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Progress in the quality of care for newly diagnosed people with HIV in Spain (2004–2019)

Belén Alejos[1], Cristina Díez[2,3,4], María J Galindo[5], Juan C López[2,3,4], Estela Moreno-García[6], Vicente Estrada[4,7], Eva Poveda[8], Mohamed Omar[9], Inmaculada Jarrín[1,4,†], Juan Berenguer[2,3,4†] For CoRIS

[1]Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain;

[2]Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain;

[3]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain;

[4]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Madrid, Spain;

[5]Infectious Diseases, Hospital Clínico Universitario de Valencia, Valencia, Spain;

[6]Infectious Diseases, Complejo Hospitalario de Navarra, Navarra, Spain;

[7]Infectious Diseases, Hospital Clínico de San Carlos, Madrid, Spain;

[8]Galicia Sur Health Research Institute (IIS Galicia Sur)-Complexo Hospitalario Universitario de Vigo, SERGAS-UVigo, Spain;

[9]Infectious Diseases, Complejo Hospitalario de Jaén, Jaén, Spain

Abstract

Background: We monitored the quality of care for newly diagnosed people with HIV (PWH) in Spain, including linkage to care within 1 month of HIV diagnosis (LC-1Mo) and viral suppression within 3 months of HIV diagnosis (VS-3Mo).
Methods: Longitudinal study based on The Cohort of the Spanish AIDS Research Network (CoRIS). We used logistic regression stratified by year of HIV diagnosis (2004–2013 and 2014–2019) to assess differences by sex, country of origin, HIV risk group, age, prior AIDS, HIV Viral Load, and CD4 cell count.
Results: The final analysis included 13,632 PWH: males 85%, men having sex with men (MSM) 61%, median age 35 years. LC-1Mo increased from 42% (95% CI, 38%–46%) in 2004 to 80% (95% CI, 77%−83%) in 2019 ($P < 0.001$). Median $CD4^+$ cell counts at ART initiation increased from <250/mm3 in 2004–2005 to >350/mm3 since 2012 ($P < 0.001$). The percentage of initial regimens based on integrase strand transfer inhibitors (INSTI) increased from 3% in 2004 to >70% from 2016 onwards ($P < 0.001$). VS-3Mo increased from 6% (95% CI, 4%–8%) in 2004 to 45% (95% CI, 41%–49%) in 2019 ($P < 0.001$). Worst results for LC-1Mo were found among PWH acquiring HIV by injection drug use and those born in Latin American Countries across all the study period.
Conclusion: Care indicators have improved among newly diagnosed PWH in Spain over the last 15 years. Removal of CD4 cell counts limitations, and probably the increasing use of INSTI-based regimens was decisive for the progress made.

[†]Contributed equally to this work

Corresponding author: Email: jbb4@me.com

Introduction

Increasing antiretroviral therapy (ART) coverage has reduced HIV incidence and mortality worldwide [1]. Nevertheless, the life expectancy of people with HIV (PWH) receiving ART remains lower than that of the general population [2,3]. This is not only HIV-related but also because of non-communicable diseases such as cardiovascular disease and different types of cancer [4,5], whose incidence is increased among PWH owing to multiple factors, including lifestyle, viral coinfections, persistent immune activation, and inflammation despite an effective ART [6–9].

The current standard of care in PWH considers the rapid initiation of ART regardless of the CD4 cell counts because this is associated with a reduction in the risk of morbidity and mortality related and not related to AIDS [10], and because achieving viral suppression prevents PWH from transmitting the infection [11–13]. These are strong reasons to implement actions to speed-up linkage to care and early ART initiation in PWH.

From a healthcare system viewpoint, the main pillars of HIV care are expanded HIV testing, prompt engagement and retainment in care, and rapid initiation of ART to achieve viral suppression [14,15]. These factors have been conceptualized in a care path known as the HIV continuum or cascade of care, a concept that has been increasingly adopted to set goals and assess HIV programs performance [16,17].

Our study aimed to analyze the quality of care for newly diagnosed PWH in the Cohort of the Spanish HIV Research Network (CoRIS) from 2004 to 2019 using previously described indicators of linkage to care and rapidness of achievement of viral suppression [18,19].

Methods

Ethics

All patients included in CoRIS have signed an informed consent approved by the Ethics Committee of Hospital General Universitario Gregorio Marañón. The CoRIS data file is registered with the Data Protection Agency in the Instituto de Salud Carlos III (ISCIII) security file (no 2,080,910,068).

