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LATE PRESENTATION AMONG A COHORT OF FEBRILE PEOPLE NEWLY HIV INFECTED DIAGNOSED, DURING 2005-2012, IN ALBANIA

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ABSTRACT

Aim: Antiretroviral therapy decreased mortality and morbidity in people living with HIV/AIDS especially when initiated early, before advanced immunodeficiency has developed. In daily practice, it's particularly challenging when dealing with HIV-positive, late presenters individuals.

The aim of our study was to determine, frequency, demographic features and factors associated with late presentation among febrile persons, newly diagnosed as HIV infected, during 2005–2012 period of time, in Albania.

Methods: All HIV-positive patients with no prior history of HIV infection, admitted to Infectious Diseases Service, University Hospital Centre "Mother Teresa" of Tirana, from January 2005 to December 2012, were target of our study. "Late presenter" was defined based on the definition of "HIV in Europe Initiative", 2009. Demographic, epidemiological, clinical characteristics, laboratory findings, and outcome data were collected.

Results: In total 87 cases (92.6%) out of 94 patients newly diagnosed with HIV were late presenters. According to univariate analysis, the age, male gender, heterosexual contact, emigration and level of education were associated with late presentation for HIV diagnosis. In the multivariate analysis, age (30-39), male gender, heterosexual contact, migration status and level of education were the only independent risk factors for late presentation.

Conclusion: A considerable proportion of people newly diagnosed HIV infected, enter late in health care, presenting advanced HIV disease and consequently are treated rather late. In order to be able to detect and treat them early as recommended by international guidelines, it's necessary to develop policies and interventions targeting social categories at high risk for late presentation.

Keywords: Febrile, HIV infection, late presentation, CD4, risk factors.

INTRODUCTION

Early commencement of antiretroviral treatment (ART) for persons living with human immune deficiency virus (HIV) or acquired immune

deficiency syndrome (AIDS) can be beneficial and can save money in the long run ^(1,2). The benefits are better realized when people present early at each stage along the continuum of care, from early

screening / testing for HIV infection, early linkage into care by those with confirmed HIV infection, to remaining in pre-ART care until timely treatment commencement decisions are made and, thereafter, maintaining high fidelity to essential long-term care and treatment contact^(3,4). Advanced HIV disease is evidenced by compromised immune status (often with CD4+ cell count < 200 cells/ml³), the presence of multiple co-morbid opportunistic infections, and poor overall functional and mental health status^(3,5-13). Despite global advances in access to care, a significant proportion (20–60%) of adults in most parts of the globe who come for the first time to HIV/AIDS care and treatment facilities, present with advanced HIV disease^(5,14-17). Evidence from immune recovery studies indicate that, even with efficacious therapies, presenting late for HIV diagnosis results in less favourable outcomes⁽¹⁸⁻²²⁾. Untreated infection with the human immunodeficiency virus (HIV) progressively destroys the immune system leading to opportunistic illnesses and death. Since potent combination antiretroviral therapy (ART) has been introduced, morbidity and mortality of HIV-infected people has drastically improved⁽²³⁻²⁵⁾. However, a substantial proportion of individuals are not aware of their HIV infection or do not present for care and treatment until the disease is advanced⁽²⁶⁾. Late initiation of cART results in less favourable outcomes^(2,18,21) and is associated with increased medical costs⁽²⁷⁾. Furthermore, untreated people may contribute to the spread of HIV for many years. In Europe, 33% to 42% and 49% to 54% of individuals were reported not to be diagnosed with HIV until having CD4 cell count values below 200 cells/mm³^(13, 28-30) and 350 cells/mm³^(26, 31, 32), respectively, and up to 30% present with an acquired immunodeficiency syndrome (AIDS) defining illness⁽³³⁾. Unfortunately, different definitions for late presentation complicate direct comparisons of the study findings⁽³⁴⁾. A recent initiative resulted in a

European consensus definition for late presentation of HIV-infected persons: Individuals presenting for care with a CD4 cell count below 350 cells/mm³ or with an AIDS-defining illness regardless of CD4 cell count should be classified as late presenters⁽³⁵⁾.

