HIV Infection and Aging

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Abstract

The median age of HIV-infected patients is increasing all over the world. Age has a significant impact on some aspects of HIV-infection when compared to younger patients. Diagnostic delay and late presentation are more frequent in older patients because some of the initial symptoms are masked by age and because older people are not considered to be a risk group for HIV infection. Despite the clinical, immunological, and virologic benefits of HAART, most studies suggest that older patients have a poorer immunological and clinical response to HAART than younger patients, despite a similar virologic response. Other problems include the frequent presence of comorbid conditions and medications that can affect the efficacy and safety of HAART as well as its pharmacokinetics and pharmacodynamics. Because no guidelines recommend a specific HAART regimen for older people, specific clinical trials and pharmacological studies should be designed to optimize HAART in these patients. **(AIDS Rev. 2010;12:218-30)**

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Key words

AIDS. HIV. Aging. Elderly. Frailty.

Introduction

Since HIV infection was first described almost 30 years ago, its epidemiology has undergone continuous change. One of the main changes today is the increasing number of older persons affected, a situation known as the "graying" of the epidemic. Although patients aged over 50 years are not considered older in most epidemiological studies, in the case of HIV-infected patients, the CDC consider them as such[1] since it was exceptional to find people of this age group in the early period of the epidemic[2].

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Data for this review were identified by searches of PubMed and references from relevant articles. No data restrictions were set in the search. We also reviewed abstracts from major meetings on HIV-1 infection during the last years. Search terms were, "aged", "aging", "antiretroviral therapy", "highly active", "comorbidity", "HIV infections", "immunosenescence", "immunity", and "pharmacokinetics". Only English and Spanish language articles were reviewed.

Epidemiology

The number of HIV infection cases diagnosed every year in the European Union is stabilizing, and has even fallen in recent years (Fig. 1). Thus, during the period 2004-2008 there was a 7.1% decrease in the number of cases of HIV infection[3]. In contrast, the number of cases diagnosed in individuals aged ≥ 50 years increased by 5% during the same period. As regards to AIDS cases, the total number of cases has fallen by 41.5%, while the number of patients aged ≥ 50 years has

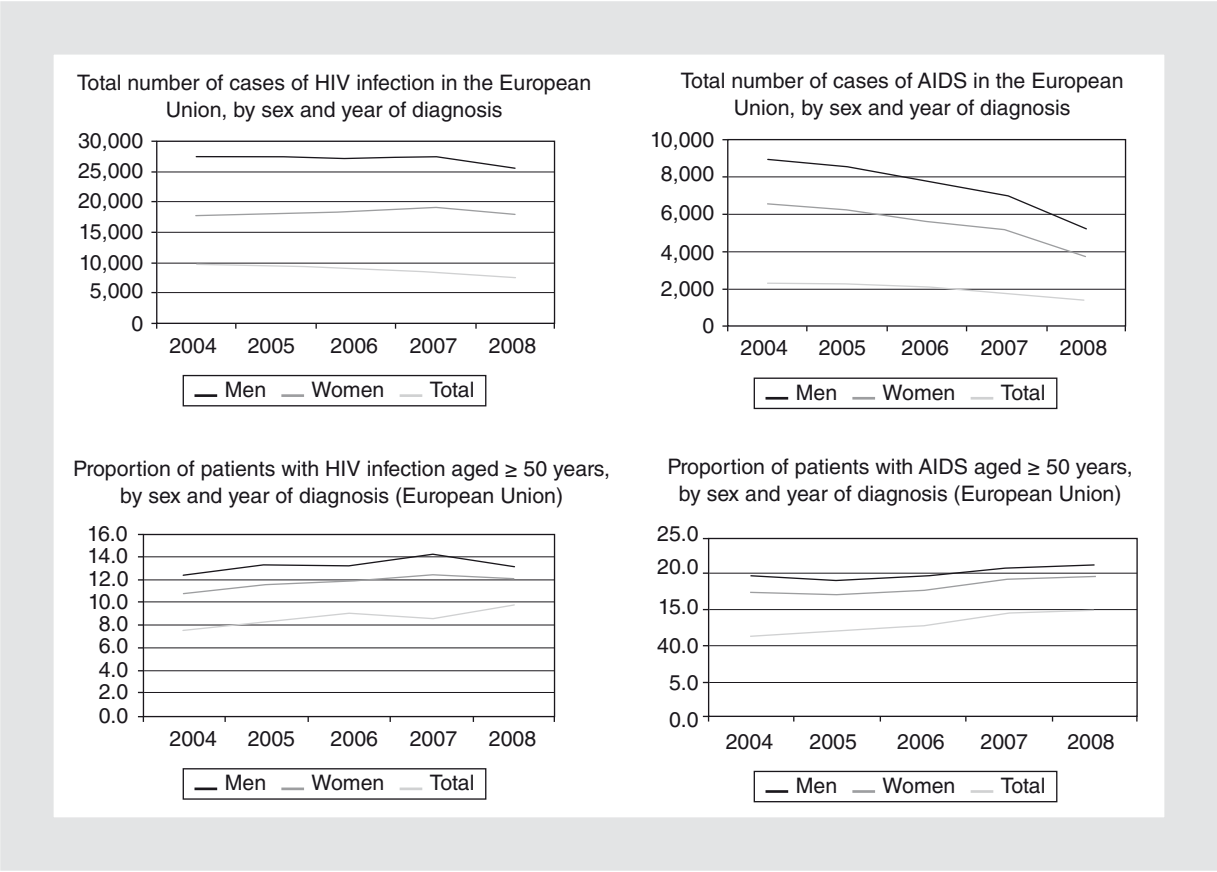

Figure 1. *Cases of HIV infection and AIDS in the European Union, by sex and year of diagnosis* (source: ECDC surveillance report 2008).

