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Older HIV-infected patients—an underestimated population in northern Greece: epidemiology, risk of disease progression and death

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SUMMARY

Objectives: HIV prevalence among older people is on the increase. The aim of this study was to evaluate the epidemiological and clinical features at diagnosis and survival of older patients.

Methods: This was a retrospective analysis of the data of 558 newly diagnosed antiretroviral-naïve patients between January 1998 and December 2008. Patients were divided into two groups according to their age at diagnosis: ≥50 years ($n = 103$) and 18–49 years ($n = 455$).

Results: The most common risk factor for older patients was heterosexual contact ($p < 0.013$). Older patients were more likely to suffer from hypertension (33.0% vs. 5.1%, $p < 0.0005$), cardiovascular disease (20.4% vs. 2.9%, $p < 0.0005$), neurological disorders (11.7% vs. 5.5%, $p = 0.02$), renal dysfunction (12.6% vs. 5.3%, $p = 0.01$), and infections (66.0% vs. 49.7%, $p = 0.003$) than their younger counterparts, and to have more hospital admissions during follow-up (47.5% vs. 19.6%, $p < 0.0005$). Older patients had a shorter survival time ($p < 0.0005$). A statistically significant increase in CD4+ cell number through time was observed in both groups ($p < 0.0005$). Younger patients reached higher magnitudes of absolute numbers of CD4+ cells during follow-up ($p < 0.0005$) after the initiation of antiretroviral therapy. The total number of patients with clinical AIDS from baseline throughout the study period was also higher in the older age group (35.9% vs. 25.0%).

Conclusions: HIV-infected people aged ≥50 years differ in epidemiological and clinical features to younger HIV-infected people. The issue of increasing prevalence of HIV infection is a matter of concern due to existing comorbidities, which probably lead to higher mortality rates and faster progression to clinical AIDS.

1. Introduction

In 2005, individuals aged ≥50 years accounted for 15% of new HIV/AIDS diagnoses and 24% of people living with HIV/AIDS.[1] The increased prevalence among older patients has been attributed to prolonged survival of those on highly active antiretroviral therapy (HAART), as well as an increasing proportion of people in midlife and late adulthood newly infected with HIV.[2–6] Given the dynamic epidemiology of HIV and the fact that HIV is nowadays considered as a chronic disease, it is important to understand the impact of age in these patients.[7]

Much attention has been paid to the prevention of HIV infection in the young population, though studies from Western Europe have presented alarming data concerning new infections in more aged people.[8] In 2007, 12.9% of newly confirmed HIV cases in Western Europe were in the population over 50 years of age, higher than in Central or Eastern Europe.[7] In Greece, the total HIV population aged over 50 years is 15.1%, as stated in the annual report of the Hellenic Center for Disease Control and Prevention (HCDCP). However, the patient's misperception of their risk and the low suspicion for this disease by clinicians may account for the underreporting of HIV cases among older people.[9,10] Currently, no previous studies have assessed the demographic and clinical characteristics of the more aged HIV-infected population in Greece. By 2015, individuals aged 50 years or more will comprise nearly half of HIV/AIDS patients in the USA.[11]

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Data from several studies have revealed conflicting results with regard to the clinical responses to HAART and HIV outcomes.[12–16] Similarly multiple studies have shown differences in the rates of HIV-1 RNA suppression, rates of CD4 cell recovery, and the magnitude between the age groups.[12,17,18] Some studies have implied that survival is significantly lower in elderly people due to deficiencies of the immune system,[19,20] while others have attributed this poor outcome to frequent late presentation of the aged people.[21,22] However, there are some large studies that have shown older people to respond similarly to HAART as their younger counterparts.[23,24] Physiological transformations attributed to ageing, including reduced immunocompetence, the presence of comorbidities that may affect the disease progress and make its management more complicated, and interactions among HAART and other co-administered drugs, underline the need for the development of age-related treatment strategies.[25]

Further research is certainly required to form and validate age-specific HIV treatment guidelines.[26] Currently, a few updated publications have summarized all the relevant issues with regard to the aged and aging HIV population and recommend general treatment strategies for integrated management of these patients.[27,28] These articles emphasize the HIV-associated non-AIDS conditions (HANA) and their association with advancing age. Moreover, they underline the need for studies that will help predict which patients are at high risk for certain complications or might need specific interventions in a multi-morbidity context and the need to enhance collaboration between HIV specialists and geriatricians.[27,28] The aim of this study was to assess the prevalence rates of comorbid conditions, mortality, survival, and immunological and virological responses in the ageing population and moreover to detect differences in clinical and epidemiological features at baseline between older and younger HIV patients.

2. Materials and methods

2.1. Study setting and design

Subjects were enrolled at the AHEPA University Hospital in Thessaloniki, Greece. This hospital provides primary and specialty care to approximately 1000 HIV-infected patients in its Infectious Diseases Division (IDD). The IDD of AHEPA Hospital is the only one in northern Greece and serves the majority of HIV-seropositive patients in this geographical area. This study was a retrospective cohort study (1998–2008).