Late presentation for care comprises two entities which are believed to be quite different from each other in terms of risk factors and interventions: (I) late HIV testing, which reflects patients who are unaware of their HIV infection, and (II) delayed presentation for care, including individuals who are aware of their HIV infection but do not seek care right away.

Recently, in their paper ‘The Beginning of the End of AIDS’, Havlir and Beyrer wrote: ‘We are at a moment of extraordinary optimism in the response to the human immunodeficiency virus (HIV).’ Several trials’ results have led many to assert that control of the HIV pandemic may be achievable⁽³⁶⁾. Early initiation of antiretroviral therapy (ART) has been found to improve individual patient outcome and reduce the risk of HIV transmission to sexual partners by 96%⁽³⁷⁾.

However, diagnosis is a critical limiting factor in the treatment and control of HIV/AIDS worldwide.

The objective of our study was to determine the frequency, demographic features, risk factors and outcomes of late presentation among the cohort of febrile people newly diagnosed HIV infected.

METHODS

Subjects

In total 166 HIV+ patients were admitted to Infectious Diseases Service (IDS), University Hospital Centre “Mother Teresa” of Tirana (UHCT), from January 2001 to December 2012 and 240 febrile episodes were registered. Patients eligible for our study were them that received HIV confirmatory Western Blot test for the first time and these cases were distributed during January 2005 - December 2012 period of time.

Data collection

Data on gender, patient's age at diagnosis moment, calendar year of HIV diagnosis, risk factors of HIV infection transmission, patient living place, CD4 cell count at diagnosis, AIDS-defining events at presentation and outcome data (days of hospitalization, mortality) were extracted from patients records and registered in database. Data were recorded in the database retrospectively until 2010 review of medical files and prospectively thereafter.

In order to ensure that the status at presentation was actually captured, CD4 cell count and/or AIDS-defining event diagnosis had to be reported.

Measurements

CDC stage clinical classification model was used. The consensus definition of the European Late Presenter Consensus Group was adopted for analysis (32). According to this definition, patients who present less than 350 CD4 cells/mm³ or an AIDS-defining event are classified as late presenters (35). Those who present less than 200 CD4+ cells/mm³ or an AIDS-defining event are classified as very late presenters and are at increased risk of death (38).

Late presentation for care comprises two entities which are believed to be quite different from each other in terms of risk factors and interventions: (a) late HIV testing, which reflects patients who are unaware of their HIV infection, and (b) delayed presentation for care, including individuals who are aware of their HIV infection but do not seek care right away. Only the first group was eligible and included in this study.

Statistical analysis

Data are presented as mean \pm SD (standard deviation) for numerical variables, number (n) or percentage (%) for categorical variables. Logistic regression models were used in order to assess predictors of late presentation. Predictors that were significantly ($p < 0.05$) associated with late presentation in univariate analyses were introduced in the multivariate model. Results of the logistic regression were reported as odds ratio

(OR) and 95% confidence interval (CI). We considered sex, transmission categories (men who have sex with men (MSM), heterosexual contact, intravenous drug user (IDU) and blood transfusions), age (<19, 20-29, 30-39, 40-49, 50-59, 60-69, 70+ years), emigration status, year of HIV infection diagnosis and educational level in the models. Categorical data were analyzed using the Chi square test. Statistical significance was considered at the level of $p \leq 0.05$. All tests were two tailed. SPSS 15.0 statistical package was used to analyze the data.

RESULTS

A total of 94 patients were diagnosed for the first time with HIV infection during the study period, 68 patients (72.3%) were male. Mean (\pm SD) age at diagnosis was 40.2 ± 12.23 years old (range: 15-71). Distribution of patients according to age is prescribed in (Figure 1). In 68.0% (64) of the patients was reported the possible route of HIV infection transmission. The most prevalent risk factor of HIV infection transmission was heterosexual contact representing 73.4% of cases (47/64). Men having sex with men (MSM) was reported in 14.1% of cases (9/64). In total 6.2% (4/64) of the patients reported multiple transfusions in their medical history, and four patients were intravenous drug users, 6.2% (4/64) ($p < 0.05$).

