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This is the peer reviewed version of the following article:

Alvaro-Meca, Alejandro; Ryan, Pablo; Martínez-Larrull, Esther; Micheloud, Dariela; Berenguer, Juan; Resino, Salvador. **Epidemiological trends of deep venous thrombosis in HIV-infected subjects (1997-2013): A nationwide population-based study in Spain**. Eur J Intern Med. 2018 Feb:48:69-74.

which has been published in final form at:

https://doi.org/10.1016/j.ejim.2017.10.012

Epidemiological trends of deep venous thrombosis in HIV-infected subjects (1997-2013): A nationwide population-based study in Spain

Running title: Deep venous thrombosis in HIV-infected patients

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Character count of Title: 131
Character count of Running Head: 47
Word count of Abstract: 244
Word count of Keywords: 6

Word count of Text: 3154
Count of References: 56
Count of Tables: 1
Count of Figures: 1
Count of supplementary files: 5

Abstract

Background: Chronic infections may be a triggering factor as well as a risk factor of deep venous thrombosis (DVT). The purpose of this study was to analyze the epidemiological trends of hospital admissions related to DVT in human immunodeficiency virus (HIV)-infected patients during the combination antiretroviral therapy (cART) era, in relation to hepatitis C virus (HCV) serological status.

Methods: We performed a retrospective study using the Spanish Minimum Basic Data Set. We selected HIV-infected subjects over 15 years old with a hospital admission and DVT diagnosis (ICD-9-CM codes: 453.4x and 453.8x) between 1997 and 2013. Patients were classified according to HCV serology. We estimated the incidence (events per 100,000 patient-years) in four calendar periods (1997-1999, 2000-2003, 2004-2007, and 2008-2013).

Results: Overall, the incidence of DVT-related hospitalizations had a significant upward trend in all HIV-infected patients (P<0.001), with significant differences between 1997-1999 and 2008-2013 [49.5 vs. 88.1 (P<0.001)]. Moreover, the incidence was higher in HIV-monoinfected patients than in HIV/HCV-coinfected patients during the entire follow-up (P<0.001). However, the incidence had a significant downward trend in HIV-monoinfected patients (P=0.002) and a significant upward trend in HIV/HCV-coinfected patients (P<0.001). Specifically, the incidence of DVT-related hospitalizations in HIV-monoinfected patients significantly decreased from 1997-1999 to 2008-2013 [142.7 vs. 103.1 (P=0.006)], whereas in HIV/HCV-coinfected patients, the incidence increased from 8.4 (1997-1999) to 70.7 (2008-2013) (P<0.001).

Conclusions: Our findings suggest that DVT is an emerging health problem among HIV-infected patients, with increasing incidence during the first 17 years after the introduction of cART, particularly in HIV/HCV-coinfected patients.

Keywords

AIDS; hepatitis C; deep venous thrombosis; cardiovascular disease; incidence; ICD9CM codes.

Introduction

Deep venous thrombosis (DVT) is a common and serious cardiovascular disease associated with higher hospital admission rates and death [1-3]. Venous thromboembolism [pulmonary embolism (PE) or DVT] may occur by a combination of factors that are specific to a given patient (anomalies of hemostasis, chronic diseases, age, etc.) and precipitating factors (surgery, catheterization, acute venous stasis, acute pathologies, etc.) [1, 4]. Chronic infections may be a triggering factor that may induce immune cell activation, inflammation-associated protein synthesis by the liver, and modification of the coagulation and fibrinolysis pathways and thus increase the risk of DTV [4].

The widespread use of combination antiretroviral therapy (cART) has resulted in a dramatic reduction of illness and mortality in human immunodeficiency virus (HIV)-infected individuals, and HIV infection has become a chronic manageable disease [5]. However, non-AIDS-related conditions, such as cardiovascular disease, have become the most frequent causes of hospitalization and death in HIV-infected persons [5]. Regarding venous thromboembolism, previous studies have reported a higher risk of venous thromboembolism in HIV-infected patients than in the general population [6-12], suggesting that HIV infection is a risk factor for venous thromboembolism. Among the factors that increase the risk of venous thromboembolism in HIV-infected individuals are HIV replication itself, cART, the existence of an active opportunistic infection, and low levels of CD4+ T-cells, all of which may induce persistent systemic inflammation, triggering upregulation of procoagulant factors and downregulation of anticoagulant and fibrinolysis factors [4, 13].

Chronic hepatitis C (CHC) has also been associated with a higher risk of thrombotic events [14, 15], particularly in cirrhotic patients [16]. The link between hepatitis C virus (HCV) infection and venous thromboembolism might be explained by several factors that may exist in patients with CHC, such as a direct endothelial damage by the HCV virus, and subsequent tissue factor activation, altered fibrinolysis and increased platelet aggregation and activation [17]. Additionally, cirrhotic patients have an alteration in portal microcirculation that may lead to thrombin activation, platelet aggregation, and clot formation [17].

