits have been documented from quitting smoking among PWLHA. In the SMART study [12], an abstinence from smoking for longer than 1 year in patients with HIV led to less risk of suffering AIDS-defining illnesses, cardiovascular disease (CVD) events, and non-AIDS-defining malignancies. In the D:A:D cohort [13], the incidence of CVD decreased more than 50 % after 3 years of abstinence. Likewise, the incidence of pneumonia in PLWHA decreased after smoking cessation [14].

There are two clear predictors of success in smoking cessation in PLWHA [6, 15]: the degree of nicotine dependence and the level of motivation. Other predictors, such as being employed and scoring lower for mood disturbance may also be important [16].

Table 13.1 European AIDS Clinical Society (EACS) guidelines 7.0, PART III, smoking cessation [18]

Brief unambiguous statement about the need to stop smoking.
If person is not contemplating, try to motivate and emphasize positive short-term aspects (more money for better things, better taste for food, better skin, less dyspnea), and long-term benefits (prevention of chronic obstructive pulmonary disease, ischemic heart disease, stroke, lung cancer).
If person is contemplating, try to fix a stop date, establish reward system.
Use nicotine substitution (patch, chewing gum, spray), varenicline, or bupropion during weaning phase if necessary. Note: both varenicline and bupropion may cause central nervous system side effects including suicide; bupropion may interact with protease inhibitors and non-nucleoside reverse transcriptase inhibitors.
Consider referring person to specialized stop smoking clinics.
Anticipate relapses, explain and consider them as part of the weaning process to final nicotine abstinence.

PLWHA who are smokers have usually perceived that HIV infection impacts more on their health than other factors (including smoking) [17] and therefore they are sensitive to the advice given by HIV physicians. Consequently, and given the chronic nature of nicotine dependence, HIV physicians, nurses, and counselors should systematically encourage patients who smoke to quit. This recommendation is highlighted by the European AIDS Clinical Society (EACS) guidelines for smoking cessation (Table 13.1) and has been increasingly incorporated into clinical care [18].

Training HIV physicians in counseling techniques for their patients with HIV who smoke within the Swiss HIV Cohort showed significant benefits in terms of tobacco consumption reduction, higher rates of abstinence, and fewer relapses [11].

Motivational interventions have shown to be more effective in reaching significant decreases in tobacco consumption

than simple health advice [19]. Intensive health counseling designed for PLWHA was twice as effective in terms of smoking abstinence as standard basic health advice [20]. The analysis of three types of counseling strategies combined with nicotine replacement therapy (NRT) among PLWHA (ie, personalized advice, on-line support, and self-help material) disclosed no significant differences in overall 1-year abstinence, showing rates of up to 29 % [16]. Other types of interventions, such as counselling delivered by cell phones, may also be effective among PLWHA [21].

An intensive approach such as that provided in specialized units for smoking cessation [22], including intensive psychological interventions [10], has proved to achieve the highest abstinence rates after 6 months of quitting (up to 62 %) amongst patients in the general population.

Hypnotherapy and acupuncture have been reported to be more effective than standard counseling among patients suffering depression in the general population [23, 24].

Some PLWHA are characterized by particular conditions that may hamper smoking cessation (eg, polypharmacy, symptomatic distress and stigma, concerns about body changes, drug abuse, and poly-tobacco use) [10]. Therefore, it appears relevant to perform clinical studies specifically addressed for this population in which adapted treatment strategies could be especially indicated [25].

13.1 Pharmacological Strategies to Treat Nicotine Dependence

A number of drugs have shown significant efficacy for nicotine dependence. First-choice drugs include:

- NRT formulations (patch, chewing gum, and spray);
- bupropion (BUP), a selective inhibitor of the reuptake of norepinephrine, dopamine, and nicotinic antagonist;
- varenicline (VAR), a partial agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes.

Other drugs such as nortriptyline (a tricyclic antidepressant) or clonidine (an α-adrenergic blocker) are used as second-choice options due to their side effects. Prior to any quit attempt, one of the first-line drugs should be prescribed in combination with health advice. This combination has shown greater efficacy and cost-effectiveness than each individual measure [26].

The efficacy of first-line drugs in HIV-positive smokers has been confirmed in several studies [10]. In one of these studies [27], the efficacy of a combination counseling-NRT regimen was compared with a control group without any intervention. After 1 year of follow-up, the abstinence rate was 38 % in the treated group, compared to 7 % in the untreated group. Four strokes and one death secondary to CVD occurred in the control group, despite a lower at baseline Framingham score, compared to the treated group. The combination of medical advice, specialized counseling, and drug therapy achieved an abstinence rate of 25 % and a significant decrease in estimated CVD risk after 1 year, irrespective of the type of drug used (NRT, BUP, or VAR) [6].

