

HIV/AIDS dopo quattro decenni: l'aumento dei Late Presenters nelle nuove diagnosi - analisi di una serie di casi dal Dipartimento di Malattie Infettive e Tropicali dell'Ospedale Universitario di Careggi, Firenze (2023-2024).

HIV/AIDS after four decades: the rise of Late Presenters in new diagnoses - A case series analysis from the Infectious and Tropical Diseases Department of Careggi University Hospital, Florence (2023-2024).

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Riassunto

Secondo i report nazionali stiamo assistendo a un incremento delle diagnosi annue di infezione avanzata da HIV nei cosiddetti "Late Presenters" cioè persone con alla diagnosi una conta di linfociti T CD4 <350 cell/mm³ o patologia diagnostica di AIDS indipendentemente dalla conta di CD4. In questo studio analizziamo le caratteristiche epidemiologiche, demografiche e cliniche dei nuovi casi riscontrati presso la Struttura di Malattie Infettive e Tropicali dell'AOU Careggi di Firenze negli ultimi due anni.

Studio monocentrico, osservazionale, retrospettivo, includente Persone che vivono con HIV (PLWH) maggiorenni, ricevuti diagnosi di infezione da HIV presso l'AOU Careggi, tra 01/01/2023 - 31/08/2024. Dati raccolti da consultazione di cartelle cliniche elettroniche. Le variabili qualitative sono state riassunte in frequenze assolute e relative, le variabili quantitative in mediana e range interquartile (IQR).

Sono state riscontrate 46 nuove diagnosi di HIV, ventotto nei primi otto mesi del 2024, con prevalenza nel genere maschile (M 78,3%), italiani (67,4%), con un caso su tre nato all'estero; età mediana di 40,5 anni.

Abstract

According to national reports, we are observing an increase of diagnoses of advanced HIV infection in so-called "late presenters", people diagnosed with CD4 T-lymphocytes below 350 cells/mm³, or with an AIDS defining disease regardless CD4 cells count. In this study, we analyze the epidemiological, demographic, and clinical characteristics of the new cases detected at the Infectious and Tropical Diseases Department of AOU Careggi in Florence over the last two years.

This is a monocentric, observational, retrospective study including adult PLWH diagnosed with HIV infection at Careggi University Hospital, Florence, between January 1, 2023, and August 31, 2024. Data was collected through the consultation of electronic clinical records. Qualitative variables were summarized as absolute and relative frequencies, while quantitative variables were presented as medians and interquartile ranges (IQR).

A total of 46 new HIV diagnoses were registered, with 28 in the first eight months of 2024.

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Il comportamento a rischio maggiormente riscontrato è stato rapporto non protetto eterosessuale nel 71.8%. In 17 casi (36,8%) lo screening è stato effettuato durante un ricovero ospedaliero. I Late Presenters sono stati il 54,3% di cui 16 casi (34,8%) con evento AIDS alla diagnosi (polmonite Pneumocystis Jirovecii in cinque casi e sarcoma di Kaposi in quattro). Alla diagnosi tre casi (6,5%) presentavano una coinfezione HIV/HBV, quattro (8,7%) una infezione occulta da HBV, cinque (10,9%) una infezione luetica attiva.

Il genotipo era disponibile per 43 pazienti, sette presentavano mutazioni maggiori per NNRTI. Un INSTI-based regimen è stata la prima terapia di scelta nel 97,8% dei casi.

La terapia antiretrovirale è stata introdotta con una mediana di 6 giorni. Non sono state riportate differenze statisticamente significative nelle caratteristiche epidemiologiche e cliniche al confronto tra late presenters e non.

I dati sono concordi alla tendenza riportata dai report di ISS e Regione Toscana.

È importante continuare a sensibilizzare la popolazione generale e gli ambienti sanitari riguardo allo screening per HIV in modo da affrontare l'aumento dei casi diagnosticati in stadi avanzati di infezione, poiché questo dato coinvolge particolarmente una popolazione, i maschi eterosessuali, che non rientra nei gruppi target più comuni a cui viene rivolto lo screening.

The majority of cases were male (78.3%), Italian (67.4%), one-third of cases originating from other Countries. The median age was 40.5 years. The most common risk behavior was unprotected heterosexual intercourse (71.8%). In 17 cases (36.8%), screening was performed during hospital admission. Late presenters accounted for 54.3%, with 16 cases (34.8%) diagnosed with an AIDS defining event (most commonly with PJP in five cases and Kaposi's sarcoma in four cases).

