Introduction

This report summarizes the Multicenter AIDS cohort study’s investigation on the relationship between hard drug use prior to highly active antiretroviral treatment (HAART) initialization and potential impact on treatment response. This prospective cohort study observes HIV-1 infection in homosexual and bisexual men recruited from four cities in the United States. Demographic information, CD4 counts, viral load, SF-36 scores, and other disease information are gathered on participants prior to HAART and then once a year for eight years.

The primary hypothesis for this report is that treatment response differs between those who report hard drug use prior to HAART initiation and those who do not. The statistical hypotheses tested were as follows: 1.) There is a meaningful difference between hard drug use between hard drug use exposure when compared to controls on the change in CD4 count after two years of treatment 2.) There is a meaningful difference between hard drug use exposure when compared to controls on the change in viral load after two years of treatment 3.) There is a meaningful difference between hard drug use exposure when compared to controls on the change in aggregate mental health scores after two years of treatment 4.) There is a meaningful difference between hard drug use exposure when compared to controls on the change in aggregate physical health scores after two years of treatment.

Methods

Data management and cleaning was completed first. Many variables had differing levels to denote missing. Responses labeled as ‘NA’ ‘9’ ‘999’ ‘-1’ were changed to blank and considered missing data. Participant 113’s BMI was considered an outlier and changed from 513 to blank. The investigator suggested re-categorization of some variables based on prior research. Variables that were condensed were race (NHW and other), income level (<10,10-40, >40), smoker (current and former/never), alcohol use (<13 drinks or >13 drinks a week), education level (high school or less and some college or greater), and adherence (>95% and <95%).

Hard drug use (n=39) and non-hard drug use (n=472) were the two groups created for the primary variable of interest. Participants that reported injection drug use (n=33) or heroin and illicit opiates (n=12) at baseline were considered hard drug users. Treatment response was measured by two laboratory outcomes and two quality of life (QoL) outcomes. Laboratory response outcomes were the change in CD4 count and viral load from baseline to year two. QoLwas measured through aggregate mental and physical health changes from baseline to year two subjectively reported with the Short Form-36. Four new variables were made to assess the change of the four outcomes from baseline to two years. The delta variables created to measure the change for each outcome were ‘leun\_d’ (CD4 cell count), ‘vload\_d’ (viral load on log10 scale), ‘agg\_md’ (aggregate mental health), and ‘agg\_pd’ (aggregate physical health).

Descriptive statistics were performed to examine potential demographic differences in drug exposure groups. For Table 1, means were used for numerical variables (age, BMI) and frequencies for categorical variables (race, income, education, smoking, alcohol use, marijuana, adherence). Bivariate statistics were then used to get estimates for outcome aggregate QoL outcomes, viral load on log10 scale, and CD4 cell count at baseline and at two years. Histograms and plots were examined to ensure outcomes did not violate assumptions of linear regression.

Four linear regression analyses were used to assess each of the four delta outcome variables and statistical hypotheses. Non-hard drug use reported at baseline was considered the reference group and a simple linear regression was used to examine the crude effect of hard drug use compared to controls on each of the delta outcome variables. Multiple linear regression analysis was conducted to assess the significance of the change for the delta outcomes adjusted by potential covariates specified by the investigator. Covariates were added to control for confounding which is an innate limitation in observational, cohort studies. The *class* statement in *proc glm* was used to dummy code all variables.

The model selection technique used was decided a priori by selecting known covariates based on the clinical knowledge and prior use in other studies by the investigator. Covariates included in the model were age, BMI, race, hash or marijuana use, alcohol use, smoking status, income all at baseline. Additionally, adherence reported at year two and the specific outcome’s baseline report was added. Partial f-tests were computed to determine if the adjusted model was significant compared to the crude. Correlations between the delta variables and covariates were then performed to assess any attenuation or strengthening that may be related to specific covariates. Multiple linear regression analysis was used because all outcome variables were continuous and the outcomes, after viral load was log transformed, fit the assumptions for linear regression. Significance level was selected at a p-value <0.025. This was to account for multiple comparisons, but it was not too conservative and still allowed for exploratory analysis. SAS University Edition with Virtual Box was used for data analysis.

Results

Demographic differences between hard drug use groups are summarized in Table 1. By year 2 of the study there were 502 men in the cohort, with 39 remaining that reported hard drug use at baseline. The hard drug use group had lower average BMI scores (23.62 [3.44] compared to 26.5 [23.5]) and had a higher percentage of current smokers (76.92%).

