

LATE DIAGNOSIS OF HIV INFECTION IN ASYMPTOMATIC PATIENTS

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Abstract Recent findings from the START Trial provided evidence that early initiation of antiretroviral treatment should be implemented as the global standard of care. However, a large proportion of patients are still being diagnosed in late stages. Our objective was to evaluate the temporal trend in the CD4+ cell count at diagnosis during a 13 year period and the factors associated with late HIV diagnosis in asymptomatic individuals tested in the Centre for Prevention, Counselling and Diagnosis of our hospital. It was a retrospective study including all asymptomatic patients with new diagnosis of HIV infection. Very late presenters (VLP) were defined as those with CD4+ counts < 200 and late presenters (LP) with CD4+ < 350 cell/mm³. We also evaluated the proportion of patients diagnosed with CD4+ cell counts below 500 cell/mm³. Between January 2002 and December 2014, 20 263 patients were tested for HIV, 1104 with a positive result of whom 995 asymptomatic individuals were included. Overall, median CD4+ count was 372 cells/mm³ and HIV-RNA 31 145 copies/ml. There was no evidence that the CD4+ count at diagnosis progressively increased over time, nor that the proportion of VLP and LP decreased. In a multivariate model older age, heterosexual transmission and intravenous drug use remained as independent factors associated with LP. In conclusion, late diagnosis of HIV infection remains prevalent among asymptomatic patients, highlighting the need to continue implementing strategies towards early diagnosis.

Key words: HIV, late diagnosis, asymptomatic patients

Resumen *Diagnóstico tardío de infección por HIV en pacientes asintomáticos.* Los resultados del estudio START han evidenciado que la iniciación temprana del tratamiento antirretroviral debe ser un estándar global. No obstante, una gran proporción de pacientes aún se diagnostican en etapas tardías. Nuestro objetivo fue evaluar la tendencia en el recuento de CD4+ al diagnóstico de infección por HIV, la proporción de presentadores tardíos entre 2002 y 2014, y los factores asociados con el diagnóstico tardío en pacientes asintomáticos en el Centro de Prevención, Asesoramiento y Diagnóstico de nuestro hospital. Se incluyeron en un estudio retrospectivo todos los sujetos asintomáticos con un diagnóstico de HIV. Se consideraron presentadores muy tardíos (PMT) a aquellos pacientes con CD4+ < 200 y presentadores tardíos (PT) con cifras de CD4+ < 350 células/mm³. Adicionalmente evaluamos la proporción de pacientes diagnosticados con recuentos de CD4+ inferiores a 500 células/mm³. Desde enero 2002 a diciembre de 2014 se testearon para HIV 20 263 pacientes, 1104 con resultado positivo, de los cuales 995 eran asintomáticos. Globalmente, la mediana de CD4+ fue 372 células/mm³ y la de HIV-ARN de 31 145 copias/ml. No hubo evidencia de que el recuento de CD4+ al diagnóstico haya aumentado en el tiempo, ni de disminución de la proporción de PT o PMT. En un modelo multivariado, la mayor edad, la transmisión heterosexual y el uso de drogas intravenosas se asociaron independientemente con PT. En conclusión, el diagnóstico tardío de infección por HIV se mantiene prevalente en pacientes asintomáticos, resaltando la necesidad de continuar implementando estrategias orientadas a favorecer el diagnóstico temprano.

Palabras clave: HIV, diagnóstico tardío, pacientes asintomáticos

The natural history of HIV infection has changed substantially with the advent of antiretroviral (ARV) treatment; increasing the life expectancy of patients and transforming it into a chronic disease¹. Defining the best moment to start treatment has been a priority item on the HIV/AIDS research agenda since the availability of treatment²⁻³.

Recent findings from the START Trial⁴ have provided strong evidence that early initiation of ARV treatment de-

creases the mortality and morbidity of HIV infection, even at high CD4 cell counts. However, epidemiological studies showed that a large proportion of patients are still being diagnosed in late stages⁵⁻¹¹ and it has a demonstrated impact not only on the survival of patients¹² and response to treatment¹³, but also on the health costs¹⁴.

Furthermore, the HIV Prevention Trials Network (HTPN) 052¹⁵ demonstrated that ARV therapy reduces the sexual transmission of HIV in serodiscordant couples by more than 96%, highlighting the importance of early diagnosis and treatment.

A Center for Prevention, Counseling and Diagnosis (CePAD), with the aim to facilitate the access to volun-

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tary testing and counseling for HIV, is available in the JM Ramos Mejía public hospital since 2002. It handles a large volume of patients, with more than 20 200 tests performed since 2002.