Globally around 20% of HIV-positive patients have chronic hepatitis C, mainly because HIV and HCV are transmitted via the same routes [18]. HIV/HCV-coinfected subjects are an important clinical subgroup that may differ from HIV-monoinfected patients in terms of risk factor distribution and inflammatory profile [10]. Furthermore, the interactions among HIV, HCV and cART are also associated with several metabolic disorders that may increase the risk of thrombotic events [19]. In fact, an increased risk of cardiovascular disease in HIV/HCV-coinfected subjects in comparison to HIV-monoinfected subjects has been reported [20, 21].

The aim of this study was to analyze the epidemiological trends of hospital admissions related to DVT in HIV-infected patients during the cART era, with particular attention to HIV/HCV-coinfected patients.

Materials and Methods

Study population

We carried out a retrospective study. We reviewed the computerized data from the Spanish Minimum Basic Data Set (MBDS) between 1997 and 2013, finding HIV-infected patients aged 16 years and older with a hospital admission and a DVT diagnosis. The study period was from January 1, 1997 to December 31, 2013, which was subdivided into four calendar periods according to the widespread use of cART among HIV-infected subjects [22]: a) from 1997 to 1999 (1997-1999); b) from 2000 to 2003 (2000-2003); c) from 2004 to 2007 (2004-2007);

and d) from 2008 to 2013 (2008-2013).

Data of patients with a diagnosis of DVT were obtained from the records of the Minimum Basic Data Set (MBDS), provided by the Ministry of Health Social Services and Equality (MSSSI). The MBDS is a clinical and administrative database containing clinical information recorded at the time of hospital discharge, which has an estimated coverage of 92% of hospital discharges registered in hospitals in Spain (84.14% from public hospitals and 15.86% from private hospitals) [23]. The National Health System (NHS) provides free medical care to 99.5% of the Spanish population, although those persons not covered by the NHS still may be attended to at the public hospitals.

The MBDS provided the encrypted patient identification number, sex, date of birth, dates of hospital admission and discharge, patients' residential postal code, medical institutions providing the services, the diagnosis and procedure codes according to the *International Classification of Diseases, 9th ed, Clinical Modification* (ICD-9-CM), and outcome at discharge. The MDBS includes up to 14 discharge diagnoses and up to 20 procedures performed during the hospital stay. The Spanish MSSSI sets standards for record-keeping and performs periodic audits.

Ethics statement

This study involves the use of patient medical data from the Spanish MBDS, which is hosted by the MSSSI. The MBDS is regulated by Spanish law, which explains how institutions are required to utilize health-related personal data. As described in detail previously [24], the data were treated with full confidentiality according to Spanish legislation. The MSSSI evaluated the protocol of our investigation and considered it to meet all ethical aspects according to Spanish legislation. Given the anonymous and mandatory nature of the dataset, it was not necessary to obtain informed consent. Furthermore, our study was approved by the Research Ethic Committee (Comité de Ética de la Investigación y de Bienestar Animal) of the Instituto de Salud Carlos III (Madrid, Spain).

ICD-9-CM codes selected and study groups

We selected subjects who were coded in the MBDS with a DVT diagnosis [453.4x and 453.8x (see **S1 Table**)], according to the criteria of White *et al.* [25]. ICD-9-CM codes were also used for defining the viral infection status: i) HIV infection (042 or V08); ii) HCV infection (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, 070.7x, or V02.62); iii) HBV infection (ICD-9-CM codes 070.2x, 070.3x, or V02.61) (see **Table S1**). Accordingly, we categorized patients as: i) HIV-infected (all HIV-infected subjects with or without HCV coinfection); ii) HIV-monoinfected (subjects exclusively infected with HIV); iii) HIV/HCV-coinfected (subjects coinfected with HIV and HCV). HBV infection was a criterion for exclusion.

Outcome variables

Hospitalization was defined as a discharge record in the MBDS with a DVT diagnosis. The index episode of a patient was the first hospital discharge encoded in MBDS with a DVT diagnosis. Patients who were readmitted with a DVT diagnosis were not counted as a new episode of DVT.

The outcome variables analyzed in this study were; 1) first DTV-related hospital admission and 2) death among patients with a DTV-related hospital admission.

Reference populations

The estimation of the number of people living with HIV/AIDS in Spain (see **Table S2**) was provided by the National Centre of Epidemiology (Instituto de Salud Carlos III, Madrid, Spain) [26]. The number of people monoinfected with HIV and coinfected with HIV and HCV in Spain was estimated using the results from the hospital survey of HIV/AIDS patients, a second-generation surveillance system in people living with HIV coordinated by the National Centre of Epidemiology [27], and the reports of two Spanish national cohorts: the "Grupo de Estudio de

Sida" (GeSIDA) [28] and the "Asociación Médica VACH de Estudios Multicentricos (AMVACH)" [29].

