HIV Treatment Report

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1 Introduction

Human immunodeficiency virus (HIV) progressively weakens the immune system by depleting CD4 cells. Therefore, CD4 count a key marker of disease severity and treatment response. Although early HIV therapies reduced mortality and infections, their long-term effectiveness has varied across patients, particularly by baseline disease stage and prior treatment exposure. Clinical evidence suggests that immune recovery may depend on both initial disease progression and the extent of prior HIV therapy use, raising questions about how treatment timing and history affect durable recovery.

This study analyzes data from a randomized clinical trial to examine whether responses to HIV therapy differ by disease stage and prior treatment exposure, and whether initiating therapy in patients with less advanced disease leads to prolonged clinical benefit. These questions are addressed using statistical models and hypothesis tests to evaluate associations between baseline characteristics, treatment history, and short- and long-term immunologic outcomes.

Our analyses show that baseline CD4 count and prior therapy duration are significant predictors of short-term CD4 response. However, neither baseline disease stage nor prior treatment exposure predicts long-term CD4 response, suggesting that early immunologic improvements may not translate into sustained long-term benefit.

2 Data

2.1 Variables

The data consist of `2,139` observations with `27` variables.

CD4 cell counts indicate how well the immune system is functioning. Because HIV attacks the immune system, we use changes in CD4 count to measure responses to HIV therapy. The response variable for the short-term analyses will be `cd4.20.delta` (`cd4.20 - cd4`), which represents the change in a patient's CD4 cell count 20 weeks after beginning therapy, while the response variable for the long-term analysis will be `cd4.96.delta` (`cd4.96 - cd4`), which represents the change in CD4 count 96 weeks after beginning therapy.

The primary covariate of interest for the analyses examining disease stage is `cd4`, the baseline CD4 count at the start of the clinical trial, as it captures initial HIV disease severity.

To examine the effect of prior HIV therapy on short-term response, we consider both the type and extent of prior treatment. Because all patients have used Drug A at some point prior to study enrollment (as seen in the **Exploratory Data Analysis**), we use `a30` (Drug A use in the 30 days prior to treatment initiation) in place of `aprior` to capture recent exposure to Drug A. We combine `a30` with `oprior` (HIV therapy other than Drug A prior to study initiation) to construct a categorical variable `prior` indicating the type of recent prior therapy (`0` = no recent therapy, `1` = Drug A only, `2` = Drug A plus another drug, `3` = other therapy only). We additionally use `hist2` to capture the duration of prior HIV therapy (`1` = no HIV therapy, `2` = >1 week but ≤52 weeks, `3` = >52 weeks). The main effects of `hist2` and its interaction with `prior` characterize how the extent and type of pre-study treatment are associated with short-term CD4 response.

Several additional variables are included as covariates to control for variation in treatment response without absorbing the effects of the primary covariates of interest. These include `age`, `wt` (weight), `race`, and `gender`, which represent baseline demographic and physical characteristics that may influence health outcomes. Treatment assignment is controlled for using `treat2` (`0` = Drug A alone, `1` = Drugs A and B, `2` = Drugs A and C, `3` = Drug B alone), as treatment regimen is known to affect CD4 response.

Baseline `cd8` is included as a covariate because CD8 cells play a regulatory role in immune response. Some CD8 cells acts as suppressor regulatory cells that can suppress or kill CD4 cells. As a result, higher baseline CD8 counts are expected to be associated with lower baseline CD4 counts and may also limit the increase in CD4 count following

treatment. This makes baseline CD8 count a confounding variable for the relationship between baseline CD4 level and CD4 response to therapy. Including `cd8` in the model helps account for this confounding and improves estimation of the effect of baseline disease severity on treatment response.

