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Late presentation of HIV infection: predictors of delayed diagnosis and survival in Eastern Sicily

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Abstract. – OBJECTIVES: Across Europe, more than one third of patients are diagnosed with HIV infection late. Late presentation for care has been associated with higher risk of clinical progression and mortality.

In the present study, we evaluated the prevalence, epidemiological characteristics and survival probability of patients with late and very late presentation, newly diagnosed with HIV infection in Catania, Italy, from 1985 to 2010.

PATIENTS AND METHODS: According to the European Consensus definition, Late Presenters (LP) were defined as subjects presenting for care with a CD4+ T-cell count below 350 cells/μl or with an AIDS-defining event, regardless of CD4+ T-cell count; patients with advanced HIV disease (Very Late Presenters) (VLP) were those presenting with a CD4+ T-cell count below 200 cells/μl or with an AIDS-defining event, regardless of CD4+ T-cell count.

RESULTS: 620 patients were included in the study. 345 (55.6%) subjects were LP, 35% of them were asymptomatic; 246 (39.7%) were VLP. In univariate analysis, late presentation was related to age ($p < 0.001$), to heterosexual exposure to HIV infection (70% of heterosexual subjects were LP) ($p < 0.005$) and to being diagnosed during the calendar period from 1991 to 2000 ($p < 0.001$). Very late presentation was related to age ($p < 0.001$), male sex ($p < 0.01$), heterosexual risk ($p < 0.001$) and to being diagnosed during the calendar period from 1991 to 2000 ($p < 0.001$). In multivariate analysis, age ($p < 0.0001$), being older than 50 years old ($p = 0.02$), years of diagnosis 1991-1995 ($p < 0.005$) and 1996-2000 ($p < 0.05$) in the subgroup of late presenters and age ($p < 0.0001$), being older than 50 years old ($p < 0.005$), male sex ($p < 0.0001$), years of diagnosis 1991-1995 ($p < 0.05$) and 1996-2000 ($p < 0.005$) in the subgroup of very late presenters maintained statistical significance.

The survival probability within LP and VLP group was statistically lower than no LP/VLP (log rank test $p < 0.0005$ and $p < 0.0001$, respectively). For both LP ($p < 0.002$) and VLP ($p < 0.0001$), survival probability was significantly lower in the pre-HAART era, in comparison with the period of mono/dual therapy and the HAART era.

CONCLUSIONS: More than fifty percent of patients in our setting were diagnosed late with HIV infection and, consequently, treated late. Late and very late presentation were associated with lower survival probability. The implementation of strategies focused on targeted prevention efforts and HIV testing programs appears fundamental to diagnose and treat HIV infection as early as possible.

Key Words:
HIV, HAART, Late presentation, Late presenter.

Introduction

Highly active antiretroviral therapy (HAART) has significantly changed the natural history of Human immunodeficiency virus (HIV) infection, leading to a great reduction of HIV-related morbidity and mortality[1]. However, HAART cannot eradicate HIV infection, because of viral persistence in latent reservoirs, which still represent a major obstacle to viral elimination[2-13]. In addition, in the last years the prevalence and mortality due to non-AIDS-related events and malignancies have significantly increased[14-32].

Across Europe, still more than one third of subjects with HIV infection are diagnosed late[33]. Late presenters (LP) have an increased risk of clinical progression and mortality and show a slow or poor immune recovery when starting HAART and a higher frequency of antiretroviral-associated toxicity[34-37]. Of importance, the number of unaware and untreated patients correlates with the level of community viral load and therefore with the risk of transmitting HIV infection[38].

In 2009, a consensus definition of late presentation has been proposed to facilitate cross-country comparisons and evaluate the impact of differ-

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ent public health care plans, identify risk factors and monitor changes in the prevalence of late presentation over time[39]. According to the definition approved by the European Consensus panel, LP were defined as patients presenting for care with a CD4+ T-cell count below 350 cells/μl or presenting with an AIDS-defining event, regardless of the CD4+ T-cell count. Very late presenters (VLP) or patients presenting with advanced HIV disease (AHD) were those presenting for care with a CD4+ T-cell count below 200 cells/μl or AIDS, regardless of CD4+ T-cell count[39].