fallen by 34.1% between 2004 and 2008 (Fig. 2)[3]. Today, the aged HIV-infected patient is typically a man who has acquired the infection through sexual contact[4-15].

One of the main problems in this group is diagnostic delay[7,8,12,15-17], although the fact that CD4 counts decline with age may also contribute to "delayed" presentation and a faster progression of the disease.

In the CoRIS cohort[18], the proportion of late diagnoses was 53% in patients aged ≥ 50 years, 39% for those aged 31-50 years, and 21% for those aged < 31 years. There are several explanations for this delay. Some of the initial symptoms (dementia, weight loss) can go unnoticed, are masked by age, or can be attributed to other diseases[6,19-21]. Therefore, as is the case with syphilis, HIV has been referred to as the "great imitator"[22]. Older people do not consider themselves a risk group for HIV infection, despite many of them having an intense and satisfactory sex life[23]. They avoid using condoms as they consider them a method of contraception rather than a means of protection against disease[15]. Furthermore, their doctors do not usually ask questions aimed at ascertaining risk factors for HIV infection[16,24]. Finally, despite the usefulness of performing HIV tests as a preventive measure in patients aged ≥ 55 years[25], < 8% of cases of HIV infection in this group are diagnosed in this way[8].

Natural history and clinical manifestations of HIV/AIDS in elderly patients

The first studies on the risk of progression to AIDS during the period before HAART revealed that older patients, especially those with hemophilia, had a greater risk of progression to AIDS[26].

The higher risk of progression to AIDS among patients aged ≥ 50 years has again been confirmed during the HAART era[5,6,24,27]. This progression is more noticeable in patients with a CD4 lymphocyte count < 200 cells/μl[6] and in those whose disease is diagnosed later[12]. Gutiérrez, et al.[28] showed how, in patients with a sustained virologic response taking HAART, the faster progression to AIDS events or death among older patients persisted after adjusting for the CD4 lymphocyte count; therefore, age played an independent role in this progression.

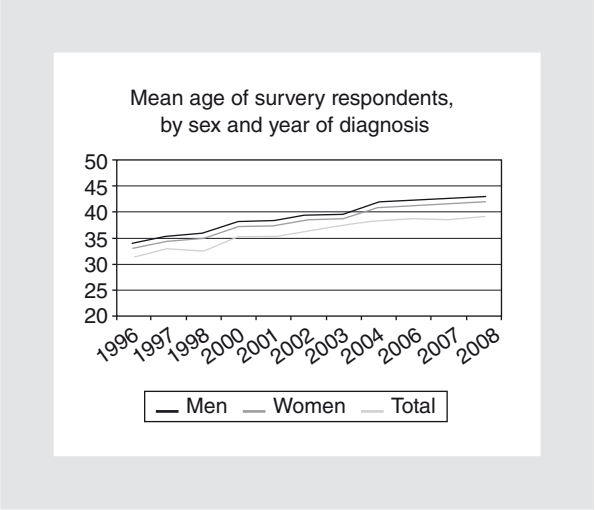

Figure 2. *Mean age of individuals attended for HIV/AIDS in the Spanish National Health System, by sex and year of diagnosis* (source: Hospital Survey 2008).

Although mortality has fallen in HIV-infected patients, it continues to be high in older patients[5,7,13,17]. This may be associated with several factors, such as age as a predictor of disease progression, diagnostic delay, comorbid conditions[9], or the presence of AIDS or non-AIDS events[9,29,30]. The same occurs with immune-virologic discordance, which is more common in patients ≥ 50 years who start HAART, and is associated with a significant increase in mortality, especially that due to non-AIDS events[30].

The pattern of opportunistic infections does not seem to differ from that of younger patients[10,31], although prognosis is poorer in patients aged ≥ 50 years[32]. In the last years, AIDS-defining events have rapidly declined in incidence[33,34]; however non-AIDS events (cardiovascular, renal, hepatic and malignancies) are increasing[33,35], mainly in elderly patients. In fact, non-AIDS events are nowadays the main cause of death[33,35].

Pathophysiology of immunosenescence

Although average life expectancy has increased in developed countries over the last 150 years, mortality due to infectious diseases continues to rise in old age. The incidence and prevalence of age-associated infectious and autoimmune diseases, together with the lack of response to vaccines, points to a deterioration of the immune system known as immunosenescence. This phenomenon affects both the innate and the adaptive immune response and is directly associated with increased morbidity and mortality in the elderly[36].