Design and patient selection

CoRIS is an open, multicenter, and prospective cohort of PWH older than 16 years, naive to ART at study entry, seen for the first time from 1 January 2004, in any of the 46 centers from 13 of 17 Regions in Spain. This database collects demographic and clinical data, HIV transmission category, ART history, previous opportunistic diseases, comorbidities, serological and immunovirological data, and specific non-AIDS diseases. To reduce losses to follow-up, participants in CoRIS who move to another participating hospital are tracked and re-included. Internal quality controls are done annually [20,21].

For this study, we included individuals diagnosed with HIV from 1 January 2004, to 30 August 2019, and followed up until 30 November 2019, the administrative censoring date. Participants from centers without active recruitment in CoRIS were not included in the analysis. We considered the following variables: age at cohort entry, sex at birth, country of origin, year of entry in the cohort, transmission category, HIV viral load and CD4 cell count at HIV diagnosis, presence of AIDS, CD4 cell count at ART initiation, and first ART regimen.

Measurements

We analyzed trends in the lag-time from HIV diagnosis to ART initiation, CD4 cell count at ART initiation, and the type of the first-line ART regimen. We also assessed two indicators of care for newly diagnosed PWH: 1) The percentage of those linked to HIV medical care within 1 month of diagnosis as suggested by the US National HIV/AIDS Strategy (NHAS); a process indicator [18]. Linkage to care was defined as the first clinical visit that coincides with the date of inclusion in CoRIS. 2) The percentage of those achieving viral suppression within 3 months of diagnosis as suggested by the Division of Disease Control, New York City Department of Health and Mental Hygiene (NYC-DHMH); an outcome indicator [19]. This last indicator was defined as ever having an HIV-RNA load <200 copies/mL in the first 3 months after HIV diagnosis.

ART regimens were classified as two nucleoside/nucleotide reverse transcriptase inhibitors [*N*(t)RTI] plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), two *N* (t)RTI plus one protease inhibitor (PI), two *N*(t)RTI plus one integrase strand transfer inhibitor (INSTI), and other combinations.

Statistics

Descriptive analysis of individuals' characteristics was carried out using frequency tables for categorical variables and median and interquartile range (IQR) for continuous variables. Multivariable logistic regression models were used to estimate adjusted odds ratios (aOR) of association between the outcomes and independent variables (sex, country of origin, HIV transmission category, age, AIDS-defining illness, HIV Viral Load, and CD4 cell count at HIV diagnosis). The selection of potential predictor variables was based on the underlying conceptual framework, and they were included in the multivariable models regardless of statistical significance. Because Spanish treatment guidelines recommended initiating ART irrespective of CD4 cell counts from 2014 onwards [22], the multivariable analyses were stratified by year of HIV diagnosis: 2004–2013 and 2014–2019. To deal with missing data we used multiple imputations by chained equations as

the primary method and by the creation of an extra category (indicator method) as a sensitivity analysis. All statistical analyses were performed using Stata software (version 15.0; Stata Corporation, College Station, Texas, USA). The STROBE guidelines were used to ensure the reporting of the study [23] (Supplementary Table S1).

Results

From 1 January 2004, to 30 November 2019, 16,759 antiretroviral naïve individuals were included in the CoRIS cohort. We excluded from the analysis 2077 (12.4%) individuals from centers not carrying active follow-up of PWH recruited in CoRIS. We also excluded 881 individuals diagnosed with HIV before 2004 and 169 diagnosed after 30 August 2019. The final analysis included 13,632 (81.3%) PWH whose characteristics are described in Table 1. A total of 212 PWH (1.56%) died before reaching viral suppression, and an additional 1215 (8.91%) were lost to follow-up or censored before this outcome.

The median age at HIV diagnosis was 35 years, 85% were males at birth, and 58% were native-born Spaniards. The most frequent HIV transmission categories were men having sex with men (MSM) in 61% and heterosexual contact in 30%. At diagnosis, 12% had a history of an AIDS-defining illness. At the time of ART initiation, the median CD4 count was 384 cells/μL.

Trends in time from HIV diagnosis to ART initiation and $CD4^+$ cell counts at ART initiation during the study period are shown in Figure 1 and Supplementary Table S2. The median lag-time from diagnosis to ART initiation varied from ≥18 months from 2004 to 2007; then, it decreased steadily, reaching 2 months in 2015, and has remained in 1 month since 2018 (*P* for trend <0.001). The median $CD4^+$ cell counts per mm3 at ART initiation were <250 in 2004 and 2005, >250 and <300 in 2006–2008, >300 and <350 in 2009–2011, and remained >350 since 2012 (*P* for trend <0.001).