In the present study, we described the prevalence of late and very late presenters in a cohort of patients newly diagnosed with HIV infection in Catania, Italy, from 1985 to 2010. We evaluated the factors associated with late/very late diagnosis as well as the survival probability of LP and VLP.

Patients and Methods

We included in our study all patients with a new diagnosis of HIV infection performed in our Unit from May 1985 to December 2010. Factors included in our analysis were sex, age, risk factors for HIV infection, CDC stage, CD4+ T-cell count at diagnosis, calendar year of presentation. Survival curve was calculated as time from first diagnosis to death. Patients alive or lost to follow up were censored at last available visit.

According to the European Consensus definition[39], Late Presenters (LP) were defined as subjects presenting for care with a CD4+ T-cell count below 350 cells/μl or with an AIDS-defining event, regardless of CD4+ T-cell count; patients with advanced HIV disease (Very Late Presenters) (VLP) were those presenting with a CD4+ T-cell count below 200 cells/μl or with an AIDS-defining event, regardless of CD4+ T-cell count.

Statistical Analysis

Continuous variables are expressed as median (interquartile range, IQR) and compared by non-parametric Mann-Whitney and Kruskal-Wallis test, when appropriate. Categorical variables are presented as number of cases (percentage) and were compared by the X2 test or Fisher's exact test, when appropriate.

Univariate regression analysis was performed to identify factors associated with late/very late presentation. Multivariate logistic regression analysis was used to identify demographic factors independently associated with late presentation. Multinomial logistic regression analysis was performed to identify factors independently associated with risk of death.

Results

From May 1985 to December 2010, 620 patients received a first diagnosis of HIV infection in our unit. Clinic and demographic features of all patients included in the study are reported in Table I.

Median CD4+ T-cell count at diagnosis was 315 (90-550) cells/μl. CD4+ T-cell count was higher among intravenous drug users (IDUs) (489 (250-744) cells/μl) in comparison with other risk groups, while heterosexual subjects had the lowest CD4+ T-cell count (232 (57-440) cells/μl, ($p < 0.005$)).

The CDC clinical stage and trend of median CD4+ T-cell count over time are summarized in Figure 1.

345 (55.6%) subjects were late presenters: 131 (38%) were AIDS presenters, 116 (33.6%) were asymptomatic. 246 (39.7%) were diagnosed with advanced disease (VLP), of them 53.2% were AIDS presenters and 15.3% were asymptomatic.

In univariate analysis, late presentation was related to age ($p < 0.001$), being older than 50 years ($p < 0.001$), to HIV risk group (70% of heterosexual patients were LP) ($p < 0.005$) and to being diagnosed during the period from 1991 to 2000 ($p < 0.001$). Age ($p < 0.0001$) and years of diagnosis 1991-1995 ($p < 0.005$) and 1996-2000 ($p < 0.05$) were still significant in multivariate analysis (Table II).

Table I. Clinic and demographic features of patients included into the study.

N	620
Male/female N(%)	457 (73.7)/163 (26.7)
Median age (years)	31 (27-40)
> 50 years old N (%)	71 (11.4)
Risk factors for HIV infection N (%)	
Heterosexual	246 (39.7)
Homosexual	170 (27.4)
Intravenous drug use	184 (29.7)
Other	20 (3.2)
CDC N (%)	
A	380 (61.3)
B	109 (17.6)
C	131 (21.1)
Median CD4+ T-cell /μl	315 (90-550)