Chronological immunosenescence involves systemic inflammation characterized by a peripheral increase in proinflammatory cytokines. Although the clinical importance of this increase is not completely clear, it is believed to contribute to the development of osteoporosis, cognitive impairment, and arteriosclerosis[37]. HIV, its treatment, and ageing also contribute to these changes[38-40].

Another abnormality reported in both groups is the reduced capacity of B lymphocytes to secrete antibodies[41]. However, B lymphocyte defects are mainly secondary to T lymphocyte functional deficit.

The thymus is the main source of T lymphocytes. It is most active at birth and its activity begins to diminish after the first year of life. Thymic involution, together with the decrease in the subpopulation of naive T lymphocytes, was the first reported characteristic of immunosenescence. The T lymphocyte population is the cell population that is most affected by aging of the immune system; therefore, thymic atrophy was considered a key part of this process. However, at the peripheral level, the CD8 population is more compromised than the CD4 population, indicating that, in addition to the reduced contribution of the thymus, peripheral abnormalities play an important role. The aged CD8 population contains terminally differentiated clonal accumulations specific for viruses that cause persistent infections and maintain an aberrant activation of the immune system (mainly herpes viruses such as cytomegalovirus [CMV] or Epstein-Barr virus [EBV])[42].

These cell populations are resistant to apoptosis and present replicative senescence; that is, they have a high effector/cytolytic capacity but are incapable of proliferating after stimulation. Lymphocytes are characterized by their loss of the expression of co-stimulatory molecules (CD28), whereas the expression of inhibitory molecules (CD57) increases considerably[43]. In individuals aged over 60 years, CD57 is expressed in up to 70% of CD8 lymphocytes. These senescent lymphocytes have a long proliferative history, and their considerably shortened telomeres lead to genetic instability and activate cell programs that prevent proliferation[43]. The combination of diminished thymus function and accumulated clonal expansion can partly account for the lymphopenia observed in elderly people, where the CD4:CD8 ratio in peripheral blood decreases. People with the immune risk phenotype characterized by a CD4:CD8 ratio < 1 have a fourfold greater mortality rate at two years[44].

In HIV infection, aberrant activation of CD8 lymphocytes is correlated with the risk of progression[45], thus

Table 1. Abnormalities in T lymphocytes characteristic of chronological immunosenescence. Similarities with HIV infection and effect of HAART

Immunological abnormalities	AGE	HIV	HIV + HAART
Risk of infection	+	++	+
Thymic function	–	–	Restored*
Virgin T lymphocytes	– –	–	Normal*
$CD4^+/CD8^+$ ratio	–	– –	–
Senescent phenotype ($CD28^-/CD57^+$)	++	++	?
Activation	+	++	+
Shortened telomeres	+	+	?
Proliferative response	–	–	?
Accumulation of $CD57^+$ effector population	++		?
Accumulation of memory population with effector functions ($CD57^+$)		++	?

*Except in patients with low-level CD4 T cell repopulation (patients under HAART with virologic response but no immune reconstitution).

showing a close parallel between HIV infection and the peripheral mechanisms leading to immunosenescence. During HIV infection, CD4 lymphopenia, which is caused by viral lytic mechanisms, accelerates decompensation between peripheral populations. This is accompanied by asymptomatic reactivation of infections caused by CMV and EBV[46]. The additional effect of these viruses reactivated by HIV viral load could be the reason why replicative senescence (CD57) appears in HIV-infected patients 20-30 years earlier than usual. The function of $CD57^+$ cells (high effector capacity) is not clear in HIV infection[46]. While terminally differentiated effector cells ($T_{EM}RA$) accumulate in asymptomatic CMV infection (chronological immunosenescence), accumulated HIV-specific cells have a predominantly memory phenotype. These anomalous memory cells express CD57 and have an effector function. The current hypothesis is that HIV interferes in differentiation processes and effector memory cells may not be as effective at clearing virus as conventional effector cells (T_{EM} and $T_{EM}RA$). This would contribute to viral escape after primary HIV infection[47]. Therefore, it is necessary to determine the real effect of the immunosenescent phenotype on disease progression and mortality in HIV-infected patients.

Effective antiviral therapy improves several aspects of the immune system and assists both in thymic rebound and peripheral repopulation[48-50]. This condition is maintained although these patients present a good virologic response[51]. Table 1 shows the T lymphocyte abnormalities that are characteristic of chronological immunosenescence, as well as their similarities with HIV infection and the effect of HAART.

In order to optimize HAART in the future, it would be necessary to determine whether premature immunosenescence is partially restored after HAART. Also important are the age at which a patient initiates HAART, the impact of age on deterioration and immune reconstitution, and the long-term effect of the senescent phenotype on morbidity and mortality.

