LATE DIAGNOSIS OF HIV INFECTION IN IAŞI COUNTY - FREQUENCY, ASSOCIATED FACTORS, THERAPEUTIC OPTIONS

A. Vâţă1, Carmen Manciuc1, Cristina Nicolau2, L. Prisacariu2, Luminiţa Vâţă1, Carmen Dorobăţ1

1. University of Medicine and Pharmacy “Gr. T. Popa” Iaşi
2. Regional HIV/AIDS Center of Iaşi

Abstract. Late diagnosis of HIV infection has unfavorable repercussions on both the patients themselves, due to higher morbidity and mortality rates, and the society as a whole, given the higher infection transmission risks and increased therapy and recovery costs. Material and methods. Our paper tackles a retrospective study conducted on naïve patients that have entered the records of the Regional HIV/AIDS Center of Iaşi in the last 10 years (2001-2010), based on the initial clinical, laboratory and therapeutic data found in the follow-up records of these patients. Late diagnosis was established when the patient presented for care with a CD4 count below 350 cells/mL or having an AIDS-defining condition. Results. 73.4% of the 192 patients included in the study were considered late presenters (58.5% with advanced HIV infection), according to the latest consensus definition. The average age of late presenters was 23.7 years, 53.9% of them being born between 1988 and 1991; M/F ratio – 1.3, U/R ratio – 1.14, average CD4 number – 130.8/cmm. The factors usually associated with late diagnosis in literature (age over 30 years, males, hepatitis co-infection) had no statistical significance in our study group. Mortality rates were considerably higher in late presenters (31.9 vs. 7.8%, p=0.002) and were correlated with a low initial number of CD4 (p<0.001), younger age (p=0.004); 57.8% of the deaths occurred within 6 months from diagnosis. ARV therapy was started by combining 2 NRTIs and PI in 52.7% of the patients, 2 NRTIs and one NNRTI in 32.1% of them, while raltegravir was only used in 3 patients. Conclusions. late diagnosis rates were higher in Iaşi County than in literature, while the risk factors detected by other authors had no statistical significance, possibly due to the regional epidemiological specificity.

Keywords: odds ratio, lethality, antiretroviral therapy

Introduction

Because the HIV infection may be asymptomatic for a long period of time and some of the initial signs and symptoms are not specific, a number of patients are diagnosed late in the course of the disease. According to some researches, 30 to 50% of the 2.3 million infected people in Europe are not yet diagnosed. [1,2]

Late HIV infection diagnosis bears negative effects on both the patients themselves and on society as a whole. Up to 90% of the AIDS-defining events occur in viremic untreated patients [3] and late diagnosis increases short-term mortality rates by 56% [4]; the lower the CD4 level, the higher the mortality rates of the following years [5]. The later the infection is acknowledged, the higher the risks of transmission, due to high viral load and to the perpetuation of risky (sexual) behaviors. Also, the costs incurred for the treatment of HIV infection and associated comorbidities are significantly higher for late presenters.

There are numerous studies worldwide that tried to establish the frequency of late HIV infection diagnosis; however they were faced with major differences concerning the definition of late diagnosis. In the literature, more than 20 different definitions have been cited for a late presenter. It (usually) relies on the initial CD4 number (vary-
ing between 50 and 350/cmm), on the presence of an AIDS-defining disease or on the time elapsed between diagnosis and AIDS.[6] Therefore, late diagnosis incidence varied considerably between 15 and 83%.[3, 7]

The discussions among numerous European experts (started in 2009) led to the publication (in April 2010) of a consensus definition. A late presenter is the patient with initial CD4 levels below 350/cmm or with an AIDS-defining manifestation. The term “advanced HIV infection” was also used for CD4 levels below 200/cmm or an AIDS-defining event.[8]

Our goal was therefore to analyze naïve patients in the records of the Regional Center of Iaşi, in order to determine the incidence of late HIV infection diagnosis, the associated factors and the initial antiretroviral (ARV) therapy of these patients.

Material and method

We conducted a retrospective study on 192 naïve patients from Iaşi County, diagnosed with HIV infection between 2001 and 2010 (November) using the data from their follow-up records. We analyzed demographic data (age, sex, background), probable transmission route, initial CD4 levels, viral load, co-infections with hepatitis viruses, initial ARV therapy regimen. We excluded the newborns and patients transferred from other centers.

We used the European 2010 consensus definition in order to determine late diagnosis and patients with advanced HIV infection [8].

