

Survival Analysis of the ACTG320 HIV Clinical Trial

BST 222 Final Report (Fall 2025)

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Abstract

This report presents a comprehensive survival analysis of the ACTG320 clinical trial, which evaluated the effectiveness of Indinavir (IDV) in delaying AIDS progression or death among HIV-positive patients with compromised immune function. Using Kaplan–Meier estimation, Cox proportional hazards models, Schoenfeld diagnostics, and advanced extensions such as time-varying coefficient and accelerated failure time (AFT) models, we investigate key prognostic factors including treatment assignment, baseline CD4 count, Karnofsky score, age, and intravenous drug use history. Sensitivity analyses and model diagnostics confirm robustness of conclusions.

1 Introduction

1.1 Clinical Background

Human Immunodeficiency Virus (HIV) is a viral infection that targets CD4-positive white blood cells, weakening immune function and leaving individuals vulnerable to opportunistic infections. Untreated HIV typically progresses to Acquired Immune Deficiency Syndrome (AIDS) within approximately ten years. Modern antiretroviral therapies suppress viral replication, delaying or preventing AIDS development entirely.

Indinavir (IDV) is an early protease inhibitor developed in the 1990s. It interferes with viral replication, creating mute reproductions of the HIV virus, and became a cornerstone therapy when combined with nucleoside analogs such as Zidovudine (ZDV) or Lamivudine (3TC), which aimed at muting reproduction entirely. The ACTG320 clinical trial evaluated whether adding IDV to the standard of care (ZDV + 3TC) improved survival among patients with advanced HIV disease.

1.2 Survival Analysis Methods

The primary methodological framework of this report is survival analysis. We analyze:

- **Time-to-event outcomes:** progression to AIDS-defining event or death.
- **Kaplan–Meier (KM) estimates:** to visualize survival differences.
- **Cox proportional hazards (PH) models:** to quantify immediate risk.

The assumptions for these methods like non-informative censoring and proportional hazards are tested in this report to verify the validity of our methods. We used a combination of clinical reasoning and statistical methods to arrive at our conclusions.

2 Data Exploration

2.1 Dataset Description

The AIDS Clinical Trial Group Study 320 (Hammer et al. (1997)) enrolled 1151 HIV-positive participants in the U.S. and Puerto Rico between January 1996 and January 1997. All participants:

- were at least 16 years old,
- had CD4 counts mostly below 200 cells/mm³ (with 90% below 200),
- had Karnofsky performance scores of at least 70,
- were previously treated with Zidovudine (ZDV),
- and had advanced HIV disease.

The composite outcome was an **AIDS-defining event or death**.

Key variables from the trial include:

- **id**: patient identifier
- **event**: event indicator for AIDS or death
- **time_event**: time to event or censoring
- **tx**: indicator for Indinavir treatment
- **ivdrug**: intravenous drug use history (never, previous, current)
 - This variable was made binary into 'previous/current' = 1 and never = 0, as there were only four 'current' patients
- **karnof**: Karnofsky score (70, 80, 90, 100)
- **priorzdv**: months of prior ZDV use
- **age**: age in years
- **cd4lvl1**: Indicator of CD4 below 50
- **base_cd4**: baseline CD4 count, (per 100 mm³ of blood)

Our composite event here is critical, AIDS and death are not independent, as someone who dies may have gone on to develop AIDS had they not experienced death. It also accounts for deaths that happen caused by t not identified as being from AIDS development. Basically, to maintain non-informative censoring, we have this composite endpoint

2.2 General Exploratory Data Analysis

Event Distribution by Treatment

Table 1 summarizes censoring and event counts by treatment group.

| | Censored | Event |
|--------|----------|-------|
| No IDV | 514 | 63 |
| IDV | 541 | 33 |

Table 1: Distribution of outcomes by treatment assignment.

Survival curves (Figure 1) show visible separation, and the log-rank test rejects the null hypothesis of equal survival functions ($p = 0.001$). We also see the KM and AE survival curves to be almost identical, hence any analysis done requiring NA survival estimate is justified by our test of the KM curve.

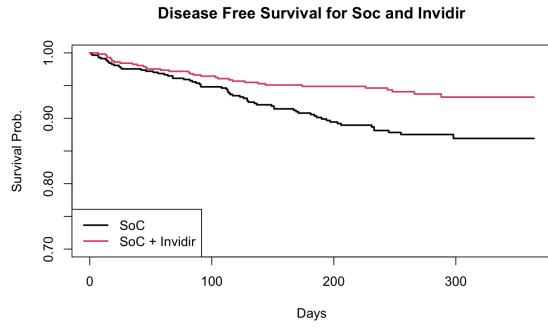


Figure 1: Kaplan–Meier survival curves by treatment group.

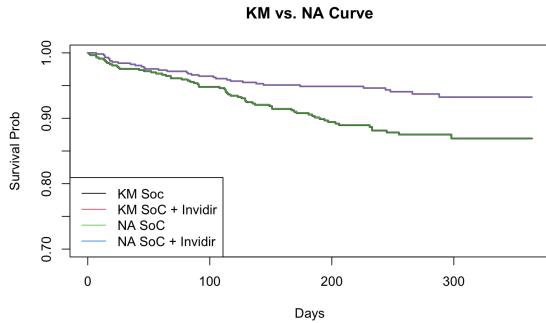


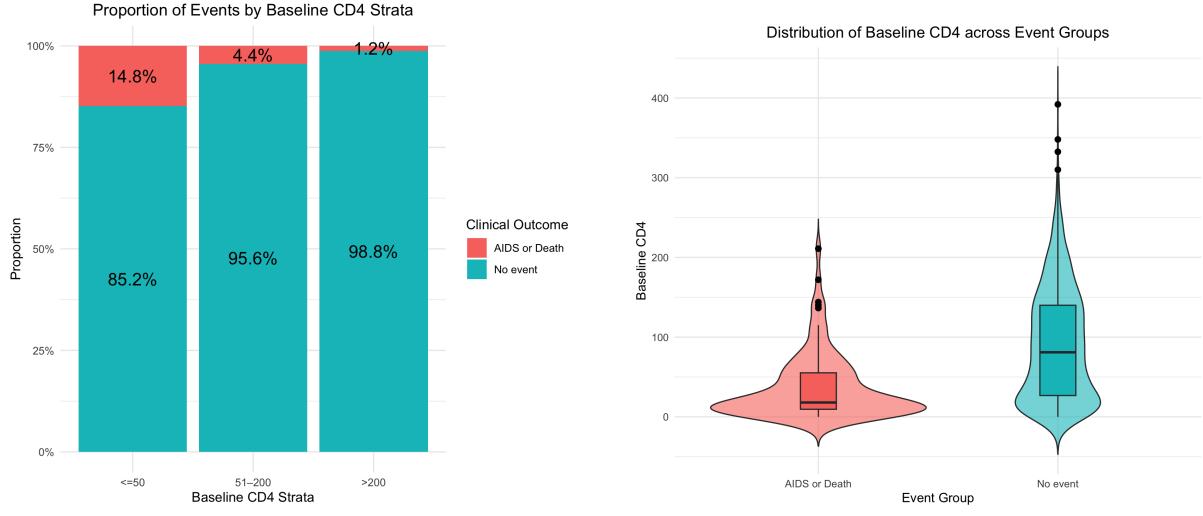
Figure 2: KM against NA Surv Curves

In this section, we explore univariate and bivariate patterns in the ACTG320 dataset, perform assumption verification, and create preliminary cox models. The goal is to identify which covariates should be included in the final cox proportional hazards and other survival models.

Baseline CD4 and Clinical Outcomes

Figure 3 provides a preliminary characterization of the relationship between baseline immunologic status and subsequent clinical outcomes. The left panel [3a] shows a strong, monotonic decline in the proportion of individuals who were diagnosed with AIDS or died as baseline CD4 level increases. Participants with CD4 level less or equal 50 exhibit a markedly elevated event rate (14.8%), roughly three times higher than those with CD4 between 51–200 (4.4%), and more than ten times higher than those with CD4 level bigger than 200 (1.2%). This steep gradient suggests that baseline CD4 level is not only clinically meaningful but also statistically influential, with the potential to serve as one of the primary prognostic covariates in the subsequent survival models.

The right panel [3b] further illustrates this relationship by displaying the full distribution of baseline CD4 level across event groups. Participants who developed AIDS or died tend to have substantially lower CD4 count levels, with distributions that are both compressed and shifted toward severe immunosuppression, near zero. In contrast, individuals who remained event-free show a broader distribution with higher median CD4 levels. The separation between the two distributions reinforces the notion that lower baseline CD4 level is strongly associated with poorer outcomes, consistent with established biological mechanisms in HIV disease progression.



(a) Proportion of clinical outcomes stratified by baseline CD4 categories.

(b) Baseline CD4 distribution stratified by clinical outcomes.

Figure 3: Exploration of baseline CD4 across strata and clinical outcomes.

Together, these visualizations provide compelling evidence that baseline CD4 level should be included in the survival analysis, potentially with careful attention to stratified form. This motivates the modeling decisions developed in later sections of the analysis.

Karnofsky Score and Outcomes

Figure 4 examines the association between Karnofsky score—a clinical measure of functional status—and subsequent clinical outcomes. This heatmap reveals a clear, monotonic pattern: as Karnofsky score increases, the proportion of participants who develop AIDS or die decreases substantially. Individuals with scores of 70 or 80 experience noticeably higher event relative frequencies compared with those scoring 90 or 100, whose event rates are markedly lower. This pattern aligns with clinical expectations, as poorer functional status at baseline generally reflects more advanced HIV disease and even greater physiological vulnerability.

