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Figure 1: Relationship between comorbidities projected on the first two components based on multiple correspondence analyses. Legend: CNS: central nervous system; AIDS: Acquired immunodifienciency syndrome; HCV: Hepatitis C virus; eGFR: estimated glomerular filtration rate in mL/min. +: comorbidity present; - comorbidity not present.

Table 1a: Description of activation, maturation and senescence markers expressed on CD4 positive and CD8 positive T lymphocytes.

| **Immune markers** | **Median (IQR\*)** |
| --- | --- |
| CD4+, VA | 579 (429 ; 759) |
| CD4+, % | 34 (27 ; 40) |
| CD4+DR+ among CD4+, % | 14 (10 ; 19) |
| CD4+DP among CD4+, % | 5 (3 ; 6) |
| CD4+CD57+CD28- among CD4+, % | 3 (1 ; 7) |
| CD4+CD28- among CD4+, % | 3 (1 ; 8) |
| CD4+TN among CD4+, % | 40 (28 ; 51) |
| CD4+TEMRA among CD4+, % | 1 (0 ; 3) |
| CD8+, VA | 671 (485 ; 922) |
| CD8+, % | 39 (33 ; 47) |
| CD8+DR+ among CD8+, % | 35 (26 ; 46)  |
| CD8+DP among CD8+, % | 13 (9 ; 20) |
| CD8+CD57+CD28- among CD8+, % | 27 (17 ; 36) |
| CD8+CD28- among CD8+, % | 39 (28 ; 51) |
| CD8+TN among CD8+, % | 38 (29 ; 48) |
| CD8+TEMRA among CD8+, % | 1. 16 ; 36)
 |

Legend: \*Interquartile Range; TN: T naïve; TEMRA: terminally differentiated T cells.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | CD4+DR+ among CD4+, % | CD4+DP among CD4+, % | CD4+CD57+CD28- among CD4+, % | CD4+CD28- among CD4+, % | CD4+TN among CD4+, % | CD4+TEMRA among CD4+, % | CD8+DR+ among CD8+, % | CD8+DP among CD8+, % | CD8+CD57+CD28- among CD8+, % | CD8+CD28- among CD8+, % | CD8+TN among CD8+, % | CD8+TEMRA among CD8+, % |
| CD4+DR+ among CD4+, % | r | 1.00 |  |  |  |  |  |  |  |  |  |  |  |
| *P* | - |  |  |  |  |  |  |  |  |  |  |  |
| CD4+DP among CD4+, % | r | 0.80 | 1.00 |  |  |  |  |  |  |  |  |  |  |
| *P* | <0.0001 | - |  |  |  |  |  |  |  |  |  |  |
| CD4+CD57+CD28- among CD4+, % | r | 0.47 | 0.31 | 1.00 |  |  |  |  |  |  |  |  |  |
| *P* | <0.0001 | <0.0001 | - |  |  |  |  |  |  |  |  |  |
| CD4+CD28- among CD4+, % | r | 0.49 | 0.33 | 0.99 | 1.00 |  |  |  |  |  |  |  |  |
| *P* | <0.0001 | <0.0001 | <0.0001 | - |  |  |  |  |  |  |  |  |
| CD4+TN among CD4+, % | r | -0.56 | -0.37 | -0.34 | -0.35 | 1.00 |  |  |  |  |  |  |  |
| *P* | <0.0001 | <0.0001 | <0.0001 | <0.0001 | - |  |  |  |  |  |  |  |
| CD4+TEMRA among CD4+, % | r | 0.38 | 0.24 | 0.81 | 0.81 | -0.19 | 1.00 |  |  |  |  |  |  |
| *P* | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | - |  |  |  |  |  |  |
| CD8+DR+ among CD8+, % | r | 0.63 | 0.51 | 0.29 | 0.31 | -0.22 | 0.25 | 1.00 |  |  |  |  |  |
| *P* | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | - |  |  |  |  |  |
| CD8+DP among CD4+, % | r | 0.44 | 0.61 | 0.22 | 0.23 | -0.10 | 0.19 | 0.71 | 1.00 |  |  |  |  |
| *P* | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0022 | <0.0001 | <0.0001 | - |  |  |  |  |
| CD8+CD57+CD28- among CD8+, % | r | 0.28 | 0.24 | 0.59 | 0.58 | -0.13 | 0.46 | 0.38 | 0.34 | 1.00 |  |  |  |
| *P* | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | - |  |  |  |
| CD8+CD28- among CD4+, % | r | 0.38 | 0.33 | 0.60 | 0.61 | -0.16 | 0.49 | 0.55 | 0.48 | 0.90 | 1.00 |  |  |
| *P* | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | - |  |  |
| CD8+TN among CD8+, % | r | -0.47 | -0.31 | -0.47 | -0.48 | 0.54 | -0.24 | -0.48 | -0.30 | -0.60 | -0.64 | 1.00 |  |
| *P* | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | - |  |
| CD8+TEMRA among CD8+, % | r | 0.33 | 0.23 | 0.61 | 0.62 | -0.13 | 0.59 | 0.43 | 0.36 | 0.82 | 0.85 | -0.52 | 1.00 |
| *P* | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | - |

