Supplemental File

Long-term alcohol use patterns and HIV disease severity in US veterans: A joint trjaectory analysis

This supplemental file includes additional information regarding the joint trajectory modeling, the weighted multinomial logistic regression analysis, the VACS tissue repository, as well as results from sensitivity analyses.

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**Determination of AUDIT-C and VACS Index Trajectories**

All values from each individual were used to estimate the distinct trajectories. Since patients had to have at least once VACS Index score and one AUDIT-C value to be included in the analysis, even a single value from a patient contributes to the trajectory estimation procedure. For each outcome, we fit four alternative group-based models, each with a different number of trajectory groups (ranging from two to five). As in previous studies [[1](#_ENREF_1), [2](#_ENREF_2)], we restricted the maximum number of groups to five due to sample size restrictions. We began with quadratic shapes for each trajectory group curve, since models with cubic polynomials failed to converge. We determined the optimal number of trajectory groups by examining model fit statistics, including the Bayesian information criterion (BIC) and the median posterior probability of group membership. Average membership probabilities greater than 0.7 indicate adequate internal reliability [[3](#_ENREF_3)]. We also applied *a priori* clinically meaningfully differences in the outcomes of interest. Specifically, we discarded models when mean scores between any two groups differed by less than 1.0 for the AUDIT-C trajectories (since the instrument is integer-based) and 5.0 for the VACS index score trajectories (representing a ≥20% difference in five-year mortality risk). Once we had selected the optimal number of groups for each outcome, we determined the final shape of each trajectory curve by dropping non-significant polynomial terms. The final AUDIT-C and VACS Index trajectory models had four classes each. In a *post hoc* analysis of models with only three trajectories each, we found that the lowest and second lowest groups remained relatively stable, whereas the two highest groups were collapsed.

**Inverse Probaility of Censoring Weights**

In the multinomial regression model, we used inverse probability of censoring weights (IPCW) to account for potential biases arising from differential loss to follow-up. In IPCW analyses, the sample is re-weighted such that the contribution of participants who share characteristics of those who drop out is inflated [[4](#_ENREF_4)]. Assuming correct model specification, IPCW estimates effects that would have been observed if all subjects had stayed in the study. The probability of remaining uncensored was modeled using logistic regression, conditional on trajectory membership and statistically significant covariates shown in Table 1.

**VACS Tissue Repository**

The VACS tissue repository has been described in detail previously [[5](#_ENREF_5), [6](#_ENREF_6)]. In brief, between 2005 and 2006, blood and DNA specimens were collected and banked from a total of 1,525 subjects enrolled in the VACS and who consented to provide blood specimens for future studies. Specimens were collected using serum separator and ethylenediaminetetraacetic acid blood collection tubes, and shipped to a central repository at the Massachusetts Veterans Epidemiology Research and Information Center in Boston, Massachusetts.

**Phosphatidylethanol (PEth) Sub-Analysis**

Phosphatidylethanol (PEth) is a validated biomarker of alcohol consumption, with high sensitivity and specificity in HIV-infected populations [[7](#_ENREF_7)]. A group of abnormal phospholipids formed in the presence of ethanol and phospholipase D, PEth provides an extended window of detection following alcohol exposure as its half-life is 4 days [[8](#_ENREF_8)]. PEth has a specificity of 95-100% for alcohol exposure in the past 21 days and provides an objective assessment of response to alcohol treatment in HIV clinics [[9](#_ENREF_9), [10](#_ENREF_10)]. PEth concentrations in collected samples were measured using dried blood spots and a liquid chromatography tandem mass spectrometric method, described in detail previously [[11](#_ENREF_11)]. As in a previous study [[12](#_ENREF_12)], we considered samples to be positive for PEth (thus indicating recent alcohol consumption) at a ≥4ng/mL limit of detection.