Although the absolute number of participants in the lower-score categories is smaller, the relative frequency of events within these groups suggests that performance status may operate as an independent predictor of progression, even after considering the baseline CD4 level.

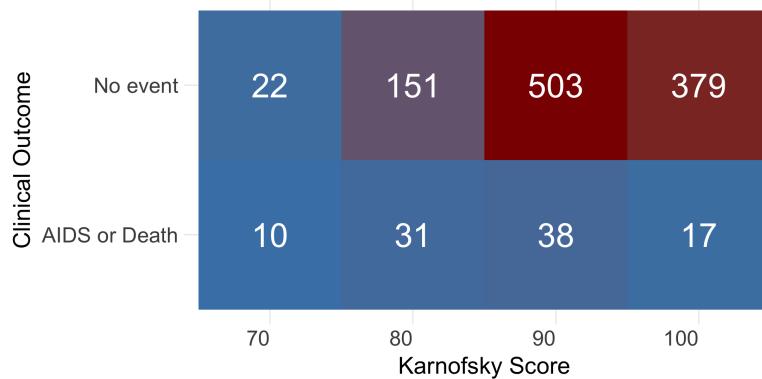


Figure 4: Clinical outcomes stratified by Karnofsky performance score.

These exploratory findings motivate the inclusion of Karnofsky score in subsequent survival models. The observed monotonic association provides strong preliminary support for functional

status as a clinically and statistically meaningful covariate in the modeling framework that follows.

Follow-Up and Censoring Patterns

Figure 5 summarizes the distribution of censored follow-up times overall and by treatment group. The left panel shows that censored times span the full range of the study period, with a concentration of censoring near the administrative end of follow-up (1 year). This pattern is consistent with non-informative administrative censoring, in which participants who do not experience the event simply remain under observation until the study concludes. The smooth distribution, with no abrupt irregularities, suggests no unexpected loss to follow-up.

The right panel compares these censoring distributions across treatment groups. The two histograms overlap almost entirely, indicating that the timing of censoring is broadly similar between those who received IVD and those who did not. This parallel behavior supports the assumption of non-informative censoring for treatment comparisons, as the likelihood and timing of censoring do not appear to depend on treatment assignment or underlying event risk.

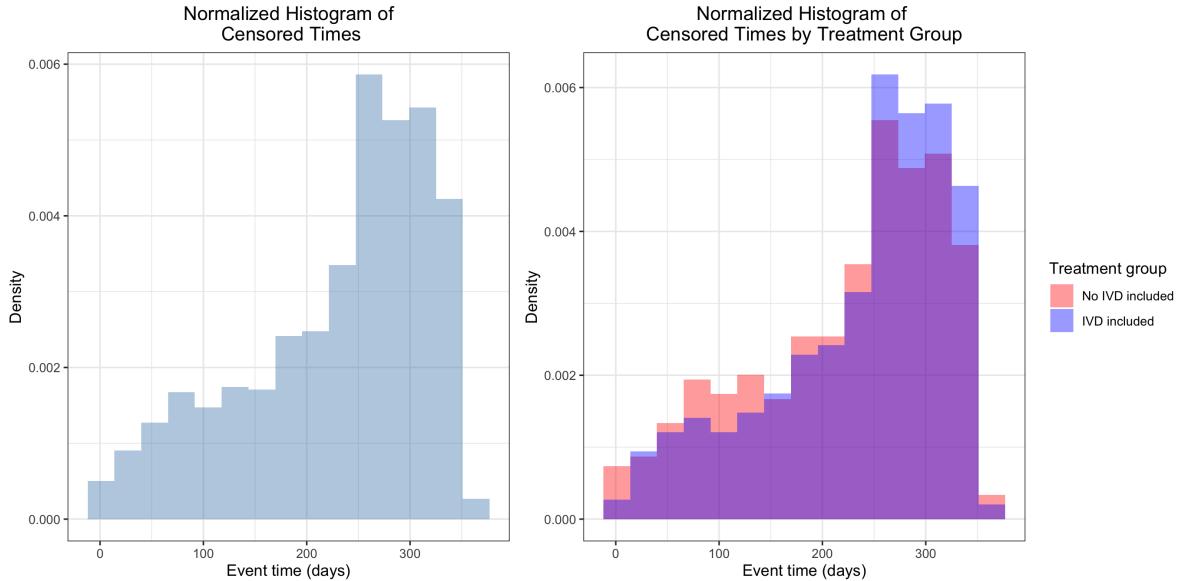


Figure 5: Density of follow-up times by treatment group.

Importantly, similar patterns are observed when examining censoring distributions across other covariates considered in this study, such as CD4 level and Karnofsky score. Across these variables, censoring tends to accumulate toward the end of the study period with no evidence of selective drop-out among higher-risk subgroups. This consistency further reinforces the validity of subsequent survival analyses, as it suggests that censoring mechanisms are unlikely to bias covariate associations or distort the interpretation of treatment effects.

Survival Differences by baseline CD4 Level strata

Figure 6 presents Kaplan–Meier survival curves stratified by baseline CD4 count, dichotomized at 50 cells/unit. The separation between the two curves is pronounced and emerges almost immediately after follow-up begins. Participants with a baseline CD4 level less or equal than 50 experience a substantially higher rate of AIDS or death throughout the study period, with survival dropping below 0.90 by approximately 125 days and continuing to decline steadily thereafter. In contrast, individuals with a baseline CD4 level greater than 50 maintain survival probabilities above 0.95 for most of the follow-up period, reflecting considerably lower short-term risk.

The non-overlapping confidence bands across much of the timeline provide strong visual evidence of a meaningful difference in survival between these two groups. The fact that the curves do not cross and decline at markedly different rates suggests that baseline CD4 level is not only a prognostic marker but one with a strong and persistent association with clinical progression. This pattern aligns with the well-established role of severe immunosuppression as a driver of adverse outcomes in HIV-infected individuals.

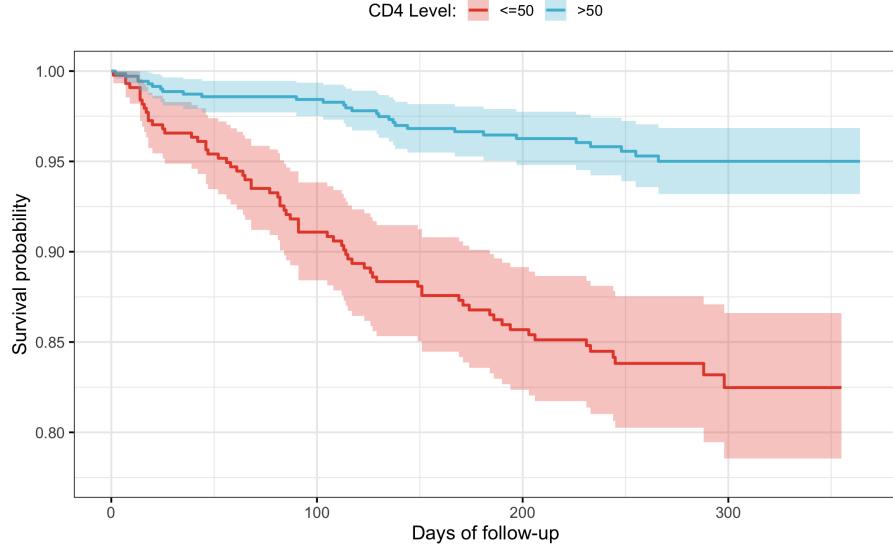


Figure 6: Kaplan–Meier curves stratified by baseline CD4 category (above/below 50).

These results reinforce the importance of including baseline CD4 level as a primary covariate in subsequent Cox proportional hazards models. Moreover, the shape of the curves motivates examining whether CD4 should be treated as a continuous predictor rather than relying solely on dichotomization, as the risk pattern observed earlier (Figures 3a, 3b and 4) suggests potentially threshold-driven effects that may not be fully captured by a simple binary split.

2.3 Preliminary Cox Model and Covariate Analysis

The 'add1' method was tested on a cox proportional hazards model regressed only on tx in order to narrow our original variable set.

| Variable | Df | AIC | LRT | p-value) |
|------------|----|--------|--------|-----------|
| <none> | – | 1308.2 | – | – |
| sex | 1 | 1310.1 | 0.042 | 0.83802 |
| hemophil | 1 | 1310.2 | 0.008 | 0.92877 |
| ivdrug_bin | 1 | 1308.4 | 1.800 | 0.17976 |
| karnof | 3 | 1274.7 | 39.469 | 1.381e-08 |
| priorzdv | 1 | 1309.8 | 0.369 | 0.54329 |
| age | 1 | 1306.8 | 3.399 | 0.06523 |
| race | 1 | 1312.2 | 3.946 | 0.41339 |
| base_cd4 | 1 | 1247.7 | 62.539 | 2.612e-15 |

Table 2: Likelihood Ratio Tests for Adding Predictors to Cox Model

We notice that the explicitly harmful variables in terms of AIC include sex, hemophil, ivdrug, priorzdv, and race. We chose to keep all of the non-AIC harmful variables, as well as ivdrug and priorzdv, as they are clinically relevant, which is to be elaborated on later, and also their AIC

harm is minimal. Any following analysis examining residuals was done using a cox proportional hazards model of the form (mid-model):

$$\text{surv_actg} \sim tx + ivdrug_bin + karnof + age + base_cd4 + priorzdv.$$

This model did not violate the proportional hazards assumption, passing a global schoenfeld residuals test at p=0.254, making it appropriate for the below analysis.

| Variable | Coef | exp(Coef) | SE(Coef) | z | Pr(> z) | Sig |
|------------|------------|-----------|-----------|--------|----------|-----|
| tx | -0.6683142 | 0.5125719 | 0.2154219 | -3.102 | 0.001920 | ** |
| ivdrug_bin | -0.5517430 | 0.5759451 | 0.3225978 | -1.710 | 0.087208 | . |
| karnof80 | -0.4440832 | 0.6414120 | 0.3666398 | -1.211 | 0.225809 | |
| karnof90 | -1.1361865 | 0.3210410 | 0.3654950 | -3.109 | 0.001880 | ** |
| karnof100 | -1.5638754 | 0.2093233 | 0.4092885 | -3.821 | 0.000133 | *** |
| priorzdv | -0.0001723 | 0.9998277 | 0.0037957 | -0.045 | 0.963798 | |
| age | 0.0220339 | 1.0222784 | 0.0112514 | 1.958 | 0.050193 | . |
| base_cd4 | -0.0144282 | 0.9856754 | 0.0025349 | -5.692 | 1.26e-08 | *** |

Table 3: Mid Model Results

Linearity of Continous Variables

Martingale residuals were used to check the linearity of each continuous covariate.

