Recupero immunologico e soppressione virologica nei "late presenters": uno studio retrospettivo monocentrico sulle nuove diagnosi HIV dal 2018 al 2023.

Immune and virological recovery in late presenters: a retrospective monocentric study in HIV-naive persons from 2018 to 2023.

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Riassunto

Negli ultimi anni sono stati ottenuti notevoli miglioramenti nel trattamento e nella prognosi dei pazienti con diagnosi precoce di HIV. Tuttavia, la presentazione tardiva rimane un grave problema sanitario ed è associata ad esiti peggiori e a un recupero immunologico e virologico più lento. L'obiettivo dello studio è stato quello di confrontare il recupero immunologico e la soppressione della viremia nel gruppo dei "late presenters" rispetto a quello dei "non-late presenters".

Abbiamo condotto uno studio di coorte retrospettivo monocentrico in cui abbiamo analizzato le caratteristiche di 113 persone con HIV (PWH) che hanno ricevuto una nuova diagnosi di HIV e hanno iniziato la terapia antiretrovirale (ARV) presso la Clinica di Malattie Infettive di Perugia tra il 2018 e il 2023.

Le PWH sono state suddivise, in base alla conta dei CD4 alla diagnosi, in gruppo "late presenters" (≤350 CD4/microL alla diagnosi) e gruppo "non-late presenters" (PWH >350 CD4/microL alla diagnosi).

Confrontando questi due gruppi, abbiamo utilizzato il test x^2 per valutare l'associazione tra variabili.

In base allo stato immunovirologico al momento della diagnosi: 72/113 PWH (63.7%) erano late presenter, mentre 41/113 (36.3%) erano non-late presenters.

Confrontando i due gruppi per la variabile età, la differenza tra i due gruppi è risultata significativa (p<0.001): l'età mediana nei late presenters era più alta (44.5 anni) rispetto al gruppo dei non late presenter (32 anni).

Abbiamo confrontato il tempo di soppressione della viremia HIV (in mesi) e il recupero dei CD4 a 6 mesi nei due gruppi: è stata riscontrata una soppressione virologica significativamente più

Abstract

In the last years significant improvements have been achieved in the treatment and prognosis of patients with early diagnosis of HIV. However, late presentation remains a serious health issue and is associated with worse outcome and slower immune and virological recovery. The objective of the study was to compare immunologic recovery and viremia suppression in "late presenters" versus "non late presenters" group.

We performed a single-centre retrospective cohort study in which we analysed the characteristics of 113 people with HIV (PWH) who received new diagnosis of HIV and started anti-retroviral (ARV) therapy at Perugia Infectious Diseases Clinic between 2018 and 2023.

PWH were defined, based on CD4 count at diagnosis, as "late presenters" (≤350 CD4/microL at diagnosis) and "non-late presenters" (PWH >350 CD4/microL at diagnosis). Comparing these two groups, we used the x^2 test to assess the association between categorical variables.

According to the immuno-virological status at diagnosis: 72/113 PWH (63.7%) were late presenters, while 41/113 (36.3%) were non-late presenters.

Comparing the two groups for the age variable, the difference between the two groups was significant (p<0.001): the median age in late presenters was higher (44.5 years) than in non-late presenter group (32 years).

We compared HIV-viremia suppression time (in months) and CD4 recovery at 6 months in the two groups: a slower

lenta (>6 mesi) nel gruppo dei late presenters (p=0.02); inoltre, nei late presenters il recupero dei CD4 è stato inferiore rispetto al gruppo dei non late presenter (p=0.01).
In conclusione, la presentazione tardiva rimane una sfida per la sanità pubblica. È necessario compiere ulteriori sforzi per garantire una diagnosi precoce dell'infezione da HIV.
La diagnosi precoce consente una più rapida riduzione della carica virale a livelli non rilevabili e un migliore recupero immunitario.

virological recovery (>6 months) was significantly high in late presenter group (p=0.02).
In late presenters the CD4 increase was lower than in non-late presenters (p=0.01).
Late presentation remains a challenge for public health. Further efforts must be made to ensure an early diagnosis of HIV infection. Early diagnosis allows a faster reduction of viral load to undetectable levels and a better immune recovery.

