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| **Supplemental Digital Content 1.** Variables included in the group-based and machine learning models to identify risk variables for the CD4/CD8 T-cell ratio subgroups. | | |
| **Demographic/HIV Clinical** | Leg agility | Programmed cell death protein-1 |
| Days infected | Leg strength | TIM-3 |
| Days from exposure to ART initiation | **Mood/QOL** | Intercellular adhesion molecule |
| Days from enrollment to ART initiation | PHQ-9 items 1-9 | Monocyte chemotactic protein-1 |
| Blood HIV viral load\* | PHQ-9 item 10 - impact | Macrophage inflammatory protein-3 |
| Blood HIV viral load (log10) | Quality of Life items 1-25 | MIP-1α |
| Mode of HIV transmission | **Substance Use** | MIP-1β |
| Gender | Ecstasy | RANTES |
| Biological sex\* | Meth (by pill) | TNFα-HS |
| Age at enrollment | Meth (by smoking) | IFNα-HS |
| Education level | Meth (by injecting) | Soluble glycoprotein-130 |
| Marital status | Opium (by smoking) | sTNFR-I |
| Fiebig stage\* | Opium (by injecting) | sTNFR-II |
| ART vs MEGAHAART | Ketamine | GCSF |
| **Cognitive Testing** | Gamma hydroxybutyrate | GMCSF |
| Color Trails 1 | Marijuana | IFNα-2 |
| Color Trails 2 | Cocaine | IFN-γ |
| Pegboard – nondominant hand | Kratom | IL-1α |
| Trail Making A | Alcohol | IL-1β-HS |
| **Neuro Exam** | Erectile dysfunction drugs | Interleukin-1 receptor |
| Facial expression | Poppers | IL-2 |
| Neuropathy symptoms | **Laboratory Values** | IL-5 |
| Smooth pursuits | White blood cell count (10^3)\* | IL-6\* |
| Concentration | Blood neutrophils % | sIL-6Rα |
| Reading | Blood lymphocytes % | IL-8 |
| Memory | Blood monocytes % | IL-10 |
| Speech | Eosinophils % | IL-12\* |
| Gait | Basophils % | IL-15 |
| Upper extremity coordination | Hemoglobin g/dL | IL-17 |
| Involuntary movement | Hematocrit % | IL-21 |
| Mood | Platelet count (10^3 cells/ul) | IL-23 |
| Social apathy | Cholesterol (mg/dL) | CD-27\* |
| Agitation | Triglycerides (mg/dL) | CD-152 |
| Response slowing | High-density lipoprotein (mg/dL) | sCD-14\* |
| Postural stability | Hepatitis C antibody | sCD-163\* |
| Deep tendon reflexes | Total bilirubin (mg/dL) | Neopterin\* |
| Severity of sensory loss | Direct bilirubin (mg/dL) |  |
| Type of neuropathy | SGPT ALT |  |
| Bradykinesias | Hepatitis B surface antibody |  |
| Arm rigidity | Hepatitis B surface antigen |  |
| Finger tapping | **Immune Markers** |  |
| \*Included in the group-based comparisons. All variables were considered as potential predictors in the machine learning analysis. Patient Health Questionnaire-9 (PHQ-9); serum glutamic-pyruvic transaminase alanine transaminase (SGPT ALT); T-cell immunoglobulin and mucin domain (TIM-3); regulated upon activation, normal T-cell expressed and secreted (RANTES); tumor necrosis factor alpha-high sensitivity (TNFα-HS); interferon alpha-high sensitivity (IFNα-HS); soluble tumor necrosis factor receptors (sTNFR); granulocyte colony-stimulating factor (GCSF); granulocyte-macrophage colony-stimulating factor (GMCSF); interleukin 1 beta-high sensitivity (IL-1β-HS); soluble interleukin-6 receptor alpha (sIL-6Rα). | | |

**Supplemental Figure 1.** Partial dependency plots depicting linear and nonlinear associations between predictors of CD4/CD8 inversion (ratio < 1.0). Red color represents membership in the low CD4 subgroup (Cluster 4). Blue color represents membership in the high CD8 subgroup (Cluster 5).