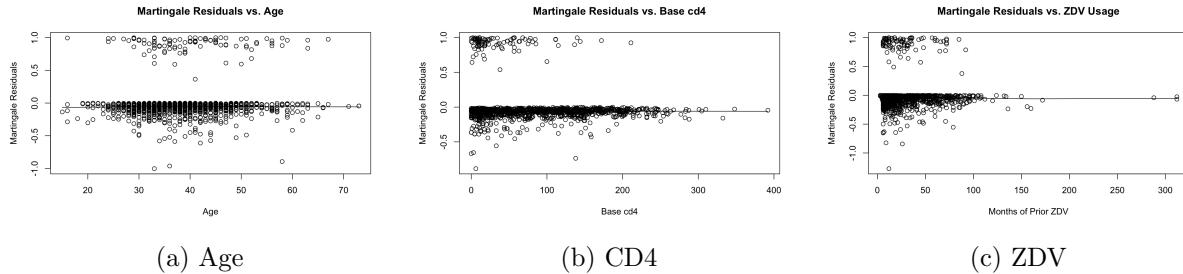


Figure 7: Martingale Residuals for Continuous Covariates

We see no obvious transformation to be made for any of the variables. The collection of points in the upper left hand corner are individuals with early events, not unusual covariate values.

Prior ZDV Use

Although clinically relevant, priorzdv use did not improve mid model fit, as seen above. In an effort to justify its clinical relevance statistically, we investigated if priorzdv had a connection to CD4. The reasoning here is that priorzdv use may be a mask for time with disease, the longer someone is on medicine, likely the longer they have HIV. HIV may effect more than just one's CD4 count, indicating a relationship between CD4 and priorzdv. Additionally, the effect of zdv may dull over time, also effecting a patient's CD4 count.

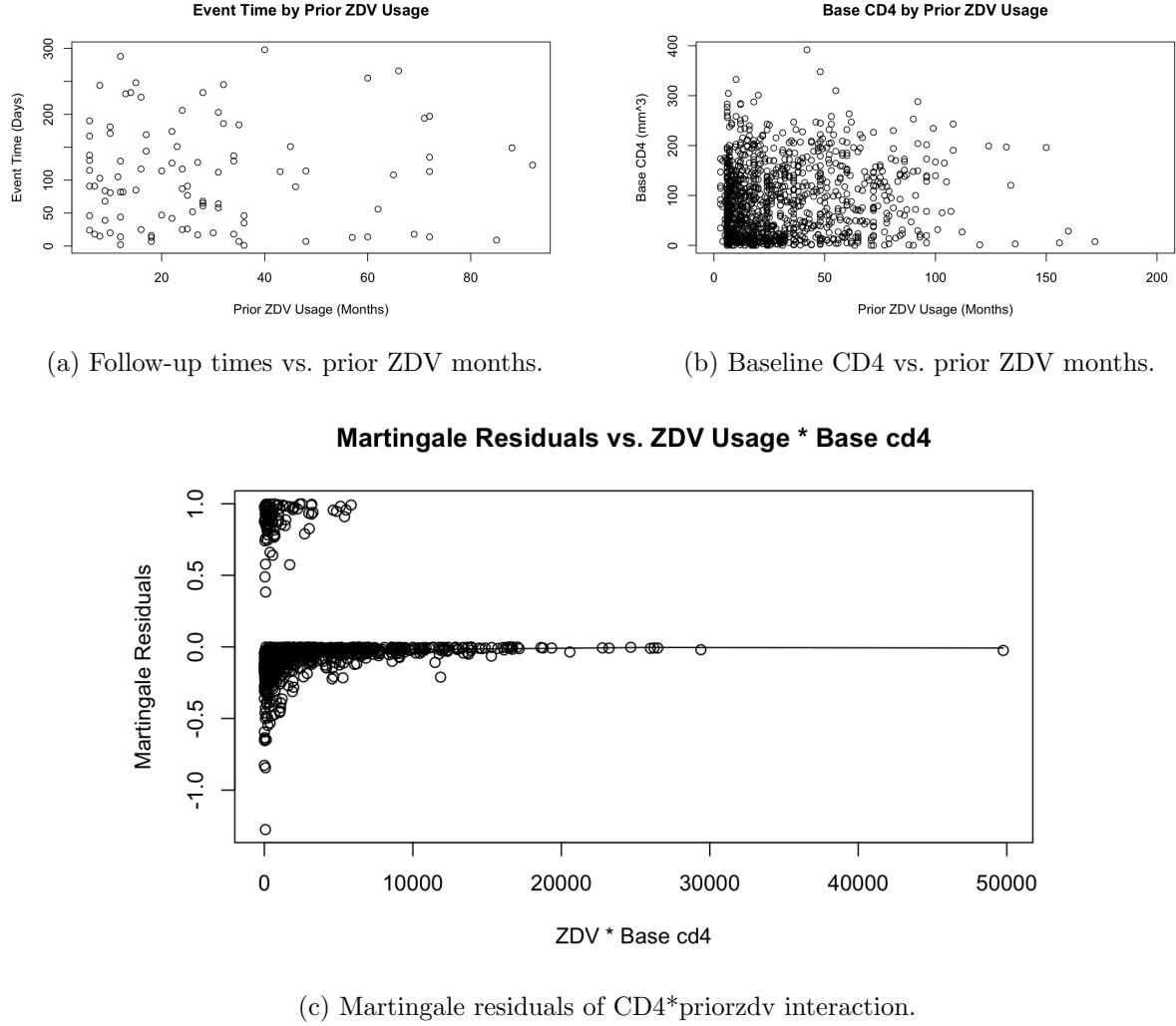
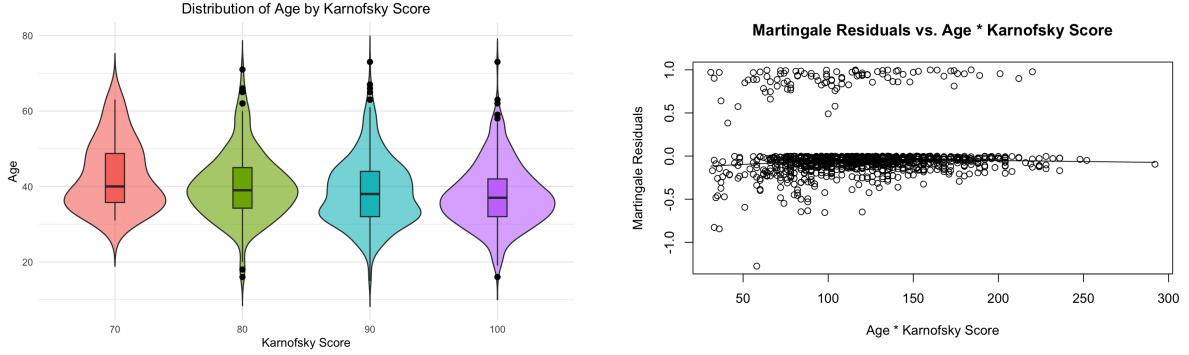


Figure 8: Plots involving prior ZDV use.

A model fit with an interaction term between priorzdv and CD4 was fit, and was insignificant. We see no correlation of priorzdv with event times or CD4 in patients. After examining the martingale residuals of the interaction term, we found no linear transformation helpful, hence, we have strong reason to remove priorzdv from consideration. **Thus, prior ZDV was excluded from the final model.**

Age and Karnofsky Score

Age and Karnofsky score are intuitively correlated: older patients may have lower functional status, making proportional sampling across ages tough. Also an interaction between age and karnofsky score is possible; older patients with the same score as younger patients are less healthy likely. However, the sample shows wide variation across ages within each Karnofsky category (Figure 9a).



(a) Relationship between age and Karnofsky score. (b) Martingale Residuals of Age * Karnofsky

Figure 9: Side-by-side comparison of plots.

After testing interactions and transformations, none were significant. Thus, both variables were included independently in the Cox model.

Code for the models fit with the interaction terms can be found in the appendix for this section. Summaries are not provided for sake of redundancy, as models are identical apart from insignificant interaction terms. Now we proceed to choose our best Cox Model, and its extensions.

3 Methodology

3.1 Selected Cox Proportional Hazards Model

We first further assessed whether the proportional hazards (PH) assumption was appropriate for tx, our variable of interest. Figure 10 shows complementary log-log (cloglog) transformed survival curves for key covariates. The approximate parallelism across groups suggests that the PH assumption is reasonable.

