

Workshop on HIV Infection and Aging: What Is Known and Future Research Directions

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Highly active antiretroviral treatment has resulted in dramatically increased life expectancy among patients with HIV infection who are now aging while receiving treatment and are at risk of developing chronic diseases associated with advanced age. Similarities between aging and the courses of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome suggest that HIV infection compresses the aging process, perhaps accelerating comorbidities and frailty. In a workshop organized by the Association of Specialty Professors, the Infectious Diseases Society of America, the HIV Medical Association, the National Institute on Aging, and the National Institute on Allergy and Infectious Diseases, researchers in infectious diseases, geriatrics, immunology, and gerontology met to review what is known about HIV infection and aging, to identify research gaps, and to suggest high priority topics for future research. Answers to the questions posed are likely to help prioritize and balance strategies to slow the progression of HIV infection, to address comorbidities and drug toxicity, and to enhance understanding about both HIV infection and aging.

The success of HAART has dramatically enhanced life expectancy among HIV-infected individuals [1]; by 2015, more than one-half of all HIV-infected individuals in the United States will be aged >50 years (figure 1). Age influences the course of HIV infection. The likelihood of seroconversion to HIV decreases with age [3] (figure 2), but mean CD4⁺ T cell counts decrease with age [4], and the time from HIV infection to the development of AIDS is shorter [5–10]. Even in the HAART era, the time from acquisition of HIV infection to AIDS or death is shorter in older patients [11]. Aging individuals with HIV infection experience HIV infection as a complex chronic disease, often with multiple comorbidities [12]. Accelerated

age-related conditions, including cirrhosis, cardiovascular disease (CVD), renal disease, and cancer, have been noted. Many HIV-infected individuals are people of color and, thus, are at high risk for the adverse effects of hypertension and diabetes.

EFFECTS OF HIV INFECTION AND AGING ON IMMUNITY

Both aging and HIV infection are associated with profound changes in immunity and host defense, with marked similarities and some differences (table 1). The T cell compartment, particularly in the gastrointestinal tract, is most disrupted by HIV infection and aging, but nearly all aspects of immunity are affected.

B cells and antibody production. With age or HIV infection, the number of memory B cells may vary, but the naive B cell repertoire decreases. Increased baseline activation of resting naive B cells in HIV-infected patients persists, even during HAART [13–15], but the effect of age on these cells is unknown [16].

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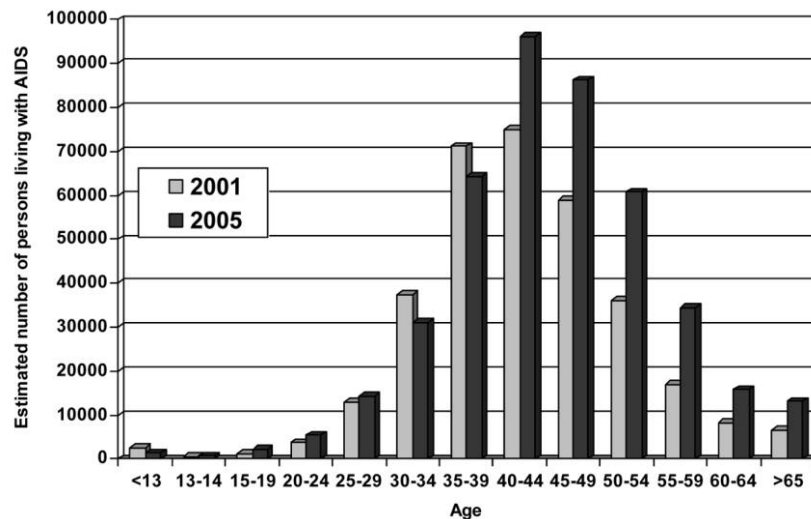


Figure 1. Age distribution (in years) of HIV-infected individuals living in the United States (reproduced with permission from Luther et al. [2]).