Immune, virologic, and clinical response to HAART

Despite the clinical, immunological, and virologic benefits of antiretroviral therapy, the exact effects of age remain unknown. For immune recovery, most studies suggest that older patients have a poorer response to HAART[4,6,10,52-59], although not all authors have observed this worse response[5,7,11-13,60-64]. The higher rate of diagnostic delay reported in older patients may be responsible for their poorer immune response[7,8,12,15,16,18].

Similarly, for the virologic response, some authors have found no differences with younger patients[7,11,12,14,53,55,57,60-62], whereas others have reported a better response in older patients[5,6,9,10,13,52,54,63] that could be due to a better adherence to HAART[13,61,65,66], despite older patients being more likely to receive other medications (e.g. antihypertensive agents, antidiabetic agents). Silverberg, et al.[13] attribute the better virologic control during the first year of HAART in patients ≥ 50 years to better adherence. However, Godkin, et al.[54] found that better virologic control was independent of the degree of adherence, regimen administered, and CDC stage.

One of the problems we face is the lack of specific study designs for this population. Study designs are heterogeneous and few include a sufficiently high number of patients (Table 2). In addition, the age cutoffs vary and some analyses do not take account of late diagnosis or comorbid conditions, which could lead to a worse immune response and poorer prognosis[10-12,21,63].

Comorbid conditions

Age acts as a risk factor for comorbid conditions and many of these conditions will be aggravated by HIV[7,9,13,31,62]. In a retrospective study of patients aged > 55 years, 89% presented at least one comorbid condition (mean, 2.0-2.5 conditions per person) and 81% were receiving medication not associated with

Table 2. Studies that evaluate the immunological and virologic response to antiretroviral therapy

Reference	Study type	Follow-up, months	Number of patients			Age groups	
			Total	Controls	Cases	Controls	Cases
Manfredi[57]	Case-control	12	105	84	21	≤ 35	≥ 55
Knobel[52]	Cohort	24	699	671	28	≤ 40	≥60
Viard[4]	Cohort	24-36	1,956	–	–	< 33	≥ 45
Yamashita[53]	Cohort	3-33	397	–	–	≤ 45	≥ 45
Grabar[6]	Cohort	Median 32	3,015	2,614	401	< 50	≥ 50
Goodkin[54]	Cross-sectional	Adjusted for ART	135	63	72	18-39	≥ 50
Kalayijan[55]	Cohort	48	92	46	46	18-30	≥ 45
Nogueras[10]	Cohort	66	455	419	36	13-40	≥ 50
Perez[5]	Cohort	36	770	535	253	<50	≥ 50
Tumbarello[62]	Case-control	–	174	116	58	20-35	≥ 50
Tumbarello[7]	Case-control	6-72	596	476	120	20-35	> 50
Cuzin[12]	Cohort	6	639	257	99	< 50	≥ 50
Navarro[63]	Cohort	48	5,004	4,511	493	< 50	≥ 50
Brañas[64]	Cohort	100	112	82	30	< 65	≥ 65
Manfredi[61]	Cross-sectional	≥ 12 months on ART	57	44	13	55-65	> 65
Silverberg[13]	Cohort	72	17,630	2,259*/ 1,834	997	18-39*/40-49	≥ 50

ART: antiretroviral therapy; VL: viral load; ns: non-significant.
*p < 0.05.
†p < 0.01.
‡p < 0.005.
§p < 0.001.

HIV[31]. In the series of Silverberg, et al.[13], 20% of patients aged 18-39 years had a Charlson comorbidity index of ≥ 1; this index increased significantly with age.

Cardiovascular disease

HIV-infected patients may experience a greater number of cardiovascular events[67-71]. Indeed, together with traditional cardiovascular risk factors (some of them higher in HIV patients), HIV has been also considered another risk factor[72] with a negative effect on vascular endothelium that may accelerate vascular aging. The vessels of HIV-infected patients are the same as those of non-HIV-infected individuals 25 years older[73]. Regarding HAART, its benefits outweigh the cardiovascular risk. In this sense HAART does not seem to influence another cardiovascular risk factor such as hypertension[74,75].