Statistical analysis

The incidence (new DVT diagnosis in the MBDS) was estimated as the ratio between the number of events within each calendar period and the number of persons at risk within each calendar period. The case fatality rate (CFR) was estimated as the proportion between the number of DVT-related deaths and the number of hospitalized patients with DVT diagnosis.

Categorical data and proportions were analyzed using chi-squared test or Fisher's exact test, as required. T-Test or Mann-Whitney U test was used to compare continuous variables. Temporal trends of incidence rates of DVT were evaluated using the Extended Mantel Haenszel Chi Square for linear trend. We also calculated the odds for in-hospital death in patients with DVT diagnosis according to calendar period by using logistic regression models, which were adjusted by age, sex, tobacco usage, and the Charlson co-morbidity index (CCI) [30].

Statistical analysis was performed using the R statistical package version 3.1.1 (GNU General Public License) [31]. All tests were two-tailed with p-values <0.05 considered significant.

Results

Characteristics of study population

We identified a total of 218,933 patients discharged from Spanish hospitals with a DVT diagnosis from 1 January 1997 to 31 December 2013. Among those patients, 1,481 (0.67%) were infected with HIV (1,006 HIV-monoinfected and 475 HIV/HCV-coinfected). In comparison with HIV-monoinfected subjects, HIV/HCV-coinfected subjects were younger, had a higher frequency of tobacco abuse, chronic pulmonary disease and liver disease and had a lower frequency of diabetes and a shorter length of hospital stay (P<0.050) (**Table 1**). The frequency of PE was 15.9% and was similar between groups (p=0.176).

Table 1. Epidemiological and clinical characteristics of HIV-infected subjects (HIV-monoinfected and HIV/HCV-coinfected) with a hospital admission and DVT diagnosis from 1997 to 2013 in Spain.

	All HIV-infected	**HIV-monoinfected**	**HIV/HCV-coinfected**	**p-value**
No. of subjects	1481	1006	475	
Gender (male)	1178(79.5%)	789 (78.4%)	389 (81.9%)	0.140
Age (years)	43.2 (42.7; 43.7)	44.1 (43.4; 44.8)	41.3(40.6; 41.9)	**<0.001**
Substances of abuse at admission				
Illicit drugs	5 (0.3%)	2 (0.2%)	3 (0.6%)	0.39
Alcohol	21 (1.4%)	12 (1.2%)	9 (1.9%)	0.406
Tobacco	395 (26.7%)	237 (23.6%)	158 (33.3%)	**<0.001**
Length of hospital stay (days)	18.8 (17.5; 20.1)	19.9 (18.3; 21.6)	16.4 (14.2; 18.6)	**0.012**
Surgical conditions	59 (4%)	40 (4%)	19 (4%)	0.999
Charlson Comorbidity Index	1.51 (1.39; 1.62)	1.17 (1.04; 1.3)	1.11 (0.91; 1.3)	0.607
Major comorbid diseases				
Cerebrovascular Disease	33 (2.2%)	25 (2.5%)	8 (1.7%)	0.432

Pulmonary embolism	235 (15.9%)	169 (16.8%)	66 (13.9%)	0.176
Chronic Pulmonary Disease	140 (9.5%)	80 (8%)	60 (12.6%)	**0.005**
Liver Disease	200 (13.5%)	85 (8.4%)	115 (24.2%)	**<0.001**
Diabetes	71 (4.8%)	56 (5.6%)	15 (3.2%)	**0.028**
Renal Disease	50 (3.4%)	33 (3.3%)	17 (3.6%)	0.886
Cancer	270 (18.2%)	197 (19.6%)	73 (15.4%)	0.059
Metastatic Carcinoma	103 (7%)	68 (6.8%)	35 (7.4%)	0.749

Values were expressed as absolute number (percentage) and median (percentile 25th; percentile 75th). P-values were calculated by Chi-squared test and Mann-Whitney U test. Statistically significant differences are shown in bold.
Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; DVT, deep venous thrombosis.

Incidence of DVT-related hospitalizations

The incidence of DVT-related hospitalizations (events per 100,000 patient-years) in HIV-infected patients during the four study periods are shown in **Fig 1** (full description in **Table S3**).