Eligible patients had to have entered HIV care at AHEPA IDD between January 1, 1998 and December 31, 2008, and had to have available CD4 cell counts and HIV-RNA levels, and to have attended for at least one visit each year during the follow-up. Other inclusion criteria were age $\geq$18 years, to be antiretroviral-naïve, and to have a complete clinical record during the follow-up. Five hundred fifty-eight patients from the IDD who met the inclusion criteria were included and analyzed in this study. Two age groups were defined according to the age at the time of diagnosis. The first group consisted of HIV-infected people aged 18–49 (n = 455), and the second group consisted of patients aged $\geq$50 years (n = 103) at diagnosis. The cut-off for the age (50 years) was decided on the basis of the data of previous HIV studies, since most significant immunological diversities take place at that time.[29–32]

2.2. Variables evaluated

Demographic parameters included gender, sex, race (Greek and non-Greek), age at diagnosis, HIV transmission risk factors (heterosexual contact, men who have sex with men (MSM), and injecting drug use (IDU)), number of hospitalizations after diagnosis, cause of hospitalization, HAART intake (initiation of HAART regimen) and time to HAART initiation from HIV diagnosis, HIV-defining morbidity (hairy leukoplakia, lymphadenopathy, oral thrush, thrombopenia, prolonged diarrhea, herpes zoster, etc.), HANA (progression to cirrhosis, cardiovascular disorders, lipoatrophy and dyslipidemia, blood disorders, infection-related cancers, peripheral neuropathy, dementia, osteoporosis, and nephropathy), AIDS-defining diseases, and data of death. Clinical variables also collected by review of inpatient and outpatient medical records were: other comorbid conditions, including hepatitis B and C, diabetes mellitus, hypertension, psychological dysfunctions, malignancy history, and all infections other than those that are HIV-defining.

The selection of HANAs and other comorbid conditions to be included in our analysis was based upon the most common interactions with HIV infection and the side effects of antiretroviral agents, according to the literature. We characterized cardiovascular disease as the presence of hypertension requiring medication, any existing ischemic cardiovascular disorder, or former angioplasty. Diabetes mellitus referred to hyperglycemia treated either with insulin or oral hypoglycemic drugs. Neurological dysfunctions included peripheral neuropathy, epilepsy, dementia, and residual clinical manifestations of a central nervous system attack (infection, tumors), while psychological impairment was defined as any condition requiring continuous treatment (psychotropics or antidepressants) or psychological support.

Blood disorders refer to thrombocytopenia (relative decrease of platelets in blood below 150×10^9 platelets per liter) or anemia (hemoglobin thresholds: women $<$12 g/dl, men $<$13 g/dl). Liver impairment/damage includes severe acute chronic viral hepatic infections (liver inflammation due to hepatitis B virus (HBV) or hepatitis C virus (HCV)) or dysmetabolic function (inflammation of the liver with concurrent fat accumulation in the liver in the context of alcoholic liver disease or metabolic syndrome) and renal damage/dysfunction refers to chronic renal insufficiency with creatinine clearance $\leq$80 ml/min or proteinuria (presence of an excess of serum protein in the urine, over 30 mg/dl) or nephrotic syndrome (proteinuria at least 3.5 g per day per 1.73 m^2 body surface area, hypoalbuminemia, hyperlipidemia, and edema) or any glomerular disease (inflammation of the glomeruli or small blood vessels in the kidneys, regardless of cause). Hyperlipidemia refers to high blood lipids (total cholesterol above 200 mg/dl, triglycerides above 150 mg/dl, or both). High blood uric acid (hyperuricemia) is considered as a blood level of uric acid above 6 mg/dl for women and 6.8 mg/dl for men.

Moreover, we evaluated the observed AIDS-free interval (time period from HIV diagnosis to AIDS progression) and mortality (time from HIV diagnosis to death). The 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults, as well as the HIV and Aging Consensus Project were used to specify HANAs and AIDS-associated morbidities. Clinical AIDS refers to the onset of an infection or a malignancy that defines the progression to the integrated AIDS syndrome, irrelevant of CD4 cell count. Laboratory screening included CD4 cell counts and HIV-1 RNA levels at entry and throughout the follow-up time. Changes in the CD4 cell count from baseline were measured at clinic visits every 6 months. CD4 counts at these intervals were estimated by averaging all CD4 cell counts recorded within 8 weeks before and after that time period. Late presentation or late diagnosis was considered as a CD4 cell count $<$350 cells/ml at baseline visit.

2.3. Statistical analysis

Age group comparisons were performed using the Chi-square test for qualitative data. However, if a cell of the table had few expected cases ($<$5), Fisher's exact test was used. All continuous

variables were compared by Student's *t*-test; the Mann–Whitney *U*-test was used when their distributions were not normal. Kaplan–Meier and log rank tests were used to estimate and to compare survival functions between the two groups.

The mean increase in CD4 cell count and the mean decrease in viral load over time were studied using a mixed analysis of variance (ANOVA) procedure. Two-way ANOVA from random factors was used, where age group and time were fixed factors, and patient was a random factor. This model studies the effect of age, time, and the interaction between age and time, on CD4 cell count or viral load. The independency and normality of residuals were verified.

The survival analysis included Kaplan–Meier estimates and Cox proportional hazards models using the AIDS-free interval and all-cause mortality as the outcomes of interest. The estimated time to an event was calculated as the time from diagnosis to each outcome. Each outcome was analyzed using multivariate Cox proportional hazard models using clinical and demographic variables believed to be potential confounders. All multivariate regressions were adjusted for all variables that were significantly different between age groups. All reported *p*-values are two-sided and all statistical analyses were carried out using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

3. Results

One hundred and three individuals ≥50 years old (18.4%) and 455 aged <50 years (81.6%) met the study criteria. The median ages of patients aged ≥50 years and <50 years were 56 years (interquartile range (IQR) 50.78) and 32 years (IQR 20.47), respectively. Older patients were more likely to have become infected through heterosexual contact (35.0% vs. 22.4%, $p < 0.01$) than younger patients (Table 1).