Mean (\pm SD) CD4 cell count at diagnosis was 123.19 ± 114.23 cells/mm³, (range from 511-1). CD4 cell count was higher among MSM group (179.0 ± 195.2 cells/ μ l) in comparison with other risk groups, while transfused subjects had the lowest CD4 cell count (104.0 ± 66.14 cells/ μ l) ($p < 0.005$) (Figure 2). The CDC clinical stage and CD4 cell count are presented in (Figure 3).

In total 87 patients (92.6%) had CD4 counts < 350 cells/mm³ or a clinical AIDS-defining event at the time of their first positive HIV test result and were considered to be late or very late presenters for HIV diagnosis. According to the CD4 cell count there were 9(10.3%) late presenters subjects, 51

(58.6%) very late presenters and 27(31.0%) cases had only a clinical AIDS-defining event.

[Table 1] compares the characteristics of late presenters for HIV diagnosis with those of early presenters.

The proportion of late presenters among all patients receiving a first HIV diagnosis was highest in 2012: 20.69%, and lowest in 2006: 2.29%. The highest proportion of late presenters was observed in heterosexual contact group: 51.7% of all late presenters. [Table 2] present the distribution of late presenters according to the CD4 cell count.

According to univariate analysis, age, male gender, heterosexual contact (95.7% of patients engaged in heterosexual relationship were late presenters) and calendar year of diagnosis were associated with late or very late presentation for HIV diagnosis. Factors associated with late presentation according to multivariate logistic analysis are presented in [Table 3]. Distribution of not late, late and very late presenters reflecting the CDC clinical stage classification is expressed in [Table 4].

Male subjects were at higher risk of “late presentation” compared to female ones (OR = 2.08). Patients 30-39 years old were at higher risk compared to those less than 19 years old (OR = 17.6). Compared to MSM, patients in heterosexual contact transmission category were at higher risk of “late presentation” (OR = 2.81). Compared to non-emigrant subjects, emigrant subjects were more likely to be diagnosed late (OR = 6.89). Compared to the subjects with a university degree, subjects who have attended the high school were more likely to be diagnosed late (OR = 17.3). Compared to subjects living in urban areas, subjects living in rural areas were at higher risk of “late presentation” (OR = 1.18).

Late and very late presentation were related to male sex, heterosexual relationship, age between 30 and 39 years old, emigration and living in the rural areas.

In total 14.9% (13) of late presenters, died during the admission and they represented all deaths registered in our cohort.

Potentially HIV-related symptoms prior to the test were present in 93.1% (81) of cases. The prevalence of the most frequent symptoms is shown in (Figure 4).

DISCUSSION

Late presentation for HIV diagnosis has been reported to be high worldwide^(11,32,39-46). In Western Europe, about 50% of newly diagnosed HIV-positive individuals are diagnosed at a late stage of disease and enter in care late.

Our results showed that 92% of individuals newly diagnosed HIV infected were late presenters; among these, 58.6% were in an advanced stage of HIV disease and 31.0% was diagnosed with AIDS. The proportion of late presenters at HIV diagnosis observed in our study was higher to that reported in other European countries, this is may be due to our restricted cohort including only febrile HIV positive subjects. Globally, up to 90% of people living with HIV may be unaware of their status⁽⁴⁷⁾ with estimates ranging from 21 to 30% in developed nations^(48,49).

In a study performed in Germany, Zoufaly *et al.*⁽³²⁾ reported, 49.5% late presenters for HIV diagnosis. An Italian cohort confirmed this, with 63% of patients being defined as diagnosed late, using the European Consensus definition⁽⁴¹⁾ of these, 16% were AIDS-presenters. A study run to Greece reported a frequency 52.5% of late presenters⁽⁵⁰⁾.

In two above mentioned studies, predictors of being diagnosed late were older patients, heterosexuals from low prevalence country and migrants for the German cohort⁽³²⁾ and older age, non-Italian origin, high HIV RNA and unemployment for the Italian Cohort⁽⁴¹⁾. In 2011, in Belgium, 42% of patients were diagnosed with CD4 <350/mm³ and 38% of those patients presented with AIDS. Risk factors associated to Heterosexual contact and intravenous drug use, compared to MSM, conferred increased risk by a

factor of 48% and 19%, respectively. Immigrant status conferred increased risk by a factor of 65%⁽⁵⁰⁾. Although the HIV epidemic in Greece predominantly affects MSM, populations such as persons who inject drugs and immigrants are at higher risk for late presentation possibly due to barriers in healthcare^(34,51).