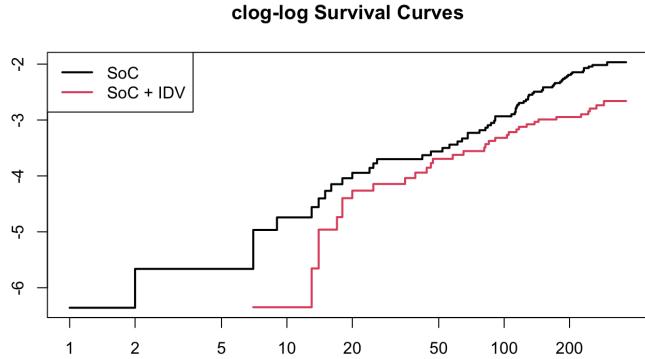


Figure 10: Cloglog-transformed survival curves used to assess the proportional hazards assumption.

Using additive model selection (`add1`), clinical reasoning, and the analysis shown above, we see keeping the karnofsky score, base_cd4, and age are helpful to the model, ivdrug_use and priorzdv are borderline. Moreover, a likelihood ratio test was conducted on a model including priorzdv to test again whether priorzdv is needed. From the result in Table 13, the

p-value=0.9637 is quite large, that means we can drop priorzdv for a more interpretable model, in accordance with the analysis above, and regardless of its clinical significance:

$$\text{surv_actg} \sim tx + ivdrug_bin + karnof + age + base_cd4.$$

Estimated coefficients and hazard ratios are presented in Table 4. Several covariates show clear associations with hazard. Indinavir treatment, higher Karnofsky scores, and greater baseline CD4 counts are all linked to lower risk, whereas older age is associated with a slight increase in hazard. In magnitude, Indinavir treatment reduces risk by about 48.75%, a Karnofsky score of 100 corresponds to roughly 79.06% lower hazard, and a 100 mm^3 increase in CD4 level is associated with about a 75.58% reduction in risk. As a final note, this model has an AIC of 1228.129, lower than any of the add1 models, and the mid-model.

One result appears counterintuitive: the “previous/current” IV drug use group shows lower hazard. This is largely because the group is dominated by *previous* users, who enter the study with higher baseline CD4 levels and more stable health status (Figure 11).

| Variable | Coef | exp(Coef) | p-value | Sig. |
|------------|---------|-----------|----------|------|
| tx | -0.6685 | 0.5125 | 0.0019 | ** |
| ivdrug_bin | -0.5520 | 0.5758 | 0.0870 | . |
| karnof80 | -0.4433 | 0.6419 | 0.2261 | |
| karnof90 | -1.1355 | 0.3213 | 0.0019 | ** |
| karnof100 | -1.5633 | 0.2094 | 0.0001 | *** |
| age | 0.0220 | 1.0223 | 0.0503 | . |
| base_cd4 | -0.0144 | 0.9857 | 1.06e-08 | *** |

Table 4: Cox proportional hazards model estimates

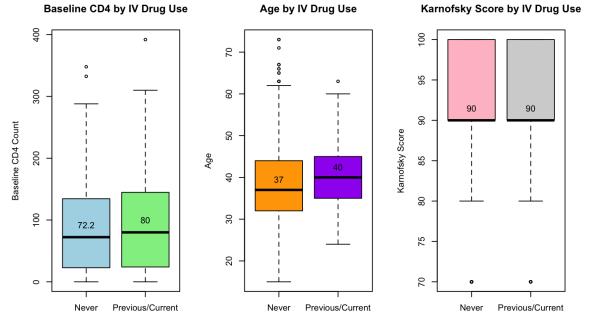


Figure 11: Baseline CD4 distribution by IV drug use

More assessment of the proportional hazards assumption using Schoenfeld residuals (Table 5) revealed no evidence of violation for any covariate, and the global test (p-value = 0.180) further supports the adequacy of the PH model. The overall model fit was strong, with the Likelihood Ratio, Wald, and Score tests all reaching high levels of statistical significance. In addition, the concordance index of 0.783 (Table 6) indicates satisfactory discriminatory performance.

| Covariate | Chi-square | df | p-value |
|---------------|----------------|----------|--------------|
| tx | 1.9046 | 1 | 0.168 |
| ivdrug_bin | 0.0071 | 1 | 0.933 |
| karnof | 2.0843 | 3 | 0.555 |
| age | 2.5442 | 1 | 0.111 |
| base_cd4 | 3.6164 | 1 | 0.057 |
| Global | 10.1532 | 7 | 0.180 |

Table 5: Schoenfeld residual tests for proportional hazards assumption

| Test | Statistic | p-value |
|-----------------------|--------------|-----------------------|
| Likelihood Ratio Test | 102.8 | $< 2 \times 10^{-16}$ |
| Wald Test | 85.66 | 1×10^{-15} |
| Score (Log-rank) Test | 102.8 | $< 2 \times 10^{-16}$ |
| Concordance (C-index) | 0.783 | SE = 0.023 |

Table 6: Model significance tests and discrimination for the Cox model.

We also evaluated a stratified Cox model based on CD4 categories (≤ 50 , $51\text{--}200$, > 200). Stratification markedly reduced model discrimination (concordance decreasing from 0.783 to 0.674) and eliminated the quantitative effect of CD4. Given the resulting loss in both predictive performance and clinical interpretability, CD4 is more appropriately treated as a continuous covariate rather than as a stratification factor.

3.2 Time-Varying Coefficient Cox Models

Although the proportional hazards (PH) assumption held overall in the reduced Cox model, the Schoenfeld test for baseline CD4 was borderline significant ($p = 0.057$). Because CD4 is biologically expected to have a changing effect over time—declining with progression or improving with treatment—we explored **time-varying coefficient (TVC)** extensions of the Cox model.

Clinical Motivation

CD4 count is a dynamic biological marker:

- Without treatment, CD4 levels generally decline over time.
- With effective therapy, CD4 may increase.
- Its protective effect is therefore expected to diminish or evolve during follow-up.

Thus, a TVC model allows us to assess whether the effect of baseline CD4 changes with time.

Model 1: CD4 \times log(t) Interaction

We first consider a model where the effect of baseline CD4 varies with $\log(t)$:

$$\text{surv_actg} \sim tx + ivdrug_bin + karnof + age + base_cd4 + (\text{base_cd4}) \cdot \log(t).$$

The results are shown in Table 7.

| Variable | Coef | exp(Coef) | SE | z | p-value | Sig. |
|---------------------------|-----------|-----------|----------|--------|---------|------|
| tx | -0.667969 | 0.512749 | 0.215396 | -3.101 | 0.00193 | ** |
| ivdrug_bin | -0.549405 | 0.577293 | 0.322564 | -1.703 | 0.08852 | . |
| karnof80 | -0.432216 | 0.649069 | 0.366318 | -1.180 | 0.23804 | |
| karnof90 | -1.121711 | 0.325722 | 0.365450 | -3.069 | 0.00214 | ** |
| karnof100 | -1.545351 | 0.213237 | 0.409443 | -3.774 | 0.00016 | *** |
| age | 0.021931 | 1.022173 | 0.011238 | 1.951 | 0.05101 | . |
| base_cd4 | -0.031306 | 0.969179 | 0.012170 | -2.572 | 0.01010 | * |
| (base_cd4) \cdot log(t) | 0.003836 | 1.003844 | 0.002626 | 1.461 | 0.14400 | |

Table 7: Time-varying coefficient Cox model with CD4 \times log(t).

The time-varying term has a p -value of 0.144, which is not statistically compelling.

Model 2: CD4 \times t Interaction

We next consider a linear time interaction:

$$\text{surv_actg} \sim tx + ivdrug_bin + karnof + age + base_cd4 + (\text{base_cd4}) \cdot t.$$

Results are reported in Table 8.

| Variable | Coef | exp(Coef) | SE | z | p-value | Sig. |
|----------------------|-----------|-----------|-----------|--------|----------|------|
| tx | -0.66668 | 0.5133 | 0.2154 | -3.096 | 0.00196 | ** |
| ivdrug_bin | -0.5493 | 0.5773 | 0.3226 | -1.703 | 0.08856 | . |
| karnof80 | -0.4295 | 0.6509 | 0.3663 | -1.172 | 0.24104 | |
| karnof90 | -1.1171 | 0.3272 | 0.3655 | -3.057 | 0.00224 | ** |
| karnof100 | -1.5410 | 0.2142 | 0.4094 | -3.764 | 0.00017 | *** |
| age | 0.02190 | 1.0221 | 0.01124 | 1.949 | 0.05134 | . |
| base_cd4 | -0.02085 | 0.9794 | 0.00470 | -4.439 | 9.03e-06 | *** |
| (base_cd4) \cdot t | 5.416e-05 | 1.00000 | 3.018e-05 | 1.795 | 0.072688 | . |

Table 8: Time-varying coefficient Cox model with CD4 \times t.

This specification improves the significance of the time-varying term ($p = 0.0727$), providing moderate evidence that the protective effect of baseline CD4 weakens over time.

Given its clinical plausibility and improved fit, we proceed with the $\mathbf{CD4} \times t$ model.

Time-Varying Hazard Ratio of CD4

Figure 12 visualizes the estimated time-varying hazard ratio for baseline CD4.

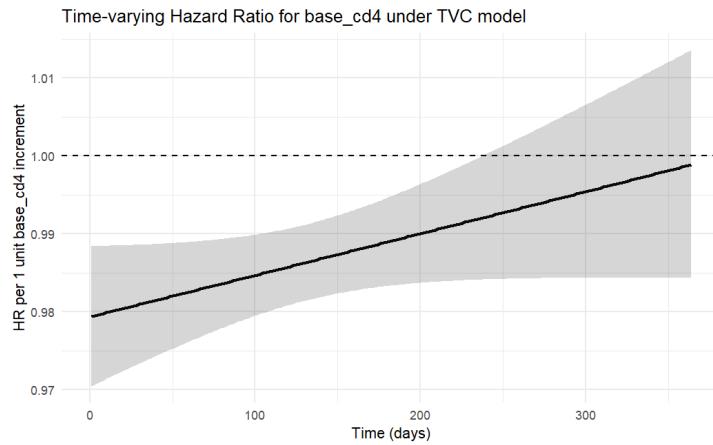


Figure 12: Estimated hazard ratio $HR(t)$ for baseline CD4 under the time-varying coefficient model.