More than half of the patients during the study period received a late diagnosis, however late presentation did not differ significantly between the two groups (56.8% vs. 61.8%, $p < 0.565$). There was no statistical difference between groups ($p = 0.479$) with regard to clinical AIDS presentation at baseline.

The prevalence of infections was higher in older patients than in their younger controls at baseline evaluation. The rate of other comorbid conditions identified was higher in the older age group, with the exception of infection with HCV at baseline.

Older patients were more likely to suffer from certain comorbidities and HANA conditions at baseline, as seen in Table 2. They were more likely to suffer from hypertension (33% vs. 5.1%, $p < 0.0005$), cardiovascular disease (20.4% vs. 2.9%, $p < 0.0005$), neurological disorders (11.7% vs. 5.5%, $p = 0.02$), and renal dysfunction (12.6% vs. 5.3%, $p = 0.01$) than their younger counterparts.

Major events like death, clinical AIDS, hospital admission, AIDS-defining infection, HAART intake, and malignancy are described in Table 3. Concerning mortality during the follow-up, there was a significant difference between the two age groups. Twenty-five patients (5.4%) under 50 years of age died, compared to 18 patients aged ≥50 years (17.4%) ($p < 0.0005$). Most deaths were attributed to non-AIDS-related causes in the more aged group, in comparison with their younger counterparts (11.65% vs. 2.64%, $p < 0.0005$), while AIDS-related causes of death did not seem to differ dramatically (5.82% vs. 2.86%, $p = 0.133$).

The presence of an AIDS-defining infection was more often seen in older patients (45.6% vs. 34.9%, $p = 0.054$) throughout the observation period. AIDS-defining malignancy did not differ between the groups, but patients ≥50 years seemed to be diagnosed with non-AIDS malignancies more frequently (11.7% vs. 1.1%, $p = 0.0005$) from baseline to the end of the study period. The most frequent types of non-AIDS-associated malignancies were lung cancer and colon cancer for both sexes, followed by liver cancer. In the female population, two cases of breast cancer were also recorded. During the follow-up period, the majority of the patients (83.7%) started antiretroviral therapy. There was no statistically significant difference between the two age groups concerning the mean time until first HAART initiation (11.7 months vs. 11.08 months, $p = 0.177$). Older patients were more likely to develop clinical AIDS during follow-up (17.5% vs. 9.5%, $p = 0.03$).

Older patients were significantly more often hospitalized (more than two hospital admissions, 47.5% vs. 19.6%, $p < 0.0005$) and less likely have no hospital admissions (28.3% vs. 52.0%, $p < 0.0005$) than the younger patients. The main causes of hospitalization in the first group were *Pneumocystis jiroveci* pneumonia (14%), pneumonia of all other causes (21%), wasting syndrome (14%), tuberculosis (9%), herpes zoster infection (7%) and Kaposi's sarcoma (5.5%). In older patients, the main causes of hospitalization were *P. jiroveci* pneumonia (8%), pneumonia of all other causes

Table 1
Demographic and clinical characteristics of patients at baseline, stratified by age group

	<50 years old (*n* = 455, 81.5%)	≥50 years old (*n* = 103, 18.5%)	Total population (*n* = 558, 100%)	*p*-Value
Age at diagnosis, years, mean (SD)	32.78 (7.12)	57.74 (6.72)	37.35 (11.92)	-
Sex, *n* (%)				
Male	372 (81.8)	83 (80.6)	455 (81.5)	0.779
Female	83 (18.2)	20 (19.4)	103 (18.5)	
Nationality, *n* (%)				
Greek	424 (93.2)	96 (93.2)	520 (93.2)	1.000
Other	31 (6.8)	7 (6.8)	38 (6.8)	
HIV risk factor, *n* (%)				
Heterosexual sex	102 (22.4)	36 (35.0)	138 (24.7)	0.013[a]
MSM	273 (60.0)	54 (52.4)	327 (58.6)	
IDU	29 (6.4)	1 (1.0)	30 (5.4)	
Unknown	51 (11.2)	12 (11.7)	63 (11.3)	
CD4 cell count, cells/ml, at baseline, mean (SD)	339.64 (243.50)	303.86 (236.22)	332.96 (242.34)	0.179
CD4 cell count, cells/ml, at baseline, *n* (%)				
<350	252 (56.8)	63 (61.8)	315 (57.7)	0.213
350–500	87 (19.6)	23 (22.5)	110 (20.1)	
>500	105 (23.6)	15 (15.7)	121 (22.2)	
Clinical AIDS at baseline, *n* (%)	71 (15.6)	19 (18.4)	90 (16.1)	0.479
Plasma viral load, $\log_{10}$ copies/ml, at baseline, mean (SD)	4.77 (0.94)	4.91 (0.93)	4.80 (0.94)	0.208

IDU, injecting drug users; MSM, men having sex with men; SD, standard deviation.
[a] $p < 0.01$ for heterosexual sex.