The initial ART regimens distribution during the study period is shown in Figure 2 and Supplementary Table S3. Regimens based on 2 *N*(t)RTI plus 1 INSTI were the less frequently prescribed from 2004 to 2013, but their use increased after that, becoming the most prescribed regimens since 2014, varying between 41% and 84% (*P* for trend <0.001). In contrast, regimens based on 2 *N*(t)RTI plus 1 NNRTI were the most frequent initial regimens from 2004 to 2013, varying between 44% and 59%, but declined after that and were the less frequently used regimens from 2015 onwards, accounting for 1% of all initial regimens in 2019 (*P* for trend <0.001). Regimens based on 2 *N*(t)RTI plus 1 PI were the second most commonly prescribed initial regimens during the study period; their use decreased steadily from 34% in 2004 and 2005 to 9% in 2016 but increased after that, reaching 15% in 2019 (*P* for trend <0.001).

Table 1. Characteristics of 13,632 people with HIV participating in the study.

Variable	Total N° of PWH = 13,632
Age at HIV diagnosis (years); *n* (%)	
<30	4,272 (31)
30–50	7,814 (57)
>50	1,546 (11)
Median (Q1, Q3)	35 (28; 43)
Sex at birth; *n* (%)	
Male	11,561 (85)
Female	2,071 (15)
Region of birth; *n* (%)	
Spain	7,893 (58)
Latin America	2,786 (20)
Europe	1,940 (14)
Sub-Saharan Africa	706 (5)
Northern Africa	172 (1)
Other	70 (1)
Unknown	65 (<1)
HIV transmission mode; *n* (%)	
Men sex with men	8,347 (61)
Heterosexual	4,074 (30)
Injection drug use	644 (5)
Other	133 (1)
Unknown	434 (3)
Clinical AIDS at HIV diagnosis; *n* (%)	
No	11,889 (87)
Yes	1,602 (12)
Unknown	141 (1)
$CD4^+$ cells/μL; *n* (%)[a]	
<200	3,015 (22)
200–500	5,143 (38)
≥500	4,091 (30)
Unknown	1,383 (10)
Median (Q1, Q3)	384 (203; 576)
HIV-RNA load, copies/mL; *n* (%)[a]	
<20,000	3,335 (24)
20,000–100,000	3,901 (29)
≥100,000	4,523 (33)
Unknown	1,873 (14)
Median (Q1, Q3)	61,800 (16,366; 203,000)

PWH, people with HIV; Q1, first quartile; Q3, third quartile.
[a]At the time of initiation of antiretroviral therapy.

Trends in the two care indicators from 2004 to 2019 are shown in Figure 3 and Supplementary Tables S4 and S5. The percentage of PWH linked to care within 1 month from diagnosis increased from 42% (95% CI, 38%–46%) in 2004 to 80% (95% CI, 77%−83%) in 2019 (*P* for trend <0.001). Likewise, the percentage of PWH achieving viral suppression within 3 months of diagnosis increased

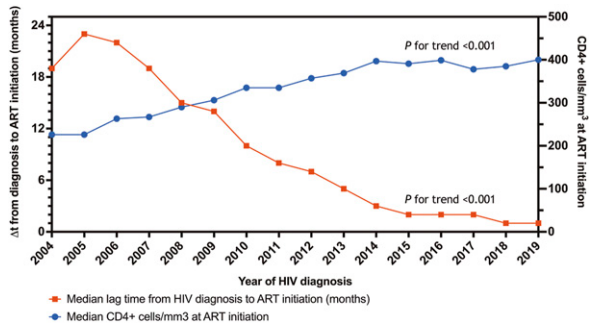

Figure 1. Trends in time from HIV diagnosis to ART initiation and CD4$^+$ cell counts at ART initiation during the study period. Δt, interval of time; ART, antiretroviral therapy

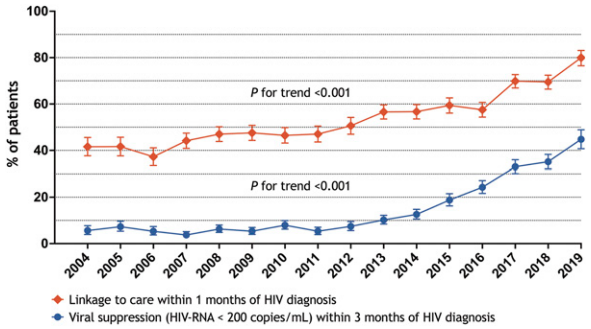

Figure 3. Trends in the two indicators of care from 2004 to 2019. Linkage to care within 1 month of HIV diagnosis and viral suppression within 3 months of diagnosis