Many variables were excluded from the analysis. `homo` (homosexual activity) and `drugs` (intravenous drug use) were excluded because, while they may be related to HIV acquisition, there is no clear reason they would directly affect CD4 response to therapy. `hemo` (hemophilia) was excluded because it is not expected to influence HIV treatment outcomes. `karnof` (baseline Karnofsky score) and `symptom` (baseline symptomatic status) were excluded from the disease-stage models because both reflect baseline disease severity and are strongly related to `cd4`. Including them could partially adjust away the effect of baseline CD4 on response (i.e., block part of the pathway from disease severity to treatment response). The variable `cens` (indicator of an unfavorable clinical event) was excluded from the regression models because it may be affected by the covariates of interest and therefore could act as a mediator. However, `cens` is used during EDA to assess whether `offtreat` (off-treatment before 96 ± 5 weeks) and `nocd4.96` (missing 96-week CD4) are plausibly due to death. If so, missing long-term CD4 values may be replaced with 0. Several variables were excluded because they are redundant with other included measures and could result in unnecessary overfitting to our data if included, including `hist`, `aprior`, `oprior`, `predays`, `treat`, and `days`.

2.2 Exploratory Data Analysis

variable_raw	0	1	2	3
aprior	0	2139	-	-
oprior	2092	47	-	-
nocd4.96	797	1342	-	-
offtreat	1363	776	-	-
cens	1618	521	-	-
gender	368	1771	-	-
treat	532	1607	-	-
hist	886	1253	-	-
hist2	-	886	410	843
treat2	532	522	524	561

Table 1: Value counts of categorical variables. Notably, `aprior` only takes on one value, and very few people had HIV therapy other than drug A prior to initiation of the study.

`Table 1` shows the value counts of the categorical variables. Interestingly, `aprior` only takes value `1`, which means that all patients in the dataset have used drug A before the study. Further, only `47` of `2139` observations have a value of `1` for `oprior`, while the rest are `0`, which means that almost all patients took only drug A before study initiation. Because the sample size of observations with prior treatments besides drug A alone is so small, `a30` is used in creating the `prior` variable alongside `oprior` in place of `aprior`. The lack in variation in `oprior` and especially `aprior` are limitations in our data because they limit the power and precision to estimate the effects of pre-study HIV therapy, restricting the strength of conclusions we make about prior treatment exposure.

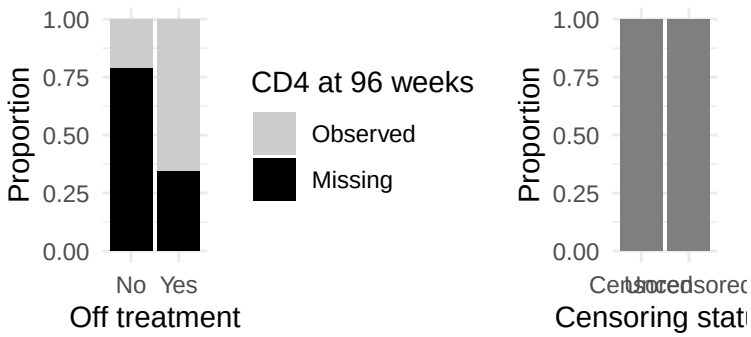

Figure 1: Investigation of missing CD4 cell counts at 96 weeks. Missing counts do not appear to be due to only death of patient.

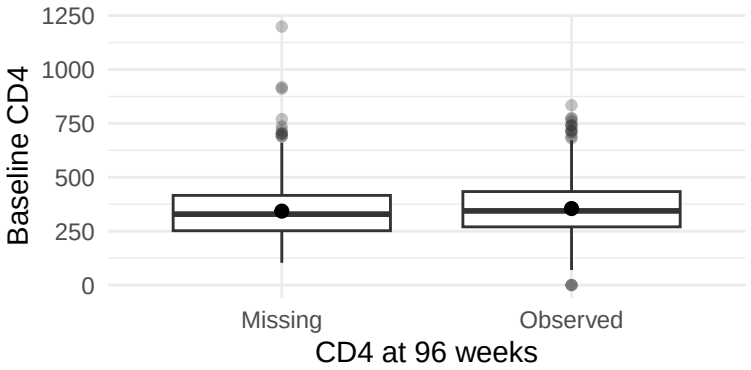

Figure 2: There appears to be no relationship between missingness of CD4 levels after 96 weeks and initial CD4 levels. This suggests that missing CD4 counts at 96 weeks are not only due to death of patients.