The objective of this study was to evaluate the temporal trend in the CD4+ cell count at diagnosis and the proportion of late presenters during the period 2002-2014, as well as the factors associated with late HIV diagnosis in asymptomatic individuals tested in the CePAD.

Materials and methods

This is a retrospective study using data from the CePAD of the public hospital J.M. Ramos Mejía. Inclusion criteria comprised all asymptomatic individuals (CDC Category A) with a new diagnosis of HIV infection performed in our centre from 1 January 2002 to 31 December 2014 were included. Patients for whom HIV testing was requested upon hospitalisation and individuals younger than 16 and with a reported or presumed prior HIV diagnosis were excluded from analysis.

Computerized records provided the following information on these patients: date of HIV diagnosis, return for HIV test results, date of birth, gender, nationality, education level, sexual orientation, substance abuse, current or previous co-infection with other sexual transmitted diseases. Electronic records of patient visits, CD4 cell counts and viral load at diagnosis were available for a quarter of all patients. Subsequently, paper records of clinical history were searched to complete this information for the other patients.

CD4 cell count and viral load at diagnosis were defined as the nearest CD4 cell count or viral load respectively to within 6 months of HIV diagnosis. Rationale for choosing this cut-off was to maximize the number of eligible patients with all information available without compromising the biological rationale.

All CD4 cell counts were performed by flow cytometry at the Central Laboratory of the Hospital.

We defined 'very late presenters' (VLP) as individuals with CD4+ cell counts below 200 cell/mm³, 'late presenters' (LP) as those with CD4+ cell counts below 350 cell/mm³. We also evaluated the proportion of patients who were diagnosed with CD4+ counts below 500 cell/mm³, the former threshold of ARV initiation.

Sexual orientation was annotated as **heterosexual, men having sex with men (MSM)** or **'no information about sexual orientation'** for all male patients. For female patients a categorisation of sexual orientation could not be made because of low numbers in the different categories (98.7% of the patients for whom this information was available reported to be heterosexual). Age was categorized as followed: 16-19 years, 20-29 years, 30-39 years, 40-49 years, 50 > years.

Data are described using absolute and relative frequency values, means (SD) and medians (25th and 75th percentiles) for non-normally distributed variables.

Univariate logistic regression was used to explore associations between patient characteristics and late HIV diagnosis as well as availability of CD4 cell counts within 6 months. Variables included were: age, risk category (female, MSM, heterosexual male, transgender, male; no information about sexual orientation), calendar year of diagnosis, attained education level, drugs and alcohol abuse.

Factors were included in a multivariate logistic regression model based on (biological) plausibility and/or because they were individually associated with late HIV diagnosis ($P < 0.3$). A forward selection procedure using maximum likelihood estimation was applied to derive a parsimonious model of

factors that were independent predictors of response to iron intervention. A 5% significance level was used, but we also explored the effect of using a more liberal criterion of $p < 0.10$.

All statistical analyses were performed using IBM SPSS Statistics 20.

The study was revised and approved by the Ethics Committee at the Ramos Mejía Hospital. Patients' information was anonymized and de-identified prior to the analysis.

Results

Of 20 263 tests performed, 11 04 individuals tested positive during the study period and 993 patients (88.4%) were asymptomatic.

The number of tests performed increased per year, from 570 in 2002 to 2339 in 2014. The number of patients with a CD4+ cell count available at diagnosis increased over time, from 58.3% in 2002 to 72.7% in 2014. Patients without CD4+ cell counts available were further divided in patients who did not return for their test results (14.8%); patients that did collect the test result, but did not come back for a visit in the first year after diagnosis, representing a minority of 1.0% of all cases; and patients who collected their test results and had a least one visit within the first year after their HIV diagnosis (20.6%).

Of note, since the introduction of the rapid test technology in 2014, there were no patients in the category 'test results not withdrawn'. Patients without CD4 test available were less likely to have finished secondary school or attained higher education levels ($P = 0.028$, 95% CI 0.539-0.965). Also risk category was associated with CD4 cell counts being available within 6 months ($P < 0.001$): patients without CD4 cell count were less likely to be MSM or women, but more likely to be transgender. There were no associations with age, intravenous drug use, alcohol abuse or history of sexually transmitted diseases.