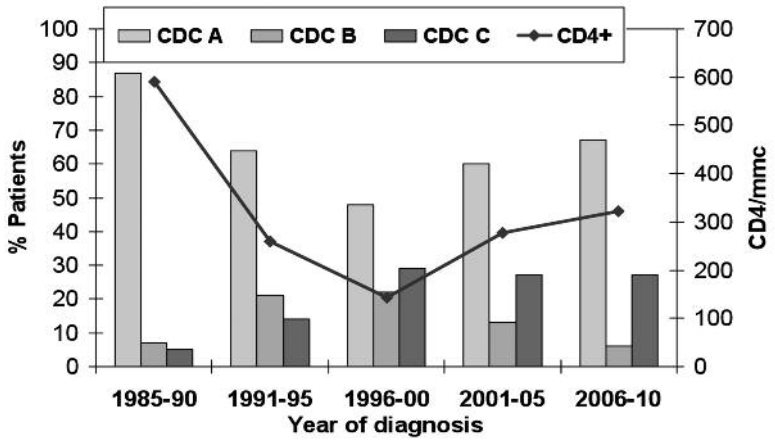

Figure 1. CDC stage and median CD4+ T-cell count over time.

Very late presentation (VLP) was related to male sex ($p < 0.01$), heterosexual risk ($p < 0.001$), age ($p < 0.001$), being older than 50 years ($p < 0.001$) and having been diagnosed from 1991 to 2000 ($p < 0.001$). Age ($p < 0.0001$), being older than 50 years old ($p < 0.005$), male sex ($p < 0.0001$), years of diagnosis 1991-1995 ($p < 0.05$) and 1996-2000 ($p < 0.005$) were significant even in multivariate analysis.

Survival analysis included 557 patients: 314 (56.4%) were late presenters, 226 (40.6%) very late presenters, 121 (21.7%) AIDS presenters. Globally, 174 (31.7%) patients died (Figure 2).

115 (36.6%) LP died and they represented 66.1% of total deaths observed during the period in which survival analysis was performed. Survival probability among LP was lower than no LP (log rank test $p < 0.0005$) (Figure 3). Median survival in the LP group was 61.5 (23.7-148.4) months *vs* 83.1 (IQR 28.8-158.6) months in the group of no LP ($p = 0.012$).

97 (42.9%) VLP died and they represented 55.7% of total deaths registered during the period in which survival analysis was performed. Survival probability among VLP was statistically lower than no LP (log rank test $p < 0.0001$) (Fig-

Table II. Factors associated with late presentation in multivariate analysis.

		Or	95% CI	p
1990-95	vs 1986-90	2.35	1.4-3.9	0.0011
1996-00	vs 1986-90	2.49	1.35-4.6	0.0035
2001-05	vs 1986-90	1.75	0.94-3.26	0.0788
2006-10	vs 1986-90	1.52	0.84-2.77	0.1695
eterosex	vs MSMs	1.39	0.91-2.15	0.1306
IVDU	vs MSMs	0.78	0.46-1.32	0.3584
other risks	vs MSMs	0.89	0.30-2.6	0.8307
age > 50 yrs	vs younger	2.06	1.12-3.8	0.0202

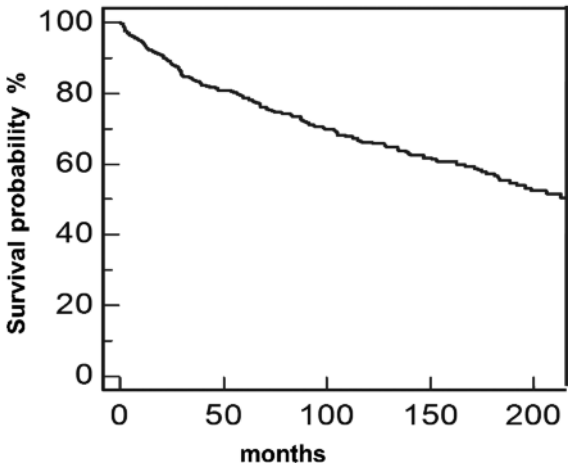

Figure 2. Kaplan Meier survival curve for all the patients included in the study.

