Appendix Project Codes

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2025-05-09

```r
# ------------------------
# Helper Functions
# ------------------------

### Smooth ES Curve for Martingale residuals
smoothSEcurve <- function(yy, xx) {
  xx.list <- min(xx) + ((0:100)/100)*(max(xx) - min(xx))
  yy.xx <- predict(loess(yy ~ xx), se=T, newdata=data.frame(xx=xx.list))
  quantile.t = qt(0.975, yy.xx$df)
  lines(yy.xx$fit ~ xx.list, lwd=2)
  lines(yy.xx$fit - quantile.t*yy.xx$se.fit ~ xx.list, lty=2)
  lines(yy.xx$fit + quantile.t*yy.xx$se.fit ~ xx.list, lty=2)
}


# ---- Extractor Functions ----
extract_metrics_cox <- function(model) {
  ll <- logLik(model)
  data.frame(
    Log_Likelihood = as.numeric(ll),
    Degrees_of_Freedom = attr(ll, "df"),
    AIC = AIC(model),
    Concordance = summary(model)$concordance[1]
  )
}


extract_metrics_aft <- function(model) {
  ll <- logLik(model)
  data.frame(
    Log_Likelihood = as.numeric(ll),
    Degrees_of_Freedom = attr(ll, "df"),
    AIC = AIC(model),
    Concordance = NA
  )
}

# Compute vertical lines for mean and median survival
get_stats <- function(fit, label) {
  tbl <- summary(fit)$table
  if (is.matrix(tbl)) {
    # Multi-group (e.g., ~ drug)
    data.frame(
      group = rownames(tbl),
      rmean = tbl[, "rmean"],
      median = tbl[, "median"]
    )
  } else {
    # Single group (e.g., ~1)
    data.frame(
      group = label,
      rmean = tbl["rmean"],
      median = tbl["median"]
    )
```

```
  }
}

# ------------------------
# Data Preprocessing
# ------------------------
attach(aids.id)
attach(aids)
myseed = set.seed(1995)
myid = sample(aids.id$patient, 400)
myaids.id = subset(aids.id, patient %in% myid)
myaids = subset(aids, patient %in% myid)
glimpse(myaids.id)
```

```
## Rows: 400
## Columns: 12
## $ patient <fct> 1, 2, 3, 4, 6, 8, 10, 11, 12, 14, 15, 16, 17, 18, 19, 23, 24, ~
## $ Time    <dbl> 16.97, 19.00, 18.53, 12.70, 1.90, 9.57, 16.43, 2.40, 18.10, 2.~
## $ death   <int> 0, 0, 1, 0, 1, 1, 0, 1, 0, 1, 0, 1, 0, 0, 1, 1, 0, 1, 0, 0, 0,~
## $ CD4     <dbl> 10.677078, 6.324555, 3.464102, 3.872983, 4.582576, 3.464102, 1~
## $ obstime <int> 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,~
## $ drug    <fct> ddC, ddI, ddI, ddC, ddC, ddI, ddI, ddC, ddI, ddI, ddI, ddC, dd~
## $ gender  <fct> male, male, female, male, female, female, male, male, male, ma~
## $ prevOI  <fct> AIDS, noAIDS, AIDS, AIDS, AIDS, noAIDS, AIDS, AIDS, noAIDS, no~
## $ AZT     <fct> intolerance, intolerance, intolerance, failure, failure, intol~
## $ start   <int> 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,~
## $ stop    <dbl> 6.00, 6.00, 2.00, 2.00, 1.90, 2.00, 2.00, 2.40, 2.00, 2.00, 2.~
## $ event   <dbl> 0, 0, 0, 0, 1, 0, 0, 1, 0, 0, 0, 0, 0, 0, 1, 1, 0, 1, 0, 0, 0,~
```

```
glimpse(myaids)
```

```
## Rows: 1,211
## Columns: 12
## $ patient <fct> 1, 1, 1, 2, 2, 2, 2, 3, 3, 3, 4, 4, 4, 4, 6, 8, 8, 8, 10, 10, ~
## $ Time    <dbl> 16.97, 16.97, 16.97, 19.00, 19.00, 19.00, 19.00, 18.53, 18.53,~
## $ death   <int> 0, 0, 0, 0, 0, 0, 0, 1, 1, 1, 0, 0, 0, 0, 1, 1, 1, 1, 0, 0, 0,~
## $ CD4     <dbl> 10.677078, 8.426150, 9.433981, 6.324555, 8.124038, 4.582576, 5~
## $ obstime <int> 0, 6, 12, 0, 6, 12, 18, 0, 2, 6, 0, 2, 6, 12, 0, 0, 2, 6, 0, 2~
## $ drug    <fct> ddC, ddC, ddC, ddI, ddI, ddI, ddI, ddI, ddI, ddI, ddC, ddC, dd~
## $ gender  <fct> male, male, male, male, male, male, male, female, female, fema~
## $ prevOI  <fct> AIDS, AIDS, AIDS, noAIDS, noAIDS, noAIDS, noAIDS, AIDS, AIDS, ~
## $ AZT     <fct> intolerance, intolerance, intolerance, intolerance, intoleranc~
## $ start   <int> 0, 6, 12, 0, 6, 12, 18, 0, 2, 6, 0, 2, 6, 12, 0, 0, 2, 6, 0, 2~
## $ stop    <dbl> 6.00, 12.00, 16.97, 6.00, 12.00, 18.00, 19.00, 2.00, 6.00, 18.~
## $ event   <dbl> 0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0, 1, 0, 0, 0,~
```

```
# ------------------------
# Kaplan-Meier Model
# ------------------------

# No assumption null model
km_fit <- survfit(Surv(Time, death) ~ 1, data = myaids.id, conf.type = "log-log")
summary(km_fit)$table
```

```
##      records      n.max      n.start      events      rmean    se(rmean)
```

Table 1. Baseline Characteristics by Treatment Group (ddC vs ddI)

Variable	Subcategory	ddC	ddI
Time (mean ± SD)		12.9 ± 5	12.5 ± 5
CD4 (mean ± SD)		6.9 ± 4.6	7.2 ± 4.7
Deaths (%)		73 (36.7%)	89 (44.3%)
Gender	female	20	17
	male	179	184
Previous Infection	noAIDS	66	71
	AIDS	133	130
AZT	intolerance	121	131
	failure	78	70

```
## 400.0000000 400.0000000 400.0000000 162.0000000   15.7664366    0.3558219
##        median       0.95LCL      0.95UCL
##            NA   17.2700000           NA
```

```r
# Model stratified with treatment group
km_fit_drug <- survfit(Surv(Time, death) ~ drug, data = myaids.id, conf.type = "log-log")
summary(km_fit_drug)$table
```

```
##            records n.max n.start events    rmean se(rmean) median 0.95LCL 0.95UCL
## drug=ddC       199   199     199     73 16.14124 0.5056964     NA   17.27      NA
## drug=ddI       201   201     201     89 15.38718 0.4991256  18.53   14.13      NA
```

```r
# Extract survival data
df_all <- surv_summary(km_fit, data = myaids.id) %>%
  mutate(group = "Overall")

df_drug <- surv_summary(km_fit_drug, data = myaids.id) %>%
  mutate(group = strata) %>%
  mutate(group = gsub("drug=", "", group))

# Combine
km_data <- bind_rows(df_all, df_drug)

vlines <- bind_rows(
  get_stats(km_fit, "Overall"),
  get_stats(km_fit_drug, "ddC"),
  get_stats(km_fit_drug, "ddI")
) %>% pivot_longer(cols = c(rmean, median), names_to = "type", values_to = "time") %>%
  mutate(linetype = ifelse(type == "median", "solid", "dashed"))

# Color map
color_map <- c("ddC" = "#E69F00", "ddI" = "#008080", "Overall" = "black")

# Plot
ggplot(km_data, aes(x = time, y = surv, color = group)) +
  geom_step(linewidth = 0.6) +
  geom_ribbon(aes(ymin = lower, ymax = upper, fill = group),
              alpha = 0.2, color = NA) +
  geom_point(data = filter(km_data, n.censor > 0),
             aes(x = time, y = surv), shape = 3, size = 0.7) +
```

```r
  geom_vline(data = vlines, aes(xintercept = time, color = group,
                                linetype = linetype), linewidth = 0.6) +
  scale_color_manual(values = color_map) +
  scale_fill_manual(values = color_map) +
  scale_y_continuous(limits = c(0, 1), expand = c(0.01, 0)) +
  coord_cartesian(ylim = c(0, 1)) +
  scale_linetype_manual(values = c("solid" = "solid", "dashed" = "dashed"),
                        labels = c("solid" = "Median", "dashed" = "Mean")) +
  labs(x = "Time (months)", y = "Survival probability", color = "Group",
       linetype = "Line Type") +
  theme_classic(base_size = 7)
```
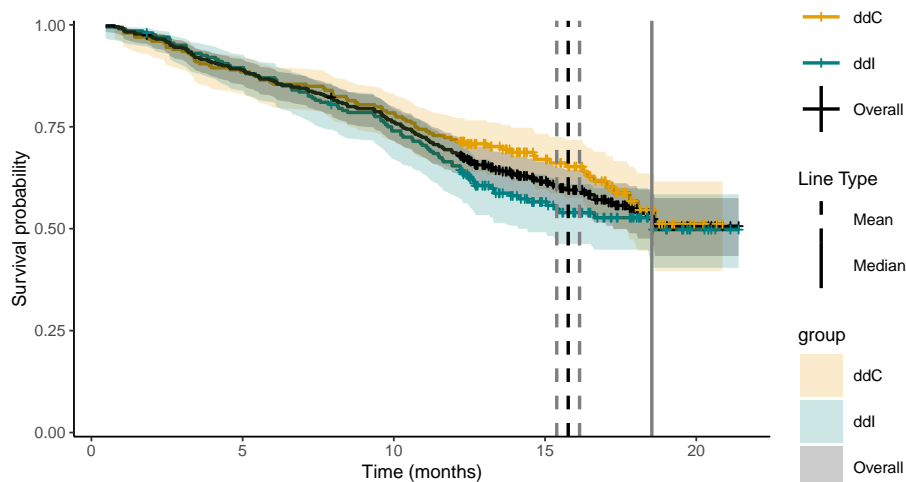

Figure 1: Kaplan–Meier survival curves with 95% confidence intervals for overall and drug-specific survival (ddC vs ddI). Dashed lines: mean survival; solid lines: median survival. Overall is shown in black. NA values were found for Median and Upper CI

```r
# ----------------------------
# Time independent Cox model
# ----------------------------

## Model Selection

### Null Model
cox_ti_null <- coxph(Surv(Time, death) ~ 1, data = myaids.id)
summary(cox_ti_null)

## Call:  coxph(formula = Surv(Time, death) ~ 1, data = myaids.id)
##
## Null model
##   log likelihood= -911.3012
##   n= 400

paste0("AIC of Null Model: ", AIC(cox_ti_null))

## [1] "AIC of Null Model: 1822.60235408444"

### Full model with Univariates
cox_full_ti_uni <- coxph(Surv(Time, death) ~ CD4 + drug + gender + prevOI + AZT,
                         data = myaids.id)
summary(cox_full_ti_uni)
```

4

```
## Call:
## coxph(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
##     AZT, data = myaids.id)
##
##   n= 400, number of events= 162
##
##                 coef exp(coef) se(coef)      z Pr(>|z|)
## CD4         -0.13200   0.87634  0.02538 -5.201 1.98e-07 ***
## drugddI      0.27572   1.31748  0.15886  1.736  0.08264 .
## gendermale  -0.45685   0.63328  0.25335 -1.803  0.07136 .
## prevOIAIDS   0.79223   2.20831  0.25483  3.109  0.00188 **
## AZTfailure   0.23853   1.26939  0.17513  1.362  0.17318
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##            exp(coef) exp(-coef) lower .95 upper .95
## CD4           0.8763     1.1411    0.8338     0.921
## drugddI       1.3175     0.7590    0.9650     1.799
## gendermale    0.6333     1.5791    0.3854     1.041
## prevOIAIDS    2.2083     0.4528    1.3401     3.639
## AZTfailure    1.2694     0.7878    0.9006     1.789
##
## Concordance= 0.716  (se = 0.02 )
## Likelihood ratio test= 93.46  on 5 df,   p=<2e-16
## Wald test            = 71.18  on 5 df,   p=6e-14
## Score (logrank) test = 81.36  on 5 df,   p=4e-16
```

```r
paste0("AIC of Main Effects (Univariate) Model: ", AIC(cox_full_ti_uni))
```

```
## [1] "AIC of Main Effects (Univariate) Model: 1739.14143463543"
```

Functional form of CD4 using Martingale model

Raw CD4 martingale

```r
mart_full_ti <- resid(cox_full_ti_uni, type = "martingale")
```