The statistical analysis relied on descriptive statistical indicators (mean values, confidence intervals 95%) and comparative tests (t Student, $\chi^2$, odds ratio) calculated using well-established computer programs (SPSS and Microsoft Excel + Analyse-It). $p<0.05$ was considered significant.

Results

A high percentage, namely 73.4% (141), of the 192 naïve patients diagnosed with HIV infection in Iaşi County over the ten-year period were considered late presenters, according to the consensus definition.

If we consider a CD4 level of 200 or the presence of an AIDS-defining event as the threshold value, 113 patients (58.5% of the whole group) may be considered as suffering from advanced HIV infection (table I).

About one third of the patients (32.6%) had initial CD4 lymphocyte levels below 50/cmm.

The annual numbers of late presenters (LP) varied between 23 and 9, with a significant decrease over the last 4 years ($p=0.008$) (figure 1).

The patients’ age varied between 11 and 65 years, with a mean value of 23.7 years (CI 95 21.5 – 25.9). More than half of the LP (53.9%) were born between 1988 and 1991. The male patients (M/F = 1.31) and the urban origin (U/R = 1.14) prevailed in the LP group.

The average number of CD4 lymphocytes amounted to 130.8/cmm (CI 95 112.7 - 148.8). Figure 2 shows patient distribution depending on initial CD4 levels.

The viral load varied between $2 \times 10^3$ and $10^7$ copies/ml, with an average of $10^6$ (CI 95 $5.1 \times 10^5$ - $1.51 \times 10^6$).

In the LP group 45 deaths occurred over the survey interval, a considerably higher number than in the group of non-late presenters (NLP) = 31.9% vs. 7.8% ($\chi^2 = 9.85$, $p = 0.0017$). Most of the deaths (57.8%) occurred during the first 6 months from diagnosis (24.4% in the first month). Among the

<table>
<thead>
<tr>
<th>CD4 Cells Categories</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>36</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 1. Patient distribution according to the CDC classification (no. cases)
Late Diagnosis of HIV Infection in Iaşi County

![Diagram of factors associated with late diagnosis (odds ratio)](figure 3)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deceased</th>
<th>Alive</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4/cmm</td>
<td>73.4</td>
<td>168.6</td>
<td>4.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VL (copies/ml)</td>
<td>2.2x10⁶</td>
<td>8.4x10⁵</td>
<td>1.86</td>
<td>0.0672</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.2</td>
<td>25.9</td>
<td>2.92</td>
<td>0.0041</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>62.2</td>
<td>54.1</td>
<td>0.52</td>
<td>0.473</td>
</tr>
</tbody>
</table>

Table II. Variables associated with death risks (mean values)

![Diagram of ARV therapy of late presenters](figure 4)

Figure 4. ARV therapy of late presenters

Discussion

If they do not receive ARV therapy, most of the HIV infected patients will slowly progress to AIDS in the following 10 years on average, as this risk factors associated with death in the LP group we noticed low CD4 levels at the time of diagnosis (p<0.0001) and younger age (p=0.0041) (table II). Relying on literature data that associated some variables (males, over 30 years of age, hepatitis co-infection) with a higher risk of late diagnosis, we drew a comparison between the two groups of patients (LP and NLP) by calculating the odds ratio. The male gender was not associated in our group with high risks of late diagnosis, as the M/F ratio was similar among both the LP and the NLP (OR=0.918; 95 CI: 0.455 - 1.845). Although the number of people over 30 years old was higher among the LP, this had no statistical significance (OR=1.49; 95 CI: 0.659-3.426). Associated B or C hepatitis virus infections were more frequent in the NLP group, and they seem to have a protective effect for late diagnosis (OR=0.465; 95 CI: 0.200-1.085).

As we considered access to specialized medical services more difficult in rural areas, we also calculated the OR for this variable (OR=1.013; 95 CI: 0.493-2.083). Comparing the frequency of HIV diagnosis during the hot season (May - September) with the cold season, we found no statistically significant differences in our group of patients (OR=0.897; 95 CI: 0.425-1.904).

The only factor revealed by us, which had a significant influence on the late HIV infection diagnosis risk, was the year of birth between 1988 and 1991 – OR=1.969; 95 CI: 1.021-3.799.

Antiretroviral (ARV) therapy was administered in all our cases (either immediately after diagnosis, or after the cure of the associated conditions). In most of the cases (52.7%), 2 NRTIs were administered together with one PI, while in 32.1% of the cases 2 NRTIs and one NNRTI were preferred (figure 4).
interval largely depends on factors related to the host and the virus. A gradual CD4 count drop of about 60-100/year occurs during the natural HIV infection course.