Interpretation

- At early times, $HR(t) < 1$, indicating that higher baseline CD4 strongly reduces the hazard of AIDS or death.
- Over time, $HR(t)$ approaches 1, meaning the protective effect diminishes.
- This pattern aligns with clinical understanding: initial CD4 reflects disease severity at enrollment, but its protective effect decays as biological changes occur during therapy.

Conclusion: The time-varying Cox model supports a weakening protective effect of baseline CD4, consistent with biological expectations and statistical evidence.

3.3 Accelerated Failure Time (AFT) Models

Motivation

The Accelerated Failure Time (AFT) framework models **survival time directly**, rather than the hazard function. This approach is commonly used when:

- large sample sizes produce very low event probabilities at each time point,
- events are guaranteed with sufficiently long follow-up (as in engineering failure),
- the proportional hazards assumption may be questionable for certain CD4.

In the ACTG320 study, every patient is expected to eventually experience AIDS progression or death given enough time, much like “failure” in reliability engineering. Thus, the AFT model provides a meaningful alternative perspective.

Candidate AFT Models

We evaluated four commonly used AFT models:

- Gumbel (extreme value),
- Weibull,

- Log-normal,
- Log-logistic.

Each model was fitted with the same covariates as the reduced Cox model.

Table 9 shows the Akaike Information Criterion (AIC) values used to compare models.

| Model | df | AIC |
|----------------|----|----------|
| Gumbel Extreme | 9 | 1735.003 |
| Weibull | 9 | 1621.059 |
| Log-normal | 9 | 1622.750 |
| Log-logistic | 9 | 1619.771 |

Table 9: AIC comparison of AFT models.

The log-logistic model has the lowest AIC and is therefore selected as the best-fitting AFT model.

Final Log-Logistic AFT Model

The selected model can be written as:

$$\log(T) = \beta_0 + \beta_1 tx + \beta_2 ivdrug_bin + \beta_3 karnof + \beta_4 age + \beta_5 base_cd4 + \sigma\epsilon,$$

where $\epsilon \sim \text{Logistic}(0, 1)$.

Parameter estimates are shown in Table 10.

| Variable | Coefficient |
|------------|-------------|
| Intercept | 6.42521 |
| tx | 0.87228 |
| ivdrug_bin | 0.75411 |
| karnof80 | 0.70487 |
| karnof90 | 1.62012 |
| karnof100 | 2.11731 |
| age | -0.02822 |
| base_cd4 | 0.01830 |
| Log(scale) | 0.16933 |

Table 10: Coefficient estimates for the log-logistic AFT model.

Interpretation and Comparison with the Cox Model

The AFT results closely mirror those from the Cox model:

- **IDV treatment (tx):** increases survival time (positive coefficient).
- **Higher Karnofsky score:** strongly increases survival time.
- **Older age:** reduces survival time slightly.
- **Higher baseline CD4:** increases survival time.

Because the AFT model directly models $\log(T)$, a positive coefficient indicates a longer expected survival time, while a negative coefficient indicates shorter survival.

Why Cox is preferred despite similar findings:

- The Cox model requires fewer distributional assumptions.
- The AFT model requires specifying a full parametric form for the survival distribution.
- AIC is slightly higher for AFT compared to the reduced Cox model.
- Interpretation of “acceleration factors” is less standard in clinical research.

Thus, while the AFT analysis reinforces the Cox model findings, it does not provide substantial advantages and is therefore treated as a secondary analysis.

3.4 Influential Observation Diagnostics

To assess the robustness of the Cox proportional hazards model, we examined influential observations using multiple diagnostics:

- dfbeta values for each coefficient,
- deviance residuals,
- visual inspection of outlying covariate patterns.

Summary of Influential Observations

A set of six potentially influential observations was identified based on martingale residual, dfbeta magnitude and deviance residual size using the Cox model from section 3.1.(Figure 13):

610, 633, 638, 671, 680, 996.

Table 11 reports dfbeta values and deviance residuals for the reduced Cox model.

Table 11: Influence diagnostics: dfbeta values and deviance residuals.

| ID | dfbeta (influence on each coefficient) | | | | | | | Dev.Res |
|-----|--|------------|----------|----------|-----------|---------|----------|---------|
| | tx | ivdrug.bin | karnof80 | karnof90 | karnof100 | age | base_cd4 | |
| 610 | 0.0322 | -0.0080 | 0.0028 | 0.0070 | 0.0687 | 0.0006 | -0.00027 | 2.584 |
| 633 | 0.0292 | -0.0167 | -0.0944 | -0.0978 | -0.0964 | -0.0012 | 0.00001 | 1.686 |
| 638 | 0.0203 | 0.0268 | 0.1213 | 0.1167 | 0.1156 | -0.0024 | 0.00017 | -1.595 |
| 671 | 0.0317 | -0.0173 | -0.1018 | -0.1043 | -0.1025 | -0.0015 | -0.00004 | 2.266 |
| 680 | -0.0137 | -0.0192 | -0.0995 | -0.1013 | -0.1020 | -0.0009 | 0.00005 | 2.246 |
| 996 | -0.0190 | -0.0106 | 0.0025 | 0.0255 | -0.0010 | 0.0030 | 0.00049 | 2.073 |

Across all coefficients, dfbeta values remain small in absolute magnitude, indicating that removing any of these observations would not meaningfully alter the coefficient estimates.

Clinical Review of Influential Patients

To better understand the flagged observations, Table 12 summarizes their clinical characteristics.

Table 12: Characteristics of observations flagged as potentially influential.

| Obs | txgrp | ivdrug | Karnofsky | Age | Baseline CD4 | Time to Event |
|-----|---------|--------|-----------|-----|--------------|---------------|
| 610 | idv_zdv | never | 100 | 43 | 5.5 | 18 |
| 633 | idv_zdv | never | 70 | 33 | 18.0 | 65 |
| 638 | zdv | never | 70 | 58 | 6.0 | 290 |
| 671 | idv_zdv | never | 70 | 31 | 8.0 | 14 |
| 680 | zdv | never | 70 | 36 | 23.0 | 9 |
| 996 | zdv | never | 90 | 67 | 136.5 | 129 |

Interpretation

Several patterns explain why these observations appear influential:

- **Extremely low CD4 values:** Many flagged patients have $CD4 \leq 25$, indicating severe immunosuppression.
- **Low Karnofsky scores:** Most have scores of 70, the minimum allowed for trial inclusion.
- **Early events:** Observations 610, 671, and 680 experience events within 20 days—consistent with severe baseline illness.
- **Not statistical outliers:** Their clinical profiles (low CD4, low functional status, early event) are realistic and expected for advanced HIV.

Despite their early events and poor baseline health, **dfbeta values are uniformly small**. This indicates the model is **robust** to their inclusion.

Conclusion: None of the flagged observations exert undue influence on the Cox model. Their extreme clinical profiles are consistent with expected disease behavior, and excluding them would not meaningfully change the model conclusions. Therefore, no observations were removed.

4 Final Conclusions

This report presents a comprehensive survival analysis of the ACTG320 HIV clinical trial, identifying key prognostic factors and evaluating the effect of Indinavir (IDV) treatment on progression to AIDS or death.

4.1 Key Findings

- **IDV significantly improves survival.** In the Cox model, IDV reduces the hazard by approximately 49%. This effect remains significant across all model specifications.
- **Baseline CD4 is the strongest predictor of clinical outcomes.** Higher CD4 substantially reduces the hazard, and a 100-unit increase in CD4 corresponds to a roughly 75% reduction in risk. Event-free patients had much higher CD4 values, and CD4 alone produced strong separation in Kaplan–Meier curves.
- **The effect of baseline CD4 may weaken over time.** Time-varying coefficient models suggest that the protective effect of baseline CD4 declines as follow-up progresses. This pattern is clinically intuitive: CD4 levels naturally change with disease progression and therapy response.
- **Higher Karnofsky scores strongly predict better survival.** Patients with scores of 100 experience about 79% lower hazard than those with a score of 70.
- **Older age is associated with slightly increased risk.** Although borderline significant, age remained clinically meaningful and was retained.
- **IV drug use history is not harmful in this cohort.** The “previous/current” group appears healthier primarily because it consists almost entirely of **previous** users who entered the trial in stable condition, had earlier diagnosis, and were monitored more frequently.
- **Proportional hazards assumption holds.** Schoenfeld residual tests show no significant violations, with a global p-value of 0.18.
- **The Cox model is robust to influential observations.** Despite several observations with early events or extremely low CD4, dfbeta values were small, and no observations required removal.

4.2 Advanced Models

Time-Varying Coefficient Model (TVC) Including a $CD4 \times t$ term suggested that the effect of baseline CD4 diminishes over time, consistent with the biological understanding that CD4 levels evolve during infection and treatment. We prefer this model the most, as the time varying effect of CD4 is **logical**, and **statistically relevant**.

Accelerated Failure Time (AFT) Model Although the log-logistic AFT model fit the data slightly better (lowest AIC among AFT models), it did not outperform the Cox model and required stronger distributional assumptions. The AFT results supported the same qualitative conclusions as the Cox model.

4.3 Overall Interpretation

Taken together, the analyses confirm that:

- IDV provides substantial therapeutic benefit,
- baseline immune function (CD4 count) is the dominant prognostic factor,
- functional status (Karnofsky score) plays a major role in survival,
- the proportional hazards framework provides a strong and reliable model for this dataset.