Log-transformed CD4

```r
myaids_log <- myaids.id %>%
  mutate(CD4_log = log(CD4 + 1))  # add small constant to avoid log(0)
cox_ti_log <- coxph(Surv(Time, death) ~ CD4_log + drug + gender + prevOI + AZT,
                data = myaids_log)
summary(cox_ti_log)
```

```
## Call:
## coxph(formula = Surv(Time, death) ~ CD4_log + drug + gender +
##     prevOI + AZT, data = myaids_log)
##
##   n= 400, number of events= 162
##
##                 coef exp(coef) se(coef)      z Pr(>|z|)
## CD4_log      -0.7859    0.4557   0.1364 -5.763 8.25e-09 ***
## drugddI       0.2788    1.3216   0.1588  1.756 0.079056 .
## gendermale   -0.4548    0.6346   0.2533 -1.796 0.072556 .
## prevOIAIDS    0.8929    2.4423   0.2521  3.542 0.000397 ***
```

```
## AZTfailure   0.2013      1.2230     0.1756   1.146 0.251734
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##            exp(coef) exp(-coef) lower .95 upper .95
## CD4_log       0.4557     2.1944    0.3488    0.5953
## drugddI       1.3216     0.7567    0.9682    1.8040
## gendermale    0.6346     1.5759    0.3862    1.0425
## prevOIAIDS    2.4423     0.4094    1.4901    4.0031
## AZTfailure    1.2230     0.8177    0.8668    1.7255
##
## Concordance= 0.716  (se = 0.02 )
## Likelihood ratio test= 92.89  on 5 df,   p=<2e-16
## Wald test            = 82.4  on 5 df,   p=3e-16
## Score (logrank) test = 90.53  on 5 df,   p=<2e-16
```

```r
#### Log CD4 martingale
mart_ti_log <- resid(cox_ti_log, type = "martingale")

aic_ti_linear <- round(AIC(cox_full_ti_uni),2)
aic_ti_log <- round(AIC(cox_ti_log),2)

### Full model with Univariates - Step
cox_full_ti_uni_step <- step(cox_full_ti_uni,
                        scope = list(upper = ~ CD4 + drug + gender + prevOI + AZT),
                        trace = 0)
summary(cox_full_ti_uni_step)
```

```
## Call:
## coxph(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI,
##     data = myaids.id)
##
##   n= 400, number of events= 162
##
##                 coef exp(coef) se(coef)      z Pr(>|z|)
## CD4         -0.13354   0.87499  0.02552 -5.232 1.68e-07 ***
## drugddI      0.25589   1.29161  0.15813  1.618    0.106
## gendermale  -0.41173   0.66250  0.25089 -1.641    0.101
## prevOIAIDS   0.91954   2.50813  0.23539  3.906 9.37e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##            exp(coef) exp(-coef) lower .95 upper .95
## CD4           0.8750     1.1429    0.8323    0.9199
## drugddI       1.2916     0.7742    0.9474    1.7609
## gendermale    0.6625     1.5094    0.4052    1.0833
## prevOIAIDS    2.5081     0.3987    1.5812    3.9784
##
## Concordance= 0.712  (se = 0.02 )
## Likelihood ratio test= 91.58  on 4 df,   p=<2e-16
## Wald test            = 68.73  on 4 df,   p=4e-14
## Score (logrank) test = 78.8  on 4 df,   p=3e-16
```

```
paste0("AIC of Main Effects (Univariate) Model with Stepwise Selection: ",
       AIC(cox_full_ti_uni_step))
```

[1] "AIC of Main Effects (Univariate) Model with Stepwise Selection: 1739.02126418427"

```
### Full model with Interactions
cox_full_ti_int <- coxph(Surv(Time, death) ~ (CD4 + drug + gender + prevOI + AZT)^5,
                         data = myaids.id)
summary(cox_full_ti_int)
```

```
## Call:
## coxph(formula = Surv(Time, death) ~ (CD4 + drug + gender + prevOI +
##     AZT)^5, data = myaids.id)
##
##   n= 400, number of events= 162
##
##                                                 coef   exp(coef)
## CD4                                          2.086e+01   1.143e+09
## drugddI                                      3.594e+02   1.245e+156
## gendermale                                   3.579e+02   2.807e+155
## prevOIAIDS                                   3.604e+02   3.296e+156
## AZTfailure                                  -1.653e+01   6.612e-08
## CD4:drugddI                                 -2.094e+01   8.068e-10
## CD4:gendermale                              -2.099e+01   7.667e-10
## CD4:prevOIAIDS                              -2.110e+01   6.879e-10
## CD4:AZTfailure                               6.822e-01   1.978e+00
## drugddI:gendermale                          -3.584e+02   2.205e-156
## drugddI:prevOIAIDS                          -3.583e+02   2.538e-156
## drugddI:AZTfailure                          -1.443e+00   2.363e-01
## gendermale:prevOIAIDS                       -3.589e+02   1.291e-156
## gendermale:AZTfailure                        2.883e+00   1.788e+01
## prevOIAIDS:AZTfailure                        1.423e+01   1.515e+06
## CD4:drugddI:gendermale                       2.097e+01   1.277e+09
## CD4:drugddI:prevOIAIDS                       2.038e+01   7.126e+08
## CD4:drugddI:AZTfailure                       1.177e+00   3.245e+00
## CD4:gendermale:prevOIAIDS                    2.112e+01   1.494e+09
## CD4:gendermale:AZTfailure                   -7.747e-01   4.608e-01
## CD4:prevOIAIDS:AZTfailure                    0.000e+00   1.000e+00
## drugddI:gendermale:prevOIAIDS                3.576e+02   1.951e+155
## drugddI:gendermale:AZTfailure                1.263e+00   3.535e+00
## drugddI:prevOIAIDS:AZTfailure                0.000e+00   1.000e+00
## gendermale:prevOIAIDS:AZTfailure             0.000e+00   1.000e+00
## CD4:drugddI:gendermale:prevOIAIDS           -2.045e+01   1.313e-09
## CD4:drugddI:gendermale:AZTfailure           -1.142e+00   3.193e-01
## CD4:drugddI:prevOIAIDS:AZTfailure            0.000e+00   1.000e+00
## CD4:gendermale:prevOIAIDS:AZTfailure         0.000e+00   1.000e+00
## drugddI:gendermale:prevOIAIDS:AZTfailure     0.000e+00   1.000e+00
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure 0.000e+00   1.000e+00
##                                               se(coef)         z Pr(>|z|)
## CD4                                          2.297e-02   908.113  < 2e-16 ***
## drugddI                                      1.581e-01  2272.696  < 2e-16 ***
## gendermale                                   2.566e-01  1394.932  < 2e-16 ***
## prevOIAIDS                                   2.220e-01  1623.074  < 2e-16 ***
```

```
## AZTfailure                                   1.578e-01   -104.749   < 2e-16 ***
## CD4:drugddI                                  2.153e-02   -972.676   < 2e-16 ***
## CD4:gendermale                               2.300e-02   -912.616   < 2e-16 ***
## CD4:prevOIAIDS                               2.711e-02   -778.345   < 2e-16 ***
## CD4:AZTfailure                               2.844e-02     23.991   < 2e-16 ***
## drugddI:gendermale                           1.576e-01  -2274.047   < 2e-16 ***
## drugddI:prevOIAIDS                           1.588e-01  -2255.657   < 2e-16 ***
## drugddI:AZTfailure                           1.818e-01     -7.938  2.06e-15 ***
## gendermale:prevOIAIDS                        1.868e-01  -1921.104   < 2e-16 ***
## gendermale:AZTfailure                        1.579e-01     18.265   < 2e-16 ***
## prevOIAIDS:AZTfailure                        1.578e-01     90.171   < 2e-16 ***
## CD4:drugddI:gendermale                       2.222e-02    943.536   < 2e-16 ***
## CD4:drugddI:prevOIAIDS                       2.908e-02    700.859   < 2e-16 ***
## CD4:drugddI:AZTfailure                       3.588e-02     32.813   < 2e-16 ***
## CD4:gendermale:prevOIAIDS                    2.645e-02    798.737   < 2e-16 ***
## CD4:gendermale:AZTfailure                    2.910e-02    -26.617   < 2e-16 ***
## CD4:prevOIAIDS:AZTfailure                    2.844e-02      0.000         1
## drugddI:gendermale:prevOIAIDS                1.606e-01   2226.981   < 2e-16 ***
## drugddI:gendermale:AZTfailure                1.856e-01      6.802  1.03e-11 ***
## drugddI:prevOIAIDS:AZTfailure                1.818e-01      0.000         1
## gendermale:prevOIAIDS:AZTfailure             1.579e-01      0.000         1
## CD4:drugddI:gendermale:prevOIAIDS            2.924e-02   -699.517   < 2e-16 ***
## CD4:drugddI:gendermale:AZTfailure            3.641e-02    -31.356   < 2e-16 ***
## CD4:drugddI:prevOIAIDS:AZTfailure            3.588e-02      0.000         1
## CD4:gendermale:prevOIAIDS:AZTfailure         2.910e-02      0.000         1
## drugddI:gendermale:prevOIAIDS:AZTfailure     1.856e-01      0.000         1
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure 3.641e-02      0.000         1
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                                              exp(coef) exp(-coef)  lower .95
## CD4                                          1.143e+09   8.748e-10  1.093e+09
## drugddI                                      1.245e+156 8.030e-157 9.134e+155
## gendermale                                   2.807e+155 3.563e-156 1.698e+155
## prevOIAIDS                                   3.296e+156 3.034e-157 2.133e+156
## AZTfailure                                   6.612e-08   1.512e+07  4.853e-08
## CD4:drugddI                                  8.068e-10   1.240e+09  7.734e-10
## CD4:gendermale                               7.667e-10   1.304e+09  7.329e-10
## CD4:prevOIAIDS                               6.879e-10   1.454e+09  6.523e-10
## CD4:AZTfailure                               1.978e+00   5.055e-01  1.871e+00
## drugddI:gendermale                           2.205e-156 4.534e+155 1.619e-156
## drugddI:prevOIAIDS                           2.538e-156 3.941e+155 1.859e-156
## drugddI:AZTfailure                           2.363e-01   4.233e+00  1.654e-01
## gendermale:prevOIAIDS                        1.291e-156 7.743e+155 8.955e-157
## gendermale:AZTfailure                        1.788e+01   5.594e-02  1.312e+01
## prevOIAIDS:AZTfailure                        1.515e+06   6.600e-07  1.112e+06
## CD4:drugddI:gendermale                       1.277e+09   7.830e-10  1.223e+09
## CD4:drugddI:prevOIAIDS                       7.126e+08   1.403e-09  6.731e+08
## CD4:drugddI:AZTfailure                       3.245e+00   3.081e-01  3.025e+00
## CD4:gendermale:prevOIAIDS                    1.494e+09   6.695e-10  1.418e+09
## CD4:gendermale:AZTfailure                    4.608e-01   2.170e+00  4.353e-01
## CD4:prevOIAIDS:AZTfailure                    1.000e+00   1.000e+00  9.458e-01
## drugddI:gendermale:prevOIAIDS                1.951e+155 5.125e-156 1.424e+155
```

```
## drugddI:gendermale:AZTfailure                     3.535e+00  2.829e-01  2.457e+00
## drugddI:prevOIAIDS:AZTfailure                      1.000e+00  1.000e+00  7.003e-01
## gendermale:prevOIAIDS:AZTfailure                   1.000e+00  1.000e+00  7.339e-01
## CD4:drugddI:gendermale:prevOIAIDS                  1.313e-09  7.614e+08  1.240e-09
## CD4:drugddI:gendermale:AZTfailure                  3.193e-01  3.132e+00  2.973e-01
## CD4:drugddI:prevOIAIDS:AZTfailure                  1.000e+00  1.000e+00  9.321e-01
## CD4:gendermale:prevOIAIDS:AZTfailure               1.000e+00  1.000e+00  9.446e-01
## drugddI:gendermale:prevOIAIDS:AZTfailure           1.000e+00  1.000e+00  6.950e-01
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure       1.000e+00  1.000e+00  9.311e-01
##                                                    upper .95
## CD4                                                1.196e+09
## drugddI                                            1.698e+156
## gendermale                                         4.642e+155
## prevOIAIDS                                         5.094e+156
## AZTfailure                                         9.009e-08
## CD4:drugddI                                        8.415e-10
## CD4:gendermale                                     8.021e-10
## CD4:prevOIAIDS                                     7.255e-10
## CD4:AZTfailure                                     2.092e+00
## drugddI:gendermale                                 3.004e-156
## drugddI:prevOIAIDS                                 3.464e-156
## drugddI:AZTfailure                                 3.374e-01
## gendermale:prevOIAIDS                              1.863e-156
## gendermale:AZTfailure                              2.436e+01
## prevOIAIDS:AZTfailure                              2.064e+06
## CD4:drugddI:gendermale                             1.334e+09
## CD4:drugddI:prevOIAIDS                             7.544e+08
## CD4:drugddI:AZTfailure                             3.482e+00
## CD4:gendermale:prevOIAIDS                          1.573e+09
## CD4:gendermale:AZTfailure                          4.879e-01
## CD4:prevOIAIDS:AZTfailure                          1.057e+00
## drugddI:gendermale:prevOIAIDS                      2.673e+155
## drugddI:gendermale:AZTfailure                      5.086e+00
## drugddI:prevOIAIDS:AZTfailure                      1.428e+00
## gendermale:prevOIAIDS:AZTfailure                   1.363e+00
## CD4:drugddI:gendermale:prevOIAIDS                  1.391e-09
## CD4:drugddI:gendermale:AZTfailure                  3.429e-01
## CD4:drugddI:prevOIAIDS:AZTfailure                  1.073e+00
## CD4:gendermale:prevOIAIDS:AZTfailure               1.059e+00
## drugddI:gendermale:prevOIAIDS:AZTfailure           1.439e+00
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure       1.074e+00
##
## Concordance= 0.736  (se = 0.019 )
## Likelihood ratio test= 132.4  on 31 df,   p=2e-14
## Wald test            = 34395827  on 31 df,   p=<2e-16
## Score (logrank) test = 309.4  on 31 df,   p=<2e-16
```

```r
paste0("AIC of Interactions Model: ", AIC(cox_full_ti_int))
```

```
## [1] "AIC of Interactions Model: 1752.21545241238"
```

```r
### Full model with Interactions - Step
cox_full_ti_int_step <- step(cox_full_ti_int,
                  scope = list(upper = ~ (CD4 + drug + gender + prevOI + AZT)^5),
```

```
                            trace = 0)
summary(cox_full_ti_int_step)

## Call:
## coxph(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
##      AZT + CD4:drug + CD4:gender + CD4:prevOI + CD4:AZT + drug:gender +
##      drug:prevOI + drug:AZT + gender:prevOI + gender:AZT + CD4:drug:gender +
##      CD4:drug:AZT + CD4:gender:prevOI + CD4:gender:AZT + drug:gender:prevOI +
##      drug:gender:AZT + CD4:drug:gender:AZT, data = myaids.id)
##
##   n= 400, number of events= 162
##
##                                     coef  exp(coef)  se(coef)       z
## CD4                             5.679e-01  1.765e+00  3.500e-01   1.622
## drugddI                         1.061e+01  4.052e+04  5.695e+00   1.863
## gendermale                      8.893e+00  7.282e+03  5.941e+00   1.497
## prevOIAIDS                      1.155e+01  1.037e+05  5.547e+00   2.082
## AZTfailure                     -2.178e+00  1.133e-01  1.531e+00  -1.422
## CD4:drugddI                    -6.384e-01  5.281e-01  3.341e-01  -1.911
## CD4:gendermale                 -6.641e-01  5.147e-01  3.585e-01  -1.852
## CD4:prevOIAIDS                 -7.793e-01  4.587e-01  3.044e-01  -2.560
## CD4:AZTfailure                  6.538e-01  1.923e+00  2.874e-01   2.275
## drugddI:gendermale             -9.225e+00  9.853e-05  5.751e+00  -1.604
## drugddI:prevOIAIDS             -9.217e+00  9.931e-05  4.902e+00  -1.880
## drugddI:AZTfailure             -1.686e+00  1.853e-01  2.189e+00  -0.770
## gendermale:prevOIAIDS          -9.700e+00  6.130e-05  5.590e+00  -1.735
## gendermale:AZTfailure           2.663e+00  1.433e+01  1.605e+00   1.659
## CD4:drugddI:gendermale          6.263e-01  1.871e+00  3.432e-01   1.825
## CD4:drugddI:AZTfailure          1.262e+00  3.534e+00  5.222e-01   2.417
## CD4:gendermale:prevOIAIDS       7.562e-01  2.130e+00  3.133e-01   2.414
## CD4:gendermale:AZTfailure      -7.297e-01  4.821e-01  3.013e-01  -2.422
## drugddI:gendermale:prevOIAIDS   8.012e+00  3.016e+03  4.943e+00   1.621
## drugddI:gendermale:AZTfailure   1.648e+00  5.199e+00  2.279e+00   0.723
## CD4:drugddI:gendermale:AZTfailure -1.253e+00  2.856e-01  5.354e-01  -2.341
##                                 Pr(>|z|)
## CD4                              0.1047
## drugddI                          0.0625 .
## gendermale                       0.1344
## prevOIAIDS                       0.0373 *
## AZTfailure                       0.1549
## CD4:drugddI                      0.0560 .
## CD4:gendermale                   0.0640 .
## CD4:prevOIAIDS                   0.0105 *
## CD4:AZTfailure                   0.0229 *
## drugddI:gendermale               0.1087
## drugddI:prevOIAIDS               0.0601 .
## drugddI:AZTfailure               0.4413
## gendermale:prevOIAIDS            0.0827 .
## gendermale:AZTfailure            0.0972 .
## CD4:drugddI:gendermale           0.0680 .
## CD4:drugddI:AZTfailure           0.0156 *
## CD4:gendermale:prevOIAIDS        0.0158 *
## CD4:gendermale:AZTfailure        0.0155 *
```

```
## drugddI:gendermale:prevOIAIDS        0.1051
## drugddI:gendermale:AZTfailure        0.4696
## CD4:drugddI:gendermale:AZTfailure    0.0193 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                                  exp(coef) exp(-coef) lower .95 upper .95
## CD4                              1.765e+00  5.667e-01 8.886e-01 3.504e+00
## drugddI                          4.052e+04  2.468e-05 5.759e-01 2.851e+09
## gendermale                       7.282e+03  1.373e-04 6.392e-02 8.295e+08
## prevOIAIDS                       1.037e+05  9.640e-06 1.969e+00 5.466e+09
## AZTfailure                       1.133e-01  8.829e+00 5.632e-03 2.278e+00
## CD4:drugddI                      5.281e-01  1.894e+00 2.744e-01 1.017e+00
## CD4:gendermale                   5.147e-01  1.943e+00 2.549e-01 1.039e+00
## CD4:prevOIAIDS                   4.587e-01  2.180e+00 2.526e-01 8.331e-01
## CD4:AZTfailure                   1.923e+00  5.200e-01 1.095e+00 3.377e+00
## drugddI:gendermale               9.853e-05  1.015e+04 1.255e-09 7.735e+00
## drugddI:prevOIAIDS               9.931e-05  1.007e+04 6.672e-09 1.478e+00
## drugddI:AZTfailure               1.853e-01  5.396e+00 2.537e-03 1.354e+01
## gendermale:prevOIAIDS            6.130e-05  1.631e+04 1.070e-09 3.513e+00
## gendermale:AZTfailure            1.433e+01  6.976e-02 6.165e-01 3.333e+02
## CD4:drugddI:gendermale           1.871e+00  5.346e-01 9.547e-01 3.665e+00
## CD4:drugddI:AZTfailure           3.534e+00  2.829e-01 1.270e+00 9.836e+00
## CD4:gendermale:prevOIAIDS        2.130e+00  4.695e-01 1.153e+00 3.936e+00
## CD4:gendermale:AZTfailure        4.821e-01  2.074e+00 2.671e-01 8.701e-01
## drugddI:gendermale:prevOIAIDS    3.016e+03  3.316e-04 1.870e-01 4.863e+07
## drugddI:gendermale:AZTfailure    5.199e+00  1.923e-01 5.965e-02 4.531e+02
## CD4:drugddI:gendermale:AZTfailure 2.856e-01 3.502e+00 1.000e-01 8.156e-01
##
## Concordance= 0.737  (se = 0.019 )
## Likelihood ratio test= 129.7  on 21 df,   p=<2e-16
## Wald test            = 114.8  on 21 df,   p=6e-15
## Score (logrank) test = 301.6  on 21 df,   p=<2e-16
```

```r
paste0("AIC of Interactions Model with Stepwise Selection: ", AIC(cox_full_ti_int_step))
```

```
## [1] "AIC of Interactions Model with Stepwise Selection: 1734.89585749095"
```