A PLWHA group who initiated treatment with BUP showed an abstinence rate of 38 % after 1 year and no relevant interactions between ART and BUP [28].

In a multicenter study assessing the efficacy and safety of VAR in a HIV-positive group, the abstinence rate reached 42 % (a success rate similar to those reported in the general population). Most common adverse events included nausea (33 %), abnormal dreams (31 %), emotional lability (19 %), and insomnia (19 %) [29].

In a recent study, 213 patients with HIV were randomized to receive VAR or placebo. The abstinence rate in the VAR group was significantly higher (18 % vs 7.2 %) at 48 weeks. Drug-related effects (such as psychiatric and gastrointestinal side effects) appeared in a similar proportion in both study groups [30].

Before prescribing BUP or VAR, it is necessary to consider eventual contraindications and interactions. Prescription of VAR requires assessment of the psychiatric status of the patient before and during treatment, since VAR-related neuropsychiatric effects include depression and suicidal ideation. Table 13.2 shows interactions of clinical interest.

Table 13.2 Contraindications and drug interactions of bupropion and varenicline in the context of HIV infection

	Contraindications	Drug interactions
BUP	Epilepsy (current or in the past). Conditions able to lower the seizure threshold: • Intracranial lesions (eg, toxoplasmosis, tuberculosis, cryptococcosis, primary brain lymphoma). • Withdrawal of alcohol or benzodiazepine. • Concomitant MAOIs (eg, up to 30 % of PLWHA suffer depression). • Serious hepatic disease (eg, HCV or HBV coinfected PLWHA).	• Any PI when boosted with ritonavir could potentially decrease BUP concentrations as it is metabolized by CYP2B6 and ritonavir induces CYP2B6 (eg, LPV AUC ↓57 %). • EFV decreases AUC of BUP up to 55 %, which warrants an increased BUP dosage according to clinical response and its maximal dosage recommended. Similar interaction is predicted between NVP and BUP, thus monitoring clinical response is advised. No significant interactions between BUP and DTG, ETR, or RIL have been identified. • Little potential of interaction between BUP and ELV/COB. In the unlikely case, it would lead to an increased BUP concentration warranting monitoring for clinical response. • No significant interactions with NRTIs or with MRV [31]. • Linezolid may behave as a reversible MAOI, thus in combination with BUP, there is higher risk of serotonin syndrome, a major adverse event. This combination is contraindicated. • Risk of seizures is associated with CIP and BUP, therefore this combination must be avoided. • RIF may reduce BUP concentration. Monitoring clinical efficacy of BUP is recommended [32].

VAR	Depression or psychiatric disorders at baseline are not contraindications but high caution is recommended when depressive symptoms appear.	No significant interaction with any antiretroviral drug has been so far identified.

Note: no significant interaction between BUP or VAR is predictable or has been observed with any of the following compounds: cotrimoxazol, fluconazol, aciclovir, isoniazid, or ceftriaxon [32]

AUC area under the curve, *BUP* bupropion, *CIP* ciprofloxacin, *DTG* dolutegravir, *EFV* efavirenz, *ELV/COB* elvitegravir/cobicistat, *ETR* etravirine, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *LPV* lopinavir, *MAOIs* monoamine oxidase inhibitors, *MRV* maraviroc, *NRTIs* Nucleotide/nucleoside reverse transcriptase inhibitors, *NVP* nevirapine, *PLWHA* people living with HIV or AIDS, *RIF* rifampicin, *RIL* rilpivirine, *VAR* varenicline

Prevention of relapse in PLWHA treated with BUP or VAR and re-treatment with pharmacotherapy for relapses occurring soon after quitting should be considered [25].

There is no scientific literature available on the effects of battery-driven inhalers named by the WHO as electronic nicotine delivery systems (ENDS) on patient health. Theoretically, ENDS reduce the amount of carcinogens that usual tobacco smokers inhale as a result of combustion, but other elements contained in ENDS may also induce cytotoxic effects. Other reasons for skepticism about the potential benefits of ENDS include paradoxical hindering of tobacco smoking cessation, inhalation of propylene glycol, unexpectedly high plasma nicotine levels, and inadequate information about ENDS contents or their chemical environmental contamination [33].

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Chapter 14
Self-management

Giovanni Guaraldi and Ana Rita Silva

Key Points

- The WHO defines chronic disease as a long-lasting condition, with a fluctuating course, that can be controlled but not cured.
- Human immunodeficiency virus (HIV) can be considered a chronic disease that may benefit from self-management programs.
- Self-rated successful aging in adults with HIV is related to better physical and mental health functioning, increased happiness, greater resilience, optimism, personal mastery, better attitudes toward aging, fewer depressive symptoms, and less perceived stress.
- Empowerment of the patient requires changing the roles in the traditional medical system. Promoting

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patient empowerment and self-management includes addressing complex issues, such as medication adherence and prevention of transmission.
- Clinicians can help improve patient well-being by focusing on interventions that enhance positive psychological traits.