Introduction

Despite improvements in the diagnosis and treatment of HIV infection over the years, a large number of new HIV diagnoses worldwide, and also in Italy, occurs at a late stage. [1,2]
In accordance with the scientific literature, a "late presenter" is a person with HIV presenting for care with a CD4 count below 350 cells/microL or presenting with an AIDS-defining event, regardless of the CD4 cell count. [3]
In addition, the definition of "presentation with advanced HIV disease" is a person presenting for care with a CD4 count below 200 cells/microL or presenting with an AIDS-defining event, regardless of the CD4 cell count. [3]
Regarding Italy, 888 new diagnoses of HIV infection were reported in 2022, representing an incidence of 3.2 new diagnoses per 100,000 residents.
There has been a decrease in new HIV diagnoses since 2012, which appears most evident from 2018 to 2020, with a slight increase in the last two years post-COVID-19.
In 2022, in terms of incidence of new HIV diagnoses, Italy was below the estimated incidence of Western European and European Union countries (5.1 cases per 100,000 residents in both areas). [2,4]
In 2022 in Italy, 40.6% of people newly diagnosed with HIV infection were late diagnoses, with a CD4 lymphocyte count of less than 200 cells/microL; 58.1% had a CD4 count of less than 350 cells/microL; it is a higher percentage than late presenters in Western Europe (46.2%), Central Europe (44.5%) and Eastern Europe (55.1%).
In 2022 in Italy, nearly half of newly diagnosed HIV-infected people were tested for suspected HIV disease or presence of HIV-related symptoms (41.2%), pointing out the need to spread HIV testing to asymptomatic people at risk of infection. [2,4]

Methods

We performed a single-centre retrospective cohort study where we analysed the characteristics of people who received new diagnosis of HIV at Perugia Infectious Diseases Clinic between 2018 and 2023.
The objective of the study was to compare characteristics, immunologic recovery and viremia suppression in "late presenters" (≤350 CD4/microL at diagnosis) versus "non late presenters" group (>350 CD4/microL at diagnosis) or presenting with an AIDS-defining event. We used demographic and medical records data from clinical Netcare software; virological data (cp/mL) and lymphocyte cell counts (cells/microL) were extracted from Virology laboratory reports.
We compared immuno-virological recovery in the two groups: 1) late presenters, 2) non-late presenters.
We defined viremia suppression as HIV-RNA <50 copies/mL.
Virological recovery defined as viremia suppression time (in months) was compared in the two groups as a dichotomous variable (≤6 months and >6 months). In cases where viremia suppression was not achieved at the time of observation, the entire observation time was considered.
Categorical and discrete variables were described as frequency and %, continuous variables as mean and standard deviation (mean ± SD) if normally distributed, as median and interquartile range (IQR) if not normally distributed.
In the crude analysis comparing intervention groups, we used the x^2 test to assess the association between categorical variables; t-test was used to compare continuous variables with normal distribution.
Data analysis was performed by SPSS statistics software ver. 23.

Results

We enrolled 113 people who were newly diagnosed with HIV between 2018 and 2023 and who started ARV therapy at Infectious Diseases Day Hospital of Perugia.

Eighty-eight patients were male, the median age at diagnosis was 40 years (18-75). Population characteristics are described in **Table 1**.

We analysed the immuno-virological status at diagnosis: 72/113 (63.7%) had ≤350 CD4/microL, defined as "late presenters", while 41/113 (36.3%) had >350 CD4/microL, defined as "non-late presenters".