The most important findings of our study can be summarized as follows:

- Late presentation for HIV diagnosis was high (92%) and related to:
 - Male sex
 - Heterosexual contact
 - Age: being between 30 and 39 years old
 - Being emigrant or living in the rural areas.

All above were independent risk factors for late presentation.

As already reported by other authors⁽⁵²⁻⁵⁶⁾, older age was associated with higher risk of late presentation. Late presentation was more common among men and was associated with heterosexual exposure to HIV infection, in comparison with other risk categories. Reduced perception of individual risk and subsequent reduced uptake of HIV testing are likely to contribute to late diagnosis among heterosexual males. Several studies have shown the proportion of late diagnosis to be lower among men who have sex with men (MSM)^(53,57). More testing among the (MSM) is likely to be a major reason for this, as overall they were much more likely to have had a recent HIV test^(32,39-41).

In our sample, emigrants and people living in rural areas of the country were more likely to be diagnosed later, suggesting a low access to HIV testing sites, or a poor perception of exposures at risk for HIV, or the presence of cultural or socio-economic barriers. In our study, complaining of clinical conditions associated with HIV infection was the main reason for undergoing HIV testing. Confirming the relevant role of healthcare professionals (especially general practitioners) in recommending HIV testing not only in presence of

AIDS-defining diseases but also for specific HIV indicator conditions⁽⁵⁸⁾.

Several published studies demonstrated also that late presentation for HIV diagnosis is linked with poor outcomes. The risk increases with lower CD4 cell counts at ART initiation and remains elevated even years after initiation of ART^(59,60). If a person is diagnosed early and HIV treatment is introduced early in the course of infection before severe impairment of the immune system has occurred, life-expectancy may approach that of the general population⁽⁶¹⁾. In the UK, 25% of HIV infections are undiagnosed, undermining efforts to reduce transmission⁽⁶²⁾. Late diagnosis is also an important cause of HIV-related morbidity,⁽⁶³⁾ mortality⁽⁶⁴⁾ and healthcare costs⁽⁶⁵⁾. In our study death was registered in 14.9% of cases among late presenters.

The healthcare cost for late presentation goes beyond cART / outpatient care including also more inpatient care / non-ARV drugs. These costs not only reflect lifelong legacy costs of the residual morbidities from some AIDS conditions but also reflect the costs of complex social and medical issues that contributed to late presentation⁽²⁷⁾. Late presentation for HIV diagnosis also plays a significant role in ongoing HIV transmission. It was estimated that people who are unaware of their HIV positive status are responsible for more than 50% of the new HIV infections occurring in the population, mainly through engaging in high-risk behaviours. This was confirmed by a meta-analysis of 11 independent studies⁽⁶²⁾. Studies have revealed that people who are aware of their HIV-positive status are less likely to transmit the disease because early access to healthcare / treatment results subsequently in lower viral load levels and safer sexual practices⁽⁶⁶⁻⁶⁸⁾. The higher the viral load, the higher the rate of transmission⁽⁶⁹⁾.

There are some limitations in our study. Our data are collected retrospectively and the study was designed after the data collection was ended. It's a limited cohort including only febrile HIV positive

subjects. We were unable to assess the impact of other predictors which may be relevant, for late presentation such as socio-economical status and origin instead of living place/residence.

CONCLUSIONS

Our study suggests a high proportion of late presenters for HIV diagnosis in Albania. Considering that late presenters are at the increased risk of clinical progression and death, it's essential to potentiate targeted prevention efforts and HIV testing programs, in order to diagnose and treat HIV infection as early as possible and so on to reduce HIV morbidity, mortality and transmission. Development of policies and wide implementation of interventions, targeting social categories at high risk for late presentation are recommended.