The WHO defines a chronic disease as a prolonged condition, with a fluctuating course, that is rarely cured completely [1–3]. Thus, chronic disease management also aims to control the disease symptoms and prevent functional impairment [4] through interventions that include managing physical symptoms, improving independence, and increasing quality of life [5, 6]. Patients dealing with multiple chronic conditions face multiple challenges in managing their health, including poor coordination of medical care, managing multiple medications (polypharmacy), and increased risk of aggravating one condition by symptoms or treatment of another.

When thinking and planning for living well with increasing age, the patient needs to recognize and accept these changes and adapt their lifestyle to this new stage. This leads to a shift from the 'traditional' disease treatment paradigm to patients assuming an active and informed role in managing the multivaried physical, psychological, and social aspects of health.

Self-management is considered by the WHO as the best practice to improve clinical care and outcomes for chronic conditions [7]. Patient empowerment means changing the roles in the traditional medical system [8]. In this setting, patients are responsible for talking their medications properly, changing their behavior to improve symptoms or slow disease progression, interpreting and reporting symptoms correctly, adjusting to new social and economic circumstances, coping with emotional consequences, participating in treatment decisions, and preventing transmission of contagious diseases [9].

Several studies have shown that self-management programs are associated with reduced morbidity, lower number of visits to acute medical services, and improvement in organ

Table 14.1 The JUSTRI Wellness Checklist [12]

Wellness Checklist
Daily
1. Could I exercise more today?
2. Have I bought the right food?
3. Should I drink less alcohol today?
4. Am I doing the right things to help me sleep properly?
5. Am I doing something new today?
6. Am I keeping my brain active?
Weekly
1. Am I doing something nice with a friend this week?
2. What is my weight and is it changing?
3. Have I planned an active weekend?
4. Am I eating healthily?
Every 3–4 months
1. Do I feel well or unwell?
2. Have I had my check up at the clinic?
3. What are my blood results?
4. Have I stopped smoking?
5. Are my finances in order?
6. How has my mood been recently?
7. What are my plans for the next few months?

function and quality of life [10, 11]. Consequently, these programs not only improve patient outcomes, but also reduce the burden on health care system resources and capacities.

An interesting example of patient empowerment is the Wellness Checklist (Table 14.1), suggested by JUSTRI (a not-for-profit

organization established to work with allies in the health care and patient communities), as a periodical self-assessment to increase awareness of aging and promote successful aging.

HIV has been recognized as a chronic illness since the advent of antiretroviral therapy (ART) [13–16], but it is still not universally included in chronic illness lists and discussions [3, 17, 18].

For the older patient with HIV, a recognized potential barrier to effective disease management is the increased complexity in managing ART regimens, as well as the often numerous medications necessary for concurrent chronic conditions. Successful aging in this population is a therefore complex and dynamic concept (Fig. 14.1).

Baltes and Baltes [19] used eight factors in defining successful aging: length of life, biological health, cognitive efficiency, mental health, social competence, productivity, personal control, and life satisfaction. Vance et al. [20] explored how HIV, medication side effects, and lifestyle choices interfere with these pathways to successful aging (Fig. 14.2).

Successful cognitive aging (SCA) involves a dynamic interaction between numerous factors, and has been defined as aging without subjective or objective cognitive impairment, depressive symptoms, or functional impairment [21, 22]. Among people aging with HIV, SCA is associated with better mental quality of life [21], medication adherence, and capacity to interact with health professionals [22]. Cognitive decline (which may be inevitable in the aging population) is associated negatively with SCA. Decline in cognitive function is partially related to poor medication adherence [23]. This can lead to antiretroviral (ARV) resistance and result in poor physical health, which in turn can lead to decreased survival. Poor medication adherence can also lead to a lapse in HIV control, with compromised control of central nervous system HIV effects resulting in further cognitive decline. Worsening of cognitive efficiency can also result in decreased social competence, productivity, and mental health (which interact to further exacerbate these declines). As a consequence, people living with HIV (PLWH) feel powerless and live with uncertainty [24]. The feeling of powerlessness further contributes to ill health [25].

