# Title page

**Title**: Trends in pulmonary embolism in patients infected with HIV during the combination antiretroviral therapy era in Spain: A nationwide population-based study

**Running Head**: Pulmonary embolism and HIV infection

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**Supplementary Table 1**. Epidemiological incidence trends of PE-related hospitalizations (events per 100,000 patients/year) in Spain (1997 to 2013) stratified by HIV and HCV infection status.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **HIV-infected** | | **HIV-monoinfected** | | **HIV/HCV-coinfected** | |  |
|  | **No.** | **Rate (95%CI)** | **No.** | **Rate (95%CI)** | **No.** | **Rate (95%CI)** | **p-value** (\*) |
| Whole follow-up | 1356 | 64.5 (61.1; 68.0) | 899 | 98.7 (92.2; 105.1) | 457 | 38.4 (34.9; 41.9) | **<0.001** |
| 1997-1999 | 241 | 73.7 (64.4; 83.0) | 204 | 203.6 (175.7; 231.6) | 37 | 16.3 (11; 21.6) | **<0.001** |
| 2000-2003 | 276 | 59.9 (52.5; 67.0) | 192 | 119.5 (102.6; 136.4) | 84 | 27.7 (21.8; 33.6) | **<0.001** |
| 2004-2007 | 315 | 63.4 (56.4; 70.4) | 180 | 83.8 (71.6; 96.1) | 135 | 47.8 (39.8; 55.9) | **<0.001** |
| 2008-2013 | 524 | 64.5 (58.9; 70.0) | 323 | 74.2 (66.1; 82.3) | 201 | 53.3 (45.9; 60.6) | **<0.001** |
| **P-values** (\*) |  |  |  |  |  |  |  |
| Differences: 97-99 vs. 00-03 |  | 0.096 |  | **<0.001** |  | **0.035** |  |
| Differences: 97-99 vs. 04-07 |  | 0.480 |  | **<0.001** |  | **<0.001** |  |
| Differences: 97-99 vs. 08-13 |  | 0.532 |  | **<0.001** |  | **<0.001** |  |
| Differences: 00-03 vs. 04-07 |  | 0.999 |  | **0.004** |  | **<0.001** |  |
| Differences: 00-03 vs. 08-13 |  | 0.999 |  | **<0.001** |  | **<0.001** |  |
| Differences: 04-07 vs. 08-13 |  | 0.999 |  | 0.999 |  | 0.999 |  |
| **P-values** (§) |  |  |  |  |  |  |  |
| Linear trend |  | 0.361 |  | **<0.001** |  | **<0.001** |  |

Values are 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; PE, pulmonary embolism.

**Supplementary Table 2**. Epidemiological mortality trends of PE-related hospitalizations (events per 100,000 patients/year) in Spain (1997 to 2013) stratified by HIV and HCV infection status.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **HIV-infected** | | **HIV-monoinfected** | | **HIV/HCV-coinfected** | |  |
|  | **No.** | **Rate (95%CI)** | **No.** | **Rate (95%CI)** | **No.** | **Rate (95%CI)** | **p-value** (\*) |
| Whole follow-up | 210 | 10.0 (8.6; 11.3) | 147 | 16.1 (13.5; 18.7) | 63 | 5.3 (4; 6.6) | **<0.001** |
| 1997-1999 | 46 | 14.1 (10.0; 18.1) | 42 | 41.9 (29.2; 54.6) | 4 | 1.8 (0; 3.5) | **<0.001** |
| 2000-2003 | 42 | 9.1 (6.3; 11.8) | 28 | 17.4 (11; 23.9) | 14 | 4.6 (2.2; 7) | **<0.001** |
| 2004-2007 | 39 | 7.8 (5.4; 10.3) | 27 | 12.6 (7.8; 17.3) | 12 | 4.3 (1.8; 6.7) | **0.001** |
| 2008-2013 | 83 | 10.2 (8.0; 12.4) | 50 | 11.5 (8.3; 14.7) | 33 | 8.7 (5.8; 11.7) | 0.225 |
| **P-values** (\*) |  |  |  |  |  |  |  |
| Differences: 97-99 vs. 00-03 |  | 0.241 |  | **0.002** |  | 0.473 |  |
| Differences: 97-99 vs. 04-07 |  | **0.045** |  | **<0.001** |  | 0.726 |  |
| Differences: 97-99 vs. 08-13 |  | 0.517 |  | **<0.001** |  | **0.002** |  |
| Differences: 00-03 vs. 04-07 |  | 0.999 |  | 0.999 |  | 0.999 |  |
| Differences: 00-03 vs. 08-13 |  | 0.999 |  | 0.498 |  | 0.248 |  |
| Differences: 04-07 vs. 08-13 |  | 0.999 |  | 0.999 |  | 0.165 |  |
| **P-values** (§) |  |  |  |  |  |  |  |
| Linear trend |  | 0.199 |  | **<0.001** |  | **<0.001** |  |