Overall, the incidence of DVT-related hospitalizations had a significant upward trend in all HIV-infected patients (P<0.001), with a significant difference between 1997-1999 and 2008-2013 [49.5 vs. 88.1 (P<0.001)]. When the population was stratified by HCV status [**Fig 1** (full description in **Table S3**)], the incidence of DVT-related hospitalizations was higher in HIV-monoinfected patients than in HIV/HCV-coinfected patients during the entire follow-up (P<0.001). However, incidence rates of DVT-related hospitalizations had a significant downward trend in HIV-monoinfected patients (P=0.002) and a significant upward trend in HIV/HCV-coinfected patients (P<0.001). Specifically, the incidence of DVT-related hospitalizations in HIV-monoinfected patients significantly decreased from 1997-1999 and 2008-2013 [142.7 vs. 103.1 (P=0.006)], whereas in HIV/HCV-coinfected patients increased from 8.4 (1997-1999) to 70.7 (2008-2013) (P<0.001).

Case fatality rate of DVT-related hospitalizations

The case fatality rate for DVT-related hospitalizations are shown in **Table S4**. The trend of the case fatality rate did not show any change during follow-up (1997-2013) in all study groups (HIV-infected, HIV-monoinfected, and HIV/HCV-coinfected patients). Moreover, case fatality rates were similar in these three study groups. When adjusted logistic regression was performed, the odds of death were not significantly higher in HIV/HCV-coinfected patients than in HIV-monoinfected patients (see **Figure S1**).

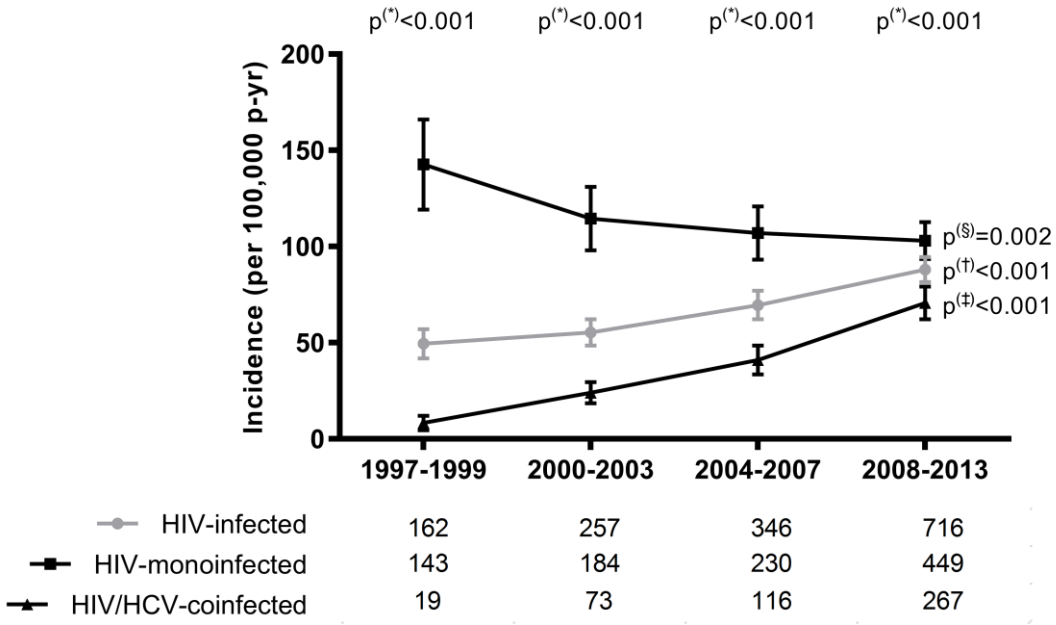

Fig 1. Incidence of DVT in HIV-infected patients in Spain (1997-2013) stratified by HCV status. P-values: (*), differences between HIV-monoinfected patients and HIV/HCV-coinfected patients by the exact confidence intervals for incidence; (§), linear trend from 1997-1999 to 2008-2013 in HIV-monoinfected patients by the Extended Mantel Haenszel Chi Square; (†), linear trend from 1997-1999 to 2008-2013 in HIV-infected patients by the Extended Mantel Haenszel Chi Square; (‡), linear trend from 1997-1999 to 2008-2013 in HIV/HCV-coinfected patients by the Extended Mantel Haenszel Chi Square. The numbers at the base of the panels are the total numbers of hospitalizations in each calendar period and study group. Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Discussion

Our study shows the epidemiological trends of DVT-related hospitalizations by examining adults discharged from Spanish hospitals during the cART era (1997-2013). The major findings of this study were: 1) the incidence of DVT-related hospitalizations increased in all HIV-infected patients; 2) the incidence was lower in HIV/HCV-coinfected patients than in HIV-monoinfected patients; 3) the incidence increased in HIV/HCV-coinfected patients and decreased in HIV-monoinfected patients, but HIV/HCV-coinfected patients still had a lower incidence than HIV-monoinfected patients in the last cART period (2008-2013); and 4) the case fatality rate did not change during follow-up and was similar for all groups. To our knowledge, this is the first nationwide study assessing temporal trends of the DVT incidence in HIV-infected patients who were stratified by HCV serostatus.