Characteristics of the 993 asymptomatic individuals included in our study are shown in Table 1; 631 (63.5%) had CD4+ cell counts available within 6 months of HIV diagnosis; of whom 120 (19.0%) were VLP, 167 (26.5%) were LP, 136 (21.6%) were presenters below WHO recommendations to start ART and 208 (33.0%) had CD4+ counts between 350 and 499 cell/mm³ or higher. Overall, a quarter of the patients were women, 28.0% were MSM, 34.7% heterosexual men and 15.0% transgender. The proportion of MSM increased over time, whereas the proportion of heterosexual men decreased.

Median age of patients was 31.5 years, 2.9% were below twenty years of age and 7.4% were 50 years or older. The proportion of elderly individuals with a HIV positive result increased slightly over time; 49.3% of the patients completed secondary or attained higher education levels, 20 patients (2.0%) reported to be intravenous drug users.

There is no evidence that CD4 cell count progressively increased over time (Fig. 1), nor that the proportion of late presenters, very late presenters and presenters with

TABLE 1.– Characteristics of asymptomatic patients with new HIV diagnosis; 2002-2014

	All patients n:993	CD4+ available n: 631 n: 120	VLP: CD4+ < 200 cells/mm ³ n: 167	LP: CD4+ < 350 cells/mm ³ n: 136	CD4+ < 500 cells/mm ³ n: 208	CD4+ > = 500 cells/mm ³
CD4+ cell count (cells/mm ³) at diagnosis		372 (235-549)	120 (52-160)	287 (245-322)	406 (377-438)	640 (551-811)
Viral load (copies/ml) at diagnosis		31 145 (10 134-98 000)	96 980 (31 897-325 903)	32 094 (13 911-123 178)	27 334 (6 486-59 187)	17 892 (5 176-47 318)
Age (years)	31(25-39)	33(26-39)	34(28-40)	32 (26-40)	33 (25-39)	29(24-37)
Risk category (%)						
Women	25.1	26.9	23.3	24.6	30.9	28.4
Heterosexual men	26.0	25.8	32.5	35.3	20.6	17.8
Men having sex with men	28.0	31.8	27.5	26.9	35.3	38.9
Transgender	15.0	10.3	14.2	8.4	11.0	9.1
No information available	2.0	4.1	2.5	4.8	2.2	5.8
Education level (%)						
No information	18.8	17.0	17.5	16.8	22.1	13.5
Primary incomplete	5.9	5.9	7.5	6.6	5.1	4.8
Primary complete	18.4	18.1	20.8	20.4	17.6	14.9
Secondary incomplete	16.8	15.8	11.7	16.2	18.4	16.3
Secondary complete	23.7	25.4	28.3	25.1	18.4	28.4
Tertiary/University incomplete	8.7	10.5	8.3	7.8	13.2	12
Tertiary/University complete	7.5	7.5	5.8	7.2	5.1	10.1
Intravenous drug use (%)	2.0	1.9	5.8	2.4	0.0	0.5
Alcohol abuse (%)	8.9	8.1	13.3	5.4	10.3	4.8

Values represent median (25th and 75th percentile) and percentage of the number of individuals per category (first row), unless otherwise stated. VLP: Very Late Presenters; LP: Late Presenters

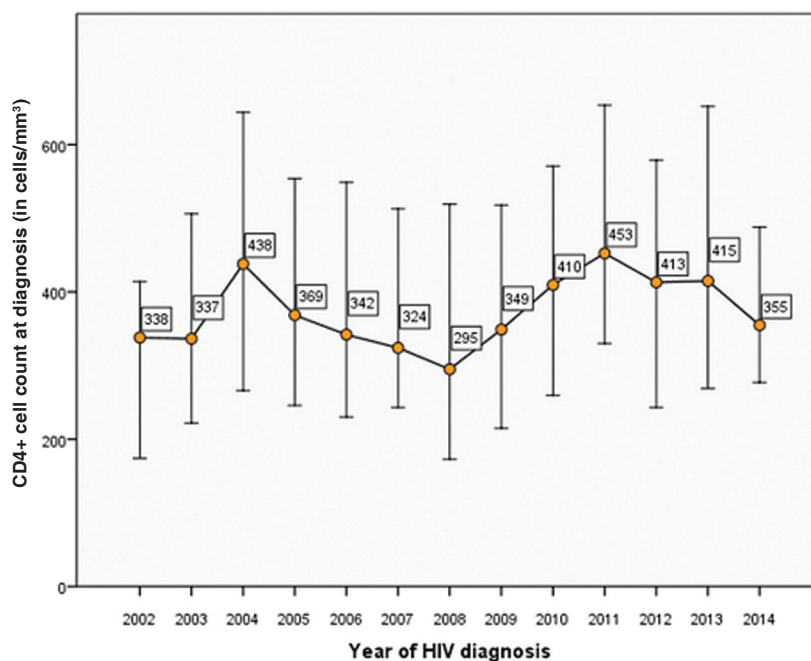


Fig. 1.– Median and interquartile range of CD4+ cell count (cells/mm³) at diagnosis, 2002-2014.