Final Time Independent Cox Model

```r
cox_ti_final <- coxph(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
    AZT + CD4:drug + CD4:gender + CD4:prevOI + CD4:AZT + drug:gender +
    drug:prevOI + drug:AZT + gender:prevOI + gender:AZT + CD4:drug:gender +
    CD4:drug:AZT + CD4:gender:prevOI + CD4:gender:AZT + drug:gender:prevOI +
    drug:gender:AZT + CD4:drug:gender:AZT, data = myaids.id)
summary(cox_ti_final)
```

```
## Call:
## coxph(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
##     AZT + CD4:drug + CD4:gender + CD4:prevOI + CD4:AZT + drug:gender +
##     drug:prevOI + drug:AZT + gender:prevOI + gender:AZT + CD4:drug:gender +
##     CD4:drug:AZT + CD4:gender:prevOI + CD4:gender:AZT + drug:gender:prevOI +
##     drug:gender:AZT + CD4:drug:gender:AZT, data = myaids.id)
##
##   n= 400, number of events= 162
```

```
## 
##                                 coef exp(coef)  se(coef)      z
## CD4                           5.679e-01 1.765e+00 3.500e-01  1.622
## drugddI                       1.061e+01 4.052e+04 5.695e+00  1.863
## gendermale                    8.893e+00 7.282e+03 5.941e+00  1.497
## prevOIAIDS                    1.155e+01 1.037e+05 5.547e+00  2.082
## AZTfailure                   -2.178e+00 1.133e-01 1.531e+00 -1.422
## CD4:drugddI                  -6.384e-01 5.281e-01 3.341e-01 -1.911
## CD4:gendermale               -6.641e-01 5.147e-01 3.585e-01 -1.852
## CD4:prevOIAIDS               -7.793e-01 4.587e-01 3.044e-01 -2.560
## CD4:AZTfailure                6.538e-01 1.923e+00 2.874e-01  2.275
## drugddI:gendermale           -9.225e+00 9.853e-05 5.751e+00 -1.604
## drugddI:prevOIAIDS           -9.217e+00 9.931e-05 4.902e+00 -1.880
## drugddI:AZTfailure           -1.686e+00 1.853e-01 2.189e+00 -0.770
## gendermale:prevOIAIDS        -9.700e+00 6.130e-05 5.590e+00 -1.735
## gendermale:AZTfailure         2.663e+00 1.433e+01 1.605e+00  1.659
## CD4:drugddI:gendermale        6.263e-01 1.871e+00 3.432e-01  1.825
## CD4:drugddI:AZTfailure        1.262e+00 3.534e+00 5.222e-01  2.417
## CD4:gendermale:prevOIAIDS     7.562e-01 2.130e+00 3.133e-01  2.414
## CD4:gendermale:AZTfailure    -7.297e-01 4.821e-01 3.013e-01 -2.422
## drugddI:gendermale:prevOIAIDS 8.012e+00 3.016e+03 4.943e+00  1.621
## drugddI:gendermale:AZTfailure 1.648e+00 5.199e+00 2.279e+00  0.723
## CD4:drugddI:gendermale:AZTfailure -1.253e+00 2.856e-01 5.354e-01 -2.341
##                               Pr(>|z|)
## CD4                            0.1047
## drugddI                        0.0625 .
## gendermale                     0.1344
## prevOIAIDS                     0.0373 *
## AZTfailure                     0.1549
## CD4:drugddI                    0.0560 .
## CD4:gendermale                 0.0640 .
## CD4:prevOIAIDS                 0.0105 *
## CD4:AZTfailure                 0.0229 *
## drugddI:gendermale             0.1087
## drugddI:prevOIAIDS             0.0601 .
## drugddI:AZTfailure             0.4413
## gendermale:prevOIAIDS          0.0827 .
## gendermale:AZTfailure          0.0972 .
## CD4:drugddI:gendermale         0.0680 .
## CD4:drugddI:AZTfailure         0.0156 *
## CD4:gendermale:prevOIAIDS      0.0158 *
## CD4:gendermale:AZTfailure      0.0155 *
## drugddI:gendermale:prevOIAIDS  0.1051
## drugddI:gendermale:AZTfailure  0.4696
## CD4:drugddI:gendermale:AZTfailure  0.0193 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## 
##                               exp(coef) exp(-coef) lower .95 upper .95
## CD4                           1.765e+00  5.667e-01 8.886e-01 3.504e+00
## drugddI                       4.052e+04  2.468e-05 5.759e-01 2.851e+09
## gendermale                    7.282e+03  1.373e-04 6.392e-02 8.295e+08
## prevOIAIDS                    1.037e+05  9.640e-06 1.969e+00 5.466e+09
```

```
## AZTfailure                            1.133e-01  8.829e+00 5.632e-03 2.278e+00
## CD4:drugddI                           5.281e-01  1.894e+00 2.744e-01 1.017e+00
## CD4:gendermale                        5.147e-01  1.943e+00 2.549e-01 1.039e+00
## CD4:prevOIAIDS                        4.587e-01  2.180e+00 2.526e-01 8.331e-01
## CD4:AZTfailure                        1.923e+00  5.200e-01 1.095e+00 3.377e+00
## drugddI:gendermale                    9.853e-05  1.015e+04 1.255e-09 7.735e+00
## drugddI:prevOIAIDS                    9.931e-05  1.007e+04 6.672e-09 1.478e+00
## drugddI:AZTfailure                    1.853e-01  5.396e+00 2.537e-03 1.354e+01
## gendermale:prevOIAIDS                 6.130e-05  1.631e+04 1.070e-09 3.513e+00
## gendermale:AZTfailure                 1.433e+01  6.976e-02 6.165e-01 3.333e+02
## CD4:drugddI:gendermale                1.871e+00  5.346e-01 9.547e-01 3.665e+00
## CD4:drugddI:AZTfailure                3.534e+00  2.829e-01 1.270e+00 9.836e+00
## CD4:gendermale:prevOIAIDS             2.130e+00  4.695e-01 1.153e+00 3.936e+00
## CD4:gendermale:AZTfailure             4.821e-01  2.074e+00 2.671e-01 8.701e-01
## drugddI:gendermale:prevOIAIDS         3.016e+03  3.316e-04 1.870e-01 4.863e+07
## drugddI:gendermale:AZTfailure         5.199e+00  1.923e-01 5.965e-02 4.531e+02
## CD4:drugddI:gendermale:AZTfailure 2.856e-01  3.502e+00 1.000e-01 8.156e-01
##
## Concordance= 0.737  (se = 0.019 )
## Likelihood ratio test= 129.7  on 21 df,   p=<2e-16
## Wald test            = 114.8  on 21 df,   p=6e-15
## Score (logrank) test = 301.6  on 21 df,   p=<2e-16
```

```r
paste0("AIC Final Selected Model: ", AIC(cox_ti_final))
```

```
## [1] "AIC Final Selected Model: 1734.89585749095"
```

```r
# ---------------------------
# Time dependent Cox model
# ---------------------------
# Create survival object with start-stop format
surv_td <- Surv(time = myaids$start, time2 = myaids$stop, event = myaids$event)


### Null Model
cox_td_null <- coxph(surv_td ~ 1, data = myaids)
summary(cox_td_null)
```

```
## Call:  coxph(formula = surv_td ~ 1, data = myaids)
##
## Null model
##   log likelihood= -911.3012
##   n= 1211
```

```r
paste0("AIC of Null Model: ", AIC(cox_td_null))
```

```
## [1] "AIC of Null Model: 1822.60235408444"
```

```r
### Full model with Univariates
cox_full_td_uni <- coxph(surv_td ~ CD4 + drug + gender + prevOI + AZT, data = myaids)
summary(cox_full_td_uni)
```

```
## Call:
## coxph(formula = surv_td ~ CD4 + drug + gender + prevOI + AZT,
##     data = myaids)
##
##   n= 1211, number of events= 162
```

```
## 
##               coef exp(coef) se(coef)      z Pr(>|z|)
## CD4        -0.15180   0.85916  0.02774 -5.473 4.43e-08 ***
## drugddI     0.32778   1.38788  0.15918  2.059   0.0395 *
## gendermale -0.55332   0.57503  0.25305 -2.187   0.0288 *
## prevOIAIDS  0.79932   2.22403  0.25182  3.174   0.0015 **
## AZTfailure  0.20847   1.23179  0.17550  1.188   0.2349
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## 
##            exp(coef) exp(-coef) lower .95 upper .95
## CD4           0.8592     1.1639    0.8137    0.9072
## drugddI       1.3879     0.7205    1.0159    1.8960
## gendermale    0.5750     1.7390    0.3502    0.9443
## prevOIAIDS    2.2240     0.4496    1.3577    3.6433
## AZTfailure    1.2318     0.8118    0.8733    1.7375
## 
## Concordance= 0.719  (se = 0.019 )
## Likelihood ratio test= 99.09  on 5 df,   p=<2e-16
## Wald test            = 69.93  on 5 df,   p=1e-13
## Score (logrank) test = 80.75  on 5 df,   p=6e-16
```

```r
paste0("AIC of Main Effects (Univariate) Model: ", AIC(cox_full_td_uni))
```

```
## [1] "AIC of Main Effects (Univariate) Model: 1733.51489997613"
```