In our study, we found a statistically significant decline in incidence rates for DVT-related hospitalizations in HIV-monoinfected patients. Several factors may have influenced these findings. Firstly, high plasma HIV viral load and/or low CD4+ cell counts have been found to increase the risk of venous thromboembolism in HIV-infected individuals [6, 10, 32]. Due to widespread use of antiretroviral therapy, the percentage of HIV-infected individuals receiving cART in Spain has increased significantly over the last decade, with a higher proportion of patients with undetectable HIV viral load, higher CD4+ T-cell counts, and less advanced CDC clinical stage [27]. This improvement could be responsible for the decrease in DVT, however, low levels of immune activation and inflammation persists in virally suppressed HIV-infected patients, which may contribute to an increased risk for venous thrombosis [19, 33]. Secondly,

cardiovascular disease has been recognized by clinicians as a major health problem in HIV-infected individuals after the introduction of cART, and the improvement in preventive interventions for reducing the cardiovascular risk has resulted in a steady reduction in cardiovascular mortality in high-income countries [34]. Thirdly, antiretroviral drugs with less metabolic side effects could have contributed to a decrease in the DVT risk [33].

Another remarkable finding was the temporal trends of the DVT incidence in HIV/HCV-coinfected patients. At the beginning of the study period, the DVT rate was far lower in HIV/HCV-coinfected patients than in HIV-monoinfected patients; but in the ensuing years, the DVT rate increased significantly in HIV/HCV-coinfected patients. At the end of the study period, the DVT rate continued being lower in HIV/HCV-coinfected patients than in HIV-monoinfected patients. We cannot infer any explanation about this epidemiological trend of the DVT rate in HIV/HCV-coinfected patients with the data to which we have access through the MBDS. One possibility is that over the study period the screening for HCV infection could have been different in patients admitted to hospitals due to DTV (e.g., more HCV testing among HIV-positive patients in the later periods than during the early period). However, testing for HCV antibodies in HIV-infected patients in Spain has not changed significantly over the last 13 years and has always been over 95% [35, 36]. Another possibility is that death could have been a major competing risk for DVT in HIV/HCV-coinfected patients from 1997-1999 to 2004-2007. However, we could not do a statistical analysis of competing risk for DVT to test this hypothesis in this patient subgroup, although this hypothesis, in our view, is much more likely and may be supported by observational studies. In a previous report by Berenguer et al. [37], they found that the mortality trend for HIV-infected individuals in Spain declined significantly from 1997 to 2008, at the expense of HIV-monoinfected patients, since they did not observed a decline in mortality rates among HIV/HCV-coinfected patients [37]. Moreover, the predominant mode of HIV acquisition in patients with HCV antibodies has been, and continues to be, injection drug use [27, 35, 36]. This means that these patients have a high risk of death due to AIDS-related and liver-related complications and lifestyle factors including substance abuse, accidents, and suicide [36]. Moreover, in the last years of the study, the use of simpler, more efficacious and safer cART regimens for all clinical scenarios [38], and the increasing use of anti-HCV therapy in coinfected patients [36] could have diminished the burden of comorbidities and death in this population. Both factors have been associated with reductions in liver-related and non-liver-related mortality among HIV/HCV-coinfected individuals [39-42]; and they could have contributed to decreasing mortality rates among HIV/HCV-coinfected patients, and consequently to lessen the competing risk of death. In any case, we have presented real data even if we were unable to clearly demonstrate what factors influence the epidemiological values and the data trends.

Both DVT and PE are manifestations of VTE, but in the present study we considered separating these two forms of VTE when taking into account the differences in frequency and prognosis of the two entities [1]. We focused on DVT as main outcome variable, which is a more common form of VTE and less severe disorder than PE. Moreover, DVT may progress to PE, a life-threatening complication, but not all DVT progress to PE, and occasionally PE may present without there being evidence of DVT [1]. In our study, around 16% of patients also had PE, but no significant differences were found between the two study groups (HIV-monoinfected versus HIV/HCV-coinfected patients).

Also of interest, HCV infection is associated with lower serum levels of total cholesterol and LDL cholesterol, which is clearly a protective factor against atherosclerosis [43, 44]. Thus, HCV eradication may have different effects on atherogenesis: reversion of inflammation and endothelial dysfunction [45] and rebound of LDL and total cholesterol to levels associated with an increased risk of coronary [43, 46]. Moreover, thrombotic events have been associated with alpha-interferon therapy for patients with chronic HCV infection [47]. However, in our study

we did not have data regarding HCV treatment and if the patient had active HCV infection, and we did not evaluate the impact of HCV therapy in eliminating the virus. Further studies should be performed to assess the possible impact of new therapies against HCV for reducing the risk of DVT in HIV/HCV-coinfected patients.