These findings align with the original ACTG320 conclusions and support the clinical adoption of IDV-containing regimens, which contributed to major improvements in HIV/AIDS therapy.

As an aside, the original ACTG320 study went ahead with a Cox PH model with CD4 stratified at 50. Obviously, they also found significant improvement in patients taking Indinavir. Today, many of the patients in the study would have been deemed to have had AIDS already due to their low CD4; we wouldn't wait for them to have an AIDS defining event. In terms of future analysis, we may consider a competing risks model in order to separate death and an AIDS event, as individuals who die from unrelated causes are not relevant to the drug treatment process.

References

- Hammer, S., Squires, K., Hughes, M., Grimes, J., Demeter, L., Currier, J., Eron, J. J., Feinberg, J., Balfour, H. J., Deyton, L., Chodakewitz, J., Fischl, M., and Team, A. C. T. G. . S. (1997). A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and cd4 cell counts of 200 per cubic millimeter or less. *New England Journal of Medicine*, 337(11):725–733.
- Stanford University / HIV Drug Resistance Database (2025). Actg 320 clinical study data. Accessed: 2025-11-19.
- Su, S. and Core Team, R. (2025). *GLDreg: Fit GLD Regression/Quantile/AFT Model to Data*. R package version 1.1.2.

Appendices

Plots and Tables

| Model | logLik | Chisq | Df | p-value |
|-------|---------|--------|----|---------|
| 1 | -607.06 | | | |
| 2 | -607.06 | 0.0021 | 1 | 0.9637 |

Table 13: Model comparison based on likelihood ratio test.

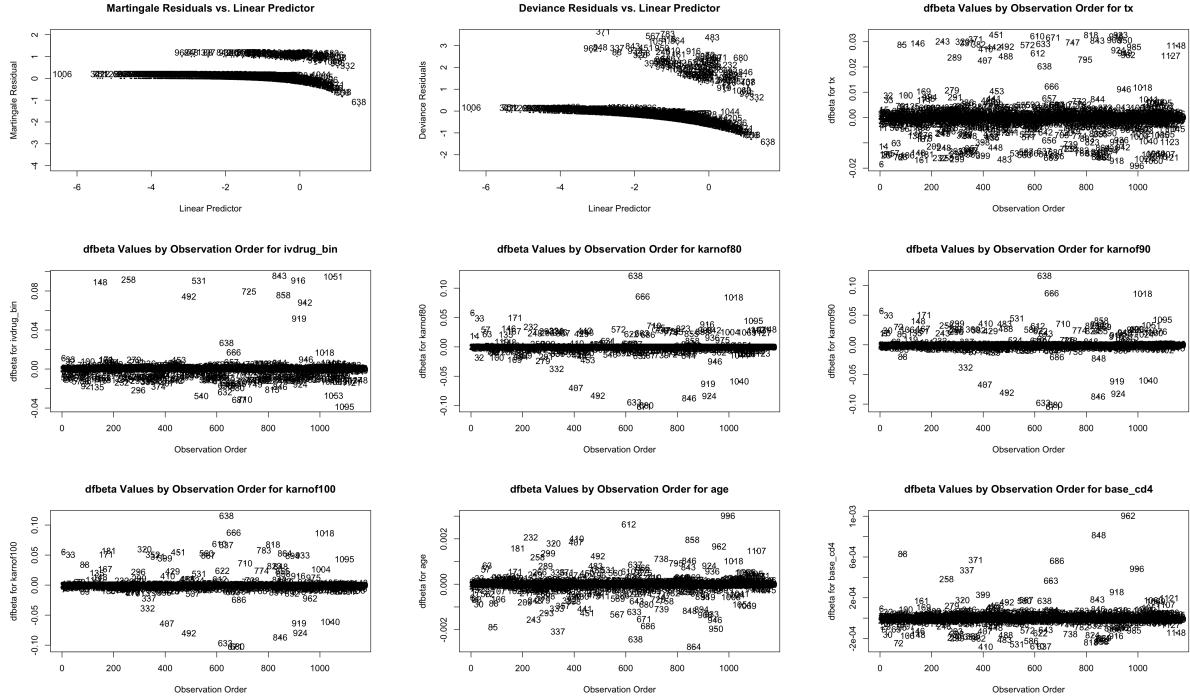


Figure 13: Residual and dfbeta diagnostics for the Cox proportional hazards model.

Code

Data Cleaning

```
1 suppressWarnings(suppressPackageStartupMessages(library(tidyverse)))
2 suppressWarnings(suppressPackageStartupMessages(library(GLDreg)))
3 suppressWarnings(suppressPackageStartupMessages(library(survival)))
4
5 edit_actg <- actg
6
7 edit_actg <-
8   edit_actg |>
9   mutate(
10     txgrp = factor(txgrp, levels = 1:4, labels = c('zdv', 'idv_zdv', 'd4t', ,
11       idv_d4t')), #3TC is included in all trt groups, so redundant in labels
12     cd4_lvl = factor(strat2, levels = 0:1, labels = c('<=50', '>50')),
13     sex = factor(sex, levels = 0:1, labels = c('male', 'female')),
14     race = factor(raceth, levels = 1:6, labels = c('wnh', 'bnh', 'h', 'api',
15       ai', 'other')),
16     ivdrug = factor(ivdrug, levels = 1:3, labels = c('never', 'currently',
17       previously)),
18     event = censor,
19     time_event = time,
20     death = censor_d,
21     time_death = time_d,
22     base_cd4 = cd4,
23     ivdrug_bin = ifelse(actg$ivdrug == 1, 0, 1)
24   ) |>
25   select(-c(raceth, strat2, time, time_d, censor, censor_d, cd4))
26
27 ##### References to ACTG dataset from here on will be referencing this cleaned
28 dataset
```

2.2 General EDA

```
1 ##### KM Curves
2
3 table(actg_c$tx, actg_c$event)
4
5 surv_actg <- Surv(actg_c$time_event, actg_c$event)
6
7 survfit_actg <- survfit(surv_actg ~ tx, data = actg_c)
8 survfit_na_actg <- survfit(surv_actg ~ tx, data = actg_c, type = 'fleming-
9   harrington')
10
11 survfit_actg |>
12   plot(main = "Disease-Free Survival for Soc and Invidir",
13     col = 1:2, lwd = 2,
14     conf.int = FALSE,
15     xlab = 'Days',
16     ylab = 'Survival_Prob.',
17     ylim = c(0.7, 1))
18 legend('bottomleft', c('SoC', 'SoC+Invidir'), col = 1:2, lwd = 2)
19
20 survfit_actg |>
21   plot(main = 'KM vs. NA Curve',
22     col = 1:2, lwd = 2,
23     xlab = 'Days',
24     ylab = 'Survival_Prob',
25     ylim = c(0.7, 1))
26 lines(survfit_na_actg, col = 3:4)
```

```

26 legend('bottomleft', c('KMSoc', 'KMSoc+uInvidir', 'NASoc', 'NASoc+u
    Invidir'), col = c(1:4), lwd = 1)
27
28 survdiff(surv_actg ~ tx, data = actg_c)
29
30
31 #####
32
33 # Install 'scales', 'survminer' and 'patchwork' packages only if it is not
   already installed
34 lapply(c("scales", "survminer", "patchwork"), function(p) {
35   if (!requireNamespace(p, quietly = TRUE)) install.packages(p)
36 })
37 suppressWarnings(suppressPackageStartupMessages(library(scales)))
38 suppressWarnings(suppressPackageStartupMessages(library(survminer)))
39 suppressWarnings(suppressPackageStartupMessages(library(patchwork)))
40
41 # Create a copy of the ACTG dataset for EDA
42 edit_actg_EDA = edit_actg
43 edit_actg_EDA$outcome_clean <- factor(edit_actg$event, # Recode the event
   variable as a factor with descriptive labels
   levels = c("1", "0"),
   labels = c("AIDSorDeath", "Noevent"))
44 )
45
46
47 # Create CD4 strata based on clinically meaningful cutpoints
48 edit_actg_EDA <- edit_actg_EDA %>%
49   mutate(
50     cd4_strata = cut(
51       base_cd4,
52       breaks = c(-Inf, 50, 200, Inf),
53       labels = c("<=50", "51-200", ">200")
54     )
55   )
56
57
58 # Compute counts and proportions of outcomes within each CD4 stratum
59 plot_df <- edit_actg_EDA %>%
60   group_by(cd4_strata) %>%
61   count(outcome_clean) %>%
62   mutate(prop = n / sum(n)) # convert counts to within-stratum proportions
63
64 # Plot stacked proportional bar chart of outcomes by CD4 strata
65 ggplot(plot_df, aes(x = cd4_strata, y = prop, fill = outcome_clean)) +
66   geom_col(position = "fill") +      # create proportional stacked bars
67   geom_text(
68     aes(label = scales::percent(prop, accuracy = 0.1)), # add percentage labels
69     position = position_fill(vjust = 0.5),
70     size = 5
71   ) +
72   scale_y_continuous(labels = scales::percent) +      # convert y-axis to % format
73   labs(
74     title = "ProportionofEventsbyBaselineCD4Strata",
75     x = "BaselineCD4Strata",
76     y = "Proportion",
77     fill = "ClinicalOutcome"
78   ) +
79   theme_minimal() +          # clean and minimalistic theme
80   theme(plot.title = element_text(hjust = 0.5)) # center the plot title
81
82 ## Visualize the distribution of baseline CD4 across outcome groups (AIDS/Death
   vs No event)
83 ggplot(edit_actg_EDA, aes(x = outcome_clean, y = base_cd4, fill = outcome_clean
   )) +