Clinical evidence of B cell dysfunction is apparent in both HIV-infected and older adults, as manifested by increased risk of serious infection (pneumonia), particularly infection due to *Streptococcus pneumoniae*. The ability of polysaccharide antigens (e.g., pneumococcal polysaccharide vaccine) to activate B cells, to generate effective antibody responses, and to provide clinical protection is also impaired in both groups [17–19].

The V_H gene repertoire that defines the range of antibody responses is similar among uninfected, HIV-infected, and older adults [20, 21]. Both older and HIV-infected individuals exhibit elevations in total serum levels of IgG and, sometimes, IgM, although to a lesser degree in uninfected older individuals. The dominant type of HIV-specific antibody-secreting cells express IgG [22]; the HIV-specific IgA level is very low, and IgA is specific for gp160, but the function of IgA antibodies is not known. Total IgA serum levels are higher only in patients with AIDS [23].

T cell function. The thymus involutes both with age [24] and with HIV infection [25]. The number of naive T cells ($CD4^+$ and $CD8^+$ T cells) decreases with age or HIV infection; HIV infection reduces levels to those typically found in an uninfected adult aged 20–30 years older than the HIV-infected patient [26]. With age or HIV infection, T cells become hyporesponsive, exhibiting decreased proliferative capacity and IL-2 production, altered receptor signaling, and altered cell surface markers, including the loss of CD28 expression [27]. The number of $CD8^+$ cytotoxic T lymphocytes (CTLs) increases in both young and old HIV-infected adults, but it decreases somewhat in uninfected aging adults [26]. Although the number of naive $CD8^+$ T cells decreases with age and HIV infection, the decrease in older HIV-infected adults is not statistically significant, compared with that in age-matched seronegative control subjects [26]. During chronic infection, repeated expansions of $CD8^+$

T cells lead to loss of CD27 and CD28 on T cells; moreover, the pattern of subsets defined by CD45RA and CD45RO changes in complex ways during both chronic infection and aging [26, 28]. Eventually, the cells reach replicative senescence [29–32], with short telomeres, very low telomerase activity, and production of high levels of proinflammatory cytokines. These cells work through bystander mechanisms to accelerate memory cell turnover and death [33] and to impede maturation and/or proliferation of naive T cells [34, 35]. High proportions of $CD8^+CD28^-$ CTLs predict early mortality [36, 37] and poor response to influenza vaccine [38–40] in uninfected elderly patients and faster progression to AIDS in HIV-infected patients [27], although causality has not been proven. Despite these similarities, it is not known whether the mechanisms that underlie replicative senescence in HIV infection and aging are similar [41, 42].

Mucosal immunity and gastrointestinal lymphoid tissues.

Mucosal host defenses are profoundly affected by HIV infection. Regardless of the route of infection, HIV replicates most intensely in gut-associated lymphoid tissue (GALT) [43], with rapid depletion of $CD4^+$ T cells in the GALT long before that in the peripheral blood. During chronic infection, $CD8^+$ CTL response in the gut is <5% of that seen in other lymphoid organs. The population of central memory cells in the gut predicts the rate of disease progression and AIDS events [44]. Reduced numbers of $CD4^+$ T cells in the GALT do not reconstitute after HAART as they do in the peripheral blood. The effects of aging on GALT are poorly understood [45], but clinical evidence of increased risk of infection due to organisms in which gastrointestinal immunity plays a vital role (e.g., *Clostridium difficile* colitis [46]) suggests that there are likely to be age-related changes in GALT as well.