CD4+ cell counts below WHO recommendations to start ART decreased (Fig. 2).

In univariate logistic regression analysis older age, heterosexual transmission and intravenous drug use had the strongest associations with LP. There was no evidence that alcohol abuse and history of sexually transmitted diseases were associated with LP in this study. Exponentiation of regression coefficients obtained by logistic regression analyses yielded odds ratios of the outcome (LP) with one-unit increases in the patient characteristics measured. For example, for each year the patient was older, the odds of being a late presenter increased by 2.8% (Table 2).

The variables age, risk category and intravenous drug use, education level and year of HIV diagnosis were included in multivariate model. With a retention criterion of $p = 0.05$ age, risk category and intravenous drug use remained as independent predictors of LP.

Discussion

Several studies have shown that late diagnosis of HIV infection remains prevalent^{8,11,16}. A major strength of our study is that it focused on asymptomatic patients, and nearly half of these subjects were late presenters (CD4 < 350 cells/mm³). Furthermore, if we take into consideration

the previous standards of ART initiation with CD4 below 500 cell/mm³ this proportion reaches 67.0%.

In Argentina, until recently late presentation was defined as a person diagnosed with an AIDS defining event at or within 12 months of HIV diagnosis¹⁷. Not until 2012, the data on CD4 count was included as a proxy for late HIV diagnosis in the official epidemiological report form. During the period 2012-2013, 30.7% of men and 22.5% of women were diagnosed with an AIDS defining event or related symptoms of immune deterioration. Furthermore, a third of those subjects had a CD4 count lower than 200, 56.0% lower than 350 and 74.9% lower than 500 cell/mm³.

Analysis of risk factors in our study revealed that older age, heterosexual transmission and intravenous drug use were independently associated with late presentation. This coincides with findings from studies performed in different populations¹⁸⁻²⁰.

Trends in diagnoses can be biased by changes in testing behaviours. In this study we see a significant increase in diagnoses among transgender people in 2008. This likely reflects an increase in testing, due to the implementation of a health care programme targeting transgender people between September 2007 and November 2008. This programme aimed to facilitate the access to HIV testing and counselling and promote early diagnosis of HIV and other STD infections in this specific population²¹.

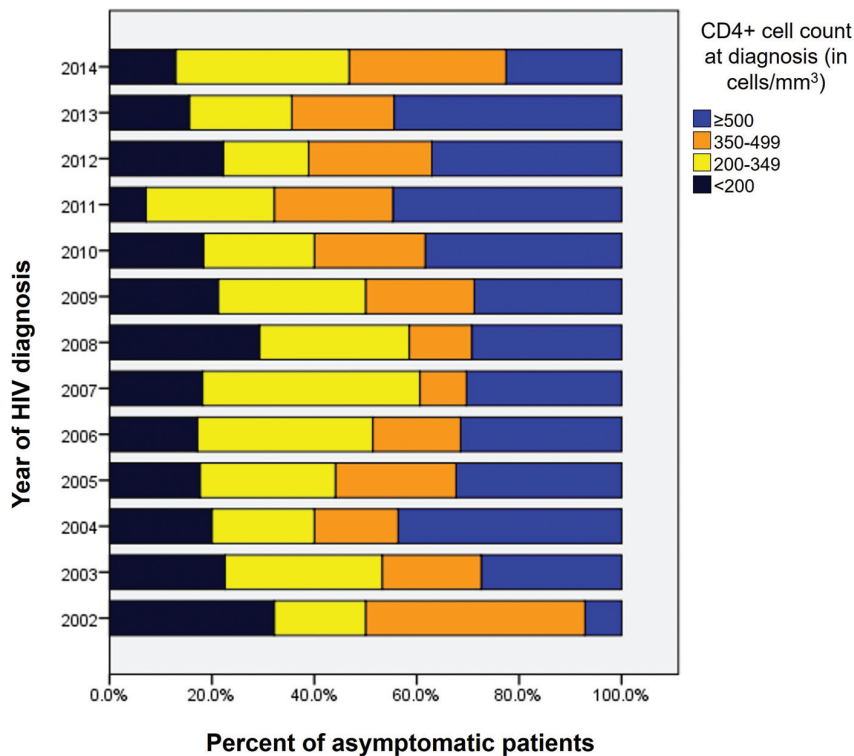


Fig. 2.– Proportion of patients in selected categories for CD4+ cell count at HIV diagnosis.