```

```

84   geom_violin(trim = FALSE, alpha = 0.6) +      # violin plot of CD4
85     distribution by outcome
86   geom_boxplot(width = 0.15, outlier.color = "black", outlier.size = 2) + #
87     overlay boxplot
88   labs(x = "Event_Group", y = "Baseline_CD4") +
89   ggtitle("Distribution_of_Baseline_CD4_across_Event_Groups") +
90   theme_minimal() +
91   theme(legend.position = "none") +
92   theme(plot.title = element_text(hjust = 0.5))
93
94 ##### Cross-tabulation of Karnofsky score and clinical outcome
95 # Create contingency table of Karnofsky score vs clinical outcome
96 tab_karnof_outcome <- table(edit_actg_EDA$karnof, edit_actg_EDA$outcome_clean)
97
98 # Convert the contingency table to a data frame for plotting
99 df_karnof_outcome <- as.data.frame(tab_karnof_outcome)
100 colnames(df_karnof_outcome) <- c("Karnofsky", "Outcome", "Count")
101
102 # Heatmap of counts by Karnofsky score and clinical outcome
103 ggplot(df_karnof_outcome, aes(Karnofsky, Outcome, fill = Count)) +
104   geom_tile() +                                # heatmap tiles
105   geom_text(aes(label = Count), color = "white", size = 10) + # show counts
106     inside tiles
107   scale_fill_gradient(low = "steelblue", high = "darkred", guide = "none") +
108   labs(
109     y = "Clinical_Outcome",
110     x = "Karnofsky_Score") +
111   theme_minimal() +
112   theme(plot.title = element_text(hjust = 0.5)) +
113   theme(
114     plot.title = element_text(hjust = 0.5, size = 15),
115     axis.text.x = element_text(size = 18, hjust = 1),
116     axis.text.y = element_text(size = 18),
117     axis.title.x = element_text(size = 20, margin = margin(t = 6)),
118     axis.title.y = element_text(size = 20, margin = margin(r = 6)))
119
120 ## Distributions of Censoring times
121 event_times <- edit_actg_EDA %>% filter(event == 0) # Subset to censored
122   observations (event == 0)
123 # Histogram of censoring times (overall)
124 p1 <- ggplot(event_times, aes(x = time_event)) +
125   geom_histogram(aes(y = after_stat(density)),
126                 bins = 15,
127                 alpha = 0.4,
128                 position = "identity",
129                 fill = "steelblue") +
130   labs(title = "Normalized_Histogram_of\nCensored_Times",
131         x = "Event_time_(days)",
132         y = "Density") +
133   theme_bw() +
134   theme(plot.title = element_text(hjust = 0.5)); p1
135
136 # Histogram of censoring times stratified by treatment group (tx)
137 p2 <- ggplot(event_times, aes(x = time_event, fill = factor(tx))) +
138   geom_histogram(aes(y = after_stat(density)),
139                 bins = 15,
140                 alpha = 0.4,
141                 position = "identity") +
142   labs(title = "Normalized_Histogram_of_\nCensored_Times_\u2225by\u2225Treatment\u2225Group",
143         x = "Event_time_(days)",
144         y = "Density",
145         fill = "Treatment_group") +

```

```

143 theme_bw() +
144   scale_fill_manual(values = c("red", "blue"), labels = c("No IVD included", "IVD included")) +
145   theme(plot.title = element_text(hjust = 0.5))
146 p1 + p2 # combine the two histograms
147
148 ##### Survival curves
149 # Kaplan-Meier model for dichotomized CD4 level (cd4_lvl must be precomputed)
150 fit2 <- survfit(Surv(time_event, event) ~ cd4_lvl, data = edit_actg_EDA)
151
152 # Plot Kaplan-Meier survival curves for the two CD4 levels
153 ggsurv2 <- ggsurvplot(
154   fit2,
155   conf.int = TRUE,
156   censor = FALSE, # no censoring marks on the curve
157   risk.table = FALSE,
158   palette = c("#E64B35", "#4DBBD5"), # only 2 colors (one per CD4 group)
159   legend.title = "CD4_Level",
160   legend.labs = c("<=50", ">50"), # labels for dichotomized CD4 levels
161   ggtheme = theme_bw(base_size = 14),
162   xlab = "Days_of_follow-up",
163   ylab = "Survival_probability"
164 )
165
166 # Aesthetic adjustments and y-axis range restriction
167 ggsurv2$plot <- ggsurv2$plot +
168   coord_cartesian(ylim = c(0.775, 1)) +
169   theme(
170     plot.title = element_text(hjust = 0.5, size = 16),
171     legend.position = "top",
172     legend.title = element_text(size = 13),
173     legend.text = element_text(size = 11)
174   )
175 ggsurv2 # print the ggsurvplot object

```

2.3 Preliminary Cox Model and Covariate Analysis

```

1 ##### Mid Model Creation
2
3 add1(small_cox_actg, scope = ~ tx + sex + hemophil + ivdrug_bin + karnof +
4       priorzdv + age + race + base_cd4, test = "Chisq")
5
6 mid_cox_actg <- coxph(surv_actg ~ tx + ivdrug_bin + karnof + priorzdv + age +
7   base_cd4, data = actg_c)
8 summary(mid_cox_actg)
9
10 cox.zph(mid_cox_actg)
11
12 ##### Mart Res for Linearity
13
14 mres_priorzdv <- residuals(coxph(surv_actg ~ tx + ivdrug_bin + karnof + age +
15   base_cd4, data = actg_c))
16 mres_age <- residuals(coxph(surv_actg ~ tx + ivdrug_bin + karnof + priorzdv +
17   base_cd4, data = actg_c))
18 mres_basecd4 <- residuals(coxph(surv_actg ~ tx + ivdrug_bin + karnof + priorzdv +
19   + age, data = actg_c))
20
21 plot(actg_c$priorzdv, mres_priorzdv,
22   xlab = 'Months_of_Prior_ZDV',
23   ylab = 'Martingale_Residuals',
24   main = 'Martingale_Residuals_vs_ZDV_Usage')
25 lines(lowess(actg_c$priorzdv, mres_priorzdv))

```

```

21 plot(actg_c$age, mres_age,
22       xlab = 'Age',
23       ylab = 'Martingale_Residuals',
24       main = 'Martingale_Residuals_vs._Age')
25 lines(lowess(actg_c$age, mres_age))
26
27 plot(actg_c$base_cd4, mres_basecd4,
28       xlab = 'Base_cd4',
29       ylab = 'Martingale_Residuals',
30       main = 'Martingale_Residuals_vs._Base_cd4')
31 lines(lowess(actg_c$base_cd4, mres_basecd4))
32
33 ###### Prior ZDV Analysis
34
35 summary(coxph(surv_actg ~ tx + ivdrug_bin + (priorzdv * base_cd4) + age +
36                 karnof, data = actg_c))
37
38 plot(actg_c$priorzdv, actg_c$base_cd4,
39       xlim = c(0, 200),
40       xlab = 'Prior_ZDV_Usage_(Months)',
41       ylab = 'Base_CD4_(mm^3)',
42       main = 'Base_CD4_by_Prior_ZDV_Usage')
43
44 plot((actg_c$priorzdv * actg_c$base_cd4), mres_mid,
45       xlab = 'ZDV_*_Base_cd4',
46       ylab = 'Martingale_Residuals',
47       main = 'Martingale_Residuals_vs._ZDV_Usage*_Base_cd4')
48 lines(lowess((actg_c$priorzdv * actg_c$base_cd4), mres_mid))
49
50 actg_c_eventonly <- actg_c[actg_c$event == 1, ]
51 plot(actg_c_eventonly$priorzdv, actg_c_eventonly$time_event,
52       main = 'Event_Time_by_Prior_ZDV_Usage',
53       xlab = 'Prior_ZDV_Usage_(Months)',
54       ylab = 'Event_Time_(Days)')
55
56 ##### Age and Karnofsky Score Analysis
57
58 summary(coxph(surv_actg ~ tx + ivdrug_bin + priorzdv + base_cd4 + (age * karnof
59 ), data = actg_c))
60
61 mres_mid <- residuals(mid_cox_actg, type = 'martingale')
62
63 plot((actg_c$age * as.numeric(actg_c$karnof)), mres_mid,
64       xlab = 'Age_*_Karnofsky_Score',
65       ylab = 'Martingale_Residuals',
66       main = 'Martingale_Residuals_vs._Age_*_Karnofsky_Score')
67 lines(lowess((actg_c$age * as.numeric(actg_c$karnof)), mres_mid))

```

3.1 Cox Model

```

1 cox_reduced <- coxph(surv_actg ~ tx + ivdrug_bin + karnof + age + base_cd4,
2                         data = actg_c)
3 anova(cox_reduced, mid_cox_actg, test = "LRT")
4 anova(cox_reduced, mid_cox_actg, test = "Rao")
5
6 summary(cox_reduced)
7 cox_reduced_zph <- cox.zph(cox_reduced)
8 cox_reduced_zph
9
10 actg_c$cd4_strata3 <- cut(
11     actg_c$base_cd4,