Immunity to chronic viral infection. Both HIV infection

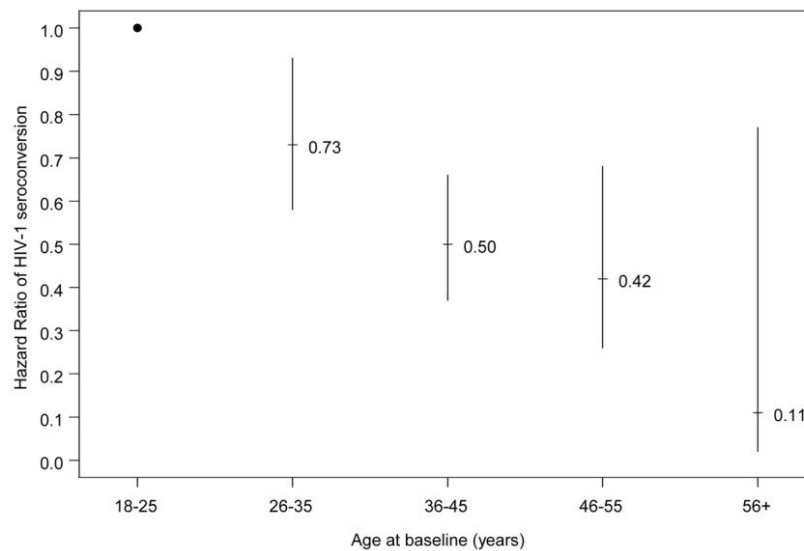


Figure 2. Risk for HIV seroconversion by age (based on data from Plankey et al. [3])

and aging are characterized by immune system changes related to chronic infections caused by viruses, such as cytomegalovirus (CMV) and varicella-zoster virus (VZV). Although HIV-infected patients mount a strong CD8⁺ T cell response to CMV, the response becomes “exhausted.” CMV-specific CD8⁺ T cells expand, and expression of other CMV-specific markers increases over time. A high percentage of CMV-specific CD8⁺ CTLs herald the onset of CMV-associated end-organ disease. Similarly, CMV-driven replicative senescence and immunologic changes in CTLs occur in older HIV-uninfected adults, but older people rarely develop end-organ CMV disease, perhaps because of differences in CMV-specific CD4⁺ T cell counts [28]. Although they reach a state of terminal differentiation after repeated stimulation, as judged by CD28 loss, CD4⁺ T cells do not expand to the same degree as do CD8⁺ T cells. The percentage of CD4⁺ T cells that are CD28⁻ rarely exceeds 10% in older individuals, whereas CD28⁻ T cells can represent >70% of CD8⁺ T cells during very advanced age [47].

The consequences of T cell senescence are profound, and loss of previous control over chronic viral infections is apparent. For example, the incidence and severity of VZV reactivation increase with age [48–60]. Cellular immunity to VZV, but not antibody immunity, decreases with age [61], but the specific correlates of protection and the mechanism(s) causing the decrease remain unclear. Clinical reactivation (shingles) and vaccination can restimulate cellular responses and maintain an immunity level needed to prevent VZV reactivation [58], but the degree of vaccine-induced stimulation decreases with age [61]. The incidence of VZV infection has not clearly been affected by HAART; some studies show a decrease [62, 63], whereas others do not [64]. Similarly, the association of age with zoster is less clear in HIV-infected persons, with some

data suggesting that the risk and incidence of zoster increase with age among HIV-infected patients [65]; other studies have found no age effect on incidence but an unexpectedly high risk of complications, particularly postherpetic neuralgia because of the age of the HIV-infected cohort [64, 66].

IMMUNOLOGIC RESPONSES TO HAART

The immunologic response to HAART predicts clinical outcomes [67–69]. Older patients are perhaps less likely than younger patients to experience failure of an initial HAART regimen, possibly because of better adherence [26], but they achieve less CD4⁺ T cell restoration [70–75]; in addition, data from the early HAART era suggest that the degree and speed of immune recovery is reduced in older patients [76–79]. Studies of virologic suppression and CD4⁺ T cell response to HAART in older patients, compared with younger patients, have yielded mixed results (table 2) [76–89], but these studies included few older adults, and none of the studies adjusted for HAART regimen [76]. When stratified by baseline viral load and CD4⁺ T cell count, better virologic responses were seen in older patients, compared with younger patients, but CD4⁺ T cell reconstitution lagged in the aged patients [76, 80]. Studies of the influence of age on HIV progression and mortality in the HAART era have also yielded mixed results (table 2). One study found no difference in 3-year survival between older and younger patients receiving HAART [78], but others found that, despite higher rates of virologic suppression, older patients had an increased risk of death and new opportunistic infections, compared with younger patients [76, 80, 90, 91].