Status at diagnosis		Response to Antiretroviral Therapy	
Immunological (mean CD4+)	**Virologic (mean log)**	**Immunological**	**Virologic**
No difference	No difference	23.8% of patients and 4.8% of controls had an increase of ≤ 200 CD4+ or an increase of ≤ 10% over baseline	71.4% of patients and 73.8% of controls ≤ 50 copies/ml
No difference	No difference	Mean increase ± standard deviation of 196 ± 100 CD4+ in patients and 228 ± 145 in controls	67% of patients and 51% of controls ≤ 50 copies/ml
No difference	No difference	Greater increase in CD4+ in the youngest*	–
–	–	Reduced CD4+ response at 3 months in those aged ≥ 45, no effects at 6 months	No difference
193 (cases) 252 (controls)§	4.88 (cases) 4.56 (controls)§	At 6 months, in patients with RNA < 5 log, mean monthly increase in CD4+ per month from 15.5 in patients to 17.9 in controls§. This trend is maintained at > 5 log and after 6 months	At 6 months, 76.6% of patients and 70.6% of controls ≤ 500 copies/ml
–	–	–	50% of patients and 31.75% of controls ≤ 50 copies/ml
–	–	Mean increase in CD4+ of 48 in patients and 85 in controls*	66.7% of controls and 57.7% of cases ≤ 50 copies/ml
180.8 (cases) 366.9 (controls)§	4.5 (cases) 4.1 (controls)	373 ± 76 (cases) 484 ± 335 (controls)§	2.88 ± 1.82 (cases) 3.26 ± 1.59 (controls)*
289 (cases) 244 (controls)*	4.3 (cases) 4.5 (controls)*	No HAART 300 (cases) vs. 290 (controls) HAART 273 (cases) vs. 224 (controls)*	No HAART 4.4 (cases) vs. 4.4 (controls). On HAART 4.2 (cases) vs. 5.2 (controls)*
108 (cases) 187 (controls)‡	4.97 (cases) 4.88 (controls)	69% of cases and 79% of controls had an increase > 200 CD4+ (ns)	79% of cases and 72% of controls ≤ 50 copies/ml (ns)
107 (cases) 178 (controls)†	4.65 (cases) 4.74 (controls)	73% of cases 79% of controls had an increase > 200 CD4+	82% of cases and 75% of controls ≤ 50 copies/ml
189.4 (cases) 228.5 (controls)	4.52 (cases) 4.4 (controls)	+100 (cases) vs. +104 (controls)	66.7% of cases and 68.6% of controls ≤ 200 copies/ml
< 200 CD4+ in 54.2% of cases and 34.1% in controls§	VL > 500 in 94.8% of cases and in 91.9% of controls*	Mean increase in CD4+ of 254 in cases and 196 in controls (at 4 years)§	Better control in patients ≥ 50 years, sustained at 4 years§
186 (cases) 265.5 (controls)	5.13 (cases) 4.95 (controls)	Poorer recovery in cases	No difference
122.3 (cases) 143.2 (controls)	3.9 (cases) 4.2 (controls)	Reduced CD4+ response in patients ≥ 65 years at 3, 6, 9, and 12 months	No difference
No difference	RNA > 10,000 copies/ml 66.3%; 62.6% and 61.6% (cases)†	Greater increase in CD4+ in patients aged 18-39 years; persists at 3 years if adjustment for adherence†. No difference at 6 years.	Cases 18-39 years have 15% greater probability of < 500 copies/ml[2] (adjusted for adherence, ns)

Neurological diseases

Older HIV-infected individuals have a higher risk of dementia and other cognitive abnormalities[76]. In the CHARTER study[77], 45% of patients had some type of neurocognitive disorder despite taking HAART. These disorders were more common in patients with more comorbidities, in patients with AIDS, or in those with low $CD4^+$ lymphocyte counts. In the NeuroSigma study[78], which included patients > 60 years taking HAART with a low $CD4^+$ count at diagnosis (median, 113 cells/mm^3) but good immunological (median, 522 $CD4^+$) and virologic control (< 50 copies/ml) at the time of assessment, 51% had some type of neurocognitive disorder (mainly cortical involvement). Valcour, et al.[76] reported that patients aged > 50 years have double the risk of HIV-associated dementia than younger patients. One possible explanation could be that both age and HIV

infection reduce cerebral blood flow and this reduction is greater as age increases[79].

Older patients also have double the risk of depression than the general population[80]. During their lifetime, between 20-37% experience a depressive episode[81]. This problem may be associated to other factors such as alcoholism, which is prevalent[54,82] and underestimated[81].

Lastly, another manifestation in these patients is neuropathy[19,79,83]. In the CHARTER study[84], the incidence of polyneuropathy remained high in the HAART era (57%). Multivariate analysis revealed the main risk factor was age, followed by use of HAART, history of use of or dependence on opiates, and a low $CD4^+$ lymphocyte count.

Cancer

From the start of the epidemic, HIV-infected patients have had a greater risk of cancers such as Kaposi's sarcoma or non-Hodgkin's lymphoma[6]. HAART seems to prevent this type of tumor, but not AIDS-defining tumors[85-87]. At present, non-AIDS-related tumors are the most common cancer diseases in HIV-infected patients[87-89] and have the greatest mortality[87,89]. These include tumors related to HIV or associated coinfections (Hodgkin's lymphoma, anal cancer, liver cancer) or with smoking (lung, kidney, larynx)[90,91]. In the coming years, we may observe a notable increase in the incidence of cancer, possibly as a result of longer patient survival.

Bone disease

The prevalence of reduced bone mineral density increases with age and varies depending on the characteristics of the population studied, being particularly high in postmenopausal women. A large body of evidence indicates that HIV-infected patients have a higher prevalence of osteopenia and osteoporosis. In one cohort of infected patients in the HAART era, 62% experienced a decrease in bone density, 52% had osteopenia, and 10% had osteoporosis[92]; all these conditions increase the risk of fractures[93]. Although the exact causes are unknown, both HIV and HAART may play a role[93-95]. However, the impact of HIV and HAART may be lower than that of classic risk factors, such as advanced age, lifestyle (smoking, sedentary lifestyle), hormone imbalance (hypogonadism), vitamin disorders (vitamin D deficiency), or consumption of opiates, which contribute to greater prevalence[96,97]. As HIV-infected populations age, an increase in morbidity and mortality related with reduced bone mineral density is expected.