At the time of diagnosis, three cases (6.5%) had an HIV/HBV coinfection, four cases (8.7%) had occult HBV infection, and five cases (10.9%) had untreated syphilis. Genotype results were available for 43 patients, seven of whom had major mutations for NNRTI. An INSTI-based regimen was chosen as the first-line therapy in 97.8% of cases. Antiretroviral therapy was initiated after a median of 6 days. No significant differences were found when comparing late presenters with non-late presenters.

The data are consistent with trends reported by the Italian ISS (Istituto Superiore di Sanità) and the Tuscany Region. It is important to continue raising awareness in the general population and Healthcare settings about HIV screening to face the increasing number of diagnoses at advanced stages of infection since it involves particularly a population, heterosexual males, that are not included in the most common target groups of screening.

Introduction

More than forty years have passed since the start of the HIV pandemic, which has led to approximately 40.4 million deaths and 39 million cases living globally to date, 80 million since the discovery of the infection (1-2).

However, the overall landscape of the disease has evolved significantly. While remarkable progress has been made in scientific research, clinical treatments, and - equally important - in reducing the stigma faced by people living with HIV, new and concerning challenges have emerged.

In particular, recent reports from both international and national organizations indicate a rise in the number of new HIV infections diagnosed at an advanced stage - known as "late presenters" - especially in certain regions, a trend that has been observed particularly after the COVID-19 pandemic (3-4).

Late presenters are individuals diagnosed with HIV infection who have a CD4 T-cell count below 350 cells/mm³ or who present with AIDS-defining conditions, regardless of their CD4 count (5).

This event is particularly concerning, as it indicates delays in seeking medical care but also missed opportunities for the early initiation of antiretroviral therapy (ART), an essential factor in significantly improving both prognosis and quality of life.

The causes behind this trend are not clearly defined and may be multifactorial, encompassing individual risk perceptions as well as social, economic, cultural, and healthcare-related factors. Despite the availability of highly effective treatments, efforts in prevention and early diagnosis have yet to reach their full potential. Additionally, barriers to healthcare access, gaps in public health policies, and persistent psychological and social obstacles continue to delay timely HIV testing for many individuals (6).

Focusing on Tuscany, the most recent report published in November 2023 on data from 2022 by the regional healthcare system indicates a stable number of new HIV diagnoses - currently below the European average - but a concerning increase in the number of late presenters seeking medical care over the past two years with an increase of

6.9 percentage points between the years 2017-2018 and the years 2021-2022 (7-8).

This study examines the epidemiological, demographic, and clinical characteristics of new HIV cases identified over the past two years at the Infectious and Tropical Diseases Department of AOU Careggi in Florence. Our goal is to outline current trends, evaluate the clinical and epidemiological features of these cases, and describe our approach to addressing this trend, which continues to be a significant challenge in the global fight against the HIV pandemic

Materials and Methods

This is a monocentric, observational, retrospective study involving adults (aged >18 years) diagnosed with HIV at the Infectious and Tropical Diseases Unit of Careggi University Hospital in Florence, from January 1, 2023, to August 31, 2024.

Qualitative variables are presented as absolute and relative frequencies, while quantitative variables are described using the median and interquartile range (IQR).

Results

Our study included 46 newly diagnosed HIV cases during the study period: 18 cases in 2023 and 28 cases from January 1 to August 31, 2024. The majority were male (36 individuals, 78.3%), with 7 females (15.2%) and 3 (6.5%) identifying as transgender female.

The median age was 40.5 years [IQR 21-83]. Most patients were Italian (67.4%, 31 cases), with other cases primarily from Peru (6), followed by individuals from Morocco (2) and one each from Senegal, Nigeria, Cameroon, Albania, Moldova, Ukraine, and Slovakia.

Regarding sexual orientation, 71.8% self-identified as heterosexual, 17.4% as men who have sex with men (MSM), 6.5% as sex workers, and in the 4.3% of individuals data were missing. HIV screening was performed due to symptoms in 23.8% of cases and during hospital admission in 36.8%. Only 19.2% of diagnoses resulted from individuals' own risk perception.

At diagnosis, the median CD4 count was 285 cells/mm³ [IQR 20-1370], and the median HIV RNA level was 395,000 copies/mL [IQR 1,670 to >10,000,000].

A total of 23 cases (54.3%) were classified as late

presenters, with 77.8% of these reported in 2023. AIDS was diagnosed in 34.8% (n=16) of cases, with opportunistic infections including *Pneumocystis jirovecii* pneumonia (5 cases) and Kaposi Sarcoma (4 cases).

We also reported two cases of non-tubercular mycobacteriosis caused by *Mycobacterium avium* complex, and two cases of cryptosporidiosis.