T cell restoration also varies by body site [92–94]. Even after 3 years of fully suppressive HAART, T cell numbers in the gut

Table 1. Age- and HIV-associated changes of immune responses.

	Change in HIV-infected patients, compared with age-matched control subjects	Change in aging persons, compared with young adults
Adaptive immune response		
B cells		
Naive cell number	Normal to low	Normal to low
Memory cell number	Increased	Increased
Resting activation ^a	Increased	Normal
Cytokine production (unstimulated)	Increased	Normal
CD86 (costimulatory ligand) expression	Increased	Normal
Total IgG and IgA level	Polyclonal increase	Normal
V _H gene use (naive B cells)	Normal	Normal
V _H gene mutation frequency	Few data	Normal
Primary responses	Decreased	Decreased
Memory responses	Low to normal	Normal
T cells		
CD4 cells		
Naive cell number	Low	Low
Memory cell number	Low	Normal to high
Resting activation ^a	Highly increased	Increased
Cytokine production	Low ^b	Low to normal ^b
CD28 (costimulatory receptor) expression	Low	Low
CD8 cells		
Naive cell number	Low	Low
Memory cell number	Low	Normal to high
Resting activation ^a	Highly increased	Increased
Cytokine production	Low	Normal to high
CD28 (costimulatory receptor) expression	Very low	Very low
Senescent phenotype ^c	Very high	High

NOTE. This table compiles general principles; individual patients or studies vary. Clinical evidence of impaired B cell function in HIV-infected patients included high rates of bacterial pneumonia and/or sinus infections, poor polysaccharide vaccine responses, and high rates of B cell lymphomas; such evidence in aging persons included high rates of bacterial pneumonia, poor polysaccharide vaccine responses, and increased rates of B cell lymphomas and leukemias. Clinical evidence of impaired T cell function in HIV-infected patients included high rates of *Pneumocystis jirovecii* infection, herpes-zoster reactivation, cytomegalovirus reactivation and diseases, *Mycobacterium tuberculosis* infection, and poor immune surveillance for cancer; such evidence in aging persons included high rates of herpes-zoster reactivation, *M. tuberculosis* infection, and poor immune surveillance for cancer.

^a Defined by markers of low-level activation or constitutive gene expression without specific activation.

^b Cytokine production varies by condition and cytokine measured. IL-2, a critical cytokine for T cell expansion that is typically derived from CD4 T cells, is usually present at low levels in HIV-infected patients and persons of advanced age.

^c Senescent phenotype consists of low CD28 expression, shortened telomeres, replicative incompetence, and excessive production of inflammatory cytokines.

rebound to only 50% of the normal numbers [92]. Fibrosis driven by immune activation, microbial translocation, and other factors promoting cell death could prevent immune reconstitution [95, 96].

FUNCTIONAL AND METABOLIC COMPLICATIONS OF AGING WITH HIV INFECTION

Frailty. Conceptually, frailty is a state of decreased physiologic reserves that increases patient risk of morbidity and mortality.

No clear clinical definition of “frailty” in HIV-infected patients has been agreed on, but the frailty phenotype in the aged population has been defined as the presence of at least 3 of the following characteristics: exhaustion, slowed walking speed, low activity level, weakness, and weight loss [97]. By this definition, HIV infection appears to accelerate frailty [98]; even while receiving HAART, middle-aged, HIV-infected men show reductions in exercise capacity (figure 3), functional performance [100], physical activity, and grip strength. Frailty predicts poor health outcomes in uninfected individuals [97, 99–102]. Ex-

Table 2. Studies evaluating immunologic and virologic responses to HAART, stratified by age.