Table 2
Comorbidities of patients at baseline, stratified by age group[a]

	<50 years old (*n* = 455, 81.5%)	≥50 years old (*n* = 103, 18.5%)	Total population (*n* = 558, 100%)	*p*-Value
HIV-defining morbidity, *n* (%)	246 (54.1)	61 (59.2)	307 (55.0)	0.381
Diabetes mellitus, *n* (%)	4 (0.9)	14 (13.6)	18 (3.2)	<0.0005
Hypertension, *n* (%)	23 (5.1)	34 (33.0)	57 (10.2)	<0.0005
HBV, *n* (%)	21 (4.6)	5 (4.9)	26 (4.7)	1.000
HCV, *n* (%)	23 (5.1)	4 (3.9)	27 (4.8)	0.801
CVD, *n* (%)	13 (2.9)	21 (20.4)	34 (6.1)	<0.0005
Hyperlipidemia,[b] *n* (%)	109 (24.0)	38 (36.9)	147 (26.3)	0.009
Anemia,[c] *n* (%)	18 (4.0)	12 (11.7)	30 (5.4)	0.006
Neurological disease, *n* (%)	25 (5.5)	12 (11.7)	37 (6.6)	0.029
Psychological disorder, *n* (%)	31 (6.8)	12 (11.7)	30 (5.4)	0.103
Thrombocytopenia,[d] *n* (%)	18 (4.0)	12 (11.7)	43 (7.7)	0.073
Liver damage,[e] *n* (%)	28 (6.2)	13 (12.6)	41 (7.3)	0.034
Renal damage,[f] *n* (%)	24 (5.3)	13 (12.6)	37 (6.6)	0.014
Hyperuricemia,[g] *n* (%)	10 (2.2)	5 (4.9)	15 (2.7)	0.169
Other infections,[h] *n* (%)	226 (49.7)	68 (66.0)	294 (52.7)	0.003

CVD, cardiovascular disease; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a] All analyses were performed using Fisher's exact test.
[b] Hyperlipidemia: total cholesterol >200 mg/dl, triglycerides >150 mg/dl, or both.
[c] Anemia: hemoglobin <12 g/dl in women, and <13 g/dl in men.
[d] Thrombocytopenia: platelets $<150 \times 10^9$/l.
[e] Liver damage: inflammation due to HCV or HBV, alcoholic liver disease, or metabolic syndrome.
[f] Renal damage: creatinine clearance ≤ 80 ml/min, proteinuria, nephrotic syndrome, or glomerular disease.
[g] Hyperuricemia: blood level of uric acid >6 mg/dl for women and >6.8 mg/dl for men.
[h] Other infections: all non AIDS-defining infections (hepatitis virus infections excluded).

(24%), wasting syndrome (17%), tuberculosis (11.5%), and lymphomas (4%).

Older patients had a shorter survival time than did the younger patients (mean time 169.1 months, 95% confidence interval (CI) 154.5–183.8 vs. 205.3 months, 95% CI 200.9–209.8; $p < 0.0005$) (Figure 1). The mean AIDS-free interval was shorter in older than in younger patients (mean time 160.4 months, 95% CI 151.4–169.5 vs. 125.2 months, 95% CI 105.3–145.1; $p = 0.007$), as seen in Figure 2. Twenty-five percent of younger patients were diagnosed with clinical AIDS at 63.2 months vs. 10.8 months for older patients.

With regard to the increase in CD4+ cell numbers, both age groups showed parallel profiles (age group × time: $p = 0.359$). A statistically significant increase through time was observed in both groups (time: $p < 0.0005$). Younger patients had a higher magnitude of absolute number of CD4+ cells compared with older patients only at 18 months ($p = 0.012$), 24 months ($p = 0.021$), and 48 months ($p = 0.029$) during the whole period of follow-up, as shown in Figure 3.

With regard to the increase in CD4+ cell counts in HAART-treated patients, both age groups responded in a similar way (age group × time: $p = 0.785$). A statistically significant increase through time was observed in both groups (time: $p < 0.0005$). Younger patients had the same numbers of CD4+ cells as older ones at each time point and during the whole period of follow-up (age group <50 years 476.02 ± 19.4 vs. age group ≥50 years 451.81 ± 42.27; $p = 0.649$) (Figure 4).

Concerning the decrease in plasma viral load, no difference was observed between the two age groups (age group × time: $p = 0.564$). A statistically significant decrease through time was observed in both groups (time: $p < 0.0005$), and older patients had lower viral load counts during follow-up (age group: $p = 0.035$) (Figure 5).

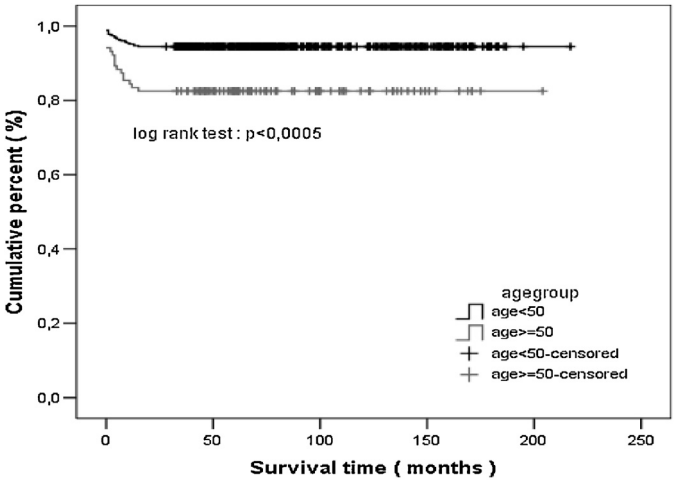
Cox proportional hazard regressions were used to identify factors associated with time to each outcome: death and progression to clinical AIDS (Table 4). In the adjusted analysis, older age was associated with a decreased likelihood of time to death (adjusted hazard ratio (aHR) 4.08, 95% CI 2.02–8.24). Older age was not statistically associated with a decreased time to clinical AIDS (aHR 1.35, 95% CI 0.88–2.08).