Figure 1 shows the relationships of `nocd4.96` with `cens` and `offtreat`. All combinations of variables are well-represented in the data, suggesting that missing CD4 counts at 96 weeks are not only due to death of patients (otherwise, `cens` and `offtreat` would each be `1` for all observations with missing CD4 counts at 96 weeks). This is further supported by **Figure 2**, which fails to suggest a relationship between missingness of CD4 levels after 96 weeks and initial disease progression (represented by baseline CD4). Therefore, observations with missing `cd4.96.delta` values will be dropped for the analysis of long-term treatment response. Regardless, lack of understanding as to why certain CD4 counts after 96 weeks are missing is a limitation in our data.

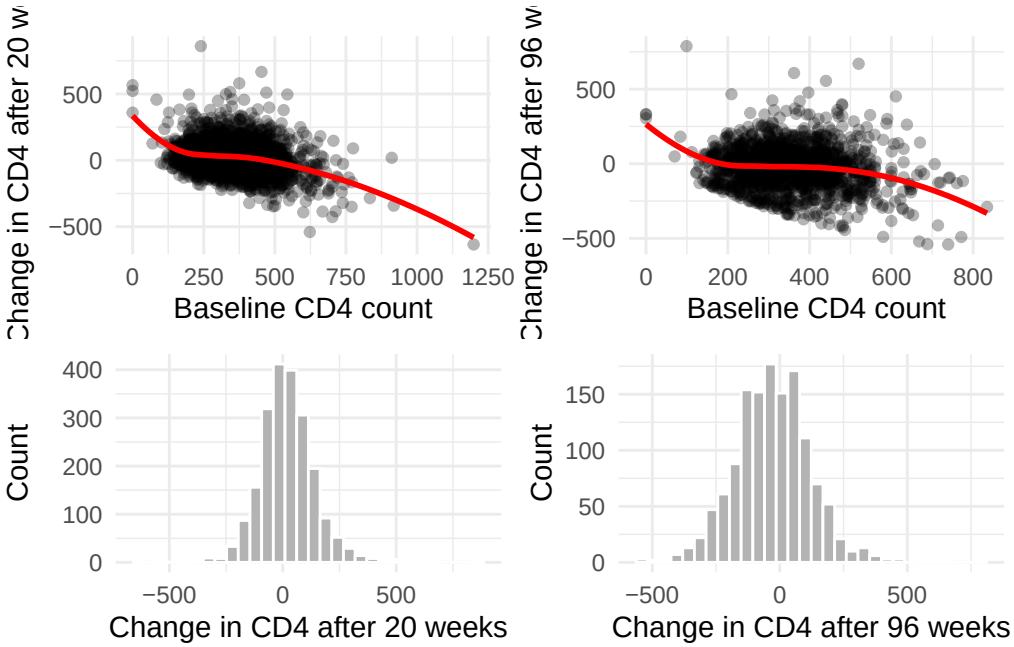

Figure 3: Distributions of and relationships between CD4 cell counts and changes in cell counts. The distributions of the changes in CD4 cell counts are quite symmetric, and, disregarding extreme observations, a slight negative or no relationship seems to exist between baseline and changes in CD4 cell counts.

Figure 3 shows the distributions of the changes in CD4 cell counts after beginning the trial, as well as their relationships with baseline CD4 cell counts. The distributions are quite symmetric, suggesting normality assumptions for the regression error terms are reasonable. Disregarding extreme observations, a slight negative or no relationship seems to exist between baseline and changes in CD4 cell counts, both in the short- and long-term.