**Table S1**: VACS index and weight of variable values

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Value** | **Points** |
| **Age (in years)** | <50 | 0 |
|  | 50-64 | 12 |
|  | ≥65 | 27 |
|  |  |  |
| **CD4+ cell count (cells/mL)** | ≥500 | 0 |
|  | 350 - 499 | 6 |
|  | 200 - 349 | 6 |
|  | 100 - 199 | 10 |
|  | 50 - 99 | 28 |
|  | <50 | 29 |
|  |  |  |
| **HIV RNA (log copies/ml)** | <500 | 0 |
|  | 500 – 10,000 | 7 |
|  | >10,000 | 14 |
|  |  |  |
| **Hemoglobin (g/dl)** | ≥14 | 0 |
|  | 12 – 13.9 | 10 |
|  | 10 – 11.9 | 22 |
|  | <10 | 38 |
|  |  |  |
| **FIB 4 ratio** | <1.45 | 0 |
|  | 1.45 – 3.25 | 6 |
|  | >3.25 | 25 |
|  |  |  |
| **eGFR (ml/min)** | >60 | 0 |
|  | 45 – 59.9 | 6 |
|  | 30 – 44.9 | 8 |
|  | <30 | 26 |
| **Hepatitis C co-infection** |  | 5 |

**Table S2**: Parameters for AUDIT-C and VACS index joint trajectory model for 3,539 HIV-infected participants in the Veterans Aging Cohort Study (VACS)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Mean group posterior probability (SD)** | | **Parameter** | | **Estimate** | | **Standard Error** | |
| **AUDIT-C Trajectories** |  | |  | |  | |  | |
| Abstainers | 0.84 (0.16) | | Intercept | | 0.00 | | 0.01 | |
|  |  | | Linear | | 0.82\*\*\* | | 0.07 | |
|  |  | |  | |  | |  | |
| Lower Risk | 0.85 (0.14) | | Intercept | | 0.97\*\*\* | | 0.09 | |
|  |  | | Linear | | -0.13\*\* | | 0.05 | |
|  |  | | Quadratic | | 0.01\* | | 0.01 | |
|  |  | |  | |  | |  | |
| Moderate Risk | 0.79 (0.16) | | Intercept | | 3.70\*\*\* | | 0.14 | |
|  |  | | Linear | | -0.10\*\*\* | | 0.02 | |
|  |  | |  | |  | |  | |
| Higher Risk | 0.86 (0.16) | | Intercept | | 7.56\*\*\* | | 0.17 | |
|  |  | | Linear | | -0.20\*\*\* | | 0.04 | |
| **VACS Index Trajectories** | |  | |  | |  | |  | |
| Low | 0.92 (0.12) | | Intercept | | 0.07 | | 0.01 | |
|  |  | | Linear | | 16.50\*\*\* | | 1.57 | |
|  |  | | Quadratic | | -1.49\*\*\* | | 0.22 | |
|  |  | |  | |  | |  | |
| Moderate | 0.90 (0.14) | | Intercept | | 18.86\*\*\* | | 0.37 | |
|  |  | | Linear | | -1.34\*\*\* | | 0.25 | |
|  |  | | Quadratic | | 0.12\*\*\* | | 0.04 | |
|  |  | |  | |  | |  | |
| High | 0.86 (0.15) | | Intercept | | 37.75\*\*\* | | 0.42 | |
|  |  | |  | |  | |  | |
| Extreme | 0.91 (0.14) | | Intercept | | 64.94\*\*\* | | 0.68 | |
|  |  | | Linear | | 1.16\* | | 0.51 | |
|  |  | | Quadratic | | -0.16\* | | 0.08 | |
| \*p<0.10; \*\*p<0.01; \*\*\*p<0.001 | | | | |  | |  | |