Fifty-five patients (48.7%) presented with AIDS-defining infectious events; the most frequent were pulmonary Pneumocystosis in 10 cases (8.8%), Kaposi sarcoma in 9 cases (8.0%), neurotoxoplasmosis in 4 cases (3.5%), invasive Citomegalovirus infection in 4 cases (3.5%), invasive Candida infection in 4 cases (3.5%).

In the whole population the median CD4 cell count at diagnosis was 218/microL (2-1132); the median viremia at diagnosis was 218000 cp/ml and the median time of viremia suppression was 5 months.

Six months after diagnosis the median CD4 number was 385/microL.

Calculating the delta (difference between the CD4 at 6 months and the CD4 at diagnosis), we obtained a median of 160/microL.

Then we compared the two groups: late presenters versus non-late presenters.

The comparison between the characteristics of the two groups is described in **Table 2**.

Viremia suppression and CD4 recovery in the two groups and in the total population is shown graphically in **Figures 1** and **2**.

Comparing the two groups for the age variable, the difference between the two groups was significant (p<0.001): the median age in late presenters was significantly higher (44.5 years) than in non-late presenter group (32 years)

We also analysed virological recovery: we compared viremia suppression time (in months) in the two groups as a dichotomous variable (≤6 months and >6 months) using the Chi-square test: a slower virological recovery (>6 months) was significantly associated with late presenter group (p=0.02).

Regarding antiretroviral therapy, the most widely chosen first-line treatment regimen included an

Population characteristics	**n=113**
Age (years), median [min-max]	40 [18-75]
Gender, n (%)	
Male	88 (77.8%)
Female	25 (22.2%)
Birth country, n (%)	
Italy	75 (66.4%)
Others	38 (33.6%)
Reason for test execution, n (%)	
AIDS-related symptoms	35 (31.0%)
Non-AIDS-related symptoms	26 (23.0%)
Screening	25 (22.1%)
HIV+ partner	8 (7.1%)
Recommended by other specialists	14 (12.4%)
Pregnancy	4 (3.5%)
CDC stage, n (%)	
A1-A2	53 (46.9%)
A3	18 (15.9%)
C3	34 (30.1%)
Others	8 (7.1%)
Late presenters, n (%)	
Yes	72 (63.7%)
No	41 (36.3%)
Main opportunistic infections, n (%)	
Pulmonary pneumocystosis	10 (8.8%)
Kaposi sarcoma	9 (8.0%)
Neurotoxoplasmosis	4 (3.5%)
Invasive CMV infection	4 (3.5%)
Invasive Candida infection	4 (3.5%)
ARV therapy at the beginning, n (%)	
Triple therapy with INI	76 (67.3%)
Triple therapy with PI	11 (9.7%)
Triple therapy with doravirine	13 (11.5%)
Dual therapy	5 (4.4%)
Other	8 (7.1%)

ARV: antiretroviral;
CMV: cytomegalovirus;
INI: integrase strand transferase inhibitors;
PI: protease inhibitors.

Table 1. Population characteristics.

Table 2. Comparison between late presenters and non-late presenters.

	Late presenters (n=72)	Non late presenters (n=41)	p
Age (years), median [min-max]	44.5 [18-75]	32.0 [21-68]	<0.001
Gender, n (%)			
male	58 (80.5%)	30 (73.2%)	
female	14 (19.5%)	11 (26.8%)	n.s.
Nadir CD4 (cell/microL), median [min-max]	97.0 [2-324]	565.0 [367-1132]	<0.001
Delta CD4 (cell/microL), median [min-max]	147.5 [-48 – 566]	238.0 [-400 – 978]	0.01
Viremia suppression at 6 months, n (%)			
Yes	47 (65.3%)	35 (85.4%)	
No	25 (34.8%)	6 (14.6%)	0.02
Time to viremia suppression* (months), median [min-max]	5 [1-29]	2 [1-17]	n.s.

Figure 1.
Median CD4 difference six months after diagnosis (cells/microL).