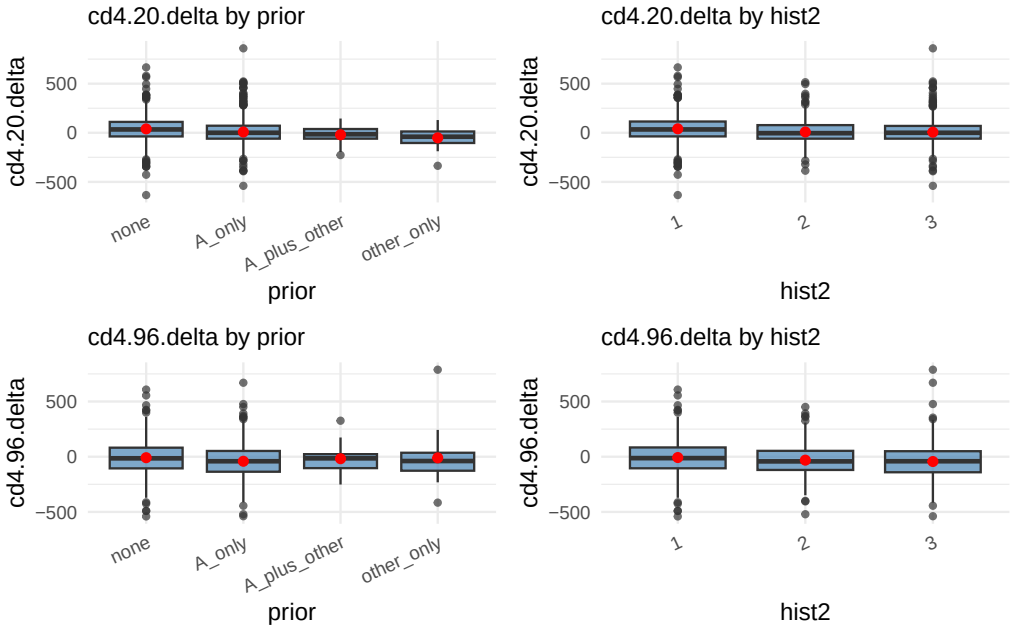

Figure 4: Distributions of CD4 cell counts appear similar across values of the categorical variables.

Figure 4 shows the relationships between the short- and long-term changes in CD4 cell counts and treatment history

(type and duration). Changes in CD4 counts appear very similarly distributed (nearly equal means, but sometimes differing variances) across prior treatment types and durations, suggesting little (unadjusted) association between prior treatment history and CD4 response. They are also symmetrically distributed around 0, suggesting that the assumption of normally distributed residuals is reasonable.

3 Methods

3.1 Overview

We examine whether immune response to HIV therapy varies by baseline disease severity and prior HIV drug exposure, and whether baseline disease severity predicts prolonged clinical benefit. Immune response is measured as the change in CD4 cell count after 20 weeks (short-term response) and 96 weeks (long-term response) following treatment initiation. Linear regression models are used throughout. All models adjust for age, weight, gender, race, and (where applicable) treatment arm.

- `prior` has three levels: *A_only*, *A_plus_other*, *other_only* (reference: *none*).
- `hist2` has three levels: *no HIV therapy*, *>1 week to ≤52 weeks*, *>52 weeks* (reference: *no HIV therapy*).

3.2 Questions 1 and 2: Short-term CD4 response (20 weeks)

Short-term immune response is defined as $\Delta\text{CD4}_{20} = \text{CD4}_{20} - \text{CD4}_{0}$.

To address Questions 1 and 2, we fit two nested linear regression models.

3.2.1 Reduced model (baseline disease severity + covariates + prior therapy type)

Let $I\{\cdot\}$ denote an indicator variable. Using none as the reference category for `prior`, the reduced model is

$$\begin{aligned}\mathbb{E}[\Delta\text{CD4}_{20,i}] = \beta_0 &+ \beta_1(\text{Baseline CD4})_i + \beta_2(\text{Age})_i + \beta_3(\text{Weight})_i \\ &+ \beta_4(\text{Gender})_i + \beta_5(\text{Race})_i \\ &+ \beta_6 I\{\text{prior}_i = \text{A only}\} + \beta_7 I\{\text{prior}_i = \text{A plus other}\} + \beta_8 I\{\text{prior}_i = \text{other only}\}.\end{aligned}$$

3.2.2 Full model (adds prior therapy duration)

Using no HIV therapy (`hist2 = 1`) as the reference category, the full model adds two duration indicators:

$$\begin{aligned}\mathbb{E}[\Delta\text{CD4}_{20,i}] = \beta_0 &+ \beta_1(\text{Baseline CD4})_i + \beta_2(\text{Age})_i + \beta_3(\text{Weight})_i \\ &+ \beta_4(\text{Gender})_i + \beta_5(\text{Race})_i \\ &+ \beta_6 I\{\text{prior}_i = \text{A only}\} + \beta_7 I\{\text{prior}_i = \text{A plus other}\} + \beta_8 I\{\text{prior}_i = \text{other only}\} \\ &+ \beta_9 I\{\text{hist2}_i = 2\} + \beta_{10} I\{\text{hist2}_i = 3\}.\end{aligned}$$

3.2.3 Question 1: Baseline disease severity

We test whether baseline CD4 count is associated with short-term CD4 response:

$$H_0^{(1)} : \beta_1 = 0 \qquad \text{vs} \qquad H_A^{(1)} : \beta_1 \neq 0.$$

This hypothesis is evaluated using the *t*-test for the baseline CD4 coefficient in the full short-term model.