TABLE 2.— Factors associated with late presentation in univariate and multivariate logistic regression

	Univariate logistic regression			Included in MLR	Multivariate logistic regression		
	OR	95% CI	p		OR	95% CI	p
Age	1.028	(1.012-1.046)	0.001	*	1.027	(1.009-1.044)	0.003
Risk category			< 0.001	*			0.006
– Women	Reference				Reference		
– Heterosexual men	2.207	(1.424-3.420)			2.057	(1.313-3.224)	
– Men, no information about sexual orientation	1.073	(0.465-2.477)			1.055	(0.450-2.475)	
– Men having sex with men	0.885	(0.584-1.341)			0.999	(0.652-1.530)	
– Transgender	1.335	(0.751-2.372)			1.558	(0.866-2.802)	
Education level			0.150	*			
– Primary incomplete	Reference						
– Primary complete	0.912	(0.433-1.918)					
– Secondary incomplete	0.591	(0.276-1.262)					
– Secondary complete	0.769	(0.375-1.575)					
– University incomplete	0.334	(0.129-0.864)					
– University complete	0.283	(0.085-0.942)					
– Unknown	0.718	(0.339-1.520)					
Intravenous drug use	13.670	(1.754-106.534)	0.013	*	7.7016	(0.967-61.320)	0.054
Alcohol abuse	1.175	(0.661-2.088)	0.583				
History of STDs	1.082	(0.622-1.883)	0.780				
Year of HIV diagnosis	0.962	(0.922-1.003)	0.070	*			

STDs: sexually transmitted diseases; MLR: multivariate logistic regression

We observed no trend over the past 13 years in patients' CD4 cell count at diagnosis. This is contrary to some studies performed in other regions²²⁻²⁴ that show a decrease in late presentation over time. It is important to note that our study specifically focused on asymptomatic patients; potentially this difference could be explained by a decrease in the number of symptomatic patients with associated low CD4 cell counts in other study populations.

Moreover, some studies suggest that there are differences between different HIV-exposure groups, e.g. a decrease in late presentation was seen among MSM and an increase among male IUDs in southern Europe²³. Unfortunately, the relatively small number of patients included in our study did not allow for subgroup analyses, but preliminary examination of data (results not shown) suggest that late diagnosis remains a serious issue across different subgroups.

In addition to late diagnosis delayed entry into care is a major concern. This regards individuals who are aware of their HIV status, but do not seek medical care. Considering large number of patients without a CD4 cell count available within 6 months of HIV diagnosis, it can be concluded that more efforts are needed to retain this group in care after diagnosis. But caution is needed to interpret these results, since this is a single site study and patients could go to other centres to receive care for their HIV.

The most important limitation of this study is the high proportion of patients without CD4 cell count at diagnosis (36.5%). The overrepresentation of women, MSM and individuals with higher education levels in our sample for analysis could have led to an overestimation of median CD4 T-cell count levels.

In conclusion, late diagnosis of HIV infection is still common in asymptomatic patients. No trend towards improvement of CD4 cell counts at diagnosis is observed so far, despite efforts to improve the access to HIV prevention, diagnosis and treatment in the city of Buenos Aires. Thus, these results highlight the need to continue implementing and reinforcing strategies towards early diagnosis.

Conflict of interests: None to declare

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[...] Y a lo que decís, señor, que vuestro hijo no estima mucho la poesía de romance [‘en lengua vulgar’, castellano] doyme a entender que no anda muy acertado en ello, y la razón es ésta: el grande Homero no escribió en latín, porque era griego, ni Virgilio escribió en griego, porque era latino; en resolución, todos los poetas antiguos escribieron en la lengua que mamaron en la leche, y no fueron a buscar las extranjeras para declarar la alteza de sus conceptos; y siendo así, razón sería se extendiese esta costumbre por todas las naciones, y que no se desestimase el poeta alemán porque escribe en su lengua, ni el castellano, ni aun el vizcaíno que escribe en la suya. [...].

Miguel de Cervantes (1547-1616)

Don Quijote de la Mancha. Segunda parte (1615). Capítulo XVI. De lo que sucedió a Don Quijote con un discreto caballero de la Mancha. Edición del IV Centenario. San Pablo, Brasil: Real Academia Española/Alfaguara, 2004, p 667