Other manifestations have been reported including a case of extrapulmonary tuberculosis with lymph nodal involvement, a case of rhinopharyngeal Non-Hodgkin Lymphoma (Plasmablastic lymphoma) associated with the presence of progressive multifocal leukoencephalopathy, a case of Cytomegalovirus retinitis, a case of cutaneous disseminated cryptococcosis without meningeal involvement.

We also recorded a case of AIDS dementia complex and a case of wasting syndrome.

Coinfections at the first evaluation included HIV/ HBV in 3 cases (6.5%), two of them late presenters, occult HBV in 4 cases (8.7%), and syphilis in 9 cases (19.6%) with five untreated people, one with ocular involvement requiring lumbar puncture and intravenous penicillin. Four individuals had a history of syphilis treatment.

Genotype was available for 43 patients revealing transmitted drug resistances for non-nucleoside reverse transcriptase inhibitors (NNRTI) in 7 patients: three with K103N, two with G190A, one with E138A and one with coexisting K103N and G190A.

No transmitted mutations were detected for nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI) and integrase strand transferase inhibitors (INSTI).

Among these seven people three of them were born abroad. Nearly all (97.8%) began antiretroviral therapy with an INSTI-based regimen, with bicitgravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) being the preferred choice (73.9%).

Dual therapy with dolutegravir/lamivudine (DTG/3TC) was started in 4 cases, all of them with a viral load below 500.000 copies/ml regardless of the CD4 cells count. One case started a PI-based regimen due to suspected partner's resistance-associated mutations (RAMs).

ART was initiated within a median of 6 days [IQR 4-10] for all individuals.

Demographic and clinical data of the study population are presented in **Tables 1** and **2**.

	Total, n = 46	2023, n= 18	2024, n= 28
Age in years , median [IQR]	40.5 [21 - 83]	42 [21 - 83]	39 [21 - 63]
Self-identified gender , n (%)			
- Cisgender Male	36 (78.3)	14 (77.8)	22 (78.5)
- Cisgender Female	7 (15.2)	2 (11.1)	5 (17.9)
- MtoF transgender	3 (6.5)	2 (11.1)	1 (3.6)
Country of Birth , n (%)			
- Italy	31 (67.4)	13 (72.2)	18 (64.3)
- Abroad	15 (32.6)	5 (27.8)	10 (35.7)
Risk behavior , n (%)			
- Unprotected intercourses in heterosexuals	36 (78.3)	14 (77.8)	22 (78.6)
- Unprotected intercourses in MSM	8 (17.4)	3 (16.6)	5 (17.8)
- Other / unknown	2 (4.3)	1 (5.6)	1 (3.6)
Reason for HIV test , n (%)			
- Risk perception	9 (19.6)	3 (16.7)	6 (21.5)
- Biological hazard source	1 (2.8)	1 (5.6)	0 (0.0)
- Blood bank screening	3 (6.5)	1 (5.6)	2 (7.1)
- Hospitalization for AIDS manifestations	11 (23.8)	5 (27.8)	6 (21.5)
- Symptoms (fever, rash, itch, swollen lymph nodes...)	17 (36.8)	8 (44.3)	9 (32.1)
- Testing for partner's diagnosis	2 (4.2)	0 (0.0)	2 (7.1)
- Pregnancy	2 (4.2)	0 (0.0)	2 (7.1)
- First approach with Healthcare in known HIV infection	1 (2.1)	0 (0.0)	1 (3.6)
Late presenters (CD4 T-cell count below 350 cells/mm³ or with AIDS-defining conditions, regardless of CD4 count) , n (%)	25 (54.3)	14 (77.8)	9 (32.14)
CD4+ T Cell Nadir (x 10⁶/L) , median [IQR]	285 [20 - 1370]	230 [20 - 910]	470 [20 - 1370]
HIV RNA Zenit (log₁₀ copies/mL) , median [IQR]	5.6 [3.2 - >7]	5.8 [3.2 - >7]	5.6 [3.6 - >7]
AIDS cases , n (%)	16 (34.8)	8 (44.4)	8 (28.6)
AIDS Defying events , n (%)			
- <i>P. jirovecii</i> pneumonia (PJP)	5 (10.9)		
- Kaposi Sarcoma	4 (8.7)		
- Mycobacteriosis	2 (4.2)		
- Cryptosporidiosis	2 (4.2)		
- Tuberculosis (lymphnode)	1 (2.1)		
- Lymphoma	1 (2.1)		
- Progressive multifocal leukoencephalopathy	1 (2.1)		
- Cytomegalovirus retinitis	1 (2.1)		
- Cryptococcosis	1 (2.1)		
- Wasting Syndrome	1 (2.1)		
- Encephalopathy, HIV related	1 (2.1)		
Coinfections , n (%)			
- HBV coinfection	3 (6.5)		
- Occult HBV infection	4 (8.7)		
- Syphilis active / previous	9 (19.6)		
- HCV	0 (0.0)		
Transmitted major resistance-associated mutations (available in 43 PLWH), n (%)			
- NRTI	0 (0.0)		
- NNRTI	7 (16.3)		
- PI	0 (0.0)		
- INSTI	0 (0.0)		
First ART regimen , n (%)			
- BIC/TAF/FTC	34 (73.9)		
- DTG/3TC	4 (8.8)		
- DTG + TDF/FTC	2 (4.3)		
-DTG + TAF/FTC	2 (4.3)		
- DTG/3TC + TDF	2 (4.3)		
- RAL + TDF/FTC	1 (2.2)		
- DRV/c/TAF/FTC	1 (2.2)		
Days to ART initiation , median (range)	6 [2 - 93]		