3.2.4 Question 2: Prior therapy duration (beyond prior therapy type)

To assess whether duration of prior HIV therapy explains additional variation in ΔCD4_{20} beyond what is already captured the reduced model, we compare the reduced and full models using a partial F-test:

$$H_0^{(2)} : \beta_9 = \beta_{10} = 0 \qquad \text{vs} \qquad H_A^{(2)} : \text{at least one of } \beta_9, \beta_{10} \neq 0.$$

Rejection of $H_0^{(2)}$ indicates that prior therapy duration is associated with short-term CD4 response after accounting for prior therapy type and other covariates.

3.3 Question 3: Long-term CD4 response (96 weeks)

Long-term immune response is defined as $\Delta\text{CD4}_{96} = \text{CD4}_{96} - \text{CD4}_0$. This analysis is restricted to patients with observed 96-week CD4 measurements.

We fit a regression model adjusting for the same covariates, and including both multi-level treatment history variables (`prior` and `hist2`) as main effects:

$$\begin{aligned}\mathbb{E}[\Delta\text{CD4}_{96,i}] = \beta_0 &+ \beta_1(\text{Baseline CD4})_i + \beta_2(\text{Age})_i + \beta_3(\text{Weight})_i \\ &+ \beta_4(\text{Gender})_i + \beta_5(\text{Race})_i \\ &+ \beta_6 I\{\text{prior}_i = \text{A only}\} + \beta_7 I\{\text{prior}_i = \text{A plus other}\} + \beta_8 I\{\text{prior}_i = \text{other only}\} \\ &+ \beta_9 I\{\text{hist2}_i = 2\} + \beta_{10} I\{\text{hist2}_i = 3\}.\end{aligned}$$

3.3.1 Hypothesis test

To determine whether baseline disease severity is associated with long-term immune recovery, we test:

$$H_0^{(3)} : \beta_1 = 0 \qquad \text{vs} \qquad H_A^{(3)} : \beta_1 \neq 0.$$

This hypothesis is evaluated using the *t*-test for the baseline CD4 coefficient in the fitted long-term model.

3.4 Diagnostics

Figures 5, 6, and 7 in the **Appendix** show the diagnostic plots for each of the models, which all shed light on the same potential concerns. There appear to be four distinct clusters of observations with varying levels of leverage. This suggests that certain subgroups within the sample data have undue influence on the regression results. Further, the Q-Q plots suggest show a heavy-tail distribution in the residuals compared to what we would expect if the residuals were truly normally distributed, which suggests that the p-values resulting from each of the analyses may be overly optimistic.

4 Results

4.1 Question 1: Baseline disease severity

Baseline CD4 count significantly predicted change in CD4 count at 20 weeks, $\beta = -0.3178937, SE = 0.0212597, t(2128) = -14.9528787, p < .001$, controlling for age, weight, gender, race, treatment arm, and prior HIV therapy exposure. Each additional CD4 cell at baseline per cubic millimeter was associated with an average decrease in -0.3178937 CD4 cells per cubic millimeter after 20 weeks (95% CI (-0.36, -0.276). Therefore, there is statistically significant evidence to reject the null hypothesis in favor of the alternative hypothesis that (short-term) response to HIV therapy varies by disease progression.

4.2 Question 2: Prior therapy duration (beyond prior therapy type)

A partial F-test comparing the reduced and full models showed that inclusion of prior HIV therapy type and duration did not significantly improve model fit for predicting short-term CD4 change, $F(2, 2128) =\backslash q2\backslash_F, p = 0.3370229$. Therefore, there is no statistically significant evidence that HIV therapy varies by extent (type and duration) of prior HIV drug exposure.