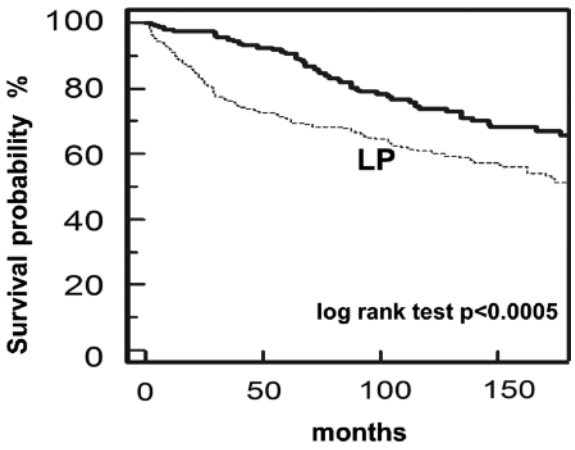

Figure 3. Kaplan Meier survival curve: late presenters (LP, dashed line) vs no LP (*continuous line*).

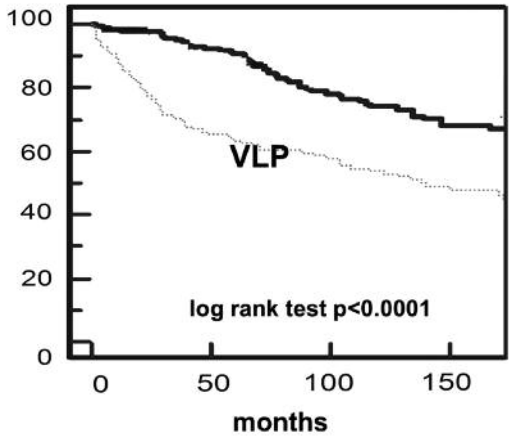

Figure 4. Kaplan Meier survival curve: very late presenters (VLP, dashed line) vs no VLP (*continuous line*).

ure 4). Median survival in VLP was 52 (20-131) months ($p < 0.0001$ *vs* no LP) .

For both LP ($p < 0.002$) and VLP ($p < 0.0001$), survival probability was significantly lower in the pre-HAART era, in comparison with the period of mono/dual therapy and the HAART era (Figures 5, 6).

Discussion

In keeping with previous reports across Europe[33], we found that more than half of patients were diagnosed with HIV infection late and were eligible for HAART initiation according to EACS

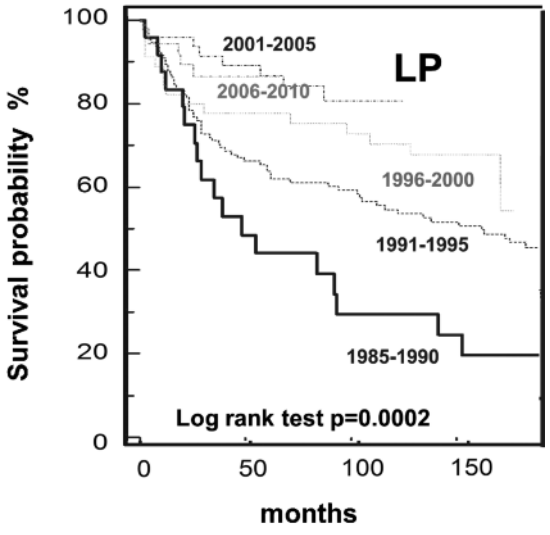

Figure 5. Kaplan Meier survival curve: late presenters in different calendar periods.