This study has several limitations. Firstly, for estimating the number of HIV-infected individuals in Spain, we did not have data from 1997 to 2013, because there was no national coverage data of HIV diagnoses in our country in this period. Instead, we used an estimation of people living with HIV provided by the National Centre of Epidemiology [26], but this estimation did not provide data of age, gender and comorbidities; and therefore, we are unable to calculate the incidence stratified by traditional cardiovascular risk factors (age, gender, diabetes, hypertension, etc.). Secondly, we did not have any information on the number of patients with DVT who did not require hospital admission for systemic anticoagulation or who died before hospital admission, since the MBDS only provides information on acute patients who were hospitalized. Indeed, a reduction in DVT-related hospitalizations may have been due to several reasons and may have affected the epidemiological trends along the study period and introduced a bias. With the emergence of better outpatient treatment options such as low molecular weight heparins and more recently direct oral anticoagulants, hospitalization can be avoided in many cases of DVT [48]. This outcome is more likely to occur for HIV-monoinfected patients than HIV/HCV-coinfected patients, due to the widespread use of cART in more recent years and because coinfection leads to more frequent liver disease requiring hospitalization. This may explain the relative increase in DVT-related hospitalization in this subgroup of patients. Thirdly, coinfection by HCV was defined by the presence of anti-HCV antibodies, and we could not estimate the proportion of patients with active HCV infection defined by the presence of HCV-RNA in serum. This is a problem frequently found in cohort studies [49, 50] and meta-analyses [51], which provides an overestimation of HCV-infected patients. Besides, we could not evaluate the impact of HCV therapy and HCV elimination on the epidemiological trend of DVT in HIV/HCV-coinfected patients. Fourthly, due to the nature of our database, we did not have access to key clinical data that could have helped us to interpret our results in a more precise way. This includes reliable information regarding illicit drug use, cART regimens and adherence, CD4+ cell counts, HIV viral loads, and DVT management. Although illicit drug use is more frequently recognized in HIV/HCV-coinfected patients than in HIV-monoinfected patients, we lacked reliable information concerning the use of intravenous opioid drugs, which is a known risk factor for DVT [52]. However, one of the strengths of this study is that the MDBS allowed us to analyze nationwide data. Our study captures hospitalizations for DVT in Spain via MBDS and ICD-9 codes, which are well-established in thromboembolism epidemiology for assessing its trends and the need for preventive and therapeutic care and for service planning, as evidenced by the numerous articles published throughout the years [3, 25, 53-56].

Conclusions

In conclusion, our findings suggest that DVT is an emerging health problem among HIV-infected patients, with increased incidence rates during the first 17 years after the introduction of cART, particularly in HIV/HCV-coinfected patients. Further studies should be performed to corroborate these findings and ascertain the effects of lifestyle factors, active HCV infection, and the possible impact of new therapies against HCV on the evolution of DVT.

Acknowledgements, conflicts of interest, and funding

Acknowledgments

We wish to thank: a) Spanish Ministry of Health and Social Policy for providing the records of the Minimum Basic Data Set (MBDS); b) National Centre for Epidemiology (Instituto de Salud Carlos III) for providing the estimation of the number of people living with HIV/AIDS in Spain.

Conflicts of interest:

The authors declare that they have no conflicts of interest.

Authorship/contributions:

Conceptualization: SR.

Formal analysis: AAM.

Data curation: AAM.

Writing – original draft preparation: AAM, PR, and SR.

Writing – Review & Editing: DM, EML, and JB.

Visualization, supervision and funding acquisition: SR.

Financial support:

This work has been supported by a grant from "Instituto de Salud Carlos III" (grant numbers PI14/01094, PI14CIII/00011). The study was also funded by the RD16CIII/0002/0002 and RD16/0025/0017 projects as part of the Plan Nacional R + D + I and cofunded by ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER).

JB is an investigator from the Programa de Intensificación de la Actividad Investigadora en el Sistema Nacional de Salud (I3SNS), Refs INT15/00079 and INT16/00100.

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Supporting Information

Table S1. Summary of ICD-9-CM coding used for baseline comorbidities investigated in this study.