Functional form of CD4 using Martingale model

Raw CD4 martingale
```r
mart_td <- resid(cox_full_td_uni, type = "martingale")
```

Log CD4 martingale
```r
myaids_log <- myaids %>% mutate(CD4_log = log(CD4 + 1))
cox_td_log <- coxph(surv_td ~ CD4_log + drug + gender + prevOI + AZT, data = myaids_log)
mart_td_log <- resid(cox_td_log, type = "martingale")
```

AIC Comparison
```r
aic_td_linear <- round(AIC(cox_full_td_uni),2)
aic_td_log <- round(AIC(cox_td_log),2)
```

Full model with Univariates - Step
```r
cox_full_td_uni_step <- step(cox_full_td_uni,
                   scope = list(upper = ~ CD4 + drug + gender + prevOI + AZT),
                   trace = 0)
summary(cox_full_td_uni_step)
```

```
## Call:
## coxph(formula = surv_td ~ CD4 + drug + gender + prevOI, data = myaids)
## 
##   n= 1211, number of events= 162
## 
##                coef exp(coef) se(coef)      z Pr(>|z|)
## CD4        -0.15330   0.85787  0.02775 -5.524 3.32e-08 ***
```

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```
## drugddI        0.31154    1.36552  0.15851  1.965    0.0494 *
## gendermale -0.51525    0.59735  0.25080 -2.054    0.0399 *
## prevOIAIDS  0.91278    2.49124  0.23122  3.948 7.89e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##             exp(coef) exp(-coef) lower .95 upper .95
## CD4            0.8579     1.1657    0.8125    0.9058
## drugddI        1.3655     0.7323    1.0009    1.8630
## gendermale     0.5973     1.6741    0.3654    0.9766
## prevOIAIDS     2.4912     0.4014    1.5834    3.9195
##
## Concordance= 0.715  (se = 0.019 )
## Likelihood ratio test= 97.66  on 4 df,   p=<2e-16
## Wald test            = 68.15  on 4 df,   p=6e-14
## Score (logrank) test = 78.73  on 4 df,   p=3e-16
```

```r
paste0("AIC of Main Effects (Univariate) Model with Stepwise Selection: ",
       AIC(cox_full_td_uni_step))
```

```
## [1] "AIC of Main Effects (Univariate) Model with Stepwise Selection: 1732.94301975638"
```

Full model with Interactions
```r
cox_full_td_int <- coxph(surv_td ~ (CD4 + drug + gender + prevOI + AZT)^5, data = myaids)
summary(cox_full_td_int)
```

```
## Call:
## coxph(formula = surv_td ~ (CD4 + drug + gender + prevOI + AZT)^5,
##     data = myaids)
##
##   n= 1211, number of events= 162
##
##                                        coef  exp(coef)   se(coef)
## CD4                               -2.382e-01  7.881e-01  3.685e-01
## drugddI                            2.702e-01  1.310e+00  2.720e+00
## gendermale                        -2.134e+00  1.184e-01  2.671e+00
## prevOIAIDS                         1.393e+00  4.027e+00  2.814e+00
## AZTfailure                        -1.569e+01  1.541e-07  4.374e+03
## CD4:drugddI                        1.467e-01  1.158e+00  3.834e-01
## CD4:gendermale                     2.142e-01  1.239e+00  3.783e-01
## CD4:prevOIAIDS                    -1.416e-01  8.680e-01  5.212e-01
## CD4:AZTfailure                     9.002e-01  2.460e+00  1.279e+03
## drugddI:gendermale                 1.567e+00  4.795e+00  2.885e+00
## drugddI:prevOIAIDS                -4.069e-02  9.601e-01  3.146e+00
## drugddI:AZTfailure                -8.523e-01  4.265e-01  2.593e+00
## gendermale:prevOIAIDS              1.177e+00  3.245e+00  2.959e+00
## gendermale:AZTfailure              2.684e+00  1.464e+01  1.678e+00
## prevOIAIDS:AZTfailure              1.336e+01  6.369e+05  4.374e+03
## CD4:drugddI:gendermale            -2.317e-01  7.932e-01  3.968e-01
## CD4:drugddI:prevOIAIDS            -2.289e-01  7.954e-01  5.971e-01
## CD4:drugddI:AZTfailure             6.274e-01  1.873e+00  6.599e-01
## CD4:gendermale:prevOIAIDS         -2.964e-02  9.708e-01  5.355e-01
## CD4:gendermale:AZTfailure         -8.602e-01  4.231e-01  4.389e-01
## CD4:prevOIAIDS:AZTfailure         -1.196e-01  8.873e-01  1.279e+03
```

```
## drugddI:gendermale:prevOIAIDS                    -1.763e+00  1.715e-01  3.330e+00
## drugddI:gendermale:AZTfailure                     6.974e-01  2.008e+00  2.675e+00
## drugddI:prevOIAIDS:AZTfailure                            NA         NA  0.000e+00
## gendermale:prevOIAIDS:AZTfailure                         NA         NA  0.000e+00
## CD4:drugddI:gendermale:prevOIAIDS                  3.534e-01  1.424e+00  6.168e-01
## CD4:drugddI:gendermale:AZTfailure                 -5.683e-01  5.665e-01  6.784e-01
## CD4:drugddI:prevOIAIDS:AZTfailure                        NA         NA  0.000e+00
## CD4:gendermale:prevOIAIDS:AZTfailure                     NA         NA  0.000e+00
## drugddI:gendermale:prevOIAIDS:AZTfailure                 NA         NA  0.000e+00
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure             NA         NA  0.000e+00
##                                                      z Pr(>|z|)
## CD4                                             -0.646    0.518
## drugddI                                          0.099    0.921
## gendermale                                      -0.799    0.424
## prevOIAIDS                                       0.495    0.621
## AZTfailure                                      -0.004    0.997
## CD4:drugddI                                      0.383    0.702
## CD4:gendermale                                   0.566    0.571
## CD4:prevOIAIDS                                  -0.272    0.786
## CD4:AZTfailure                                   0.001    0.999
## drugddI:gendermale                               0.543    0.587
## drugddI:prevOIAIDS                              -0.013    0.990
## drugddI:AZTfailure                              -0.329    0.742
## gendermale:prevOIAIDS                            0.398    0.691
## gendermale:AZTfailure                            1.599    0.110
## prevOIAIDS:AZTfailure                            0.003    0.998
## CD4:drugddI:gendermale                          -0.584    0.559
## CD4:drugddI:prevOIAIDS                          -0.383    0.701
## CD4:drugddI:AZTfailure                           0.951    0.342
## CD4:gendermale:prevOIAIDS                       -0.055    0.956
## CD4:gendermale:AZTfailure                       -1.960    0.050 .
## CD4:prevOIAIDS:AZTfailure                        0.000    1.000
## drugddI:gendermale:prevOIAIDS                   -0.530    0.596
## drugddI:gendermale:AZTfailure                    0.261    0.794
## drugddI:prevOIAIDS:AZTfailure                       NA       NA
## gendermale:prevOIAIDS:AZTfailure                    NA       NA
## CD4:drugddI:gendermale:prevOIAIDS                0.573    0.567
## CD4:drugddI:gendermale:AZTfailure               -0.838    0.402
## CD4:drugddI:prevOIAIDS:AZTfailure                   NA       NA
## CD4:gendermale:prevOIAIDS:AZTfailure                NA       NA
## drugddI:gendermale:prevOIAIDS:AZTfailure            NA       NA
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure        NA       NA
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                                                 exp(coef) exp(-coef) lower .95
## CD4                                             7.881e-01  1.269e+00 0.3827731
## drugddI                                         1.310e+00  7.632e-01 0.0063436
## gendermale                                      1.184e-01  8.448e+00 0.0006304
## prevOIAIDS                                      4.027e+00  2.483e-01 0.0162090
## AZTfailure                                      1.541e-07  6.491e+06 0.0000000
## CD4:drugddI                                     1.158e+00  8.635e-01 0.5461706
## CD4:gendermale                                  1.239e+00  8.072e-01 0.5901607
```

```
## CD4:prevOIAIDS                                 8.680e-01  1.152e+00 0.3125264
## CD4:AZTfailure                                  2.460e+00  4.065e-01 0.0000000
## drugddI:gendermale                              4.795e+00  2.086e-01 0.0167997
## drugddI:prevOIAIDS                              9.601e-01  1.042e+00 0.0020145
## drugddI:AZTfailure                              4.265e-01  2.345e+00 0.0026456
## gendermale:prevOIAIDS                           3.245e+00  3.082e-01 0.0098276
## gendermale:AZTfailure                           1.464e+01  6.832e-02 0.5455070
## prevOIAIDS:AZTfailure                           6.369e+05  1.570e-06 0.0000000
## CD4:drugddI:gendermale                          7.932e-01  1.261e+00 0.3644734
## CD4:drugddI:prevOIAIDS                          7.954e-01  1.257e+00 0.2468233
## CD4:drugddI:AZTfailure                          1.873e+00  5.340e-01 0.5137888
## CD4:gendermale:prevOIAIDS                       9.708e-01  1.030e+00 0.3398486
## CD4:gendermale:AZTfailure                       4.231e-01  2.364e+00 0.1789775
## CD4:prevOIAIDS:AZTfailure                       8.873e-01  1.127e+00 0.0000000
## drugddI:gendermale:prevOIAIDS                   1.715e-01  5.832e+00 0.0002511
## drugddI:gendermale:AZTfailure                   2.008e+00  4.979e-01 0.0106045
## drugddI:prevOIAIDS:AZTfailure                         NA        NA        NA
## gendermale:prevOIAIDS:AZTfailure                      NA        NA        NA
## CD4:drugddI:gendermale:prevOIAIDS               1.424e+00  7.023e-01 0.4250626
## CD4:drugddI:gendermale:AZTfailure               5.665e-01  1.765e+00 0.1498708
## CD4:drugddI:prevOIAIDS:AZTfailure                     NA        NA        NA
## CD4:gendermale:prevOIAIDS:AZTfailure                  NA        NA        NA
## drugddI:gendermale:prevOIAIDS:AZTfailure              NA        NA        NA
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure          NA        NA        NA
##                                               upper .95
## CD4                                               1.623
## drugddI                                         270.639
## gendermale                                       22.230
## prevOIAIDS                                     1000.360
## AZTfailure                                          Inf
## CD4:drugddI                                       2.455
## CD4:gendermale                                    2.601
## CD4:prevOIAIDS                                    2.411
## CD4:AZTfailure                                      Inf
## drugddI:gendermale                             1368.357
## drugddI:prevOIAIDS                              457.607
## drugddI:AZTfailure                               68.740
## gendermale:prevOIAIDS                          1071.315
## gendermale:AZTfailure                           392.763
## prevOIAIDS:AZTfailure                               Inf
## CD4:drugddI:gendermale                            1.726
## CD4:drugddI:prevOIAIDS                            2.563
## CD4:drugddI:AZTfailure                            6.826
## CD4:gendermale:prevOIAIDS                         2.773
## CD4:gendermale:AZTfailure                         1.000
## CD4:prevOIAIDS:AZTfailure                           Inf
## drugddI:gendermale:prevOIAIDS                   117.073
## drugddI:gendermale:AZTfailure                   380.395
## drugddI:prevOIAIDS:AZTfailure                        NA
## gendermale:prevOIAIDS:AZTfailure                     NA
## CD4:drugddI:gendermale:prevOIAIDS                 4.770
## CD4:drugddI:gendermale:AZTfailure                 2.141
## CD4:drugddI:prevOIAIDS:AZTfailure                    NA
```