4.3 Question 3: Long-term CD4 response (96 weeks)

Baseline CD4 count significantly predicted change in CD4 count at 96 weeks, $\beta = -0.2254084, SE = 0.0346477, t(1331) = -6.5057241, p < .001$, adjusting for age, weight, gender, race, treatment arm, and prior HIV therapy exposure. Each additional CD4 cell at baseline per cubic millimeter was associated with an average decrease in -0.2254084 CD4 cells per cubic millimeter after 96 weeks (95% CI (-0.293, -0.157). Therefore, there is statistically significant evidence to reject the null hypothesis in favor of the alternative hypothesis that long-term response to HIV therapy varies by initial disease progression.

5 Discussion

Based on the results of the statistical analysis, strong evidence was found that baseline CD4 levels are associated with short-term treatment response, and that patients with less advanced HIV disease experience greater long-term clinical benefit (96-week CD4 response) after treatment. However, no statistically significant evidence was found that the duration or extent of prior HIV therapy significantly predicts short-term CD4 outcomes. These findings suggest that while baseline immune status is important for short- and long-term outcomes, post-treatment outcomes do not seem to depend on treatment history.

However, several limitations may have influenced the accuracy of these findings.

First, CD4 counts at 96 weeks were missing for a substantial number of patients. Because these observations were removed, Model 3 may suffer from non-random missingness, potentially biasing estimates if patients with missing long-term CD4 counts differ systematically, especially if missingness relates to certain health outcomes, such as death.

Second, our sample population consists only of patients who have taken drug A and primarily of patients who have only taken drug A pre-trial. As a result, the analysis could not fully address how different pre-study regimens interact with current treatment.

Finally, differences in CD4 counts were used as the sole measure of treatment response. Although common in HIV research, they do not capture broader clinical outcomes such as symptom progression, quality of life, or survival.

6 Appendix

6.1 Tables

Term	b	SE	t	p
(Intercept)	181.250	19.257	9.41	< .001
cd4	-0.318	0.021	-14.95	< .001
age	-0.176	0.291	-0.60	= 0.546
wt	-0.078	0.196	-0.40	= 0.689
gender1	-8.167	7.101	-1.15	= 0.250
race1	-17.377	5.790	-3.00	= 0.003
priorA_only	-42.547	5.152	-8.26	< .001
priorA_plus_other	-73.292	26.046	-2.81	= 0.005
priorother_only	-115.751	22.599	-5.12	< .001

Table 1: Regression results for reduced full-term.

Term	b	SE	t	p
(Intercept)	183.416	19.317	9.50	< .001
cd4	-0.318	0.021	-14.95	< .001
age	-0.171	0.292	-0.59	= 0.558
wt	-0.090	0.196	-0.46	= 0.647
gender1	-8.220	7.118	-1.15	= 0.248
race1	-17.771	5.803	-3.06	= 0.002
priorA_only	-23.996	13.600	-1.76	= 0.078
priorA_plus_other	-54.122	29.112	-1.86	= 0.063
priorother_only	-96.829	25.987	-3.73	< .001
hist22	-18.717	13.817	-1.35	= 0.176
hist23	-20.818	14.187	-1.47	= 0.142

Table 2: Regression results for full short-term.

Term	b	SE	t	p
(Intercept)	36.928	31.884	1.16	= 0.247
cd4	-0.225	0.035	-6.51	< .001
age	0.209	0.476	0.44	= 0.660
wt	0.516	0.338	1.53	= 0.127
gender1	-3.000	11.805	-0.25	= 0.799
race1	-16.336	9.645	-1.69	= 0.091
priorA_only	-12.255	22.675	-0.54	= 0.589
priorA_plus_other	5.977	45.480	0.13	= 0.895
priorother_only	7.679	42.332	0.18	= 0.856
hist22	-15.858	23.063	-0.69	= 0.492
hist23	-32.433	23.606	-1.37	= 0.170

Table 3: Regression results for the long-term model.