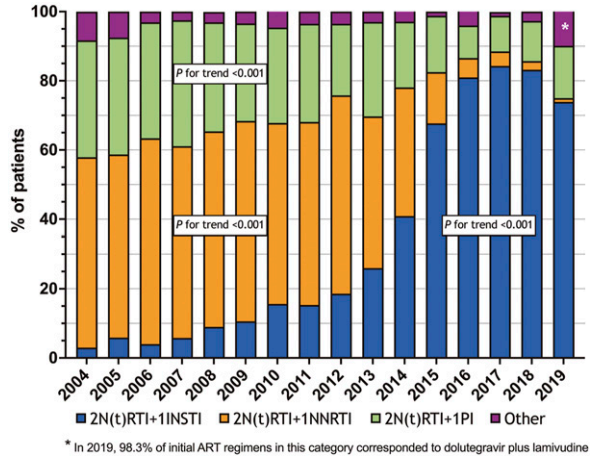

Figure 2. Distribution of initial ART regimens during the study period. *N* (t)RTI, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor

from 6% (95% CI, 4%–8%) in 2004 to 45% (95% CI, 41%–49%) in 2019 (*P* for trend <0.001).

Results from multivariable logistic regression for the association between independent factors and indicators of care in both calendar periods are shown in Table 2. Significant associations were found between the HIV transmission category, region of birth, clinical AIDS, CD4$^+$ cell count, and HIV-RNA load at HIV diagnosis with care indicators. Taking MSM as the reference category, IDU was associated with lower odds of linkage to care within 1 month from diagnosis in both calendar periods and lower odds of achieving viral suppression within 3 months of diagnosis in the second calendar period. As for the region of birth, taking Spain as the reference category, higher odds of achieving both care indicators in the two calendar periods were found for other European countries. In contrast, birth in Latin American countries was associated with lower odds of linkage to care in both calendar periods. Regarding HIV-related variables, the presence of AIDS-defining conditions and a CD4 cell count lower than 200 cells/μL at HIV diagnosis were associated with higher odds of achieving both care indicators across all the study period. As for HIV viral load, taking less than 20,000 copies per mL as the reference category, higher odds of linkage to care within 1 month of diagnosis, and lower odds of viral suppression within 3 months of diagnosis was associated with HIV viral load higher than or equal to 100,000 copies per mL. The sensitivity analysis results in which the indicator method was used to deal with missing data did not change the findings of the primary analysis (Supplementary Table S6).

Discussion

We found a significant improvement in care indicators for newly diagnosed PWH in Spain between 2004 and 2019. During the first years, less than half of PWH were linked to care within 1 month of diagnosis, and no more than 10 percent achieved viral suppression within the first trimester after diagnosis. A continuous improvement followed this, particularly after 2013, to the point that almost 80% of PWH were linked to care within 1 month from diagnosis in the last year of the study period, and approximately half reached viral suppression within 3 months of this time point.

These improvements followed changes in recommendations on ART initiation in asymptomatic PWH. During the first years of the study period, the recommendation was to initiate ART with a CD4 count below 350 cells/uL, a threshold that was increased to ≤500 cells/uL in 2013 [24], followed 1 year later by the recommendation of universal treatment irrespective of the CD4 count [22]. A decrease in the time to linkage to care and viral suppression after diagnosis has also been reported in the US following universal treatment recommendations in PWH [19,25].

Table 2. Results from multivariable logistic regression for the association between independent factors and indicators of care stratified by calendar period of HIV diagnosis. Multiple imputations by chained equations were used to deal with missing data.