```
## CD4:gendermale:prevOIAIDS:AZTfailure                     NA
## drugddI:gendermale:prevOIAIDS:AZTfailure                 NA
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure             NA
##
## Concordance= 0.74  (se = 0.018 )
## Likelihood ratio test= 126.9  on 25 df,   p=1e-15
## Wald test            = 106.1  on 25 df,   p=6e-12
## Score (logrank) test = 178.4  on 25 df,   p=<2e-16
```

```r
paste0("AIC of Interactions Model: ", AIC(cox_full_td_int))
```

```
## [1] "AIC of Interactions Model: 1745.68990671712"
```

```r
### Stepwise on Interaction Model
cox_full_td_int_step <- step(cox_full_td_int,
                             scope = list(upper = ~ (CD4 + drug + gender + prevOI + AZT)^5),
                             trace = 0)
summary(cox_full_td_int_step)
```

```
## Call:
## coxph(formula = surv_td ~ CD4 + drug + gender + prevOI + AZT +
##     CD4:gender + CD4:prevOI + CD4:AZT + drug:prevOI + gender:AZT +
##     CD4:gender:AZT, data = myaids)
##
##   n= 1211, number of events= 162
##
##                             coef exp(coef) se(coef)      z Pr(>|z|)
## CD4                     -0.12217   0.88500  0.09604 -1.272 0.203326
## drugddI                  1.24317   3.46658  0.47353  2.625 0.008656 **
## gendermale              -0.53340   0.58661  0.56688 -0.941 0.346732
## prevOIAIDS               2.04388   7.72050  0.56162  3.639 0.000273 ***
## AZTfailure              -1.56505   0.20908  0.99618 -1.571 0.116171
## CD4:gendermale           0.03784   1.03856  0.09722  0.389 0.697135
## CD4:prevOIAIDS          -0.10887   0.89685  0.07121 -1.529 0.126307
## CD4:AZTfailure           0.63024   1.87807  0.19887  3.169 0.001529 **
## drugddI:prevOIAIDS      -1.01782   0.36138  0.50448 -2.018 0.043635 *
## gendermale:AZTfailure    1.80718   6.09322  1.01972  1.772 0.076356 .
## CD4:gendermale:AZTfailure -0.65813 0.51782  0.20219 -3.255 0.001134 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                           exp(coef) exp(-coef) lower .95 upper .95
## CD4                          0.8850     1.1299   0.73315    1.0683
## drugddI                      3.4666     0.2885   1.37036    8.7694
## gendermale                   0.5866     1.7047   0.19312    1.7819
## prevOIAIDS                   7.7205     0.1295   2.56799   23.2112
## AZTfailure                   0.2091     4.7829   0.02967    1.4732
## CD4:gendermale               1.0386     0.9629   0.85838    1.2566
## CD4:prevOIAIDS               0.8968     1.1150   0.78001    1.0312
## CD4:AZTfailure               1.8781     0.5325   1.27184    2.7733
## drugddI:prevOIAIDS           0.3614     2.7672   0.13445    0.9714
## gendermale:AZTfailure        6.0932     0.1641   0.82577   44.9606
## CD4:gendermale:AZTfailure    0.5178     1.9312   0.34839    0.7696
##
```

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```
## Concordance= 0.733  (se = 0.019 )
## Likelihood ratio test= 119.3  on 11 df,   p=<2e-16
## Wald test            = 95.24  on 11 df,   p=2e-15
## Score (logrank) test = 132.9  on 11 df,   p=<2e-16
```
```r
paste0("AIC of Interactions Model with Stepwise Selection: ", AIC(cox_full_td_int_step))
```
```
## [1] "AIC of Interactions Model with Stepwise Selection: 1725.31023538143"
```
Final Time dependent Cox Model
```r
cox_td_final <- coxph(surv_td ~ CD4 + drug + gender + prevOI + AZT +
    CD4:gender + CD4:prevOI + CD4:AZT + drug:prevOI + gender:AZT +
    CD4:gender:AZT, data = myaids)
summary(cox_td_final)
```
```
## Call:
## coxph(formula = surv_td ~ CD4 + drug + gender + prevOI + AZT +
##     CD4:gender + CD4:prevOI + CD4:AZT + drug:prevOI + gender:AZT +
##     CD4:gender:AZT, data = myaids)
##
##   n= 1211, number of events= 162
##
##                             coef exp(coef) se(coef)      z Pr(>|z|)
## CD4                      -0.12217   0.88500  0.09604 -1.272 0.203326
## drugddI                   1.24317   3.46658  0.47353  2.625 0.008656 **
## gendermale               -0.53340   0.58661  0.56688 -0.941 0.346732
## prevOIAIDS                2.04388   7.72050  0.56162  3.639 0.000273 ***
## AZTfailure               -1.56505   0.20908  0.99618 -1.571 0.116171
## CD4:gendermale            0.03784   1.03856  0.09722  0.389 0.697135
## CD4:prevOIAIDS           -0.10887   0.89685  0.07121 -1.529 0.126307
## CD4:AZTfailure            0.63024   1.87807  0.19887  3.169 0.001529 **
## drugddI:prevOIAIDS       -1.01782   0.36138  0.50448 -2.018 0.043635 *
## gendermale:AZTfailure     1.80718   6.09322  1.01972  1.772 0.076356 .
## CD4:gendermale:AZTfailure -0.65813   0.51782  0.20219 -3.255 0.001134 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                           exp(coef) exp(-coef) lower .95 upper .95
## CD4                          0.8850     1.1299   0.73315    1.0683
## drugddI                      3.4666     0.2885   1.37036    8.7694
## gendermale                   0.5866     1.7047   0.19312    1.7819
## prevOIAIDS                   7.7205     0.1295   2.56799   23.2112
## AZTfailure                   0.2091     4.7829   0.02967    1.4732
## CD4:gendermale               1.0386     0.9629   0.85838    1.2566
## CD4:prevOIAIDS               0.8968     1.1150   0.78001    1.0312
## CD4:AZTfailure               1.8781     0.5325   1.27184    2.7733
## drugddI:prevOIAIDS           0.3614     2.7672   0.13445    0.9714
## gendermale:AZTfailure        6.0932     0.1641   0.82577   44.9606
## CD4:gendermale:AZTfailure    0.5178     1.9312   0.34839    0.7696
##
## Concordance= 0.733  (se = 0.019 )
## Likelihood ratio test= 119.3  on 11 df,   p=<2e-16
## Wald test            = 95.24  on 11 df,   p=2e-15
## Score (logrank) test = 132.9  on 11 df,   p=<2e-16
```

```r
paste0("AIC Final Selected Model: ", AIC(cox_td_final))
```

```
## [1] "AIC Final Selected Model: 1725.31023538143"
```

```r
layout(matrix(1:4, nrow = 2, byrow = TRUE))
par(mar = c(3.5, 3.5, 2.2, 1), oma = c(2, 2, 1, 1), mgp = c(2, 0.6, 0), tck = -0.02)

# Plot A: TI - CD4
plot(myaids.id$CD4, mart_full_ti, pch = 20, cex = 0.3, xlab = "", ylab = "",
     main = "", ylim = c(-1.5, 0.75), xlim = c(0, 20))
smoothSEcurve(mart_full_ti, myaids.id$CD4)
mtext("A. TI Cox: CD4", side = 3, line = 0.4, adj = 0, font = 2, cex = 0.75)
text(x = 15, y = -1.4, labels = paste("AIC =", round(aic_ti_linear, 2)),
     col = "red", cex = 0.85)

# Plot B: TI - log(CD4)
plot(log(myaids.id$CD4 + 1), mart_ti_log, pch = 20, cex = 0.3, xlab = "", ylab = "",
     main = "", ylim = c(-2, 1), xlim = c(0, 3))
smoothSEcurve(mart_ti_log, log(myaids.id$CD4 + 1))
mtext("B. TI Cox: log(CD4)", side = 3, line = 0.4, adj = 0, font = 2, cex = 0.75)
text(x = 2.3, y = -1.9, labels = paste("AIC =", aic_ti_log), col = "red", cex = 0.85)

# Plot C: TD - CD4
plot(myaids$CD4, mart_td, pch = 20, cex = 0.3, xlab = "", ylab = "",
     main = "", ylim = c(-1, 1), xlim = c(0, 20))
smoothSEcurve(mart_td, myaids$CD4)
mtext("C. TD Cox: CD4", side = 3, line = 0.4, adj = 0, font = 2, cex = 0.75)
text(x = 15, y = -0.9, labels = paste("AIC =", round(aic_td_linear, 2)),
     col = "red", cex = 0.85)

# Plot D: TD - log(CD4)
plot(log(myaids$CD4 + 1), mart_td_log, pch = 20, cex = 0.3, xlab = "", ylab = "",
     main = "", ylim = c(-1.5, 1), xlim = c(0, 3))
smoothSEcurve(mart_td_log, log(myaids$CD4 + 1))
mtext("D. TD Cox: log(CD4)", side = 3, line = 0.4, adj = 0, font = 2, cex = 0.75)
text(x = 2.3, y = -1.4, labels = paste("AIC =", aic_td_log),
     col = "red", cex = 0.85)

# Shared axis labels
mtext("Martingale Residuals", side = 2, outer = TRUE, line = 0.3, cex = 0.8)
mtext("CD4 or log(CD4 + 1)", side = 1, outer = TRUE, line = 0.3, cex = 0.8)

# ----------------------------------------
# Accelerated Failure Time (AFT) model
# ----------------------------------------


# ----------------------------------------
# Weibull Distribution
# ----------------------------------------


### Null model
weibull_ti_null <- survreg(Surv(Time, death) ~ 1, data = myaids.id, dist = "weibull")
```
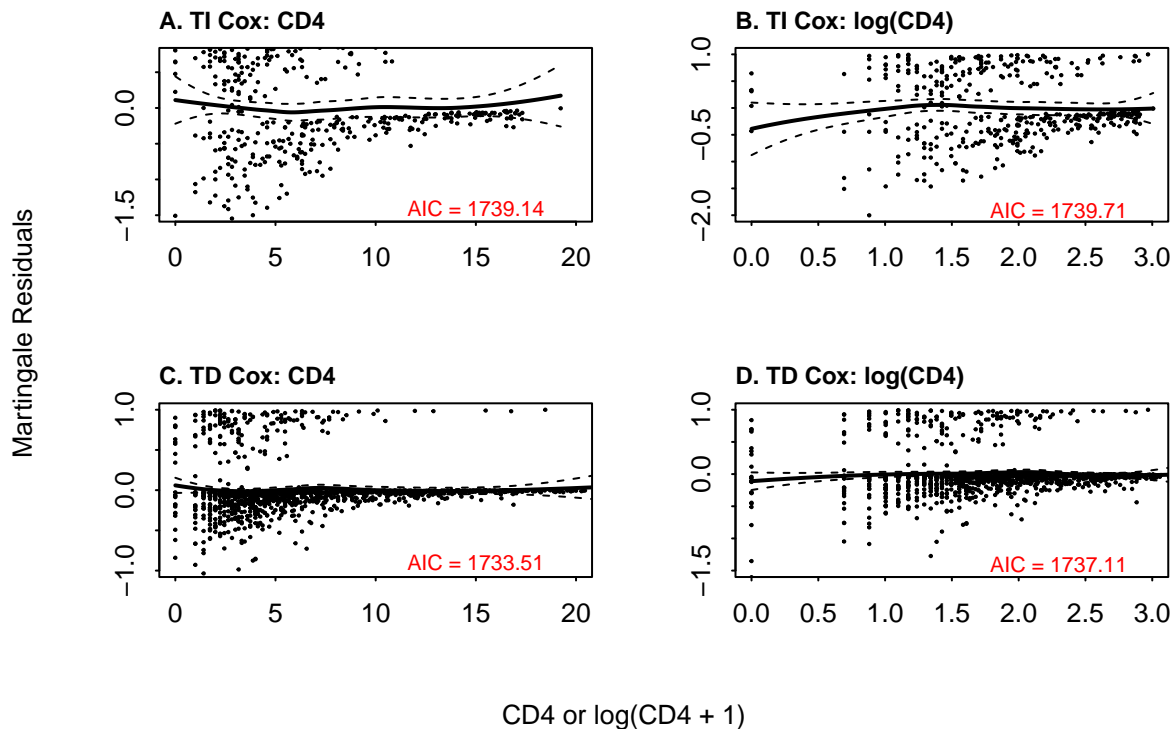
Figure 2: Martingale residuals for CD4 and log(CD4) in TI/TD Cox models. Loess fits with 95% CI shown. AIC values are annotated in red.

```r
summary(weibull_ti_null)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ 1, data = myaids.id, dist = "weibull")
##              Value Std. Error     z       p
## (Intercept)  3.2448     0.0717 45.26 <2e-16
## Log(scale)  -0.2945     0.0726 -4.06  5e-05
##
## Scale= 0.745
##
## Weibull distribution
## Loglik(model)= -712.9   Loglik(intercept only)= -712.9
## Number of Newton-Raphson Iterations: 5
## n= 400
```

```r
paste0("AIC of Null Model: ", AIC(weibull_ti_null))
```

```
## [1] "AIC of Null Model: 1429.84810629383"
```

```r
### Full model with Univariates
weibull_full_ti_uni <- survreg(Surv(Time, death) ~ CD4 + drug + gender + prevOI + AZT,
                        data = myaids.id, dist = "weibull")
summary(weibull_full_ti_uni)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
```

```
##        AZT, data = myaids.id, dist = "weibull")
##                 Value Std. Error     z       p
## (Intercept)  2.9119      0.2440 11.93 < 2e-16
## CD4          0.0916      0.0182  5.03 4.9e-07
## drugddI     -0.1889      0.1102 -1.71   0.086
## gendermale   0.3286      0.1756  1.87   0.061
## prevOIAIDS  -0.5510      0.1784 -3.09   0.002
## AZTfailure  -0.1627      0.1212 -1.34   0.179
## Log(scale)  -0.3715      0.0705 -5.27 1.3e-07
##
## Scale= 0.69
##
## Weibull distribution
## Loglik(model)= -665.5   Loglik(intercept only)= -712.9
##   Chisq= 94.83 on 5 degrees of freedom, p= 6.5e-19
## Number of Newton-Raphson Iterations: 5
## n= 400
```

```r
paste0("AIC of Main Effects (Univariate) Model: ", AIC(weibull_full_ti_uni))
```

```
## [1] "AIC of Main Effects (Univariate) Model: 1345.01438805026"
```