Study (year)	Study design	Duration of follow-up	No. of participants		Age group, years		CD4 cell count changes	Viral load after treatment	Survival, %		Adverse events, %	
			Total subjects	Control subjects	Patients	Control subjects			Patients	Control subjects		Patients
Manfredi et al. [77] (2000)	Case control	12 months	105	84	21	≤35	≥55	23.8% of patients and 4.8% of control subjects had a CD4 cell count increase of <200 cells/mm ³ or an increase of CD4 cell percentage of ≤10% vs. baseline	71.4% of patients and 73.8% of control subjects had a viral load ≤50 copies/mL	15.5	14.3	14.3
Viard et al. [78] (2001)	Cohort	24–36 months	1956	<33	≥45	For time to CD4 cell count increase >200 cells/mm ³ , the relative hazard ratio for patients was 0.8 (95% CI, 0.7–0.9)
Knobel et al. [81] (2001)	Cohort	24 months	699	671	28	≤40	≥60	Mean increase in CD4 cell count ± SD was 196 ± 100 cells/mm ³ for patients and 228 ± 145 cells/mm ³ for control subjects	67% of patients and 51% of control subjects had a viral load ≤50 copies/mL	35
Yamashita et al. [79] (2001)	Cohort	3–33 months	397	<45	≥45	Decreased CD4 response at 3 months in persons aged ≥45 years; no effect of age on CD4 cell count at 6 months	Viral load <400 copies/mL, no difference by age group
Manfredi et al. [88] (2003)	Cross-sectional	All received HAART for ≥1 year	57	44	13	55–65	>65	Decreased CD4 response in the group aged >65 years at 3, 6, 9, and 12 months	No difference by age in the reduction of HIV load
Perez et al. [89] (2003)	Cohort	3 years	770	535	253	<50	≥50	83 among untreated subjects and 89 among HAART-treated subjects (at 3 years) ^a	70 among untreated patients and 83 among HAART-treated patients (at 3 years) ^a	...
Tumbariello et al. [83] (2003)	Case control	Adjusted for HAART use	174	116	58	20–35	≥50	69% of patients and 79% of control subjects had an increase in CD4 cell count to >200 cells/mm ³ ; the P value was not statistically significant	79% of patients and 72% of control subjects had a viral load ≤50 copies/mL; the P value was not statistically significant
Goodkin et al. [87] (2004)	Cross-sectional	Adjusted for HAART use	135	63	72	18–39	≥50	...	50.00% of patients and 31.75% of control subjects had a viral load ≤50 copies/mL
Grabar et al. [80] (2004)	Cohort	Median, 32 months	3015	2614	401	<50	≥50	The mean increase in CD4 cell count was 14.1 cells/mm ³ per month for patients and 17.3 cells/mm ³ per month for control subjects	76.6% of patients and 70.6% of control subjects had a viral load ≤500 copies/mL	95.0 (at 1 year)	89.7 (at 1 year)	...
Tumbariello et al. [84] (2004)	Case control	6 months–6 years	596	476	120	20–35	>50	73% of patients and 79% of control subjects had an increase in CD4 cell count to >200 cells/mm ³	82% of patients and 75% of control subjects had a viral load ≤50 copies/mL
Kalayjian et al. [82] (2005)	Cohort	48 weeks	92	46	46	18–30	≥45	The mean increase in naive CD4 cell count was 48 cells/mm ³ for patients and 85 cells/mm ³ for control subjects

NOTE. Table adapted from Morgan et al. [65]

^a For untreated control subjects versus untreated patients, *P* < .01. For HAART-treated control subjects versus HAART-treated patients, the *P* value was not statistically significant.

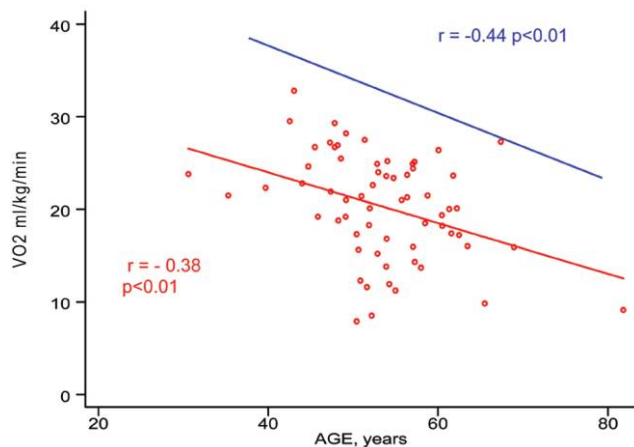


Figure 3. Reductions in aerobic capacity (VO_2) in HIV-infected patients aged 30–80 years (reproduced with permission from Oursler et al. [100]). Data on healthy subjects are shown in blue, and data on HIV-infected patients are shown in red.