Other processes

Lung diseases

HIV-infected patients may have a greater prevalence of lung diseases since HIV infection has been found to be an independent risk factor for the development of chronic obstructive pulmonary disease[98]. In addition, the incidence of recurrent acute bronchitis[99] and emphysema[100] may be higher compared with uninfected persons.

Changes in body shape

Despite the improved prognosis of HIV infection, HAART sometimes leads to changes in body fat distribution (lipodystrophy)[52,101-103], which has a marked social stigma and makes this group of patients feel even more "frail".

Frailty

Frailty is a state of physiological exhaustion that increases the morbidity and mortality of HIV-infected patients[104]. Although there is no clinical definition to explain this term, it has been defined as three or more of the following characteristics: fatigue, slow ambulation, reduced activity, weakness, and weight loss[105]. This process is accelerated in HIV-infected patients, even in those taking HAART[104,106]. Although the pathogenesis of this condition is unknown, it is more common in patients with mitochondrial disease and increased levels of cytokine inflammation mediators, and in patients with high levels of C reactive protein, D-dimer, factor VIII, fibrinogen, and interleukin 6[107,108].

Ideal HAART in older patients

Although several factors theoretically associated with age can affect the metabolism, efficacy, and safety of HAART, there is no scientific evidence indicating that HAART should be tailored in older patients[109,110]. HAART is tailored in older patients on the basis of studies performed in similar scenarios irrespective of age. Data are then extrapolated to the situation of the older patient.

It is worth remembering that older patients are affected by a series of prevalent factors that have the potential to modify the pharmacokinetics and metabolism of drugs, including HAART. Special attention must be paid to the following: alteration of some of the physiological factors involved in bioavailability and metabolism

of antiretroviral drugs (absorption in the digestive tract, liver function, kidney function), alterations of body composition affecting drug distribution (transporter proteins, quantity and distribution of water in the body, lean mass, fat mass), interaction with other drugs used in older patients for comorbid conditions, and pharmacogenetic abnormalities with modified expression of enzymes involved in metabolism or of receptors. The pharmacodynamics of drugs, particularly HAART, may also be altered. Furthermore, the pathogenesis and replication dynamics of HIV may be different in some organs or reservoirs, for example in the central nervous system. In this case, the efficacy of HAART could vary depending on its pharmacokinetic and pharmacodynamic characteristics and could justify tailoring HAART according to patient age. However, the most important pharmacodynamic abnormalities in older patients depend on greater sensitivity to toxic effects, especially when the body's adaptive capacity is compromised[111]. Once again, alteration of some physiological functions (hemopoiesis, glomerular filtration, enzyme synthesis, mitochondrial activity), phenotypic changes, and interaction with other drugs can predispose to greater antiretroviral toxicity.

Intestinal absorption

With the exception of enfuvirtide, HAART is administered orally. Absorption depends on factors associated with the formulation (concentration, dispersion, solubility) and with the patient (gastric emptying and acidity, area of absorption, blood flow). In addition, particularly in the case of protease inhibitors (PI), absorption could be altered according to the activity of cytochrome P450 and P glycoprotein in intestinal cells[112].

To date, no studies have specifically analyzed the absorption of antiretroviral drugs with respect to age. For some drugs, absorption is easier; for example, didanosine in the context of lower gastric acidity[113] or drugs in the form of delayed-release tablets in the setting of lower intestinal motility and longer absorption time. However, most are absorbed more slowly due to slow gastric emptying, lower absorption surface area, and reduced blood flow. There are no studies that adequately define the changes in transporter proteins with respect to age and the role they play in absorption of antiretroviral drugs.

Distribution

Age is accompanied by a reduction in total body mass, muscle mass, total water content (15-20%), and interstitial volume (approximately 40%). However, the amount of adipose tissue increases by up to 35%[111,114]. These changes affect the volume of distribution of drugs in older patients. Lipophilic substances have a larger volume of distribution and a longer half-life; hydrophilic substances have a lower volume of distribution. These physiological changes may be even more evident in HIV-infected patients taking HAART. There are no pharmacokinetics studies on antiretroviral drugs in older patients that demonstrate the importance of these physical changes; however, we can assume that this factor will increase variability in these patients.

Total protein and albumin content decreases with age, whereas alpha-1-acid glycoprotein remains at normal levels or increases. The latter is already higher in HIV-infected patients than in the general population. Although age-related reduced albumin concentration is estimated to be 10-15%, its pharmacokinetic relevance is scarce. However, older patients are prone to other comorbid conditions that progress with significant hypoalbuminemia. In this context, there could be an increase in exposure to and toxicity of antiretroviral drugs that bind to albumin, as is the case of nonnucleoside reverse transcriptase inhibitors (NNRTI) or PI[115], especially if these are administered together with other drugs that alter protein binding[111].