Full model with Univariates - Step

```r
weibull_full_ti_uni_step <- step(weibull_full_ti_uni,
                        scope = list(upper = ~ CD4 + drug + gender + prevOI + AZT),
                        trace = 0)
summary(weibull_full_ti_uni_step)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI,
##     data = myaids.id, dist = "weibull")
##                 Value Std. Error     z       p
## (Intercept)  2.9201      0.2456 11.89 < 2e-16
## CD4          0.0927      0.0183  5.06 4.3e-07
## drugddI     -0.1753      0.1096 -1.60 0.10976
## gendermale   0.2978      0.1738  1.71 0.08664
## prevOIAIDS  -0.6378      0.1666 -3.83 0.00013
## Log(scale)  -0.3714      0.0705 -5.27 1.4e-07
##
## Scale= 0.69
##
## Weibull distribution
## Loglik(model)= -666.4   Loglik(intercept only)= -712.9
##   Chisq= 92.99 on 4 degrees of freedom, p= 3e-19
## Number of Newton-Raphson Iterations: 5
## n= 400
```

```r
paste0("AIC of Main Effects (Univariate) Model with Stepwise Selection: ",
       AIC(cox_full_td_uni_step))
```

```
## [1] "AIC of Main Effects (Univariate) Model with Stepwise Selection: 1732.94301975638"
```