Values are 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; PE, pulmonary embolism.

**Supplementary Table 3**. Epidemiological trends of case fatality rate of PE-related hospitalizations (%) in Spain (1997 to 2013) stratified by HIV and HCV infection status.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **HIV-infected** | | **HIV-monoinfected** | | **HIV/HCV-coinfected** | |  |
|  | **No.** | **Rate (95%CI)** | **No.** | **Rate (95%CI)** | **No.** | **Rate (95%CI)** | **p-value** (\*) |
| Whole follow-up | 210 | 15.49 (13.62; 17.55) | 147 | 16.35 (14.03; 18.97) | 63 | 13.79 (10.83; 17.37) | 0.248 |
| 1997-1999 | 46 | 19.09 (14.44; 24.74) | 42 | 20.59 (15.39; 26.92) | 4 | 10.81 (3.52; 26.36) | 0.244 |
| 2000-2003 | 42 | 15.22 (11.3; 20.13) | 28 | 14.58 (10.07; 20.56) | 14 | 16.67 (9.73; 26.73) | 0.794 |
| 2004-2007 | 39 | 12.38 (9.05; 16.65) | 27 | 15 (10.28; 21.25) | 12 | 8.89 (4.88; 15.34) | 0.145 |
| 2008-2013 | 83 | 15.84 (12.88; 19.32) | 50 | 15.48 (11.81; 20) | 33 | 16.42 (11.72; 22.43) | 0.871 |
| **P-values** (\*) |  |  |  |  |  |  |  |
| Differences: 97-99 vs. 00-03 |  | 0.880 |  | 0.455 |  | 0.999 |  |
| Differences: 97-99 vs. 04-07 |  | 0.119 |  | 0.591 |  | 0.999 |  |
| Differences: 97-99 vs. 08-13 |  | 0.937 |  | 0.496 |  | 0.999 |  |
| Differences: 00-03 vs. 04-07 |  | 0.999 |  | 0.999 |  | 0.389 |  |
| Differences: 00-03 vs. 08-13 |  | 0.999 |  | 0.999 |  | 0.999 |  |
| Differences: 04-07 vs. 08-13 |  | 0.607 |  | 0.999 |  | 0.205 |  |
| **P-values** (§) |  |  |  |  |  |  |  |
| Linear trend |  | 0.367 |  | 0.242 |  | 0.510 |  |

Values are 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; PE, pulmonary embolism

**Supplementary Table 4**. 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 |

**Supplementary Figure 1.** Cross-sectional images of computed tomography (CT) used to diagnosis the acute pulmonary embolism.

Images A and B: a 35-year-old man infected with HIV with bilateral pulmonary thromboembolism with filling defects in the right main pulmonary artery and interlobar artery.

Images C and D: a 39-year-old woman co-infected with HIV and HCV who presents multiple filling defects in the pulmonary arterial tree bilaterally and signs of right ventricular overload in the CT scan.

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**Supplementary Table 5**. 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). 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 [[1](#_ENREF_1), [2](#_ENREF_2)].

(‡), The percentage of patients with HCV antibodies was collected from the “Asociación Médica VACH de Estudios Multicentricos (AMVACH)” (1999-2001) [[3](#_ENREF_3)], the “Grupo de Estudio de Sida” (GeSIDA) (2002) [[4](#_ENREF_4)], 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) [[5](#_ENREF_5), [6](#_ENREF_6)].

(†), 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.

(§), The estimation of the number of HIV-monoinfected patients in Spain was the result of subtracting the number of individuals infected with HIV and the number of patients coinfected with HIV and HCV.