Table 1b: Correlation matrix between activation, maturation and senescence immune markers expressed on CD4 positive and CD8

positive T lymphocytes.

Legend: r: Spearman correlation coefficient; *P*: p-values; TN: T naïve; TEMRA: terminally differentiated T cells.

Table 2: HIV related characteristics associated with the presence of at least three comorbidities (Univariable analysis)

| **Variables** | **OR (CI95%)** | ***P*-value** | **AIC** |
| --- | --- | --- | --- |
| Sex (female vs. male)  | 0.4 (0.2-0.7) | 0.0014 | 688.2 |
| Age (years)\* | 2.7 (2.2-3.4) | <0.0001 | 605.7 |
| Contamination | 1.0 | 0.4866 | 701.7 |
|  | MSM (vs. Heterosexual) | 1.0 (0.6-1.5) | . | . |
|  | Drug users (vs. Heterosexual) | 0.7 (0.4-1.4) | . | . |
|  | Others (vs. Heterosexual) | 1.4 (0.7-2.7) | . | . |
| Duration since first reported seropositivity (years)\*  | 1.3 (1.1-1.6) | 0.0073 | 692.7 |
| CDC classification | 1.0 | <0.0001 | 681.2 |
|  | B (vs. A) | 1.4 (0.9-2.4) | . | . |
|  | C (vs. A) | 2.9 (1.9-4.6) | . | . |
| Patients on cART | 1.0 | 0.0406 | 694.502 |
|  | 2 NRTI + 1 PI/r (vs. Others) | 0.6 (0.4-0.9) | . | . |
|  | 2 NRTI + 1 NNRTI (vs. Others) | 0.6 (0.4-1.0) | . | . |
| Time since the first cART (years)\*  | 1.6 (1.3-2.0) | <0.0001 | 679.1 |
| Duration of viral suppression (years)\*  | 1.2 (1.0-1.5) | 0.0443 | 696.2 |
| CD4+ nadir (cells/mm3)\*  | 0.8 (0.7-1.0) | 0.0351 | 695.6 |
| Time from CD4+ nadir (years)\*  | 1.3 (1.1-1.6) | 0.0051 | 692.3 |
| Last CD4+ count (cells/mm3)\*  | 1.0 (0.8-1.2) | 0.6350 | 699.9 |
| Last CD4/CD8 ratio \*  | 0.9 (0.7-1.1) | 0.1891 | 698.3 |
| Positive CMV serology (yes vs. no) | 0.8 (0.4-1.6) | 0.6080 | 578.5 |
| Hepatitis B virus infection (yes vs. no) | 0.8 (0.3-1.7) | 0.5077 | 686.1 |
| Hepatitis C virus infection (yes vs. no) | 0.7 (0.4-1.2) | 0.1997 | 687.5 |

Legend: \* odds-ratio given for a one standard deviation increase; CDC: center for disease control, cART: combination antiretroviral therapy, CMV: cytomegalovirus, NRTIs: Nucleoside Reverse Transcriptase Inhibitors, PI/r: ritonavir boosted protease Inhibitors, NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor. OR: Odds ratio; CI: confidence intervals; IRP: Immune risk profile; AIC: Akaike information criterion.