**Table S3**: Baseline characteristics, by AUDIT-C trajectory group (n, % except as noted)

| **Characteristic** | **AUDIT-C Trajectory Group** | | | | ***p*-value** |
| --- | --- | --- | --- | --- | --- |
|  | **Abstainer** | **Lower-Risk** | **Moderate Risk** | **Higher-Risk** |  |
|  | N = 854  (24%) | N = 1576   (45%) | N = 843   (24%) | N = 266   (7%) |  |
| Age (median, IQR) | 51 (46-56) | 49 (43-55) | 47 (42-53) | 49 (43-54) | <0.001 |
| Baseline VACS Index (median, IQR) |  |  |  |  |  |
| Female | 24 (2.8) | 43 (2.7) | 18 (2.1) | 5 (1.9) | 0.682 |
| Race |  |  |  |  | 0.357 |
| White | 182 (22.6) | 367 (24.1) | 218 (26.8) | 60 (23.3) |  |
| African American | 586 (72.6) | 1079 (70.8) | 547 (67.1) | 183 (70.9) |  |
| Other | 39 (4.8) | 78 (5.1) | 50 (6.1) | 15 (5.8) |  |
| Hispanic/Latino | 90 (10.5) | 124 (7.9) | 95 (11.3) | 23 (8.7) |  |
| On HAART at baseline | 649 (82.3) | 1209 (80.7) | 582 (74.2) | 175 (70.3) | <0.001 |
| CD4 count (median, IQR cells/mL) | 370 (207-560) | 369 (217-556) | 368 (220-555) | 349 (200-537) | 0.824 |
| Virally suppressed (<400 copies/mL) | 415 (48.6) | 667 (42.3) | 311 (36.9) | 89 (33.5) | <0.001 |
| HCV positive | 473 (55.4) | 760 (48.2) | 409 (48.5) | 148 (55.6) | 0.001 |
| Current smoker | 361 (42.4) | 810 (51.6) | 503 (59.8) | 206 (78.0) | <0.001 |
| Injection drug use, ever | 350 (41.9) | 451 (29.1) | 272 (32.5) | 97 (37.3) | <0.001 |
| Depressive Symptomatology† | 189 (22.5) | 324 (20.7) | 196 (23.4) | 81 (30.6) | 0.004 |
| Education, high school or less | 403 (47.2) | 596 (37.8) | 340 (40.3) | 137 (51.5) | <0.001 |
| Marital Status |  |  |  |  | 0.215 |
| Married/living with Partner | 201 (24.0) | 355 (22.8) | 201 (24.1) | 49 (18.9) |  |
| Divorced/separated/widowed | 357 (42.7) | 648 (41.7) | 318 (38.1) | 109 (42.1) |  |
| Never Married | 279 (33.3) | 553 (35.5) | 316 (37.8) | 101 (39.0) |  |
| Homeless, ever | 325 (38.3) | 591 (37.6) | 343 (40.9) | 129 (49.1) | 0.004 |
| Died during study period | 338 (39.7) | 455 (28.9) | 204 (24.3) | 108 (40.6) | <0.001 |
| Loss to follow-up | 177 (20.7) | 344 (21.8) | 205 (24.3) | 47 (17.3) | 0.076 |

Abbreviations: HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; IQR, interquartile range; VACS, Veterans Aging Cohort Study.

Note: not all cells add to 100% due to missing values.

† PHQ-9 score ≥10 indicates moderate depressive severity [13].

**Table S4**: Baseline characteristics, trajectory group membership, death, and loss to follow-up, stratified by participation in the VACS biomarker cohort

| **Characteristic** |  | **in VACS biomarker cohort** | |
| --- | --- | --- | --- |
|  | **Overall** | **Yes** | **No** |
|  | N = 3,539 | N = 1,499 (42.4%) | N = 2,040  (57.6%) |
| Age (median, IQR) | 49 (44–55) | 49 (44-54) | 50 (44-55) |
| Female | 90 (3) | 41 (3) | 49 (2) |
| Race |  |  |  |
| White | 827 (23) | 330 (23) | 497 (25) |
| African American | 2395 (68) | 1047 (72) | 1348 (69) |
| Other | 182 (5) | 74 (5) | 108 (6) |
| On HAART at baseline | 2615 (73.9) | 1195 (79.7) | 1420 (69.6) |
| CD4 count (median, IQR) | 367 (213 – 555) | 369 (223 – 560) | 367 (207 – 546) |
| Virally suppressed (<400/mL) | 1482 (42) | 632 (42) | 850 (42) |
| HCV positive | 1790 (51) | 753 (50) | 1038 (51) |
| Current smoker | 1880 (53) | 804 (54) | 1076 (53) |
| Injection drug use, ever | 1170 (33) | 493 (33) | 677 (34) |
| Depression† | 790 (22) | 313 (21) | 477 (24) |
| Education, high school or less | 1476 (42) | 628 (42) | 848 (42) |
| Marital Status |  |  |  |
| Married/living with Partner | 806 (23) | 334 (23) | 472 (23) |
| Divorced/separated/widowed | 1432 (40) | 599 (41) | 833 (41) |
| Never Married | 1249 (35) | 544 (37) | 705 (35) |
| Homeless, ever | 1388 (39) | 583 (39) | 805 (40) |
| AUDIT-C trajectory group |  |  |  |
| Abstainers | 854 (24) | 275 (18) | 579 (28) |
| Lower Risk | 1576 (45) | 717 (48) | 859 (42) |
| Moderate Risk | 843 (24) | 390 (26) | 453 (22) |
| Higher Risk | 266 (7) | 117 (8) | 149 (7) |
| VACS index trajectory group |  |  |  |
| Low | 68 (2) | 32 (2) | 36 (2) |
| Moderate | 1628 (46) | 737 (49) | 892 (44) |
| High | 1290 (36) | 572 (38) | 718 (35) |
| Extreme | 552 (16) | 158 (10) | 394 (19) |
| Died during study period | 1105 (31) | 327 (22) | 778 (38) |
| Loss to follow-up | 772 (22) | 280 (19) | 492 (24) |