exercise intervention to prevent or treat components of frailty has been studied among younger HIV-infected patients [103, 104] but not among older patients.

The mechanism(s) of frailty is unknown, but increases in the number of free radicals, mitochondrial dysfunction, and cytokines may activate inflammatory pathways, leading to frailty. Levels of C-reactive protein, D-dimer, factor VIII, fibrinogen, and IL-6 are elevated in older people with the frailty phenotype [105–107], and these increased levels are associated with frailty intermediates (e.g., wasting) in HIV-infected adults [108, 109]. Likewise, HIV infection and drug toxicities activate frailty-associated inflammatory pathways [110, 111].

Fat, metabolic changes, and CVD. HIV infection and specific antiretroviral drugs contribute differentially to fat and metabolic changes associated with increased risk of CVD. Both aging and HIV infection are associated with muscle loss, but the type of fat loss differs between aged and HIV-infected individuals [112–114]. Nucleoside reverse-transcriptase inhibitors, particularly stavudine, are associated with peripheral fat loss in HIV-infected patients [115]. There are mixed data regarding the relationship of age and lipotrophy in HIV-infected persons. All studies demonstrated an association of lipotrophy with duration of therapy and an increased risk of CVD, but some studies showed no association of lipotrophy with age [116, 117]; other studies demonstrated an association of lipotrophy with both age and duration of therapy [118].

During the pre-HAART era, HIV infection was associated with decreases in total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels, followed by increases in triglyceride levels as the infection progressed to AIDS [119]. However, HAART increases low-density lipoprotein cholesterol levels to preseroconversion levels [120],

and ritonavir-based regimens are associated with high triglyceride levels [121–123]. Lower quartiles of leg fat and higher quartiles of visceral adipose tissue are associated with higher triglyceride levels [124] in HIV-infected and uninfected men.

Unlike most infections, HIV infection is associated with less insulin resistance [125], but specific antiretroviral drugs have a direct adverse effect on glucose metabolism [123, 126]. Cumulative exposure to nucleoside reverse-transcriptase inhibitors is associated with insulin resistance and incident diabetes, regardless of the HAART regimen [127]. In one study, the incidence of diabetes or hyperglycemia was 4-fold higher in HIV-infected men than in uninfected men [128].

The prevalence of CVD increases with age among HIV-infected patients [64, 120]. Systolic blood pressure increases immediately after initiation of HAART and over time, but diastolic blood pressure increases with time in both HIV-infected patients and uninfected persons [129].

Kidney disease. Kidney function is low both in elderly patients and in HIV-infected patients, affecting drug clearance, risk of drug toxicity, and mortality associated with cardiovascular events. The incidence of kidney disease among HIV-infected individuals is increasing with age and type of HAART; both incidence increases are associated with increased risk of chronic renal insufficiency [130, 131], but the spectrum of kidney disease among older adults and the impact of comorbidities on kidney disease are poorly defined, particularly in HIV-infected patients. Accurate methods of measuring glomerular filtration rate have not been established for these populations [132].

Advanced HIV disease and hepatitis C virus (HCV) coinfection increase the risk of chronic kidney disease [133], and HCV coinfection, lower $CD4^+$ T cell count, drug toxicity, and liver disease have been associated with acute renal failure [134]. Survival of HIV-infected patients with end-stage renal disease has improved since the introduction of HAART, but the incidence of end-stage renal disease has not changed [135]. The true prevalence of end-stage renal disease among HIV-infected patients is not known, and few cohort studies have examined end-stage renal disease in aging patients.