Table 3: Immunological markers associated with the presence of at least three comorbidities (Univariable analysis)

| **Variables** | **OR (CI95%)** | ***P*-value** | **AIC** |
| --- | --- | --- | --- |
| CD4+DR+ among CD4+, %\* | 1.4 (1.1-1.6) | 0.0004 | 688.2 |
| CD4+DP among CD4+, %\* | 1.2 (1.0-1.4) | 0.0870 | 697.4 |
| CD4+CD57+CD28- among CD4+, %\* | 1.3 (1.1-1.5) | 0.0025 | 691.7 |
| CD4+CD28- among CD4+, %\* | 1.3 (1.1-1.5) | 0.0027 | 691.9 |
| CD4+TN among CD4+, %\* | 0.6 (0.5-0.7) | <0.0001 | 672.9 |
| CD4+TEMRA among CD4+, %\* | 1.1 (0.9-1.3) | 0.2099 | 698.7 |
| CD8+DR+ among CD8+, %\* | 1.4 (1.2-1.7) | 0.0001 | 685.8 |
| CD8+DP among CD4+, %\* | 1.1 (0.9-1.3) | 0.2058 | 698.6 |
| CD8+CD57+CD28- among CD8+, %\* | 1.2 (1.0-1.5) | 0.0346 | 695.7 |
| CD8+CD28- among CD4+, %\* | 1.3 (1.1-1.6) | 0.0083 | 693.2 |
| CD8+TN among CD8+, %\* | 0.5 (0.4-0.7) | <0.000 | 669.1 |
| CD8+TEMRA among CD8+, %\* | 1.3 (1.1-1.6) | 0.0042 | 692.0 |
| CIADIS score \* | 1.7 (1.4-2.1) | <0.0001 | 674.1 |
| VACS index <35 (yes vs. no) | 3.7 (2.3-5.7) | <0.0001 | 671.3 |
| IRP score ≤ 2 (yes vs. no) | 2.2 (1.4-3.4) | 0.0006 | 566.2 |

Legend: \*odds-ratio given for a one standard deviation increase; OR: Odds ratio; CI: confidence intervals; IRP: Immune risk profile; AIC: Akaike information criterion; VACS: Veterans Aging Cohort Study; IRP: immune risk profile.

Table 4a: Veterans Aging Cohort Study index (VACS index) calculated in the 876 patients included in CIADIS substudy of the ANRS CO3 Aquitaine cohort

| **Variables** |  | **n (%)** | **VACS index points** |
| --- | --- | --- | --- |
| Age (years) |    <50 | 414 (47.3) | 0 |
|  |    50-64 | 379 (43.3) | 12 |
|  |    ≥ 65 | 83 (9.5) | 27 |
| CD4 (cells/mm3) |    ≥ 500 | 566 (64.6) | 0 |
|  |    350-499 | 188 (21.5) | 6 |
|  |    200-349 | 89 (10.2) | 6 |
|  |    100-199 | 26 (3.0) | 10 |
|  |    50-99 | 5 (0.6) | 28 |
|  |    <50 | 2 (0.2) | 29 |
| Hemoglobin (g/dL) |    ≥14 | 564 (64.4) | 0 |
|  |    12-13.9 | 264 (30.1) | 10 |
|  |    10-11.9 | 42 (4.8) | 22 |
|  |    <10 | 6 (0.7) | 38 |
| FIB-4 |    <1.45 | 535 (61.5) | 0 |
|  |    1.45-3.25 | 292 (33.6) | 6 |
|  |    >3.25 | 43 (4.9) | 25 |
| eGFR (mL/min) |    ≥60 | 819 (96.5) | 0 |
|  |    45-59.9 | 23 (2.7) | 6 |
|  |    30-44.9 | 2 (0.2) | 8 |
|  |    <30 | 5 (0.6) | 26 |
| Hepatitis C virus infection |  | 203 (23.5) | 5 |

Legend: eGFR: estimated glomerula filtration rate. FIB-4 is a non-invasive marker of liver fibrosis calculated based on the age, AST levels, ALT levels and platelet count (Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology 2006;43:1317-1325.).