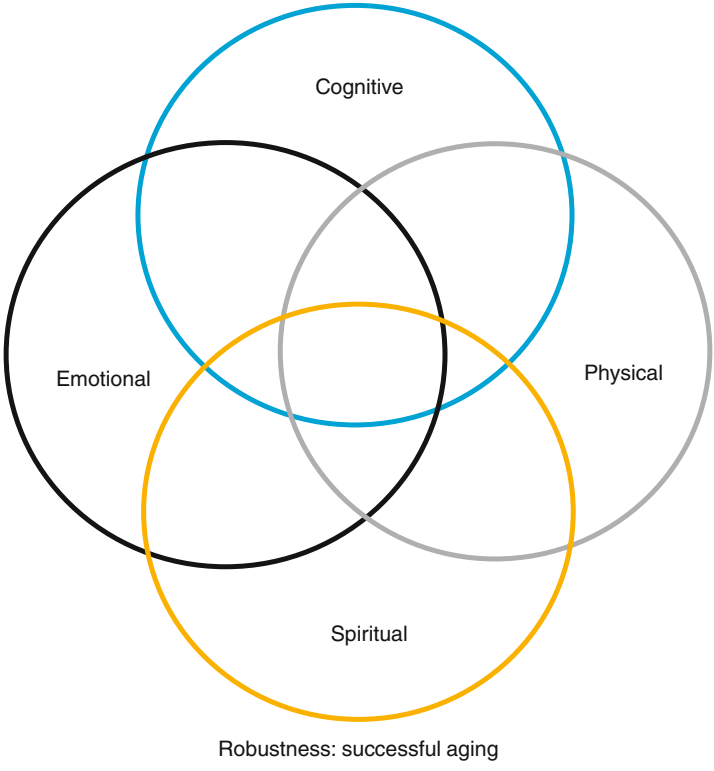

FIGURE 14.1 The multiple interactions of life domains associated with successful aging

Promoting patient empowerment and self-management for PLWH includes addressing complex issues, such as medication adherence and prevention of HIV transmission.

One of the major differences between HIV and other chronic diseases is not medical, but related to sociocultural factors. Challenges in the HIV-positive population include coping with stigma, shame, discrimination, social rejection, and strategically managing disclosure [26]. There is an increased complexity of self-management, with the need to address individual, family, and health care system factors [27].

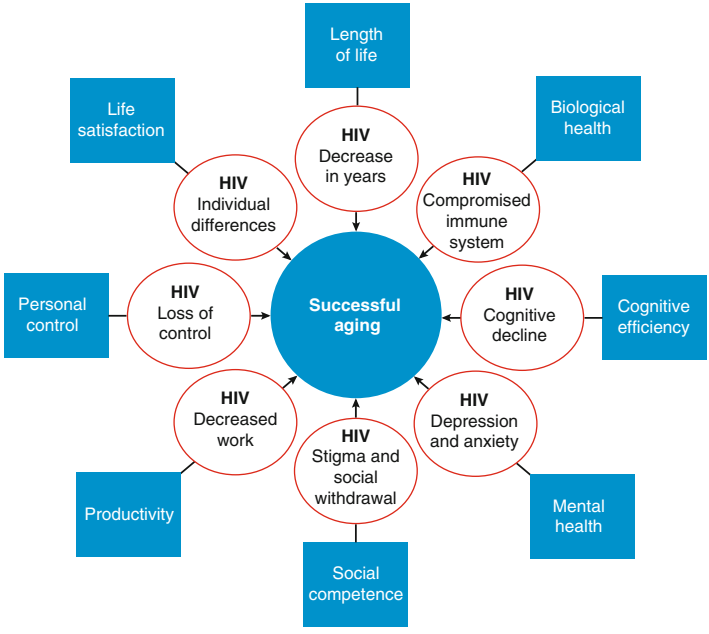

FIGURE 14.2 Factors of and obstacles to successful aging with HIV (Adapted from Vance et al. [20])

Numerous intervention studies have demonstrated success in changing health-related behaviors of PLWH, including:

- improving adherence to medication regimens [28];
- reducing risk of transmission [29, 30];
- increasing self-care (ie, nutrition, exercise, sleep);
- emotional regulation [31];
- social support [31];
- reducing substance use [32];
- improving quality of life [33];
- reducing social stigma [34]; and
- increasing immune system functioning [35].

There are several standardized assessments, which include questions about self-management knowledge, skills,

confidence, supports, and barriers [36–38], enabling the health care team to further support patient self-management efforts. These assessments should be tailored to include the diverse personal and cultural contexts [39–43] across different health care settings. Non-invasive, non-medical cognitive interventions are favored, especially since they are inexpensive and do not place medication demands on a clinical population for which there is already a heavy pharmaceutical burden [44, 45].

Recognizing HIV as a chronic disease has implications for medical care and delivery, public policy, and the well-being of PLWH. This is particularly important in low-resource settings with limited health care workforce, supplies, and facilities, where an integrative self-management framework allows PLWH to receive care without putting an additional strain on resources. However, at present there remains a significant gap in translating proven chronic disease research findings and interventions into practice. Better dissemination and implementation of evidence-based interventions is critical to truly benefit children, families, adults, and communities facing disease management challenges [46].

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