Full model with Interactions

```r
weibull_full_ti_int <- survreg(Surv(Time, death) ~ (CD4 + drug + gender + prevOI + AZT)^5,
                        data = myaids.id, dist = "weibull")
```

```r
summary(weibull_full_ti_int)
```

```
## 
## Call:
## survreg(formula = Surv(Time, death) ~ (CD4 + drug + gender + 
##     prevOI + AZT)^5, data = myaids.id, dist = "weibull")
##                                               Value Std. Error     z       p
## (Intercept)                                3.82e+02   5.79e+04  0.01   0.995
## CD4                                       -2.20e+01   3.36e+03 -0.01   0.995
## drugddI                                   -3.80e+02   5.79e+04 -0.01   0.995
## gendermale                                -3.79e+02   5.79e+04 -0.01   0.995
## prevOIAIDS                                -3.80e+02   5.79e+04 -0.01   0.995
## AZTfailure                                 1.48e+01   3.26e+04  0.00   1.000
## CD4:drugddI                                2.21e+01   3.36e+03  0.01   0.995
## CD4:gendermale                             2.21e+01   3.36e+03  0.01   0.995
## CD4:prevOIAIDS                             2.22e+01   3.36e+03  0.01   0.995
## CD4:AZTfailure                            -4.52e-01   1.99e-01 -2.28   0.023
## drugddI:gendermale                         3.79e+02   5.79e+04  0.01   0.995
## drugddI:prevOIAIDS                         3.79e+02   5.79e+04  0.01   0.995
## drugddI:AZTfailure                         7.46e-01   1.43e+00  0.52   0.602
## gendermale:prevOIAIDS                      3.79e+02   5.79e+04  0.01   0.995
## gendermale:AZTfailure                     -1.93e+00   1.07e+00 -1.79   0.073
## prevOIAIDS:AZTfailure                     -1.33e+01   3.26e+04  0.00   1.000
## CD4:drugddI:gendermale                    -2.21e+01   3.36e+03 -0.01   0.995
## CD4:drugddI:prevOIAIDS                    -2.17e+01   3.36e+03 -0.01   0.995
## CD4:drugddI:AZTfailure                    -6.76e-01   3.32e-01 -2.04   0.042
## CD4:gendermale:prevOIAIDS                 -2.22e+01   3.36e+03 -0.01   0.995
## CD4:gendermale:AZTfailure                  5.13e-01   2.08e-01  2.46   0.014
## CD4:prevOIAIDS:AZTfailure                        NA   0.00e+00    NA      NA
## drugddI:gendermale:prevOIAIDS             -3.78e+02   5.79e+04 -0.01   0.995
## drugddI:gendermale:AZTfailure             -6.28e-01   1.50e+00 -0.42   0.676
## drugddI:prevOIAIDS:AZTfailure                    NA   0.00e+00    NA      NA
## gendermale:prevOIAIDS:AZTfailure                 NA   0.00e+00    NA      NA
## CD4:drugddI:gendermale:prevOIAIDS          2.17e+01   3.36e+03  0.01   0.995
## CD4:drugddI:gendermale:AZTfailure          6.53e-01   3.44e-01  1.90   0.057
## CD4:drugddI:prevOIAIDS:AZTfailure                NA   0.00e+00    NA      NA
## CD4:gendermale:prevOIAIDS:AZTfailure             NA   0.00e+00    NA      NA
## drugddI:gendermale:prevOIAIDS:AZTfailure         NA   0.00e+00    NA      NA
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure     NA   0.00e+00    NA      NA
## Log(scale)                                -4.41e-01   7.03e-02 -6.27 3.5e-10
## 
## Scale= 0.643 
## 
## Weibull distribution
## Loglik(model)= -646.1   Loglik(intercept only)= -712.9
##  Chisq= 133.58 on 31 degrees of freedom, p= 1.1e-14 
## Number of Newton-Raphson Iterations: 20 
## n= 400
```

```r
paste0("AIC of Interactions Model: ", AIC(weibull_full_ti_int))
```

```
## [1] "AIC of Interactions Model: 1358.27156372946"
```

```
### Full model with Interactions - Step
weibull_full_ti_int_step <- step(weibull_full_ti_int,
                          scope = list(upper = ~ (CD4 + drug + gender + prevOI + AZT)^5),
                          trace = 0)
summary(weibull_full_ti_int_step)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
##      AZT + CD4:drug + CD4:gender + CD4:prevOI + CD4:AZT + drug:gender +
##      drug:prevOI + drug:AZT + gender:prevOI + gender:AZT + CD4:drug:gender +
##      CD4:drug:AZT + CD4:gender:prevOI + CD4:gender:AZT + drug:gender:prevOI +
##      drug:gender:AZT + CD4:drug:gender:AZT, data = myaids.id,
##      dist = "weibull")
##                                Value Std. Error     z       p
## (Intercept)                   9.8987     3.8546  2.57  0.0102
## CD4                          -0.3874     0.2282 -1.70  0.0896
## drugddI                      -7.1827     3.7221 -1.93  0.0536
## gendermale                   -6.0541     3.8796 -1.56  0.1186
## prevOIAIDS                   -7.8277     3.6161 -2.16  0.0304
## AZTfailure                    1.4690     1.0010  1.47  0.1422
## CD4:drugddI                   0.4330     0.2177  1.99  0.0467
## CD4:gendermale                0.4481     0.2338  1.92  0.0553
## CD4:prevOIAIDS                0.5293     0.1965  2.69  0.0071
## CD4:AZTfailure               -0.4344     0.1885 -2.30  0.0212
## drugddI:gendermale            6.2664     3.7554  1.67  0.0952
## drugddI:prevOIAIDS            6.2094     3.2004  1.94  0.0524
## drugddI:AZTfailure            0.8917     1.3921  0.64  0.5218
## gendermale:prevOIAIDS         6.6213     3.6406  1.82  0.0690
## gendermale:AZTfailure        -1.7867     1.0492 -1.70  0.0886
## CD4:drugddI:gendermale       -0.4229     0.2235 -1.89  0.0584
## CD4:drugddI:AZTfailure       -0.7276     0.3166 -2.30  0.0215
## CD4:gendermale:prevOIAIDS    -0.5142     0.2023 -2.54  0.0110
## CD4:gendermale:AZTfailure     0.4848     0.1976  2.45  0.0141
## drugddI:gendermale:prevOIAIDS -5.4163    3.2242 -1.68  0.0930
## drugddI:gendermale:AZTfailure -0.8646    1.4505 -0.60  0.5512
## CD4:drugddI:gendermale:AZTfailure  0.7209 0.3255  2.22  0.0268
## Log(scale)                   -0.4414     0.0703 -6.28 3.4e-10
##
## Scale= 0.643
##
## Weibull distribution
## Loglik(model)= -647.4   Loglik(intercept only)= -712.9
##  Chisq= 130.95 on 21 degrees of freedom, p= 6.7e-18
## Number of Newton-Raphson Iterations: 6
## n= 400
```

```
paste0("AIC of Interactions Model with Stepwise Selection: ",
       AIC(weibull_full_ti_int_step))
```

```
## [1] "AIC of Interactions Model with Stepwise Selection: 1340.89427920678"
```

```
### Final Time Independent Weibull Model
weibull_ti_final <- survreg(Surv(Time, death) ~ CD4 + drug + gender + prevOI +
```

```
      AZT + CD4:drug + CD4:gender + CD4:prevOI + CD4:AZT + drug:gender +
      drug:prevOI + drug:AZT + gender:prevOI + gender:AZT + CD4:drug:gender +
      CD4:drug:AZT + CD4:gender:prevOI + CD4:gender:AZT + drug:gender:prevOI +
      drug:gender:AZT + CD4:drug:gender:AZT, data = myaids.id,
      dist = "weibull")
summary(weibull_ti_final)
```

```
## 
## Call:
## survreg(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
##       AZT + CD4:drug + CD4:gender + CD4:prevOI + CD4:AZT + drug:gender +
##       drug:prevOI + drug:AZT + gender:prevOI + gender:AZT + CD4:drug:gender +
##       CD4:drug:AZT + CD4:gender:prevOI + CD4:gender:AZT + drug:gender:prevOI +
##       drug:gender:AZT + CD4:drug:gender:AZT, data = myaids.id,
##       dist = "weibull")
##                                   Value Std. Error     z       p
## (Intercept)                      9.8987     3.8546  2.57  0.0102
## CD4                             -0.3874     0.2282 -1.70  0.0896
## drugddI                         -7.1827     3.7221 -1.93  0.0536
## gendermale                      -6.0541     3.8796 -1.56  0.1186
## prevOIAIDS                      -7.8277     3.6161 -2.16  0.0304
## AZTfailure                       1.4690     1.0010  1.47  0.1422
## CD4:drugddI                      0.4330     0.2177  1.99  0.0467
## CD4:gendermale                   0.4481     0.2338  1.92  0.0553
## CD4:prevOIAIDS                   0.5293     0.1965  2.69  0.0071
## CD4:AZTfailure                  -0.4344     0.1885 -2.30  0.0212
## drugddI:gendermale               6.2664     3.7554  1.67  0.0952
## drugddI:prevOIAIDS               6.2094     3.2004  1.94  0.0524
## drugddI:AZTfailure               0.8917     1.3921  0.64  0.5218
## gendermale:prevOIAIDS            6.6213     3.6406  1.82  0.0690
## gendermale:AZTfailure           -1.7867     1.0492 -1.70  0.0886
## CD4:drugddI:gendermale          -0.4229     0.2235 -1.89  0.0584
## CD4:drugddI:AZTfailure          -0.7276     0.3166 -2.30  0.0215
## CD4:gendermale:prevOIAIDS       -0.5142     0.2023 -2.54  0.0110
## CD4:gendermale:AZTfailure        0.4848     0.1976  2.45  0.0141
## drugddI:gendermale:prevOIAIDS   -5.4163     3.2242 -1.68  0.0930
## drugddI:gendermale:AZTfailure   -0.8646     1.4505 -0.60  0.5512
## CD4:drugddI:gendermale:AZTfailure 0.7209   0.3255  2.22  0.0268
## Log(scale)                      -0.4414     0.0703 -6.28 3.4e-10
## 
## Scale= 0.643
## 
## Weibull distribution
## Loglik(model)= -647.4   Loglik(intercept only)= -712.9
##   Chisq= 130.95 on 21 degrees of freedom, p= 6.7e-18
## Number of Newton-Raphson Iterations: 6
## n= 400
```

```
paste0("AIC Final Selected Model: ", AIC(weibull_ti_final))
```

```
## [1] "AIC Final Selected Model: 1340.89427920678"
```

```
# --------------------------------------
# Log-Normal distribution
```

```
# ----------------------------------------

# Null model
lognorm_ti_null <- survreg(Surv(Time, death) ~ 1, data = myaids.id, dist = "lognormal")
summary(lognorm_ti_null)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ 1, data = myaids.id, dist = "lognormal")
##              Value Std. Error     z       p
## (Intercept) 3.0665     0.0854 35.92 <2e-16
## Log(scale)  0.2002     0.0623  3.21 0.0013
##
## Scale= 1.22
##
## Log Normal distribution
## Loglik(model)= -713.7   Loglik(intercept only)= -713.7
## Number of Newton-Raphson Iterations: 3
## n= 400
```

```
paste0("AIC of Null Model: ", AIC(lognorm_ti_null))
```

```
## [1] "AIC of Null Model: 1431.49602720194"
```

```
# Full model with univariates
lognorm_full_ti_uni <- survreg(Surv(Time, death) ~ CD4 + drug + gender + prevOI + AZT,
                          data = myaids.id, dist = "lognormal")
summary(lognorm_full_ti_uni)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
##     AZT, data = myaids.id, dist = "lognormal")
##               Value Std. Error     z       p
## (Intercept)  2.4940     0.2867  8.70 < 2e-16
## CD4          0.0872     0.0181  4.80 1.6e-06
## drugddI     -0.2162     0.1316 -1.64  0.1003
## gendermale   0.6297     0.2143  2.94  0.0033
## prevOIAIDS  -0.6115     0.1903 -3.21  0.0013
## AZTfailure  -0.1556     0.1508 -1.03  0.3021
## Log(scale)   0.0812     0.0611  1.33  0.1836
##
## Scale= 1.08
##
## Log Normal distribution
## Loglik(model)= -671   Loglik(intercept only)= -713.7
##  Chisq= 85.52 on 5 degrees of freedom, p= 5.9e-17
## Number of Newton-Raphson Iterations: 4
## n= 400
```

```
paste0("AIC of Main Effects (Univariate) Model: ", AIC(lognorm_full_ti_uni))
```

```
## [1] "AIC of Main Effects (Univariate) Model: 1355.97981393027"
```

```
# Stepwise selection from full univariate model
lognorm_full_ti_uni_step <- step(lognorm_full_ti_uni,
                                 scope = list(upper = ~ CD4 + drug + gender + prevOI + AZT),
                                 trace = 0)
summary(lognorm_full_ti_uni_step)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI,
##     data = myaids.id, dist = "lognormal")
##                Value Std. Error     z        p
## (Intercept)   2.4930     0.2870  8.69 < 2e-16
## CD4           0.0879     0.0182  4.84 1.3e-06
## drugddI      -0.2102     0.1314 -1.60  0.1098
## gendermale    0.6180     0.2140  2.89  0.0039
## prevOIAIDS   -0.6959     0.1727 -4.03 5.6e-05
## Log(scale)    0.0819     0.0611  1.34  0.1798
##
## Scale= 1.09
##
## Log Normal distribution
## Loglik(model)= -671.5   Loglik(intercept only)= -713.7
##   Chisq= 84.45 on 4 degrees of freedom, p= 2e-17
## Number of Newton-Raphson Iterations: 4
## n= 400
```

```
paste0("AIC of Interactions Model with Stepwise Selection: ", AIC(lognorm_full_ti_uni_step))
```

```
## [1] "AIC of Interactions Model with Stepwise Selection: 1355.04881235274"
```

```
# Full interaction model
lognorm_full_ti_int <- survreg(Surv(Time, death) ~ (CD4 + drug + gender + prevOI + AZT)^5,
                               data = myaids.id, dist = "lognormal")
summary(lognorm_full_ti_int)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ (CD4 + drug + gender +
##     prevOI + AZT)^5, data = myaids.id, dist = "lognormal")
##                                     Value Std. Error     z     p
## (Intercept)                      2.07e+02   2.70e+04  0.01 0.994
## CD4                             -1.19e+01   1.57e+03 -0.01 0.994
## drugddI                         -2.03e+02   2.70e+04 -0.01 0.994
## gendermale                      -2.03e+02   2.70e+04 -0.01 0.994
## prevOIAIDS                      -2.06e+02   2.70e+04 -0.01 0.994
## AZTfailure                       7.91e+00   1.44e+04  0.00 1.000
## CD4:drugddI                      1.18e+01   1.57e+03  0.01 0.994
## CD4:gendermale                   1.19e+01   1.57e+03  0.01 0.994
## CD4:prevOIAIDS                   1.21e+01   1.57e+03  0.01 0.994
## CD4:AZTfailure                  -5.27e-01   2.36e-01 -2.23 0.026
## drugddI:gendermale               2.03e+02   2.70e+04  0.01 0.994
## drugddI:prevOIAIDS               2.03e+02   2.70e+04  0.01 0.994
## drugddI:AZTfailure               6.22e-02   2.10e+00  0.03 0.976
## gendermale:prevOIAIDS            2.05e+02   2.70e+04  0.01 0.994
```

```
## gendermale:AZTfailure                               -2.45e+00    1.24e+00 -1.97 0.048
## prevOIAIDS:AZTfailure                                -5.88e+00    1.44e+04  0.00 1.000
## CD4:drugddI:gendermale                               -1.18e+01    1.57e+03 -0.01 0.994
## CD4:drugddI:prevOIAIDS                               -1.14e+01    1.57e+03 -0.01 0.994
## CD4:drugddI:AZTfailure                               -5.89e-01    5.01e-01 -1.18 0.240
## CD4:gendermale:prevOIAIDS                            -1.21e+01    1.57e+03 -0.01 0.994
## CD4:gendermale:AZTfailure                             6.19e-01    2.45e-01  2.53 0.011
## CD4:prevOIAIDS:AZTfailure                                   NA    0.00e+00   NA    NA
## drugddI:gendermale:prevOIAIDS                        -2.02e+02    2.70e+04 -0.01 0.994
## drugddI:gendermale:AZTfailure                        -1.47e-01    2.17e+00 -0.07 0.946
## drugddI:prevOIAIDS:AZTfailure                               NA    0.00e+00   NA    NA
## gendermale:prevOIAIDS:AZTfailure                            NA    0.00e+00   NA    NA
## CD4:drugddI:gendermale:prevOIAIDS                     1.14e+01    1.57e+03  0.01 0.994
## CD4:drugddI:gendermale:AZTfailure                     5.69e-01    5.09e-01  1.12 0.264
## CD4:drugddI:prevOIAIDS:AZTfailure                           NA    0.00e+00   NA    NA
## CD4:gendermale:prevOIAIDS:AZTfailure                        NA    0.00e+00   NA    NA
## drugddI:gendermale:prevOIAIDS:AZTfailure                    NA    0.00e+00   NA    NA
## CD4:drugddI:gendermale:prevOIAIDS:AZTfailure                NA    0.00e+00   NA    NA
## Log(scale)                                           -6.59e-03    6.09e-02 -0.11 0.914
##
## Scale= 0.993
##
## Log Normal distribution
## Loglik(model)= -650.2   Loglik(intercept only)= -713.7
##  Chisq= 127.06 on 31 degrees of freedom, p= 1.4e-13
## Number of Newton-Raphson Iterations: 18
## n= 400
```

```r
paste0("AIC of Interactions Model: ", AIC(lognorm_full_ti_int))
```

```
## [1] "AIC of Interactions Model: 1366.43313674881"
```

```r
# Stepwise interaction model
lognorm_full_ti_int_step <- step(lognorm_full_ti_int,
                      scope = list(upper = ~ (CD4 + drug + gender + prevOI + AZT)^5),
                      trace = 0)
summary(lognorm_full_ti_int_step)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
##     AZT + CD4:gender + CD4:prevOI + CD4:AZT + drug:prevOI + gender:prevOI +
##     gender:AZT + CD4:gender:prevOI + CD4:gender:AZT, data = myaids.id,
##     dist = "lognormal")
##                    Value Std. Error     z       p
## (Intercept)       4.6525     0.8149  5.71 1.1e-08
## CD4              -0.0858     0.0608 -1.41  0.1579
## drugddI          -0.8655     0.2804 -3.09  0.0020
## gendermale       -1.0702     0.8375 -1.28  0.2013
## prevOIAIDS       -3.2253     1.0062 -3.21  0.0013
## AZTfailure        1.6130     0.9655  1.67  0.0948
## CD4:gendermale    0.1602     0.0692  2.32  0.0206
## CD4:prevOIAIDS    0.3733     0.1496  2.50  0.0126
## CD4:AZTfailure   -0.6159     0.2143 -2.87  0.0041
```

```
## drugddI:prevOIAIDS         0.8318         0.3135  2.65  0.0080
## gendermale:prevOIAIDS       2.0272         1.0412  1.95  0.0515
## gendermale:AZTfailure      -2.0650         1.0033 -2.06  0.0396
## CD4:gendermale:prevOIAIDS  -0.3709         0.1566 -2.37  0.0179
## CD4:gendermale:AZTfailure   0.6968         0.2195  3.18  0.0015
## Log(scale)                  0.0161         0.0607  0.26  0.7913
##
## Scale= 1.02
##
## Log Normal distribution
## Loglik(model)= -655.5   Loglik(intercept only)= -713.7
##   Chisq= 116.43 on 13 degrees of freedom, p= 1e-18
## Number of Newton-Raphson Iterations: 4
## n= 400
```

```r
paste0("AIC of Interactions Model with Stepwise Selection: ", AIC(lognorm_full_ti_int_step))
```

```
## [1] "AIC of Interactions Model with Stepwise Selection: 1341.06676972302"
```

```r
# Final log-normal model
lognorm_ti_final <- survreg(Surv(Time, death) ~ CD4 + drug + gender + prevOI +
    AZT + CD4:gender + CD4:prevOI + CD4:AZT + drug:prevOI + gender:prevOI +
    gender:AZT + CD4:gender:prevOI + CD4:gender:AZT, data = myaids.id,
    dist = "lognormal")
summary(lognorm_ti_final)
```

```
##
## Call:
## survreg(formula = Surv(Time, death) ~ CD4 + drug + gender + prevOI +
##     AZT + CD4:gender + CD4:prevOI + CD4:AZT + drug:prevOI + gender:prevOI +
##     gender:AZT + CD4:gender:prevOI + CD4:gender:AZT, data = myaids.id,
##     dist = "lognormal")
##                            Value Std. Error     z       p
## (Intercept)               4.6525     0.8149  5.71 1.1e-08
## CD4                      -0.0858     0.0608 -1.41  0.1579
## drugddI                  -0.8655     0.2804 -3.09  0.0020
## gendermale               -1.0702     0.8375 -1.28  0.2013
## prevOIAIDS               -3.2253     1.0062 -3.21  0.0013
## AZTfailure                1.6130     0.9655  1.67  0.0948
## CD4:gendermale            0.1602     0.0692  2.32  0.0206
## CD4:prevOIAIDS            0.3733     0.1496  2.50  0.0126
## CD4:AZTfailure           -0.6159     0.2143 -2.87  0.0041
## drugddI:prevOIAIDS        0.8318     0.3135  2.65  0.0080
## gendermale:prevOIAIDS     2.0272     1.0412  1.95  0.0515
## gendermale:AZTfailure    -2.0650     1.0033 -2.06  0.0396
## CD4:gendermale:prevOIAIDS -0.3709     0.1566 -2.37  0.0179
## CD4:gendermale:AZTfailure  0.6968     0.2195  3.18  0.0015
## Log(scale)                0.0161     0.0607  0.26  0.7913
##
## Scale= 1.02
##
## Log Normal distribution
## Loglik(model)= -655.5   Loglik(intercept only)= -713.7
##   Chisq= 116.43 on 13 degrees of freedom, p= 1e-18
```

```
## Number of Newton-Raphson Iterations: 4
## n= 400
```

```r
paste0("AIC Final Selected Model: ", AIC(lognorm_ti_final))
```

```
## [1] "AIC Final Selected Model: 1341.06676972302"
```

```r
# ---- Build Model Comparison Table ----
model_comp_all <- bind_rows(
  # Cox Time-Independent
  cbind(Section = "Cox Proportional Hazards (Time-Independent)",
        Model = "Null", extract_metrics_cox(cox_ti_null)),
  cbind(Section = "Cox Proportional Hazards (Time-Independent)",
        Model = "Main Effects", extract_metrics_cox(cox_full_ti_uni)),
  cbind(Section = "Cox Proportional Hazards (Time-Independent)",
        Model = "Stepwise", extract_metrics_cox(cox_full_ti_uni_step)),
  cbind(Section = "Cox Proportional Hazards (Time-Independent)",
        Model = "Interaction Full", extract_metrics_cox(cox_full_ti_int)),
  cbind(Section = "Cox Proportional Hazards (Time-Independent)",
        Model = "Interaction Stepwise", extract_metrics_cox(cox_full_ti_int_step)),

  # Cox Time-Dependent
  cbind(Section = "Cox Proportional Hazards (Time-Dependent)",
        Model = "Null", extract_metrics_cox(cox_td_null)),
  cbind(Section = "Cox Proportional Hazards (Time-Dependent)",
        Model = "Main Effects", extract_metrics_cox(cox_full_td_uni)),
  cbind(Section = "Cox Proportional Hazards (Time-Dependent)",
        Model = "Stepwise", extract_metrics_cox(cox_full_td_uni_step)),
  cbind(Section = "Cox Proportional Hazards (Time-Dependent)",
        Model = "Interaction Full", extract_metrics_cox(cox_full_td_int)),
  cbind(Section = "Cox Proportional Hazards (Time-Dependent)",
        Model = "Interaction Stepwise", extract_metrics_cox(cox_full_td_int_step)),

  # AFT Weibull
  cbind(Section = "AFT: Weibull", Model = "Null",
        extract_metrics_aft(weibull_ti_null)),
  cbind(Section = "AFT: Weibull", Model = "Main Effects",
        extract_metrics_aft(weibull_full_ti_uni)),
  cbind(Section = "AFT: Weibull", Model = "Stepwise",
        extract_metrics_aft(weibull_full_ti_uni_step)),
  cbind(Section = "AFT: Weibull", Model = "Interaction Full",
        extract_metrics_aft(weibull_full_ti_int)),
  cbind(Section = "AFT: Weibull", Model = "Interaction Stepwise",
        extract_metrics_aft(weibull_full_ti_int_step)),

  # AFT Log-Normal
  cbind(Section = "AFT: Log-Normal", Model = "Null",
        extract_metrics_aft(lognorm_ti_null)),
  cbind(Section = "AFT: Log-Normal", Model = "Main Effects",
        extract_metrics_aft(lognorm_full_ti_uni)),
  cbind(Section = "AFT: Log-Normal", Model = "Stepwise",
        extract_metrics_aft(lognorm_full_ti_uni_step)),
  cbind(Section = "AFT: Log-Normal", Model = "Interaction Full",
        extract_metrics_aft(lognorm_full_ti_int)),
```

```r
    cbind(Section = "AFT: Log-Normal", Model = "Interaction Stepwise",
          extract_metrics_aft(lognorm_full_ti_int_step))
  ) %>%
  mutate(row_id = row_number())  # Unique ID for later reference

# ---- Get Row IDs with Lowest AIC in Each Section ----
highlight_ids <- model_comp_all %>%
  group_by(Section) %>%
  filter(AIC == min(AIC, na.rm = TRUE)) %>%
  pull(row_id)

# ---- Build GT Table ----
model_comp_all %>%
  gt(groupname_col = "Section") %>%
  tab_header(title = md("**Table A1. Model Comparison: Cox (TI/TD) and Parametric AFT Models**")) %>%
  fmt_number(columns = c(Log_Likelihood, AIC, Concordance), decimals = 3) %>%
  cols_label(
    Model = "Model",
    Log_Likelihood = "Log-Likelihood",
    Degrees_of_Freedom = "DF",
    AIC = "AIC",
    Concordance = "Concordance (C-index)"
  ) %>%
  tab_style(
    style = list(cell_fill(color = "#d0f0c0"), cell_text(weight = "bold")),
    locations = cells_body(
      rows = row_id %in% highlight_ids,
      columns = AIC
    )
  ) %>%
  tab_options(
    table.font.size = "x-small",
    data_row.padding = px(0),
    table.width = pct(100)
  ) %>%
  cols_hide(columns = row_id) %>% as_latex()

# -------------------------------------------------
# Time independent Cox model - Model Diagnostics
# -------------------------------------------------

## Influential observations
# DFBETAs (for each covariate)
dfb_ti <- residuals(cox_ti_final, type = "dfbeta")
colnames(dfb_ti) <- names(coef(cox_ti_final))
dfb_ti_df <- as.data.frame(dfb_ti)
dfb_ti_df$Observation <- 1:nrow(dfb_ti_df)
dfb_ti_long <- pivot_longer(dfb_ti_df, -Observation, names_to = "Covariate",
                            values_to = "DFBETA")
dfb_ti_extreme <- dfb_ti_long %>%
  filter(abs(DFBETA) > 0.5)

dfb_ti_extreme_summary <- dfb_ti_extreme %>%
```