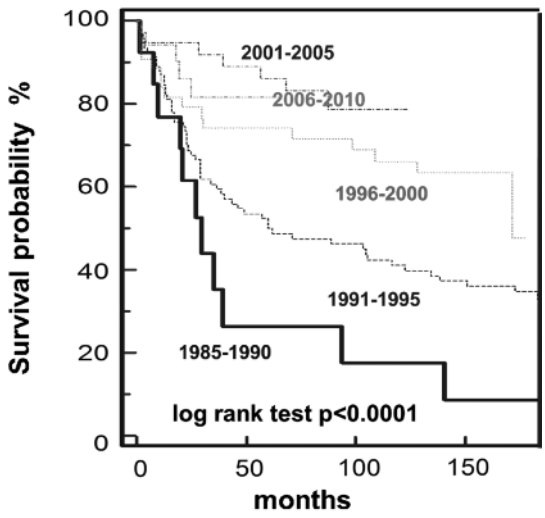

Figure 6. Kaplan Meier survival curve: very late presenters in different calendar periods.

recommendation[40]. As already reported by other authors[34,41-44], older age was associated with higher risk of late presentation. Several factors may contribute to explain this finding: older adults may not consider themselves as a risk category and may be excluded by the network of targeted sexual health information[45-46]. In addition, general practitioners may not suspect HIV infection for a long time, thus delaying diagnosis. Late presentation was more common among men and was associated with heterosexual exposure to HIV infection, in comparison with other risk categories. Again, reduced perception of individual risk and subsequent reduced uptake of HIV testing are likely to contribute to late diagnosis. Several studies have shown the proportion of late diagnosis to be lower among men who have sex with men (MSM)[41,46]. This observation may be explained by more testing among MSM; however, it should be noticed that it may reflect a higher rate of recent infections in this group. In fact, in our clinical setting, we have recently observed a rise in newly diagnosed infections among young MSM, with CD4+ T-cell count often > 350 cells/μl and a probable recently acquired infection (unpublished data).

As expected, survival probability of LP/VLP was significantly lower in the pre-HAART era, in comparison with the period of mono/dual therapy and the HAART era. However, late presentation was associated with increased risk of death, despite HAART initiation. In a recent study of d'Arminio Monforte et al[34], the authors found that patients diagnosed late had a > 5-fold greater risk of HIV progression. LP exhibit an immunological

profile characterized by increased number of activated CD38+ CD8+ T cells and decreased expression of CD127 (also known as IL-7 receptor) on CD4+ T cells[47]. Downregulation of CD127 on T cells has been associated with immune activation and increased susceptibility to apoptosis, which may reinforce CD4+ decline and disease progression[48,49]. Considering that LP are at increased risk of disease progression and poor immune reconstitution, it has been suggested to use CD127+ CD4+ percentage as an additional marker to identify and monitor late presenters[47].

The management of patients presenting very late is challenging: some of them may die because of AIDS-defining illnesses, even before having the possibility to start HAART[50,51]. Subjects with very low CD4+ T-cell count have a higher probability of developing immune reconstitution inflammatory syndrome when starting antiretroviral therapy. In addition, the global pill burden for the treatment of HIV and opportunistic infections may have a negative impact on adherence and drug interactions may negatively affect the efficacy and tolerability of treatment[50,51].

From an economic perspective, Krentz et al[52] have recently shown that the medical costs for late presenters were significantly higher in comparison with patients with a CD4+ T-cell count > 350 cells/μl over a 15-year period. This finding further underlines the need for earlier detection and access to HIV care, in order to reduce both the individual and socio-economic costs of HIV infection.

Conclusions

More than 50% of subjects diagnosed with HIV infection had a CD4+ T-cell count below the threshold at which HAART initiation is recommended by current European guidelines. Considering that late presenters are at increased risk of clinical progression and death, it is essential to potentiate targeted prevention efforts and HIV testing programs, in order to diagnose and treat HIV infection as early as possible. In additional to individual benefits, early diagnosis and treatment may have a wide impact from a social and economical point of view, as they may significantly reduce further HIV transmission, the occurrence of cancers[53-60] and medical care costs.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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