Table 1. Demographic and clinical data of people who received a new diagnosis of HIV infection from January 1, 2023, to August 31, 2024, at Careggi University Hospital, Florence, Italy.

Table 2. Comparison between late presenters and non-late presenters, diagnosed from January 1, 2023, to August 31, 2024, at Careggi University Hospital, Florence, Italy.

	Late Presenters N= 25	Not Late Presenters N=21	P
Italians , n (%)	17 (68.0)	14 (66.7)	0.923
Age in years , median, [IQR]	41 [37 - 54]	39 [29 - 45]	0.0420
Self-identified gender , n (%)			
- Cisgender Male	21 (84.0)	15 (71.4)	0.566
- Cisgender Female	3 (12.0)	4 (19.0)	
- MtoF transgender	1 (4.0)	2 (9.6)	
Risk behavior , n (%)			
- Heterosexual intercourses	20 (80.0)	16 (76.2)	0.862
- MSM intercourses	4 (16.0)	4 (19.0)	
- Other / unknown	1 (4.0)	1 (4.8)	
Coinfections , n (%)			
- HBsAg positive	2 (8.0)	1 (4.8)	0.658
- Anti HbC positive	4 (16.0)	0 (0.0)	-
- Syphilis active/previous	4 (16.0)	5 (23.8)	0.506

Discussion

Our findings reflect broader national and regional trends reported by the Italian National Institute of Health (ISS) and the Tuscany Region, which have also noted an increase in new HIV diagnoses in a late stage of infection in recent years.

In particular, the rise in new cases observed in 2024 compared to 2023 underscores the continuing need for effective HIV prevention, awareness, and early diagnosis strategies. Despite advances in HIV treatment and awareness efforts, a substantial proportion of newly diagnosed individuals still present themselves at an advanced stage of infection. In our cohort, over half of the cases were classified as late presenters, with advanced immunosuppression and, in many cases, AIDS-defining conditions.

This prevalence of late presentation highlights critical gaps in early diagnosis and suggests that individuals at risk may not be accessing testing services in a timely manner.

Notably, most new diagnoses, particularly among late presenters, were observed in cisgender heterosexual males in their forties. This demographic often falls outside the focus of traditional HIV screening and awareness campaigns, which—rightly—prioritize younger individuals, key populations, and those at higher perceived risk, such as men who have sex with men, sex workers, or individuals with a history of intravenous drug use. However, the prevalence of late presentation in mid-

dle-aged cisgender heterosexual men highlights an important gap in existing HIV prevention and screening strategies, suggesting the need to broaden efforts to include all demographics effectively.

HIV, unfortunately, remains an infection that can impact individuals across all communities, regardless of age, gender, or background. To address this, testing should be promoted universally, ensuring that everyone has access to early diagnosis and care while respecting and supporting the needs of historically marginalized groups.

Late presenters pose unique clinical challenges, as the presence of advanced-stage conditions can complicate diagnosis and treatment. Moreover, healthcare providers should be vigilant in recognizing potential indicators of HIV in clinical presentations that may initially seem unrelated, particularly in cases involving opportunistic infections or unusual clinical findings. This awareness can reduce missed diagnostic opportunities, especially in cases where patients are unaware of their risk.

In addition, our findings show the presence of resistance RAMs for NNRTI in 16% of PLWH.

This is a higher value compared to those reported in studies conducted in similar settings, which show a prevalence around 7%.

However, it is important to consider the limitations of our sample (9). Results indicate that while most patients were able to begin on standard INSTI-based

regimens, drug resistance remains a potential issue in HIV management.

In conclusion, our study underscores the importance of comprehensive HIV strategies that address both early testing and immediate treatment initiation, while also expanding the scope of awareness and screening

campaigns to reach demographics currently underrepresented in HIV prevention efforts.

The high proportion of new diagnoses among cisgender men in their forties calls for targeted interventions to ensure that this group is not overlooked. ■

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