Female gender was associated with an increased likelihood of time to death (aHR 0.31, 95% CI 0.11–0.84) and increased time to clinical AIDS (aHR 0.36, 95% CI 0.20–0.64). Non-Greek origin was

Table 3
Major events throughout the study period

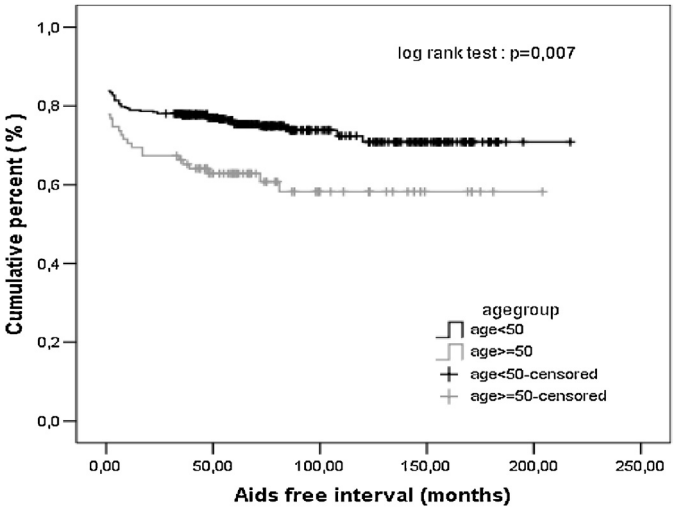
	<50 years old (*n* = 455, 81.5%)	≥50 years old (*n* = 103, 18.5%)	Total population (*n* = 558, 100%)	*p*-Value
AIDS-defining infection, *n* (%)	159 (34.9)	47 (45.6)	206 (36.9)	0.054
Malignancy, *n* (%)	5 (1.1)	12 (11.7)	17 (3.0)	<0.0005
AIDS-defining malignancy, *n* (%)	20 (4.4)	6 (5.8)	26 (4.7)	0.603
New clinical AIDS onset, *n* (%)	43 (9.5)	18 (17.5)	61 (10.9)	0.03
HAART, *n* (%)	378 (83.1)	89 (86.4)	467 (83.7)	0.463
Hospital admissions, *n* (%)				
0	225 (52.0)	28 (28.3)	253 (47.6)	<0.0005[a]
1	123 (28.4)	24 (24.2)	147 (27.6)	
>2	85 (19.6)	47 (47.5)	132 (24.8)	
Mortality, *n* (%)	25 (5.4)	18 (17.4)	43 (7.7)	<0.0005
AIDS-related death	13 (2.8)	6 (5.8)	19 (3.4)	0.133
Non-AIDS-related death	12 (2.6)	12 (11.6)	24 (4.3)	<0.0005
Total patients with clinical AIDS	114 (25)	37 (35.9)	151 (27)	0.025

HAART, highly active antiretroviral therapy.
[a] $p < 0.0005$ for 0 and 2+ hospital admissions.



Time (months)	0	6	12	18	24	30	36	42	48	54	60	66
n=age<50	444	416	370	381	368	359	324	305	264	254	231	210
n=age>50	102	91	85	84	75	79	74	67	56	57	50	45
Time (months)	72	78	84	90	96	102	108	114	120	126	132	138
n=age<50	178	166	151	144	132	122	116	109	100	94	75	64
n=age>50	42	41	37	35	31	29	28	24	24	20	14	14

Figure 1. Test of equality of survival distributions for the different age groups.



Time (months)	0	6	12	18	24	30	36	42	48	54	60	66
n=age<50	444	416	370	381	368	359	324	305	264	254	231	210
n=age>50	102	91	85	84	75	79	74	67	56	57	50	45
Time (months)	72	78	84	90	96	102	108	114	120	126	132	138
n=age<50	178	166	151	144	132	122	116	109	100	94	75	64
n=age>50	42	41	37	35	31	29	28	24	24	20	14	14

Figure 2. Test of equality of clinical AIDS-free interval distributions for the different age groups.