Survival among elderly patients receiving dialysis is low, but delayed onset of dialysis contributes to even higher morbidity and mortality. Both dialysis and transplantation are options for HIV-infected patients [136], but it is not known whether transplantation will lead to a survival advantage among HIV-infected patients. It is also not known whether controlling blood pressure and glucose level will slow kidney disease in HIV-infected individuals, as it does in the general population.

Liver disease. Liver disease is second only to direct AIDS-related complications as a cause of death in HIV-infected patients (figure 4), with up to a 4-fold increase in hepatic morbidity and mortality among older patients, compared with

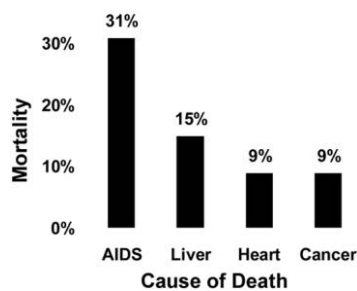


Figure 4. Causes of death in the Data Collection on Adverse Events in Anti-HIV Drugs study (based on data from Hooshyar et al. [137]).

young adults [138]. Liver volume, blood flow, hepatocyte numbers, drug metabolism, and hepatoregenerative capacity all decrease with age, whereas susceptibility to liver disease increases. The markers FIB4 and APRI have been validated to identify individuals at high risk of cirrhosis, and both are strongly associated with age [139]. Mortality associated with liver disease is high among HIV-infected patients, even in the HAART era [140, 137]. Coinfection with HIV increases the likelihood of cirrhosis in patients with hepatitis [64, 141]. HIV infection is not associated with hepatocellular cancer, but age is associated with this condition [142].

Across a variety of populations, 10%–20% of HIV-infected patients are also positive for hepatitis B surface antigen [143–147], and hepatitis B disease–associated mortality is increased among men with HIV and hepatitis B coinfection. Many treatments for HIV infection suppress—but do not eradicate—hepatitis B virus, and they are sometimes limited by adverse effects, such as drug resistance with lamivudine and kidney disease with tenofovir.

Immune dysfunction in HIV-HCV–coinfected patients differs from that associated with chronic HIV or HCV infection alone [148–150], and some comorbidities are more common among coinfecting individuals [148]. Age and kidney function influence the effectiveness and tolerability of HCV treatment [151], and age is an independent risk factor for anemia in patients treated for HCV infection [152]. The best approaches to management of viral hepatitis in older HIV-infected patients, as well as the effects of age and duration of HIV infection on the natural history of viral hepatitis, are not known. However, the combination of HAART-associated mitochondrial toxicity, HIV- and aging-associated increases in the prevalence of hepatic steatosis, and the high prevalence of other risk factors for liver disease progression in HIV-infected patients suggest that HIV and hepatitis coinfection is a critical area for investigation.

CONSIDERATIONS FOR CARE

The presence of multimorbidities, including medical, psychiatric, and substance use comorbidities, is more common in HIV-infected patients than in uninfected patients [64], but pri-

mary care guidelines rarely account for comorbid conditions [153–165]. Current strategies for prioritizing multimorbidities do not account for clinical dominance and concordance of conditions or for the presence or absence of symptoms [165–168].

The effects of age on absorption, distribution, and metabolism of drugs [169] are subtle and usually do not cause toxicity. However, renal function does decrease with age [170]; in an expanded-access study of tenofovir in France, Germany, and Italy, age was a risk factor for changes in serum creatinine level [171]. Response to HAART also might be affected by immune senescence (e.g., extrathymic sources of T cell maturation and expansion of cell numbers without replacement of the V_H repertoire) and by resistance mutations that alter the drug concentration needed for effective treatment [172].

Because HIV-infected patients age while receiving HAART and are at risk of age-associated comorbidities, they also have increased risk of toxicities and drug interactions. However, few drug trials involving aging populations have been performed, and nothing is known about drug interactions in aging HIV-infected patients. A consensus panel of experts found that most elderly patients receive at least 1 drug listed by the widely used Beers criteria as inappropriate for elderly patients with specific comorbidities [173]. Therefore, the panel has updated these criteria.