6.2 Figures

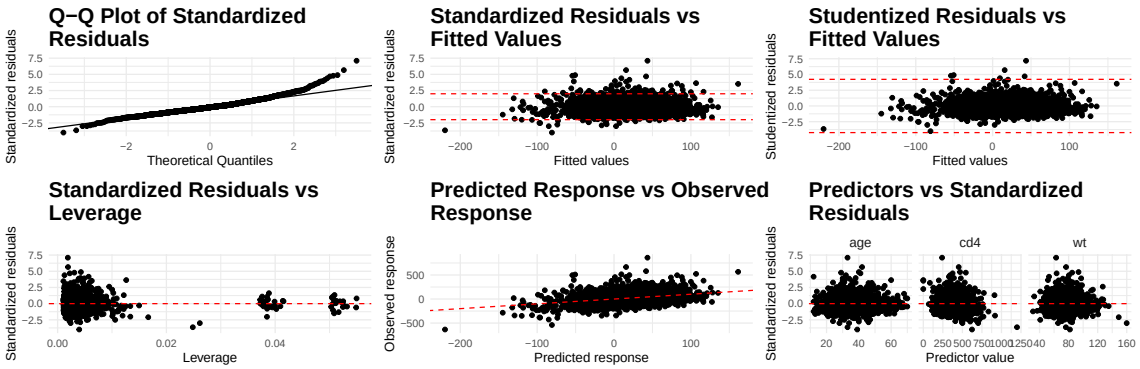

Figure 5: Diagnostics for reduced short-term model.

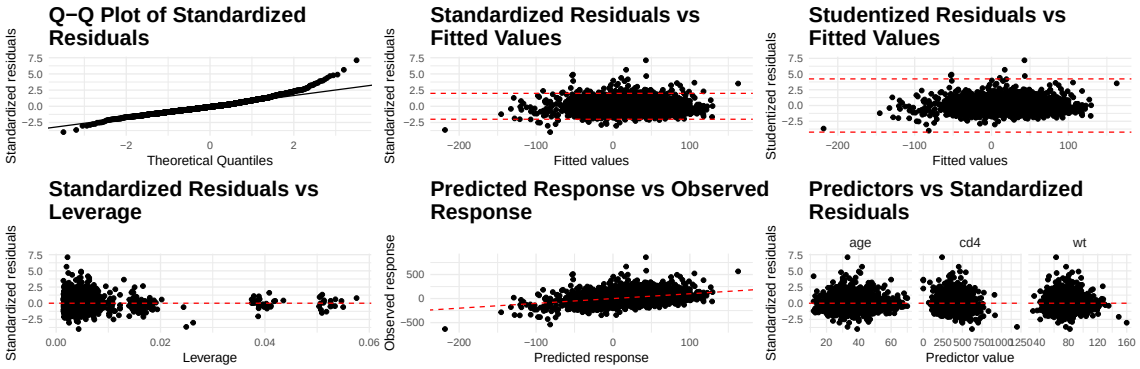

Figure 6: Diagnostics for full short-term model.

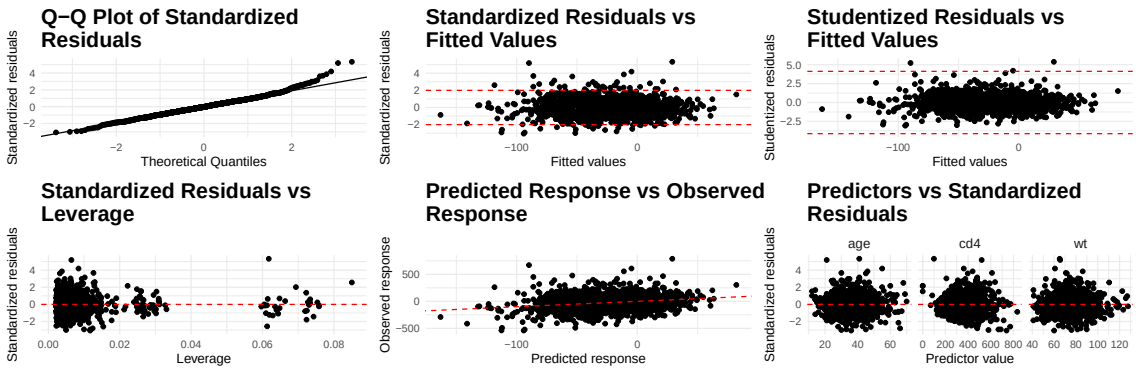

Figure 7: Diagnostics for long-term model.