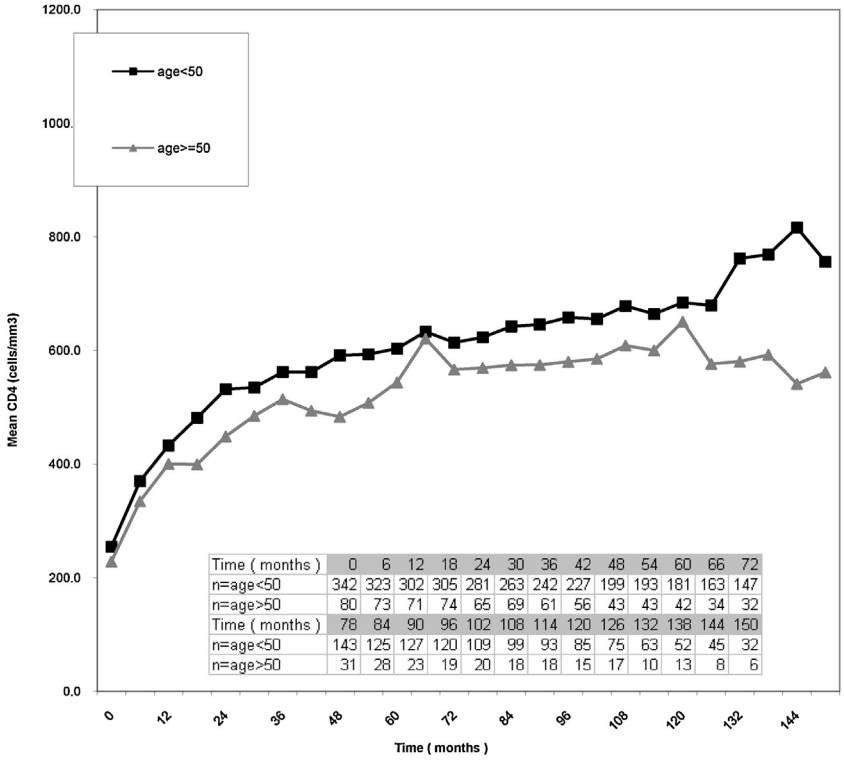
associated with a decreased time to death (aHR 3.29, 95% CI 1.54–7.02) and decreased time to clinical AIDS (aHR 1.82, 95% CI 1.02–3.25).

CD4 cell counts between 350 and 500 cells/ml (aHR 0.46, 95% CI 0.28–0.77) and above 500 cells/ml (aHR 0.49, 95% CI 0.27–0.86) were associated with an increased time to clinical AIDS compared with CD4 cell counts below 350 cells/ml, but CD4 cell count did not seem to interfere with the overall mortality.

HAART intake was associated with a decreased likelihood of time to death (aHR 3.29, 95% CI 0.74–14.63) and decreased time to clinical AIDS (aHR 7.36, 95% CI 2.75–15.45). Cardiovascular disease was associated with a decreased hazard of time to death (aHR 3.05, 95% CI 1.16–8.07).

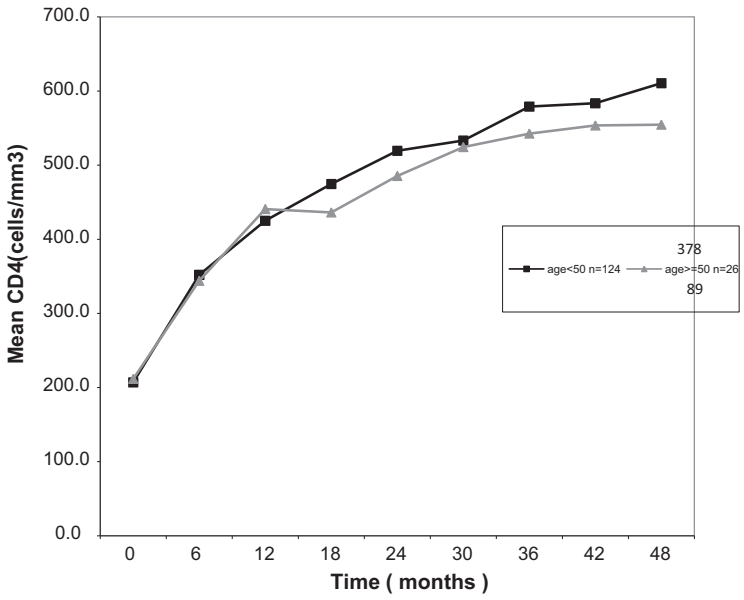
4. Discussion

Since 1996, when HAART became widely available, the morbidity and mortality of HIV-patients have decreased, and



Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72
n=age<50	342	323	302	305	281	263	242	227	199	193	181	163	147
n=age>50	80	73	71	74	65	69	61	56	43	43	42	34	32
Time (months)	78	84	90	96	102	108	114	120	126	132	138	144	150
n=age<50	143	125	127	120	109	99	93	85	75	63	52	45	32
n=age>50	31	28	23	19	20	18	18	15	17	10	13	8	6

Figure 3. Comparison of CD4+ cell numbers for the different age groups during the observation period.



Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72
n=age<50	378	323	302	305	281	263	242	227	199	193	181	163	147
n=age>50	89	73	71	74	65	69	61	56	43	43	42	34	32
Time (months)	78	84	90	96	102	108	114	120	126	132	138	144	150
n=age<50	143	125	127	120	109	99	93	85	75	63	52	45	32
n=age>50	31	28	23	19	20	18	18	15	17	10	13	8	6

Figure 4. Comparison of CD4+ cell numbers in patients receiving HAART during the observation period.

nowadays they have a prolonged survival and enjoy a good life. Also there is an increasing number of new HIV infections in older patients due to high-risk exposures.[2] The US Centers for Disease Control and Prevention identified patients aged 50 years and older as a separate age group, because this age group was so much older compared with the lower mean age of patients early in the HIV epidemic.[32] The aged HIV population has been poorly described and assessed in Greece.