```

```

11  breaks = c(-Inf, 50, 200, Inf),
12  labels = c("<=50", "51-200", ">200")
13 )
14
15 table(actg_c$cd4_strata3)
16
17 cox_strat3 <- coxph(
18   surv_actg ~ tx + ivdrug_bin + karnof + age + strata(cd4_strata3),
19   data = actg_c
20 )
21
22 summary(cox_strat3)
23
24 cox_final <- cox_reduced
25 summary(cox_final)
26
27 cox_int_cd4 <- coxph(
28   surv_actg ~ tx*base_cd4 + ivdrug_bin + karnof + age,
29   data = actg_c
30 )
31
32 summary(cox_int_cd4)
33 anova(cox_final, cox_int_cd4, test="LRT")
34
35 cox_int_karnof <- coxph(
36   surv_actg ~ tx*karnof + ivdrug_bin + karnof + age,
37   data = actg_c
38 )
39
40 summary(cox_int_karnof)
41 anova(cox_final, cox_int_karnof, test="LRT")
42
43 fit_ivdrug <- survfit(Surv(time_event, event) ~ ivdrug_bin, data = actg_c)
44
45 plot(fit_ivdrug, col = 1:2, lwd = 2, ylim = c(0.85, 1.0), xlab = "Time_(days)",
46       ylab = "Survival")
47 title("KM_Survival_Curves_for_Drug_use_history")
48 legend("bottomleft", c("Never", "Previous/Current"), col = 1:2, lwd = 2)
49 survdiff(Surv(time_event, event) ~ ivdrug_bin, data = actg_c)
50
51 par(mfrow=c(1,3))
52
53 # 1. Baseline CD4 boxplot
54 boxplot(base_cd4 ~ factor(ivdrug_bin, labels=c("Never", "Previous/Current")),
55         data=actg_c,
56         main = "Baseline_CD4_by_IV_Drug_Use",
57         xlab = "IV_Drug_Use_History",
58         ylab = "Baseline_CD4_Count",
59         col = c("lightblue", "lightgreen"))
60
61 cd4_medians <- tapply(actg_c$base_cd4,
62                         factor(actg_c$ivdrug_bin, labels=c("Never", "Previous/
63                                         Current")),
64                         median)
65
66 text(1:2, cd4_medians + 20,
67       labels = round(cd4_medians, 1),
68       col="black", cex=1)
69
70 # 2. Age boxplot
71 boxplot(age ~ factor(ivdrug_bin, labels=c("Never", "Previous/Current")),
72         data=actg_c,

```

```

72     main = "Age_by_IV_Drug_Use",
73     xlab = "IV_Drug_Use_History",
74     ylab = "Age",
75     col = c("orange", "purple"))
76
77 age_medians <- tapply(actg_c$age,
78                         factor(actg_c$ivdrug_bin, labels=c("Never", "Previous/
79                                         Current")),
80                         median)
81
82 text(1:2, age_medians + 2.5,
83       labels = round(age_medians, 1),
84       col="black", cex=1)
85
86 # 3. karnof
87 boxplot(karnof_num ~ factor(ivdrug_bin, labels=c("Never", "Previous/Current")),
88          data = actg_c,
89          main = "Karnofsky_Score_by_IV_Drug_Use",
90          xlab = "IV_Drug_Use_History",
91          ylab = "Karnofsky_Score",
92          col = c("pink", "lightgray"))
93
94 # median karnofsky scores
95 karnof_num_medians <- tapply(actg_c$karnof_num,
96                               factor(actg_c$ivdrug_bin, labels=c("Never", "Previous/
97                                         Current")),
98                               median)
99
100 text(1:2, karnof_num_medians + 1.5,
101       labels = round(karnof_num_medians, 1),
102       col="black", cex=1)
103
104 par(mfrow=c(1,1))

```

3.2 TVC Cox Model

```

1 =====
2 Part A: Time-Varying Coefficient Cox Model (TVC)
3 =====
4
5 # tt = x*log(t) (commonly used)
6
7 cox_tvc <- coxph(
8   Surv(time_event, event) ~ tx + ivdrug_bin + karnof + age + base_cd4 + tt(base
9     _cd4),
10    data = actg_c,
11    tt = function(x, t, ...) x * log(t)
12  )
13  summary(cox_tvc)
14
15 # tt = x*t
16
17 cox_tvc_1 <- coxph(
18   Surv(time_event, event) ~ tx + ivdrug_bin + karnof + age + base_cd4 + tt(base
19     _cd4),
20    data = actg_c,
21    tt = function(x, t, ...) x * t
22  )
23  summary(cox_tvc_1)
24
25 # Time-varying HR plot for base_cd4 under model cox_tvc_1

```

```

24 # HR(t) = exp( base_cd4 * (b0 + b1 * t) )
25
26
27 coefs <- coef(cox_tvc_1)
28 V <- vcov(cox_tvc_1)
29
30 b0 <- coefs["base_cd4"]
31 b1 <- coefs["tt(base_cd4)"]
32
33 var_b0 <- V["base_cd4","base_cd4"]
34 var_b1 <- V["tt(base_cd4)","tt(base_cd4)"]
35 cov_b0b1 <- V["base_cd4","tt(base_cd4)"]
36
37 times <- seq(1, max(actg_c$time_event, na.rm = TRUE), length.out = 200)
38
39 logHR_t <- b0 + b1 * times
40 se_logHR <- sqrt(var_b0 + (times^2) * var_b1 + 2 * times * cov_b0b1)
41
42 df_hr <- data.frame(
43   time = times,
44   HR = exp(logHR_t),
45   HR_lo = exp(logHR_t - 1.96 * se_logHR),
46   HR_hi = exp(logHR_t + 1.96 * se_logHR)
47 )
48
49 library(ggplot2)
50 ggplot(df_hr, aes(x = time, y = HR)) +
51   geom_line(size = 1) +
52   geom_ribbon(aes(ymin = HR_lo, ymax = HR_hi), alpha = 0.2) +
53   geom_hline(yintercept = 1, linetype = "dashed") +
54   labs(x = "Time_(days)", y = "HR_per_1_unit_base_cd4_increment",
55        title = "Time-varying Hazard Ratio for base_cd4 under TVC model")+
56   theme_minimal()
57
58
59 # Interpretation of the TVC plot:
60 # If HR(t) > 1 and increases : higher CD4 increases risk and the harmful effect
61 # becomes stronger over time.
62 # If HR(t) < 1 and decreases : higher CD4 decreases risk and the protective
63 # effect becomes stronger over time.
64 # If HR(t) crosses 1 : CD4 is protective at early times but becomes harmful
65 # later (or the opposite).
66
67 # Our result:
68 # HR(t) < 1 : higher baseline CD4 is consistently associated with lower risk (
69 # protective effect).
70 # HR(t) increases over time : the protective effect weakens over time, but CD4
71 # remains protective throughout follow-up.

```

3.3 AFT Models

```

1 =====
2 Part B: AFT (accelerated Failure Time) Models
3 =====
4
5 # load
6 library(survival)
7
8 # 1. Fit AFT models (Weibull / log-normal / log-logistic / Gumbel)
9
10 aft_weib <- survreg(Surv(time_event, event) ~ tx + ivdrug_bin + karnof + age +

```

```

11             dist = "weibull", data = actg_c)
12
13 aft_lognorm <- survreg(Surv(time_event, event) ~ tx + ivdrug_bin + karnof + age
14   + base_cd4,
15   dist = "lognormal", data = actg_c)
16
17 aft_loglog <- survreg(Surv(time_event, event) ~ tx + ivdrug_bin + karnof + age
18   + base_cd4,
19   dist = "loglogistic", data = actg_c)
20
21 aft_gumbel <- survreg(Surv(time_event, event) ~ tx + ivdrug_bin + karnof + age
22   + base_cd4,
23   dist = "extreme", data = actg_c)
24
25 # 2. Model comparison using AIC
26
27 AIC(aft_gumbel, aft_weib, aft_lognorm, aft_loglog)
28
29 summary(aft_loglog)

```

3.4 Influential Observation Diagnostics

```

1 mres <- residuals(cox_final, type = "martingale")
2 plot(actg_c$base_cd4, mres,
3   xlab = "Baseline_CD4_Count",
4   ylab = "Martingale_Residuals",
5   pch = 20, col = "black",
6   main = "Martingale_Residuals_vs_CD4")
7
8 lines(lowess(actg_c$base_cd4, mres), col = "blue", lwd = 2)
9
10 mart_res <- residuals(cox_final, type = "martingale")
11 dev_res <- residuals(cox_final, type = "deviance")
12 dfb_res <- residuals(cox_final, type = "dfbeta")
13 lp      <- predict(cox_final) # linear predictor
14
15 # 2. Martingale residuals vs Linear Predictor
16 plot(lp, mart_res, xlab = "Linear_Predictor", ylab = "Martingale_Residual",
17   ylim = c(-4,2), pch = 19, cex = 0.2)
18 title("Martingale_Residuals_vs.Linear_Predictor")
19 text(lp, mart_res+0.2, labels = rownames(actg_c))
20
21 # 3. deviance residuals vs. the linear predictor
22 plot(lp, dev_res, xlab = "Linear_Predictor", ylab = "Deviance_Residuals",
23   ylim = c(-2.5,3.5), pch = 19, cex = 0.2)
24 title("Deviance_Residuals_vs.Linear_Predictor")
25 text(lp, dev_res + 0.2, labels = rownames(actg_c))
26
27 # 4. two dfbeta values by observation order
28 coef_names <- names(coef(cox_final))
29 colnames(dfb_res) <- coef_names
30
31 for (i in 1:ncol(dfb_res)) {
32   plot(dfb_res[,i], xlab = "Observation_Order", ylab = paste0("dfbeta_for",
33     coef_names[i]), pch = 19, cex = 0.2)
34   title(paste0("dfbeta_Values_by_Observation_Order_for", coef_names[i]))
35   text(dfb_res[,i], labels = rownames(actg_c))
36 }
37
38 dfb_res[c(610, 633, 638, 671, 680, 996), ]
39 dev_res[c(610, 633, 638, 671, 680, 996)]

```

40 | `actg_c[c(610, 633, 638, 671, 680, 996),]`