Table 4b: Distribution of the VACS index in the CIADIS substudy of the ANRS CO3 Aquitaine cohort

| **VACS index score** | **n(%)** |
| --- | --- |
|    <35 | 723 (85.8) |
|    35-50 | 90 (10.7) |
|    50-70 | 24 (2.8) |
|    ≤70 | 6 (0.7) |

Table 5a: Immune risk profile score calculated in patients included in CIADIS substudy of the ANRS CO3 Aquitaine cohort (n=714)

| **Variables** | **n (%)** | **IRP points** |
| --- | --- | --- |
| Last CD4/CD8 ratio <1 | 338 (61.4) | 1 |
| Positive CMV serology\* | 638 (89.4) | 1 |
| CD4+CD57+CD28- among CD4+, % > Q3 | 220 (25.1) | 1 |
| CD4+TN among CD4+, %< Q1 | 219 (25.0) | 1 |
| CD4+TEMRA among CD4+, %> Q3 | 218 (24.9) | 1 |
| CD8+CD57+CD28- among CD4+, % > Q3 | 220 (25.1) | 1 |
| CD8+TN among CD4+, %< Q1 | 220 (25.1) | 1 |
| CD8+TEMRA among CD4+, %> Q3 | 217 (24.8) | 1 |

Legend: CMV serology was only available for 714 patients. Q3, Third quartile; Q1, first quartile

Table 5b: Distribution of the Immune risk profile score of patients included in CIADIS substudy of the ANRS CO3 Aquitaine cohort

| **IRP score** | **N(%)** |
| --- | --- |
|    0 | 30 (4.2) |
|    1 | 146 (20.4) |
|    2 | 179 (25.1) |
|    3 | 101 (14.1) |
|    4 | 90 (12.6) |
|    5 | 66 (9.2) |
|    6 | 62 (8.7) |
|    7 | 27 (3.8) |
|    8 | 13 (1.8) |

 Table 6: Factors associated with the presence of at least three comorbidities adjusted for HIV related characteristics (Multivariable analysis)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Model 1 (n=876)**AIC = 591.2AUC = 0.790 | **Model 2 (n=876)**AIC = 592.9AUC = 0.790 | **Model 3 (n=714)**AIC = 484.9AUC = 0.798 | **Model 4 (n=714)**AIC = 485.4AUC = 0.800 | **Model 5 (n=876)**AIC = 596.7AUC = 0.784 |
|  | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| **CIADIS score\*** | 1.3 (1.1-1.7) | 0.0169 | 1.3 (1.1-1.7) | 0.0176 | - | - | - | - | - | - |
| **IRP score ≤ 2** **(yes vs. no)** | - | - | - | - | 1.6 (1.0-2.6) | 0.0777 | 1.5 (0.9-2.5) | 0.0952 | - | - |
| **VACS score <35** **(yes vs. no)** | - | - | 1.2 (0.6-2.1) | 0.5993 | - | - | 1.5 (0.8-2.9) | 0.2180 | 1.2 (0.7-2.1) | 0.5500 |
| **Age (years)\*** | 2.4 (1.9-3.1) | <0.0001 | 2.3 (1.8-3.1) | <0.0001 | 2.5 (2.0-3.3) | <0.0001 | 2.3 (1.7-3.1) | <0.0001 | 2.5 (1.9-3.3) | <0.0001 |
| **Duration since seropositivity (years)** | 1.2 (0.9-1.5) | 0.1310 | 1.2 (1.0-1.5) | 0.1242 | 1.3 (1.0-1.7) | 0.0674 | 1.3 (1.0-1.7) | 0.0544 | 1.2 (0.9-1.5) | 0.1922 |
| **Gender****(F vs. M)** | 0.6 (0.3-1.1) | 0.1137 | 0.6 (0.3-1.1) | 0.1019 | 0.5 (0.2-1.0) | 0.0385 | 0.5 (0.2-0.9) | 0.0266 | 0.5 (0.3-0.9) | 0.0219 |
| **Stage A**  | 1.0 | 0.0048 | 1.0 | 0.0053 | 1.0 | 0.0112 | 1.0 | 0.0143 | 1.0 | 0.0078 |
| **Stage B** **(vs. stage A)** | 1.2 (0.7-2.0) |  | 1.2 (0.7-2.0) |  | 1.2 (0.7-2.2) |  | 1.2 (0.6-2.1) |  | 1.2 (0.7-2.1) |  |
| **Stade C** **(vs. stage A)** | 2.2 (1.3-3.7) |  | 2.2 (1.3-3.6) |  | 2.3 (1.3-3.9) |  | 2.2 (1.3-3.9) |  | 2.1 (1.3-3.5) |  |

Legend: \*odds-ratios given for a one standard deviation (SD) increase (SD of CIADIS score: 2.0; SD of age: 10.0; SD of duration since seropositivity: 7.0); OR: Odds ratio; CI: confidence intervals; IRP: Immune risk profile; AIC: Akaike information criterion; AUC: area under the receiver operator curve.