Note: not all cells add to 100% due to missing values

\* not applicable

† PHQ-9 score ≥10 indicates moderate depression severity [[13](#_ENREF_13)].

**Figure S1:** Mean phosphatidylethanol (PEth) concentration (red line) and proportion with detectable PEth in dried blood spots (blue bar) among persons participating in the VACS tissue repository (n=1,499)

Note: values ≥4 ng/mL were considered above the limit of detection.

Note: AUDIT-C group and the proportion of participants with PEth above the limit of detection were highly correlated (Cramér’s V = 0.465, χ2 = 323.40, *p* < 0.001).

**Figure S2**: Last observation carry-forward (LOCF) analysis examining AUDIT-C score trajectories among 3,539 HIV-infected participants in the Veterans Aging Cohort Study (VACS), 2002-2010

LOCF was computed for participants who were known to be alive at the end of the study period but who were lost to follow-up (defined as failing to complete a study assessment with a year prior to the end of the study period).

Note: dashed lines represent predicted values and error bars represent 95% confidence intervals for each wave’s estimate; solid lines represent empirical averages.

**Figure S3**: Last observation carry-forward (LOCF) analysis examining VACS index score trajectories among 3,539 HIV-infected participants in the Veterans Aging Cohort Study (VACS), 2002-2010

LOCF was computed for participants who were known to be alive at the end of the study period but who were lost to follow-up (defined as failing to complete a study assessment with a year prior to the end of the study period).

Note: dashed lines represent predicted values and error bars represent 95% confidence intervals for each wave’s estimate; solid lines represent empirical averages.

**Figure S4**: Effect of excluding persons who did not complete at least two assessments during the study period on AUDIT-C score trajectories among HIV-infected participants in the Veterans Aging Cohort Study (VACS), 2002-2010 (N=3,072)

Note: dashed lines represent predicted values and error bars represent 95% confidence intervals for each wave’s estimate; solid lines represent empirical averages.

**Figure S5**: Effect of excluding persons who did not complete at least two assessments during the study period on VACS index score trajectories among HIV-infected participants in the Veterans Aging Cohort Study (VACS), 2002-2010 (N=3,072)

Note: dashed lines represent predicted values and error bars represent 95% confidence intervals for each wave’s estimate; solid lines represent empirical averages.

**Figure S6**: Effect of excluding persons who died during the study period on AUDIT-C score trajectories among HIV-infected participants in the Veterans Aging Cohort Study (VACS), 2002-2010 (N=2,425)

Note: dashed lines represent predicted values and error bars represent 95% confidence intervals for each wave’s estimate; solid lines represent empirical averages.

**Figure S7**: Effect of excluding participants who died during the study period on VACS index score trajectories among HIV-infected participants in the Veterans Aging Cohort Study (VACS), 2002-2010 (N=2,425)

Note: dashed lines represent predicted values and error bars represent 95% confidence intervals for each wave’s estimate; solid lines represent empirical averages.

Supplemental File References

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