A high percentage, that is 73.4%, of the 192 patients enrolled in the study, were considered late presenters, which is far from the results of other previous European researches, where the LP percentage did not exceed 45%.[1] The fact that the latter employed different standards to define late diagnosis rends the results not fully comparable.

Romania is a unique model in Europe concerning HIV infection epidemiology, due to a massive infection phenomenon affecting numerous people, mostly children, over a short period of time (1988-1991). The fact that more than half (53.9%) of the LP, according to clinical and CD4 level criteria, were born in that interval may lead to the conclusion that they suffered a parenteral infection in their first childhood and lived with the virus for more than 10 years.

Like most of the other European countries, Romania has a well established policy for HIV testing concerning special target groups: pregnant women, blood donors, prisoners, sex workers, drug addicts. In 2010 more than 690,000 HIV tests were performed, with a positivity rate of 0.34%. (higher among prisoners – 10.77%, MSM – 7.84%)[9]. Some of the patients infected in their early childhood, between 1988-1991, are slow progressors, with minimal signs of disease, thus escaping diagnosis. As they are now reaching a sexually active, child bearing age, they could contribute to the horizontal and vertical spread of their infection. The mandatory pre-marital and obstetrical wards HIV testing should help identify some of these individuals. The practitioner should be aware of the special risk that this age group population has and efforts towards a more frequent HIV testing should be carried out.

The fact that several LP-associated factors in other European studies were not validated in our paper (male gender, over 30 years of age, hepatitis co-infection) maybe due to this epidemiological specificity. The number of declared homosexuals (5) and IV drug addicts (2) was low in our group and did not allow a valid statistical analysis.

The discovery of a chronic viral infection in an individual should lead to a larger investigation of his health status and the search for other co-infections (including HIV). This could explain why, in our group, a hepatitis co-infection was not an associated factor with LP as some authors have found [10] and why it had a tendency to be more of a protective factor (OR=0.46).

Due to certain adaptive changes to the ambient temperatures, length of day and food supply our organism is altering its immune response according to seasonal characteristics. Variation in melatonin, glucocorticoids levels and other mechanisms are cited. [11, 12, 13] The immune response is usually higher during the hot season and HIV infection diagnosis during this period could be the sign of a more affected immunity, but our results do not confirm this hypothesis (OR-0.897; 95 CI: 0.425-1.904).

The annual LP number decreased progressively over the time interval under survey, dropping to about 10 cases every year in the last 4 years. This descending trend has also been noticed by other European authors [3] and it may be due to better access to HIV testing and educational measures.

The lethality of the infection was significantly higher among the LP, which is also supported by literature data [3, 1] and was associated both with initially lower CD4 lymphocyte levels and with younger age. More than half of the deaths occurred within the first 6 months (24.4% during the first month) from HIV infection diagnosis.

These late presenters usually have high viral load and/or serious associated conditions. The antiretroviral treatment used was aimed on rapidly decreasing the viral load and on raising the CD4 levels, while taking in consideration the possibility of an immune reconstitution inflammatory syndrome and some individual characteristics.

Raltegravir, a drug that was officially launched in Romania in the summer of 2010, was used for only 3 patients. It has been recommended for naïve patients by both the American (DHHS December 2009 – as first intention therapy) and the European (2010 – as alternative therapy) guides and due to the rapid viremia drop, reduced interactions with other drugs and good tolerability, it could be especially recommendable for this type of patients (LP).

Conclusions

- the frequency of late HIV infection diagnosis in Iaşi County, between 2001 and 2010, was higher than that described in literature (73.4%)
- the factors associated by some European authors with late diagnosis (over 30 years of age, male gender, hepatitis co-infection) were not significant in the group under survey
- the fact of being born between 1988 and 1991 was significantly associated with late HIV infection diagnosis (OR=1.96 95 CI: 1.021 - 3.799)
- mortality rates were considerably higher in late presenters (31.9 vs. 7.8%, p = 0.0017) and they were associated with low CD4 counts and younger age
- ARV therapy consisted of 2 NRTIs and one PI in 52.7% of the cases, and 2 NRTIs and one NNRTI in 32.1% of the cases.
Abbreviations
NNRTI - Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI - Nucleoside reverse transcriptase inhibitors
PI – protease inhibitors
LP - late presenters
NLP - non-late presenters

References
1. Hamers FF, Phillips AN. Diagnosed and undiagnosed HIV-infected populations in Europe HIV Medicine 2008; 9 (Suppl. 2), 6–12