Table A1. Model Comparison: Cox (TI/TD) and Parametric AFT Models

Model	Log-Likelihood	DF	AIC	Concordance (C-index)
Cox Proportional Hazards (Time-Independent)				
Null	-911.301	0	1,822.602	0.000
Main Effects	-864.571	5	1,739.141	0.716
Stepwise	-865.511	4	1,739.021	0.712
Interaction Full	-845.108	31	1,752.215	0.736
Interaction Stepwise	-846.448	21	**1,734.896**	0.737
Cox Proportional Hazards (Time-Dependent)				
Null	-911.301	0	1,822.602	0.000
Main Effects	-861.757	5	1,733.515	0.719
Stepwise	-862.472	4	1,732.943	0.715
Interaction Full	-847.845	25	1,745.690	0.740
Interaction Stepwise	-851.655	11	**1,725.310**	0.733
AFT: Weibull				
Null	-712.924	2	1,429.848	NA
Main Effects	-665.507	7	1,345.014	NA
Stepwise	-666.429	6	1,344.858	NA
Interaction Full	-646.136	33	1,358.272	NA
Interaction Stepwise	-647.447	23	**1,340.894**	NA
AFT: Log-Normal				
Null	-713.748	2	1,431.496	NA
Main Effects	-670.990	7	1,355.980	NA
Stepwise	-671.524	6	1,355.049	NA
Interaction Full	-650.217	33	1,366.433	NA
Interaction Stepwise	-655.533	15	**1,341.067**	NA

```r
  group_by(Covariate) %>%
  summarise(
    n_extreme = n(),
    Obs_IDs = paste(unique(Observation), collapse = ", "),
    .groups = "drop"
  )


dfb_ti_extreme_summary %>%
  gt() %>%
  tab_header(title = md("**Table A2: Cox time-independent model –
                  Covariates with DFBETA > 0.5**")) %>%
  cols_label(
    Covariate = "Covariate",
    n_extreme = "# Influential Obs",
    Obs_IDs = "Observation IDs"
  ) %>%
  tab_options(table.font.size = "small")

### Proportional hazards assumption validation (Schoenfeld Residuals)
#### Run cox.zph() to test PH assumption
```

Table A2: Cox time-independent model - Covariates with DFBETA > 0.5

Covariate	# Influential Obs	Observation IDs
AZTfailure	5	18, 210, 244, 347, 399
drugddI	10	15, 24, 68, 96, 130, 185, 244, 298, 347, 399
drugddI:AZTfailure	6	18, 164, 210:244, 347, 399
drugddI:gendermale	10	15, 24, 68, 96, 130, 185, 244, 298, 347, 399
drugddI:gendermale:AZTfailure	6	18, 164, 210, 244, 347, 399
drugddI:gendermale:prevOIAIDS	8	15, 24, 68, 96, 185, 244, 298, 347
drugddI:prevOIAIDS	8	15, 24, 68, 96, 185, 244, 298, 347
gendermale	12	6, 15, 24, 30, 68, 96, 130, 185, 244, 298, 347, 399
gendermale:AZTfailure	5	18, 210, 244, 347, 399
gendermale:prevOIAIDS	10	6, 15, 24, 30, 68, 96, 185, 244, 298, 347
prevOIAIDS	10	6, 15, 24, 30, 68, 96, 185, 244, 298, 347

```r
ph_ti_test <- cox.zph(cox_ti_final)
#### Convert cox.zph output to a data frame
ph_ti_df <- as.data.frame(ph_ti_test$table)
ph_ti_df$Covariate <- rownames(ph_ti_df)
colnames(ph_ti_df) <- c("rho", "chisq", "p", "Covariate")
ph_ti_global <- ph_ti_df[ph_ti_df$Covariate == "GLOBAL", ]
ph_ti_df <- ph_ti_df[ph_ti_df$Covariate != "GLOBAL", ]

gt(ph_ti_df) %>%
  gt::tab_header(title = md("**Table A3. Cox time-independent model -
                      Schoenfeld Residual Test for Proportional Hazards**")) %>%
  fmt_number(columns = c("rho", "chisq", "p"), decimals = 4) %>%
  cols_label(
    Covariate = "Covariate",
    rho = "Correlation ( )",
    chisq = "Chi-squared",
    p = "p-value"
  ) %>%
  data_color(
    columns = vars(p),
    colors = scales::col_bin(
      bins = c(0, 0.05, 1),
      palette = c("tomato", "gray90")
    )
  ) %>%
  tab_source_note(md(paste0("**GLOBAL TEST**:  ² = ",
                      round(ph_ti_global$chisq, 2),
                      ", p = ",
                      round(ph_ti_global$p, 4))))

## Color    Meaning
# Tomato     p < 0.05 → potential PH violation
# Gray90     p   0.05 → no significant violation

# -------------------------------------------------
# Time dependent Cox model - Model Diagnostics
# -------------------------------------------------
```

Table A3. Cox time-independent model - Schoenfeld Residual Test for Proportional Hazards

Correlation ( )	Chi-squared	p-value	Covariate
0.1704	1.0000	0.6797	CD4
0.0944	1.0000	0.7586	drug
0.3599	1.0000	0.5486	gender
0.1843	1.0000	0.6677	prevOI
0.4246	1.0000	0.5146	AZT
0.3585	1.0000	0.5493	CD4:drug
0.0748	1.0000	0.7845	CD4:gender
0.9826	1.0000	0.3216	CD4:prevOI
1.1969	1.0000	0.2739	CD4:AZT
0.0091	1.0000	0.9242	drug:gender
0.3526	1.0000	0.5526	drug:prevOI
0.2523	1.0000	0.6155	drug:AZT
0.0126	1.0000	0.9107	gender:prevOI
0.2553	1.0000	0.6134	gender:AZT
0.0013	1.0000	0.9713	CD4:drug:gender
0.0483	1.0000	0.8260	CD4:drug:AZT
0.2130	1.0000	0.6444	CD4:gender:prevOI
0.7758	1.0000	0.3784	CD4:gender:AZT
0.0995	1.0000	0.7524	drug:gender:prevOI
0.3431	1.0000	0.5580	drug:gender:AZT
0.0680	1.0000	0.7943	CD4:drug:gender:AZT

GLOBAL TEST: $^2 = 21$, p = 0.0021

```r
## Influential observations
# DFBETAs (for each covariate)
dfb_td <- residuals(cox_td_final, type = "dfbeta")
colnames(dfb_td) <- names(coef(cox_td_final))
dfb_td_df <- as.data.frame(dfb_td)
dfb_td_df$Observation <- 1:nrow(dfb_td_df)

dfb_td_long <- pivot_longer(dfb_td_df, -Observation, names_to = "Covariate",
                            values_to = "DFBETA")
dfb_td_extreme <- dfb_td_long %>%
  filter(abs(DFBETA) > 0.5)

dfb_td_extreme_summary <- dfb_td_extreme %>%
  group_by(Covariate) %>%
  summarise(
    n_extreme = n(),
    Obs_IDs = paste(unique(Observation), collapse = ", "),
    .groups = "drop"
  )

dfb_td_extreme_summary %>%
  gt() %>%
  tab_header(title = md("**Table A4: Influential Observations in Time-Dependent Cox Model**")) %>%
```

Table A4: Influential Observations in Time-Dependent Cox Model

Covariate	# Influential Obs	Observation IDs

```r
  cols_label(
    Covariate = "Covariate",
    n_extreme = "# Influential Obs",
    Obs_IDs = "Observation IDs"
  ) %>%
  tab_options(table.font.size = "small")

### Schoenfeld Residual Test for TD
ph_td_test <- cox.zph(cox_td_final)
ph_td_df <- as.data.frame(ph_td_test$table)
ph_td_df$Covariate <- rownames(ph_td_df)
colnames(ph_td_df) <- c("rho", "chisq", "p", "Covariate")
ph_td_global <- ph_td_df[ph_td_df$Covariate == "GLOBAL", ]
ph_td_df <- ph_td_df[ph_td_df$Covariate != "GLOBAL", ]

gt(ph_td_df) %>%
  tab_header(title = md("**Table A5: Schoenfeld Residuals for TD Cox Model**")) %>%
  fmt_number(columns = c("rho", "chisq", "p"), decimals = 4) %>%
  cols_label(
    Covariate = "Covariate",
    rho = "Correlation ( )",
    chisq = "Chi-squared",
    p = "p-value"
  ) %>%
  data_color(
    columns = vars(p),
    colors = scales::col_bin(bins = c(0, 0.05, 1), palette = c("tomato", "gray90"))
  ) %>%
  tab_source_note(md(paste0("**GLOBAL TEST**:  ² = ",
                            round(ph_td_global$chisq, 2),
                            ", p = ",
                            round(ph_td_global$p, 4))))
```

Table A5: Schoenfeld Residuals for TD Cox Model

Correlation (ρ)	Chi-squared	p-value	Covariate
0.0233	1.0000	0.8786	CD4
0.0164	1.0000	0.8981	drug
0.0007	1.0000	0.9795	gender
0.0772	1.0000	0.7811	prevOI
0.2408	1.0000	0.6236	AZT
0.0866	1.0000	0.7686	CD4:gender
0.7932	1.0000	0.3731	CD4:prevOI
0.5208	1.0000	0.4705	CD4:AZT
0.0102	1.0000	0.9197	drug:prevOI
0.2228	1.0000	0.6369	gender:AZT
0.4066	1.0000	0.5237	CD4:gender:AZT

GLOBAL TEST: $\chi^2 = 11$, p = 0.9965