Table 1: Demographics for Hard Drug Use and Non-Hard Drug Use

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Overall n=502 | Non-Hard Drug Use n=472 | Hard Drug Use  n=39 |
| Age (SD) | 43 (8.79) | 43 (8.73) | 45 (9.49) |
| BMI (SD) | 26.28 (22.64) | 26.5 (23.5) | 23.62 (3.44) |
| Education (%) |  |  |  |
| High school | 110 (21.91) | 94 (20.3) | 16 (41.03) |
| Some college or more | 392 (78.09) | 369 (79.7) | 23(58.97) |
| Race (%) |  |  |  |
| White, Non-Hispanic | 317 (63.15) | 298 (64.36) | 19 (48.72) |
| Other | 185 (36.85) | 165 (35.64) | 20 (51.28) |
| Income (%) |  |  |  |
| < 10,000 | 208 (42.89) | 192 (43.05) | 16 (41.03) |
| 10- 40,000 | 105 (21.65) | 91 (20.40) | 14 (35.90) |
| > 40,000 | 172 (35.46) | 163 (36.55) | 9 (23.08) |
| Alcohol Use (%) |  |  |  |
| <13 drinks/week | 467 (93.03) | 430 (92.87) | 37 (94.87) |
| >13 drinks/week | 35 (6.97) | 33 (5.13) | 2 (5.13) |
| Adherence (%) |  |  |  |
| 95-100% | 451 (89.84) | 413 (89.20) | 38 (97.44) |
| <95% | 51 (10.16) | 50 (10.80) | 1 (2.56) |
| Smoker (%) |  |  |  |
| Never/Former | 308 (61.35) | 299 (64.58) | 9 (23.08) |
| Current | 194 (38.56) | 164 (35.42) | 30 (76.92) |
| Marijuana/Hash Use-  Yes (%) | 206 (41.04) | 194 (41.90) | 12 (30.77) |

Table 2 compares the crude estimates to the adjusted estimates for change in CD4 cell count. The crude model showed that the hard drug use group had a significant decrease in CD4 cells when compared to the controls (p=<0.0001). After holding the covariates constant, the hard drug use group still had significantly less CD4 cell increases at an average of 166.61 (31.25) less than compared to controls (p=<0.0001). However, a partial f-test gave a critical f-value of 1.579 and was not significant (p=0.228).

Table 2: Change in CD4 Cell Count

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Crude Model Estimate (SE) | P-value | Adjusted Model Estimate (SE) | P-value |
| Intercept | 182.7(8.43) | <0.0001 | 169.724 (52.76) | **0.0014** |
| Hard Drugs | -169.16 (29.68) | <0.0001 | -166.61 (31.25) | **<0.0001** |

Table 3 compares the crude estimates to the adjusted estimates for change in viral load. After holding the covariates constant, there were no significant differences between the hard drug use group and the controls (p=0.9519). Viral load at base was weakly associated with delta viral load (r=-.39, p=<.0001) and may have attenuated the crude intercept estimate. Additional weak associations included high school (r=0.1, p=0.0218), adherence (r=-0.18, p=<0.0001), and race (r=0.15, p=0.012).

Table 3: Change in Viral Load

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Crude Model Estimate (SE) | P-value | Adjusted Model Estimate (SE) | P-value |
| Intercept | -2.71 (0.06) | <0.0001 | 0.348 (.459) | 0.4483 |
| Hard Drugs | 0.01 (0.21) | 0.9446 | -0.0122 (0.2) | 0.9519 |

Table 4 compares the crude estimates to adjusted estimates for change in SF-36 aggregate mental health scores. After holding the covariates constant, there were no significant differences between the hard drug use group and the controls (p=0.7571). Aggregate mental health scores at baseline were moderately associated with the delta outcome (r= -0.57, p=<0.0001) and may be the cause of attenuation of the intercept estimate. Income and high school variables were weakly correlated (r=-0.19, p=<0.0001), suggesting collinear covariates.

Table 4: Change in Aggregate Mental Health

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Crude Model Estimate (SE) | P-value | Adjusted Model Estimate (SE) | P-value |
| Intercept | 2.15 (0.56) | 0.0001 | 20.92 (3.126) | **<0.0001** |
| Hard Drugs | 1.43 (2.01) | 0.4711 | -0.55 (1.77) | 0.7571 |

Table 5 compares the crude estimates to adjusted estimates for change in SF-36 aggregate physical health scores. After holding the covariates constant, the relationship between the hard drug use group is significantly strengthened when compared to the controls (p=0.218). The changes in physical health scores were an average 3.22 (1.4) less than controls. A partial f-test did not find the adjusted model to be significant when compared to the crude model (p=0.55).

Table 5: Change in Aggregate Physical Health

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Crude Model Estime (SE) | P-value | Adjusted Model Estimate (SE) | P-value |
| Intercept | -1.43 (0.4) | 0.0003 | 16.71 (3.69) | **<0.0001** |
| Hard Drugs | -2.43(1.41) | 0.0851 | -3.24(1.4) | **0.0218** |

Conclusions

The results of this analysis suggest that hard drug use does significantly impact laboratory measures of HAART treatment. The change in CD4 cell count after two years was significantly less (-166.61 [31.25]) in the group that reported hard drug use prior to treatment initialization (p=<0.0001) after adjusting for covariates. Even though a partial f-test found the crude model to be a better fit for the data, both models found a significant difference between hard drug use and controls. This could be consistent with prior in vitro and animal studies suggesting a biological difference for those that report using hard drugs prior to beginning treatment and CD4 cell growth. Although the hard drug use group reported significantly lower score changes on the SF-36 physical health component questions in the adjusted model, these results should be assessed for clinical significance as the partial f-test showed the adjusted model may not be the best fit for the data.

There may be some limitations to this analysis that may merit further investigation. There were 69 men that reported hard drug use at baseline. At year two, 27 of these men were lost to follow up, 20 men no longer reported hard drug use, and 11 men from the non-drug use group started reporting hard drug use. Of the 27 participants lost to follow up, 24 (88%) were injection drug users at baseline. Examination of outcome means for each of these groups showed that those lost to follow up subjectively reported the lowest average aggregate physical health scores (40.49 [9.58]). Those that stopped using hard drugs by year two reported the lowest average mental health scores (39.61 [8.23]).

Reproducible Research

https://github.com/BIOS6623-UCD/bios6623-delgoulding/tree/master/Project1