Description	ICD-9-CM
Viral infection status	
HIV infection	042 or V08
HCV infection	070.44, 070.54, 070.7x, or V02.62
HBV infection	070.2x, 070.3x, or V02.61
Conditions influencing in health status	
Surgical conditions	V42, V45
Trauma	E880* to E929*, E950 to E999*
Comorbid diseases (Charlson index)	
Myocardial Infarction	410, 412
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7, 425.8, 425.9, 428
Peripheral Vascular Disease	093.0, 437.3, 440, 441, 443.1, 443.2, 443.8, 443.9, 447.1, 557.1, 557.9, V434
Cerebrovascular Disease	362.34, 430, 431, 432, 433, 434, 435, 436, 437, 438
Chronic Pulmonary Disease	416.8, 416.9, 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 5064, 508.1, 508.8
Connective Tissue Disease-Rheumatic Disease	446.5, 710.0, 710.1, 710.2, 710.3, 710.4, 714.0, 714.1, 714.2, 714.8, 725
Mild Liver Disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, 573.9, V427
Moderate or Severe Liver Disease	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8
Diabetes without complications	250.0, 250.1, 250.2, 250.3, 250.8, 250.9
Diabetes with complications	250.4, 250.5, 250.6, 250.7
Renal Disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 585, 586, 588.0, V420, V451, V56
Cancer	140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 171, 172, 174, 175, 176, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 200, 201, 202, 203, 204, 205, 206, 207, 208, 238.6
Metastatic Carcinoma	196, 197, 198, 199
Abuse of alcohol and drugs	
Abuse of drugs	304.0,304.1,304.2,304.3,304.4,304.5,304.6,304.7,304.8,304.9,305.2,305.3,305.4,305.5,305.6,305.7,305.8,305.9,292.0 ,969.6,965.01,292.82,292.83,292.84,292.89,292.9,292.11,292.12,292.2,648.3

Abuse of alcohol	305.0,303.0,303.9,291.0,291.1,291.2,291.3,291.4,291.5,291.8,291.9,571.0,571.1,571.2,571.3,425.5,535.3,357.5,265.2, V11.3,790.3,980.0
Abuse of tobacco	305.1,V158.2

Venous thromboembolism

Pulmonary embolism	415.11, 415.19
Deep venous thrombosis	453.4x, 453.8x

Table S2. Estimation of the number of people over 15 years of age coinfected with HIV and HCV in Spain.

Year	HIV-infected patients (No.) (*)	HCV-positive antibody (%) (‡)	HIV/HCV-coinfected patients (%) (†)	HIV/HCV-coinfected patients (No.) (¥)	HIV-monoinfected (No.) (§)
1997	106.483	69	69.8	74,353	32,130
1998	109.419	69	69.4	75,962	33,457
1999	111.281	69	68.9	76,689	34,592
2000	113.130	69	68.3	77,274	35,856
2001	114.824	69	66.7	76,605	38,219
2002	116.766	65	64.4	75,286	41,480
2003	118.964	-	62.1	73,905	45,059
2004	121.038	57.1	59.9	72,524	48,514
2005	123.069	58.5	57.7	71,113	51,956
2006	125.257	53.1	55.7	69,882	55,375
2007	127.615	50.8	53.8	68,719	58,896
2008	129.765	48.7	51.6	67,018	62,747
2009	131.888	47.7	49.2	64,992	66,896
2010	134.392	45.7	47.1	63,409	70,983
2011	136.747	42.6	45.4	62,126	74,621
2012	138.978	42.8	43.6	60,723	78,255
2013	141.052	42.6	41.9	59,163	81,889

(*),The estimation of number of people living with HIV/AIDS in Spain was provided by the National Centre of Epidemiology (Instituto de Salud Carlos III, Madrid, Spain) [1]. This estimation was done using the Estimation and Projection Package (EPP) and Spectrum software, two programs developed by the Joint UNAIDS/WHO for estimating and projecting HIV prevalence at country level [2, 3].

(‡), The percentage of patients with HCV antibodies was collected from the "Asociación Médica VACH de Estudios Multicentricos (AMVACH)" (1999-2001) [4], the "Grupo de Estudio de Sida" (GeSIDA) (2002) [5], and the "Hospital survey of patients infected with HIV", a second-generation surveillance system in people living with HIV coordinated by the National Centre of Epidemiology (2004-2013) [6, 7].

(†), The final estimation of the percentage of subjects coinfected with HIV and HCV in Spain was obtained from a regression model for imputing missing values and smoothing the numbers according to the temporal trend of the data.

(¥), The estimation of the number of subjects coinfected with HIV and HCV in Spain was the result of multiplying the number of individuals infected with HIV and the percentage of patients coinfected with HIV and HCV.

Table S3. Epidemiological incidence trends of DVT-related hospitalizations (events per 100,000 patients/year) in Spain (1997 to 2013) stratified by HIV and HCV infections.