In our study, the HIV population over 50 years of age in northern Greece was 18.5%, a little bit higher than the total percentage in Greece which is 15.1%. Older HIV-infected patients presented with some differences in epidemiological variables compared to younger patients. Homosexual exposure was the main route of HIV transmission in both groups, although heterosexual contact was significantly higher in the older adults, as confirmed in other studies.[33,34] A higher proportion of IDUs was observed in the younger age group, and an approximately similar proportion mentioned no risk factor for HIV transmission in both groups. Differences in the means of transmission, since this factor is self-reported, might indicate a fear of stigma in the advanced age group, or a lack of awareness[35,36] for sexually transmitted diseases generally in the Greek population.[37]

Late presentation remains an issue for HIV patients. There are data from studies reporting that even in the era of HAART, older patients still delay seeking care. Studies reported in the literature attribute this delayed access to different factors, referring to both patients and clinicians.[24,35] In our study, despite the numerical differences in median CD4 cells counts at baseline in favor of younger patients (306 vs. 263 cells/ml), in the number of patients with CD4 count <350 cells/ml (56.8% vs. 61.8%) and the number of patients with clinical AIDS at diagnosis (15.6% vs. 18.4%) there was no statistical difference. In this specific study population, for the decade mentioned, late presentation based on a low CD4 cell count was a general public health issue that was not influenced by age. No investigation on the reasons for this observation was made, which could be a potential limitation of this study.[38]

At baseline evaluation, the rates of comorbid conditions identified were higher in the older age group, as expected, with the exception of infection with HCV. This could be attributed to the higher number of drug addicts in the younger age group.[18,39] Hypertension, diabetes mellitus, cardiovascular disease, dyslipidemia, anemia, neurological dysfunctions, liver damage, and renal impairment were significantly more frequent in the older group than in the younger patients by the time of HIV diagnosis, a has been described in other recent studies investigating comorbidities in HIV patients.[40,41] The progression of HIV and antiretroviral agent metabolism could be affected by these clinical entities as well as by their pharmaceutical regimens.[42] These findings suggest that more medical specialties should be actively involved in the care of this specific population.

Most of the patients started HAART during the follow-up period. There was no statistical difference between the two groups with regards to the number of patients and the time of HAART initiation. In our study, virological suppression did not differ by age group, confirming the results of other studies.[12,43] Concerning the immunological response, literature data are conflicting.[13,21] With regard to the increase in CD4+ cell numbers, both age groups showed parallel profiles with a statistically significant increase

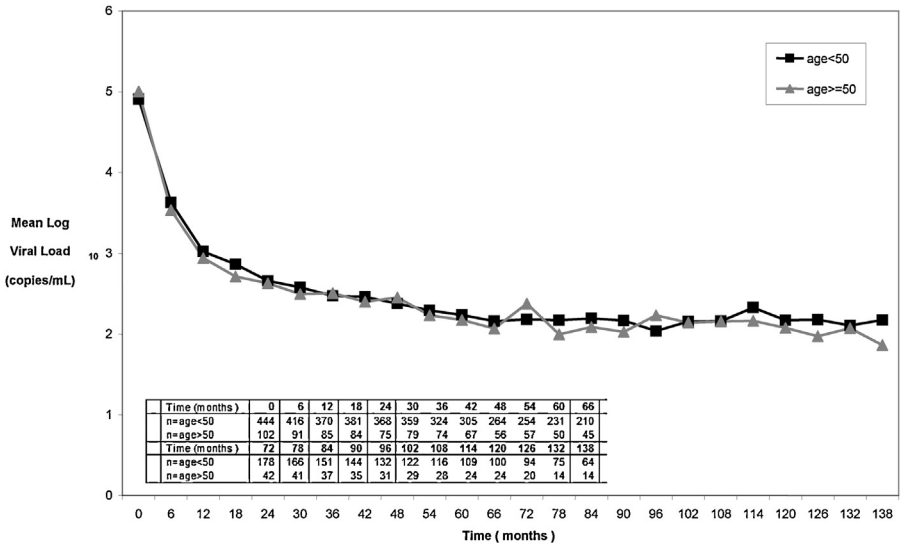


Figure 5. Comparison of plasma viral load ($\log_{10}$) in the different age groups during the observation period.

through time in both groups, but younger patients had higher absolute numbers of CD4+ cells during follow-up. More recent studies have confirmed these results.[17] CD4 cell count reconstitution has been proven to be inversely associated with age.[43] Thymic suppression is implied to be the cause of decreased immunologic responses.[44] Different clinical features and mean durations of HIV infection in the study populations are potential variables that might affect immunological reconstitution.[45]

Overall mortality was higher in the older age group. CD4 cell counts between 350 and 500 cells/ml and above 500 cells/ml were associated with an increased time to clinical AIDS, compared with CD4 cell counts below 350 cells/ml, but CD4 cell count did not play a significant role in the overall mortality in either population. AIDS-related mortality did not differ between groups. The higher overall mortality in the older patients was attributed to the non-AIDS-related mortality aspect.