Distribution of antiretroviral drugs in the central nervous system could be important for the prevention and treatment of HIV infection. Penetration of the central nervous system by these drugs varies widely with several factors, such as molecular size, protein binding, lipid solubility, degree of ionization, or the presence of transporters that limit penetration, such as P glycoprotein in the endothelial cells of brain capillaries[109]. Studies analyzing concentrations and penetration of the main antiretroviral drugs in cerebrospinal fluid show that bioavailability in the central nervous system is higher with drugs such as zidovudine, abacavir, and nevirapine[116]. Although PI generally have lower penetration associated with increased binding to proteins, distribution of amprenavir (fosamprenavir) and lopinavir seems to be better[116]. Boosting with ritonavir improves bioavailability in the central nervous system, probably because it inhibits the mechanisms by which other PI are expelled from the cell (as in intestinal absorption). Scores have been established to predict the pharmacodynamic effect of different antiretroviral regimens on neurocognitive activity and control of HIV levels in cerebrospinal fluid. Some of these scores show greater neurocognitive recovery with HAART regimens[116-118].

Liver metabolism

Aging is accompanied by a reduction in liver volume, blood flow, hepatocyte count, drug metabolism, and regenerative capacity[104]. It has been estimated that the liver's ability to metabolize diminishes by up to 30% in individuals aged ≥ 65 years[114,119]. In the absence of other functional abnormalities of the liver, this reduction does not usually involve significant changes in drug metabolism. Many antiretroviral drugs are metabolized by cytochrome P450, which is negatively associated with age[120]; therefore, these patients could be more sensitive to the toxicity of some antiretrovirals[20,121]. It is also important to remember that some drugs (nevirapine, efavirenz, lopinavir) are inducers of this cytochrome, with the result that they can reduce concentrations of agents such as macrolides and statins[109]. Glucuronidation, which is active even in situations of end-stage liver disease (< 20% of liver activity), does not vary with age[122].

Renal clearance

Renal flow decreases by approximately 1% per year after age 50[123]. Renal parenchymal mass also decreases with age, leading renal function (creatinine clearance) to fall below 50% in many older patients with no associated kidney disease. Furthermore, decreased muscle mass in older people and HIV-infected patients can lead us to underestimate renal functional abnormality evaluated according to plasma creatinine[124].

Nucleoside analogs (NRTI), with the exception of abacavir, are generally eliminated through the kidneys. In older patients with abnormal renal function, the drugs can accumulate and toxicity can increase if the dose is not adjusted. In contrast, elimination of PI, NNRTI, raltegravir, and maraviroc is not altered in patients with renal failure.

In pharmacodynamic terms, older patients are more sensitive to renal toxicity[13]. As tenofovir, atazanavir, and indinavir can cause kidney disease, close monitoring is recommended.

Drug-drug interactions

One of the problems faced by older HIV-infected patients is a greater presence of comorbid conditions. In the series of Shah, et al.[31], 81% of patients aged > 55 years were taking non-HIV-related medications. In addition to HAART, HIV-infected patients aged > 70 years also take a mean of three other drugs (range, 1-10)[103]. Therefore, given that many drugs can alter the pharmacokinetics and pharmacodynamics of antiretroviral drugs, concomitant medication must be closely monitored to avoid interactions[125,126].

Pharmacogenetics and pharmacokinetics

In older patients, variable phenotypic expression of certain genes related to drug metabolism can alter metabolism.

Few studies analyze the importance of pharmacokinetics in patients taking HAART. In addition, the scarce existing evidence is based on small, generally retrospective, non population-based or cross-sectional studies[109]. In a substudy of ACTG A5015[127] analyzing the effect of age on the metabolism of lopinavir, there was a significant correlation at week 24 between age and plasma concentrations of lopinavir (greater in older people), although these differences did not persist in subsequent weeks. However, in their study on healthy volunteers, Bertz, et al.[128] did not find a statistically significant association between age or sex and the area under the curve or the maximum concentration of lopinavir. Gibbons, et al.[129] used the menopause as a marker of age and did not find differences between pre-, peri-, and postmenopausal women and levels of lopinavir (mean concentration). However, these authors did observe differences when they analyzed levels of efavirenz (higher in postmenopausal women). The same authors stated that this could be because cytochrome CYP2B6 is affected by age, menopause, or both. In a pharmacokinetic study with atazanavir[130] and a population-based phase I-III study with maraviroc (summary of product characteristics), both of which evaluated the effect of age, there was no evidence of age-related pharmacokinetic differences. Rhee and Greenblatt[109] concluded that we do not know if there are age-related differences in the pharmacokinetics of antiretroviral drugs and that specific studies are necessary, considering that HIV-infected patients are increasingly older.

It is also important to remember that there is no correlation between the pharmacokinetics of some drugs (NRTI, integrase inhibitors, and CCR5 receptor inhibitors) and toxicity or activity. Therefore, future research lines and management of the HIV-infected patients should take into account the need for pharmacokinetic studies, especially population-based studies to analyze variability, usefulness of drug monitoring, and close monitoring of clinical safety and efficacy. Bioavailability and clinical efficacy in central nervous system manifestations could be of particular interest.