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Ethical Clearance

This study was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2000, and was approved by the ethics committee of our institution. As this was a retrospective descriptive study, and data were collected as part of patients routine care the local committee exempted the authors from the need to apply for informed consent.

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Table 1: Clinical and demographic features of patients according to the classification late presenters and not late presenters

	Not late presenters	Late presenters	p-value
Age (mean ± SD) in years	42.71 ± 13.4	40.0 ± 12.19	0.57
CD4 cell count (cells/μl)	456.0 ± 54.0	106.55 ± 87.75	< 0.0001*
Male (%)	57.1	76.1	0.50
Living in rural areas (%)	28.5	32.18	0.82
Unknown education	3 (42.8%)	33 (37.9%)	0.88
Mandatory school	2 (28.5%)	26 (29.8%)	0.72
High school	0 (0%)	22 (25.2%)	0.29
University degree	2 (28.5%)	6 (6.8%)	0.19
Risk factor for HIV infection			
• MSM	1 (14.2%)	8 (9.1%)	0.82
• Heterosexual contact	2 (28.5%)	45 (51.7%)	0.43
• Intravenous drug use	0 (0%)	4 (4.5%)	0.68
• Blood	0 (0%)	4 (4.5%)	0.68
Emigrant	0 (0%)	25 (28.7%)	0.22
Age at diagnosis			

<ul style="list-style-type: none"> • under 19 years old • 20-29 years old • 30-39 years old • 40-49 years old • Above 50 years old 	0 (0%) 2 (28.5%) 0 (0%) 3 (42.8%) 2 (28.5%)	1 (1.1%) 19 (21.8%) 26 (29.8%) 23 (26.4%) 18 (20.6%)	0.09 0.95 0.20 0.62 0.99
Year of being diagnosed <ul style="list-style-type: none"> • 2005-2007 • 2008-2010 • 2011 • 2012 	3 (42.8%) 0 (0%) 1 (14.2%) 3 (42.8%)	14 (16.0%) 38 (43.6%) 17 (19.5%) 18 (20.6%)	0.20 0.06 0.87 0.37
CDC stage of disease <ul style="list-style-type: none"> • A • B • C 	2 (28.5%) 4 (57.1%) 0 (0%)	1 (1.14%) 11 (12.6%) 75 (86.2%)	0.004* 0.01* < 0.0001*
Outcomes Days of hospitalization(mean \pm SD) Deaths	9.7 \pm 4.60 0 (0%)	17.6 \pm 12.85 13 (14.9%)	p=0.111

*p- value significant

Table 2: Distribution of late presenters according to the CD4 cell count

CD4 cell count	Late presenters (n/%)
< 50 cells/mm ³	19 (21.8%)
< 200 cells/mm ³	32 (36.7%)
< 350 cells/mm ³	9 (10.3%)

Table 3: Factors associated with late presentation in multivariate logistic analysis

Predictor	Odds ratio	95% CI	P value
Risk factor for HIV infection (reference MSM)			
<ul style="list-style-type: none"> • Heterosexual contact • Intravenous drug use • Blood transfusion 	2.81 0.62 0.62	0.22-34.8 0.02-18.8 0.02-18.8	0.42 0.78 0.78
Emigrant	6.89	0.37-125.3	0.19
Age at diagnosis (reference under 19 years old)			
<ul style="list-style-type: none"> • 20-29 years old • 30-39 years old • 40-49 years old • 50-59 years old • 60-69 years old • Above 70 years old 	2.6 17.6 2.23 2.33 1.66 1.0	0.08-82.7 0.25-1239.9 0.07-66.5 0.06-87.9 0.04-64.0 0.01-92.4	0.58 0.18 0.64 0.64 0.78 1.0
Living in rural areas	1.18	0.21-6.49	0.84
Male gender	2.08	0.43-10.04	0.35
University degree	Reference		
Unknown education	3.66	0.50-26.8	0.20
Mandatory school	4.33	0.50-37.2	0.18
High school	17.3	0.73-407.6	0.07

MSM, men having sex with men

CI: Confidence Interval

Table 4: Distribution of not late, late and very late presenters according to the CDC clinical stage classification