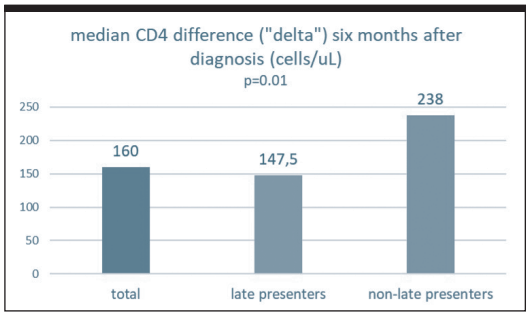
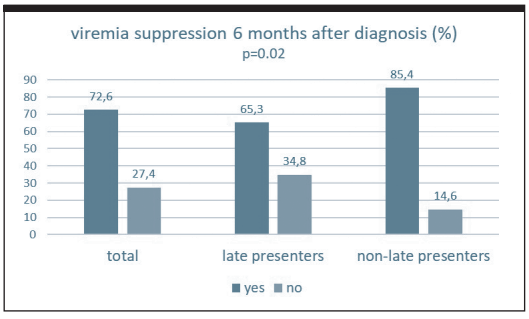


Figure 2.
Viremia suppression 6 months after diagnosis (%).



integrase inhibitor (INI) in both groups, for a total of 76 people with HIV(PWH) (67.3%) receiving INI-based regimens at the beginning. The most used INI was bictegravir, in 50 cases (44.2%).

Five PWH (4.4%) started antiretroviral therapy with a dual regimen containing dolutegravir; in all these 5 cases, viremia was suppressed at 6 months.

Regarding immunological recovery, we compared CD4 delta at 6 months in the two groups and obtained a statistically significant result: in late presenters the CD4 increase is lower than non-late presenter group (p=0.01).

Four deaths occurred, all of them were late presenters and died due to complications of advanced HIV or opportunistic infections.

Discussion

According to the latest data from the Italian National Institute of Health (Istituto Superiore di Sanità, ISS), in 2022 in Italy more than half of new HIV diagnoses were late presenters, meaning they had a CD4 count <350 cells/microL or presented with an AIDS-defining event; the findings from our study agree with Italian data. [2]

We found that late presenters are more often male, older than non-late presenters, and have worse immunologic recovery: in fact, a higher percentage had viremia still detected at 6 months, compared with non-late presenters, and CD4 recovery was lower.

This finding is in agreement with the scientific literature, particularly with the ICONA cohort data, showing that late and AIDS presenters still show a higher risk of treatment failure and have an increased mortality, especially in the first year, due to AIDS-related events [5]. However, the efficacy of antiretroviral therapy was demonstrated by the time to HIV viremia suppression that was collectively lower than 6 months in more than 50% of PWH.

Therapies of choice in naïve patients appear to be integrase strand transferase inhibitors (INI)-containing regimens in particular second generation INI (bictegravir, dolutegravir), in accordance with

international guidelines and scientific literature, which shows that INI became a key component of first-line therapy. [6,7]
The most frequent opportunistic infection at HIV diagnosis in late presenters remains pulmonary pneumocystosis, both in our study and in Italian ISS data. [2]
It seems a priority to perform more extensive screening to make earlier HIV diagnoses; some experiences described in medical literature have shown the benefits of screening in health care settings including emergency departments to facilitate early HIV diagnosis. [8,9]
Increasing early diagnosis in the general population is certainly crucial, as reported by CDC (Centers for Disease Control and Prevention), to carry out focused approaches that encourage more people who are at substantial risk for HIV to get more frequently tested for HIV. [10]
Furthermore, it is fundamental to implement innovative technologies and programs, such as self-testing, to make testing more accessible, especially in high-burden areas. [10]

Conclusions

Our data show the need to reduce the number of late HIV diagnoses; early diagnosis is indeed correlated with better immunovirological recovery.
Older age appears to correlate with later diagnosis, so there is a need to raise awareness of this category of people to perform early HIV testing if they have presented risk exposure in their lifetime. ■

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