In American and European cohorts, the causes of death in HIV patients have changed from complications of HIV to primarily non-HIV-related causes.[46] The same observation was made for malignancies; there was no difference between groups for AIDS-

Table 4
Cox proportional hazards multivariate analysis of time to onset of clinical AIDS and death

	Mortality		*p*-Value	AIDS-free interval		*p*-Value
	aHR	95% CI		aHR	95% CI	
Age at diagnosis						
<50 years	1.00		<0.0005	1.00		0.169
≥50 years	4.08	2.02–8.24		1.35	0.88–2.08	
Sex						
Male	1.00		0.022	1.00		0.001
Female	0.31	0.11–0.84		0.36	0.20–0.64	
Nationality						
Greek	1.00		0.002	1.00		0.042
Other	3.29	1.54–7.02		1.82	1.02–3.25	
HIV risk factor						
Heterosexual sex	1.00		0.033	1.00		0.032
MSM	0.42	0.18–0.96	0.040	0.58	0.36–0.94	0.026
IDU	1.35	0.46–3.98	0.57	1.16	0.58–2.31	0.678
Unknown	1.39	0.57–3.34	0.467	0.56	0.31–1.04	0.065
HAART						
No	1.00		<0.0005	1.00		0.001
Yes	3.29	0.74–14.63		7.36	2.75–15.45	
CD4 cell count, cells/ml, at baseline						
<350	1.00		0.066	1.00		0.001
350–500	0.38	0.11–1.29	0.120	0.46	0.28–0.77	0.003
>500	0.31	0.10–1.05	0.060	0.49	0.27–0.86	0.014
Hypertension at baseline			0.072			0.843
No	1.00			1.00		
Yes	0.14	0.02–1.10		1.06	0.60–1.87	
Diabetes mellitus at baseline			0.349			0.909
No	1.00			1.00		
Yes	0.47	0.1–2.30		1.05	0.45–2.43	
CVD at baseline			0.024			0.204
No	1.00			1.00		
Yes	3.05	1.16–8.07		1.54	0.80–3.08	

aHR, adjusted hazard ratio; CI, confidence interval; CVD, cardiovascular disease; HAART, highly active antiretroviral therapy; IDU, injecting drug users; MSM, men having sex with men.

defining malignancies, but a statistical difference in favor of older patients for non-HIV malignancies (11.7% vs. 1.1%, $p < 0.0005$). Recent studies have shown a dramatic increase in overall malignancies and organ-specific malignancies, particularly lung and liver malignancies.[47] In addition, certain cancers, particularly lung, breast, prostate, and colon cancers, increase with age.[48] In our cohort, lung and colon cancer cases were mostly recorded in both sexes, followed by liver cancer.

A higher proportion of older patients progressed to clinical AIDS compared to their younger counterparts (17.5% vs. 9.5%). The mean AIDS-free interval was shorter in older than in younger patients (mean time: 160.4 months vs. 125.2 months). This fact could be partially explained by the fact that aging HIV people exhibit an excess burden of multi-morbidity and a premature onset of clinical, immunological, and functional decline, due to the HIV virus and its antiretroviral influence.[28]

The elderly group of patients had a higher proportion of people who were admitted to hospital for all causes, as confirmed by other authors too.[18] In our study older patients were more frequently hospitalized, highlighting their high morbidity and the need for extensive care in aging seropositive people. AIDS-defining infections were more frequent in the older patients, although not surprisingly older patients had a worse survival than younger patients and were more often hospitalized, similar conclusions to those of previous studies,[17,18] but in contrast with others documenting a higher incidence of AIDS-defining infections in younger subjects.[12]

In the Cox proportional hazards multivariate analysis, age $\geq$50 years was related to a decreased time to death. Women were less likely to have proceeded to clinical AIDS and have a fatal outcome. Sex differences in immunological recovery, virological suppression, and clinical outcome have been observed in some previous studies, while others have not confirmed such results.[49,50] Non-Greek origin was associated with a decreased time to death and decreased time to disease progression. Poor living conditions, insurance issues for immigrants, and the fear of stigma could probably account for insufficient follow-up, underestimation of health issues, and worse outcomes in this population. HAART intake was associated with a decreased time to death and decreased time to disease progression, probably due to the fact that most treated patients presented with more a severe immunological status at diagnosis. Cardiovascular disease was associated with a decreased time to death, a fact compatible with most studies.[51]

This study was a retrospective analysis, which lacks the ability of a more targeted design. No data on the type and duration of HAART regimen were included in our analysis. Tolerance and adherence to HAART intake may also have had an impact on the clinical outcome and survival of the older people; adherence data were available for only a limited number of patients, making it difficult to draw any conclusions. Drug–drug interactions between HAART and other agents used by older patients for non-HIV comorbidities could have influenced survival. We used the age at diagnosis as the main parameter, so we could not compare individuals living with HIV at an older age to patients diagnosed with HIV at an advanced age, and maybe we should also determine the impact of HIV on aging in a future analysis.

As the individual with HIV grows older, other factors may contribute to morbidity and mortality and these factors should be taken into consideration in future analyses. Non-AIDS-defining comorbidities should be evaluated since they may be relevant to the management of older HIV-infected patients. This increase in age and comorbidities will increase the need for multiple professional competences, and the sharing of specialist medical skills. New screening test strategies for malignancies should be developed for older HIV-infected patients. Controlled clinical studies should be preformed regarding the effectiveness and safety of antiretroviral therapy in this sub-population.

Ethical approval: The study was approved by the Ethics Committee of the Medical School of Aristotle University of Thessaloniki.

Conflict of interest: We have no competing interests to declare.

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