Tolerance and toxicity

Antiretroviral drugs induce a wide variety of adverse events with varying relevance and incidence. The reasons for this variability are not clear, although there is increasing evidence that pharmacokinetics and pharmacogenetic factors could play a key role[131,132].

Although some studies do not show age to be a risk factor for the development of HAART-related toxicity[57,60,61], others show that the adverse effects of HAART are more frequent in older people[7,12,13,52]. A study of the Swiss cohort showed that 47% of patients had a clinical adverse event and 27% had a laboratory abnormality that was attributable (probable or definite) to HAART[133]. Multivariate analysis showed that age affected the presence of polyneuropathy, lipodystrophy, hyperlipidemia, and hyperglycemia. However as older people tend to have some laboratory abnormalities (e.g. dyslipidemia), it is hard to rule out the possibility that its higher frequency could have been seen anyway, regardless of initiation of HAART. Thus, these may not all be attributable to the use of HAART. Silverberg, et al.[13] showed that patients > 50 years experience a greater percentage of laboratory adverse effects. Tumbarello, et al.[7] observed the frequency and distribution of HAART-related adverse effects to be similar in older patients and the youngest age groups, although in the oldest age groups, anemia and hyperglycemia were more common. During the HAART era, the incidence of cardiovascular, metabolic, or neurological abnormalities is also significantly greater in patients aged ≥ 50 years[11].

Some authors found that rates of HAART interruptions due to drug adverse events in older patients are similar to those seen in younger patients[7,11,12,55], although they usually occur earlier in older patients[12]. The main adverse events leading to treatment discontinuations in older patients are hematological disorders, followed by neuropsychiatric disorders[12].

These results lead us to question whether it is necessary to take specific measures to prevent drug adverse events in older patients. To date, no studies have shown that older patients should be treated differently from younger patients[109,110]. However, special caution should be taken when using antiretroviral regimens including zidovudine (because of the hematological abnormalities it can induce)[134], tenofovir (due to its effects on the kidneys)[135,136], and efavirenz or stavudine (due to their effects on the nervous system)[137,138].

It is important to remember that up to 89% of HIV-infected patients have comorbid conditions that require treatment with specific non-HIV-related therapy (inhaled $ß_2$ agonists, calcium antagonists, nonsteroidal anti-inflammatory drugs, proton pump inhibitors), with the subsequent risk of interactions[31,139]. However, the presence of comorbid conditions does not seem to be associated with greater HAART-related toxicity[31].

HIV screening in older people

In developed countries, there are two different approaches to HIV testing. In Europe, the test is offered to risk groups and individuals with symptoms indicating HIV infection[140]. In the USA, universal screening is recommended in populations where the prevalence is above a specific value[141,142]. If the objective is to diagnose not only the incident population, but also people who are already infected but who are not aware of a previous risk, population screening seems more appropriate.

In individuals aged > 50 years and < 65 years, the most efficient diagnostic strategy seems to be the one recommended by the American College of Physicians, namely, offer the test universally, except when prevalence is low, as demonstrated by testing 4,000 people[142]. In patients ≥ 65 years, there is no consensus or evidence that a universal diagnostic program can fulfill the minimum requirements of screening. As long as data on efficacy and safety of HAART in older patients do not indicate the contrary, it seems logical to offer testing to those who are clearly at risk or have clinical symptoms[140]. This mixed approach is applied in all age groups in the 2008 British guidelines[143].

Prevention campaigns are worthy of note. The vast majority are aimed at young people and adolescents. In addition, given that the educational level of older people is usually lower than that of younger people[15,18], much of the currently available information may not be adapted to their educational level.

Integrated care of the older HIV-infected patient

There are no specific recommendations on prevention of opportunistic and non-opportunistic infections in older patients; therefore, the same measures are advised as for other infected individuals[125,126,144]. With regard to vaccination, most patients have received the anti-pneumococcal vaccine and anti-influenza vaccine or have taken the tuberculin skin test. In contrast, older patients take *P. jiroveci* prophylaxis less than younger patients[32].

It is important to remember that older HIV-infected patients must undergo the same screening as the rest of the population[144]. Despite the risk of colon cancer, HIV-infected patients aged ≥ 50 years are less likely to undergo endoscopy than other patients of the same age[145]. The same is true for HIV-infected women who must undergo regular gynecological check-ups (cytology, mammogram)[31,146].

Lastly, one aspect that usually goes unnoticed is malnutrition and vitamin deficiency in some older patients; this can increase the risk of acquiring an infection[147].

Outlook for the future

Given that early diagnosis is fundamental for immune recovery, knowledge and diagnostic suspicion of HIV infection must be improved (active search for infection). Specific health education and prevention programs are essential in this collective. Similarly, as recommended Gebo, et al.[139], pharmacological studies are necessary to establish the optimal dose in this population and thus reduce possible adverse effects. In this line, specific clinical trials should be designed in order to know if a specific HAART regimen is necessary for these patients.

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