AVAILABLE COHORTS AND RESOURCES FOR RESEARCH IN AGING AND HIV INFECTION

A recently formed collaborative, the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [174], is a research consortium of 22 cohorts located in the United States and Canada, and it includes >60,000 HIV-infected patients. The NA-ACCORD population is heterogeneous, with a median age of 41 years; 18% of the patients are aged 50–59 years, but only 6% are aged >60 years. NA-ACCORD cohorts with the oldest populations are the Veterans Aging Cohort Study, the Multicenter AIDS Cohort Study, and the AIDS Link to the Intravenous Experience. The Veterans Aging Cohort Study was designed to evaluate issues of HIV infection specifically in older veterans.

RECOMMENDED QUESTIONS FOR FUTURE RESEARCH

Who are the appropriate control subjects for studying HIV infection and aging? The selected group should best fit the question being studied, to control for appropriate variables. For example, the Veterans Aging Cohort Study used a group of veterans with similar risk factors for HIV infection but who were not infected with HIV, to control for substance abuse, psychiatric illness, and other disorders that are common in veterans but not in the general population.

What are appropriate surrogate markers that predict outcomes in studies of HIV infection and aging? These markers might differ significantly from the general population.

To what extent do normal aging processes result from viral infection and immune activation? The similarities and differences in the processes underlying aging and chronic viral infection and how these processes influence each other remain to be determined, but connections among inflammation, immune activation, and disease should be explored. Furthermore, the role of chronic viral infections in immune senescence in the presence or absence of HIV infection should be a priority.

How do HIV infection and aging exacerbate each other? Future research should define frailty and other age-associated events with enough specificity to provide early, easily attainable indices to allow the identification of frailty precursors in HIV-infected patients.

What are the age-associated differences in immunologic and virologic response to HAART and toxicities resulting from HAART? Identifying particular antiretroviral drugs or treatment strategies that may be more effective in older HIV-infected individuals is essential.

What changes occur in the GALT with age? Results from studies of HIV infection can inform new studies about the aging immune system within the gut and may provide information on a particularly significant subject, to examine the interaction between aging and HIV infection.

What are the biologic characteristics underlying age-associated fibrosis in multiple organ systems? The triggers for fibrosis are not known, and it is not clear whether fibrosis observed during the course of HIV infection mirrors, overlaps with, or differs from that seen during aging.

What is the role of HIV- or HAART-associated mitochondrial toxicity in age-related illnesses in HIV-infected patients? There are marked effects on mitochondrial function that are likely to be related to fatigue, comorbidities, and the frailty phenotype; HAART, particularly with nucleoside reverse-transcriptase inhibitors, may exacerbate these mechanisms.

Should the HIV treatment paradigm change for older patients? It is not clear whether CD4⁺ T cell thresholds for management decisions should be different or whether correlates of immunologic success differ in older patients. Age-associated changes on pharmacokinetics and pharmacodynamics and how toxicities offset the benefit of the early initiation of HAART also should be explored. Although older adults consistently demonstrate greater adherence to HAART, compared with young adults, the occurrence of long-term adverse effects perhaps related to HAART (e.g., diabetes, atherosclerosis) suggests that the relative risks and benefits of starting HAART at an earlier threshold in older adults is an open question.

How can primary care screening and treatment guidelines be appropriately tailored to patients with HIV infection?

Future studies should explore whether choices among preventive measures (e.g., screening for cancer of the prostate or colon) can be informed by the likelihood of the patient living long enough to benefit from the intervention.

What can be learned regarding the management of complex chronic disease in patients aging with HIV infection, and how does this type of management differ from the management of single disease entities? HIV infection could serve as a model of accelerated aging in a multiply comorbid patient that can be broadly applicable to geriatrics and gerontology. Training of additional researchers in geriatrics will facilitate integration of geriatric principles into infectious diseases research [175].

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