CDC stage of disease	Not late N (%)	Late N (%)	Very late N (%)
Stage A	2 (2.1%)	1 (1.0%)	0 (0%)
Stage B	4 (4.2%)	5 (5.3%)	6 (6.3%)
Stage C	0 (0%)	30 (31.9%)	45 (70.3%)

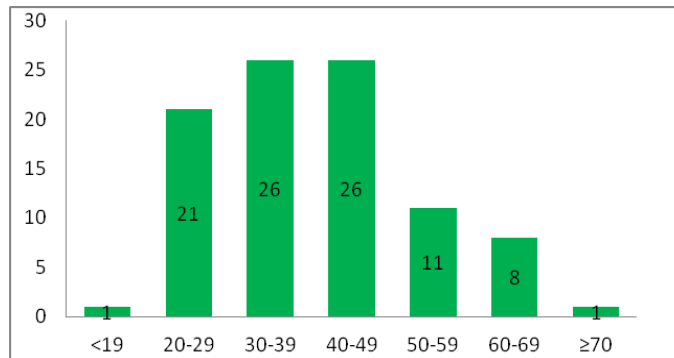


Figure 1: Distribution of patients according to age

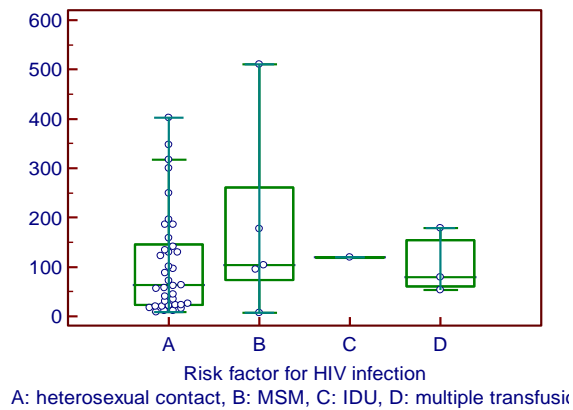


Figure 2: CD4 cell count according to the risk factor for HIV infection

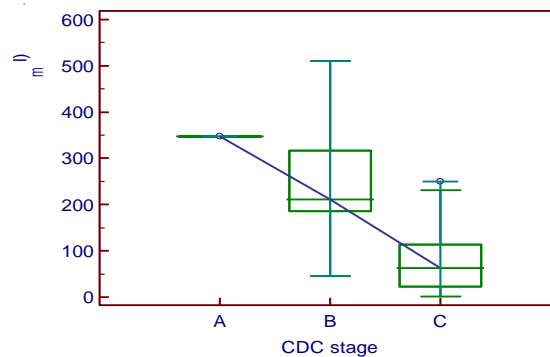


Figure 3: CD4 cell count according to the CDC stage of HIV infection

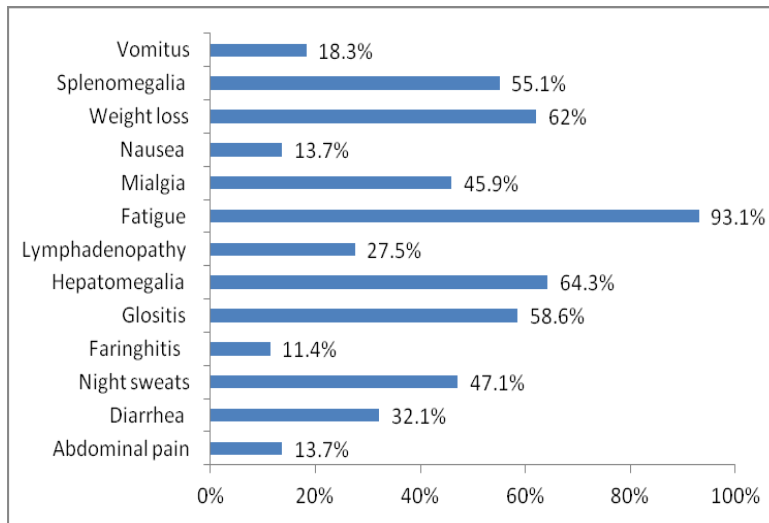


Figure 4: Prevalence of symptoms prior to HIV test among late presenters.