	HIV-infected		HIV-monoinfected		HIV/HCV-coinfected		
	No.	**Rate (95%CI)**	**No.**	**Rate (95%CI)**	**No.**	**Rate (95%CI)**	**p-value**
Whole follow-up	1481	70.5 (66.9; 74.1)	1006	110.4 (103.6; 117.3)	475	39.9 (36.3; 43.5)	**<0.001**
1997-1999	162	49.5 (41.9; 57.1)	143	142.7 (119.3; 166.1)	19	8.4 (4.6; 12.1)	**<0.001**
2000-2003	257	55.4 (48.6; 62.2)	184	114.6 (98.0; 131.1)	73	24.1 (18.6; 29.6)	**<0.001**
2004-2007	346	69.6 (62.3; 77.0)	230	107.1 (93.3; 120.9)	116	41.1 (33.6; 48.6)	**<0.001**
2008-2013	716	88.1 (81.6; 94.5)	449	103.1 (93.6; 112.7)	267	70.7 (62.3; 79.2)	**<0.001**
P-values (*)							
Differences: 97-99 vs. 00-03		0.999		0.298		**<0.001**	
Differences: 97-99 vs. 04-07		**0.002**		**0.046**		**<0.001**	
Differences: 97-99 vs. 08-13		**<0.001**		**0.006**		**<0.001**	
Differences: 00-03 vs. 04-07		**0.033**		0.999		**0.002**	
Differences: 00-03 vs. 08-13		**<0.001**		0.999		**<0.001**	
Differences: 04-07 vs. 08-13		**0.002**		0.999		**<0.001**	
P-values (§)							
Linear trend		**<0.001**		**0.002**		**<0.001**	

Values were expressed as absolute count; and rate (95% confidence interval (95% CI)).

P-values: (*), differences by the exact confidence intervals for incidence; (§), linear trend from 1997-1999 to 2008-2013 by the Extended Mantel Haenszel Chi Square. Statistical significant differences are shown in bold.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; DVT, deep venous thrombosis.

Table S4. Epidemiological trends of the case fatality rate of DVT-related hospitalizations (%) in Spain (1997 to 2013) stratified by HIV and HCV infections.

	HIV-infected		HIV-monoinfected		HIV/HCV-coinfected		
	No.	**Rate (95%CI)**	**No.**	**Rate (95%CI)**	**No.**	**Rate (95%CI)**	**p-value** (*)
Whole follow-up	97	6.55 (5.37; 7.96)	66	6.56 (5.15; 8.32)	31	6.53 (4.55; 9.24)	0.999
1997-1999	11	6.79 (3.61; 12.13)	10	6.99 (3.59; 12.82)	1	5.26 (0.28; 28.11)	0.999
2000-2003	18	7.00 (4.32; 11.03)	11	5.98 (3.17; 10.72)	7	9.59 (4.27; 19.33)	0.452
2004-2007	18	5.20 (3.20; 8.24)	10	4.35 (2.22; 8.09)	8	6.90 (3.24; 13.56)	0.452
2008-2013	50	6.98 (5.28; 9.17)	35	7.80 (5.56; 10.77)	15	5.62 (3.29; 9.29)	0.340
P-values (*)							
Differences: 97-99 vs. 00-03		0.999		0.999		0.999	
Differences: 97-99 vs. 04-07		0.999		0.999		0.999	
Differences: 97-99 vs. 08-13		0.999		0.999		0.999	
Differences: 00-03 vs. 04-07		0.999		0.999		0.999	
Differences: 00-03 vs. 08-13		0.999		0.999		0.999	
Differences: 04-07 vs. 08-13		0.985		0.366		0.999	
P-values (§)							
Linear trend		0.907		0.531		0.375	

Values were expressed as absolute count; and rate (95% confidence interval (95% CI)).

P-values: (*), differences by the exact confidence intervals for incidence; (§), linear trend from 1997-1999 to 2008-2013 by the Extended Mantel Haenszel Chi Square. Statistical significant differences are shown in bold.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; DVT, deep venous thrombosis

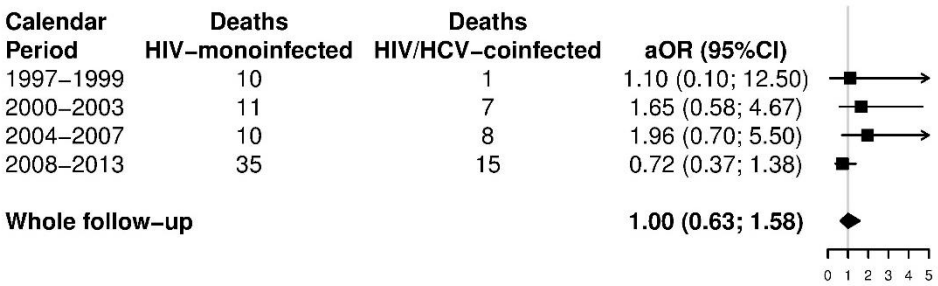

Figure S1. Adjusted likelihood of death among HIV-infected patients with DVT in Spain (1997-2013) stratified by HCV status.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus, aOR, adjusted odds ratio; 95%CI, 95% of confidence interval.