	Linkage to care within 1 month of HIV diagnosis		Viral suppression within 3 months of HIV diagnosis	
Variable	Calendar period 2004–2013	Calendar period 2014–2019	Calendar period 2004–2013	Calendar period 2014–2019
Sex at birth				
• Male	1	1	1	1
• Female	1.04 (0.90–1.21)	1.05 (0.83–1.31)	1.93 (1.50–2.48)	1.21 (0.96–1.52)
Transmission Mode				
• Men sex with men	1	1	1	1
• Injection drug use	0.81 (0.67–0.98)	0.62 (0.39–0.99)	1.10 (0.76–1.60)	0.53 (0.29–0.95)
• Heterosexual	1.26 (1.11–1.44)	1.09 (0.91–1.31)	1.15 (0.89–1.49)	1.01 (0.84–1.21)
Region of birth				
• Spain	1	1	1	1
• Other European countries	1.89 (1.66–2.14)	1.84 (1.49–2.26)	1.33 (1.04–1.71)	2.07 (1.72–2.51)
• Sub-Saharan Africa	1.12 (0.90–1.38)	0.82 (0.61–1.11)	1.05 (0.73–1.50)	0.88 (0.64–1.23)
• Northern Africa	1.64 (1.03–2.60)	0.81 (0.51–1.28)	1.14 (0.53–2.46)	0.74 (0.43–1.26)
• Latin America	0.78 (0.69–0.89)	0.83 (0.72–0.95)	1.10 (0.85–1.41)	1.12 (0.97–1.31)
Age at HIV diagnosis (years)				
• <30	1	1	1	1
• 30–50	1.08 (0.98–1.20)	0.98 (0.87–1.12)	0.92 (0.74–1.14)	1.05 (0.91–1.21)
• ≥50	1.36 (1.15–1.62)	1.14 (0.93–1.40)	1.13 (0.83–1.55)	1.10 (0.89–1.36)
Clinical AIDS at HIV diagnosis				
• No	1	1	1	1
• Yes	3.55 (2.99–4.21)	2.26 (1.74–2.93)	2.62 (2.07–3.31)	1.33 (1.06–1.65)
$CD4^+$ cells/μL				
• <200	1	1	1	1
• 200–500	0.80 (0.70–0.91)	0.73 (0.61–0.87)	0.47 (0.37–0.60)	0.86 (0.72–1.04)
• ≥500	0.73 (0.62–0.86)	0.65 (0.54–0.79)	0.18 (0.13–0.26)	0.60 (0.49–0.74)
HIV-RNA load, copies/mL				
• <20,000	1	1	1	1
• 20,000–100,000	1.63 (1.44–1.84)	1.10 (0.95–1.29)	0.94 (0.73–1.21)	0.99 (0.84–1.17)
• ≥100,000	1.28 (1.13–1.46)	1.36 (1.15–1.60)	0.50 (0.38–0.65)	0.79 (0.67–0.93)

Another factor that likely contributed to the rising trends in viral suppression during the first trimester after diagnosis was the growing use of INSTIs as anchor drugs for initial ART from less than 6% in the first years to more than 80% in the last years of the study period. INSTIs-based combinations were included among the preferred regimens for initial ART therapy in the Spanish Guidelines in 2011 [26] and were considered the only preferred category of anchor drugs since 2015 [27]. Recent real-world experience has shown faster viral suppression with initial ART regimens based on INSTIs than with regimens based on protease inhibitors [28].

Of note, the results of both HIV care indicators were significantly worst among those acquiring HIV by IDU. There is substantial evidence that individuals with prior history of IDU have lower rates of linkage and retention in HIV care [29–31], and inferior clinical and virologic outcomes [32,33] than individuals acquiring HIV by other routes. Several factors may account for these differences, including socioeconomic disadvantages, active drug use, and incarceration [33,34]. Holistic care models integrating HIV, substance use, and psychosocial services may improve retention in care, medication adherence, and HIV viral suppression among these individuals [35]. Whether integrated care through mobile clinics can improve HIV and substance use outcomes among IDUs is currently being evaluated in a NIH-funded clinical [36]. Taking native born Spaniards as reference, the finding of lower odds of linkage to care across all the study period for those born in Latin American countries are concordant with observations that social and economic determinants of health impact the continuum of care among PWH [37]. Better results in both care indicators were found among those with clinical AIDS and lower CD4 cell counts at diagnosis. We believe that this

is likely due to the confounding effect of late presentation with advanced disease defined as a CD4 count <200 cells/μL or AIDS-defining conditions at HIV diagnosis [38], as PWH within this category, are frequently diagnosed in hospitals and likely have started ART immediately after diagnosis [39]. Late presentation with advanced disease has been frequent in Spain, ranging from 33.9% in 2004–2008 to 22.7% in 2009–2012 and remained stable with a modest increase up to 23.6% during 2013–2018 [40].

Limitations of our study include the absence of information about some sociodemographic variables, including ethnicity, income, housing, work, and documentation status. Our study is also limited by not including the patient perspective in our analyses. The study's major strengths include the prospective design, the large sample size, and the large study period.

In conclusion, our findings indicate that linkage to care and time to viral suppression after HIV diagnosis has improved among PWH in Spain over the last 15 years. Removal of CD4 cell counts limitations, and increasing use of INSTIs-based regimens were critical determinants of progress. The implementation of these two care indicators could be of help to monitor progress in the continuum of care of newly diagnosed PWH.

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ORCID iD

Juan Berenguer https://orcid.org/0000-0001-8541-8200

Supplemental Material

Supplemental material for this article is available online.

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