Survival Analysis Project: HIV Clinical Trial

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Contents


```
knitr::opts_chunk$set(message=FALSE, warning=FALSE, fig.height=3, fig.width=5,
                      fig.align="center")
library(tidyverse)
library(broom)
library(plyr)
library(survival)
library(survminer)
library(coxed)


aids <- read.csv( "http://pages.pomona.edu/~jsh04747/courses/math150/AIDSdata.csv")
dim(aids)
```

```
## [1] 851  16
```

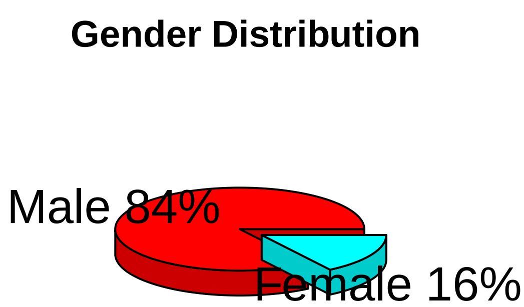
```
summary(aids)
```

```
##        id              time           censor             time_d
##  Min.   :   1.0   Min.   :  1.0   Min.   :0.00000   Min.   :  1.0
##  1st Qu.: 287.5   1st Qu.:179.5   1st Qu.:0.00000   1st Qu.:199.5
##  Median : 581.0   Median :257.0   Median :0.00000   Median :266.0
##  Mean   : 579.5   Mean   :231.8   Mean   :0.08108   Mean   :243.4
##  3rd Qu.: 873.0   3rd Qu.:300.0   3rd Qu.:0.00000   3rd Qu.:306.0
##  Max.   :1156.0   Max.   :362.0   Max.   :1.00000   Max.   :362.0
##    censor_d            tx             txgrp          strat2
##  Min.   :0.0000   Min.   :0.0000   Min.   :1.000   Min.   :0.0000
##  1st Qu.:0.0000   1st Qu.:0.0000   1st Qu.:1.000   1st Qu.:0.0000
##  Median :0.0000   Median :1.0000   Median :2.000   Median :1.0000
##  Mean   :0.0235   Mean   :0.5041   Mean   :1.504   Mean   :0.6157
##  3rd Qu.:0.0000   3rd Qu.:1.0000   3rd Qu.:2.000   3rd Qu.:1.0000
##  Max.   :1.0000   Max.   :1.0000   Max.   :2.000   Max.   :1.0000
##       sex            raceth          ivdrug          hemophil
##  Min.   :1.000   Min.   :1.000   Min.   :1.000   Min.   :0.00000
##  1st Qu.:1.000   1st Qu.:1.000   1st Qu.:1.000   1st Qu.:0.00000
##  Median :1.000   Median :1.000   Median :1.000   Median :0.00000
```

```
##  Mean   :1.157   Mean   :1.706   Mean   :1.317   Mean   :0.03408
##  3rd Qu.:1.000   3rd Qu.:2.000   3rd Qu.:1.000   3rd Qu.:0.00000
##  Max.   :2.000   Max.   :5.000   Max.   :3.000   Max.   :1.00000
##      karnof            cd4            priorzdv           age
##  Min.   : 70.00   Min.   :  0.00   Min.   :  3.00   Min.   :15.00
##  1st Qu.: 90.00   1st Qu.: 22.25   1st Qu.: 11.00   1st Qu.:33.00
##  Median : 90.00   Median : 75.00   Median : 21.00   Median :38.00
##  Mean   : 91.34   Mean   : 86.45   Mean   : 30.63   Mean   :38.81
##  3rd Qu.:100.00   3rd Qu.:135.75   3rd Qu.: 44.00   3rd Qu.:44.00
##  Max.   :100.00   Max.   :348.00   Max.   :288.00   Max.   :73.00
```

The data set contains a sample size equal to 851 participants and 16 different variables.

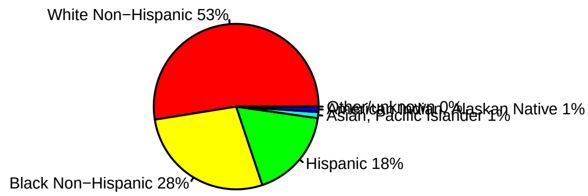
```r
library(plotrix)
male<-sum(aids$sex==1)
female<-sum(aids$sex==2)
slices <- c(male, female)
lbls <- c("Male", "Female")
pct <- round(slices/sum(slices)*100)
lbls <- paste(lbls, pct)
lbls <- paste(lbls,"%",sep="")
pie3D(slices,labels=lbls,explode=0.1,
   main="Gender Distribution ", cex.lab=0.1)
```



The Pie Chart represents the gender distribution in the sample, with 84% male and 16% female. This shows the potential for the data to not be able to correctly represent the difference of the data variance by gender, if there were to be one. Therefore, gender is something to look into in future data analysis.

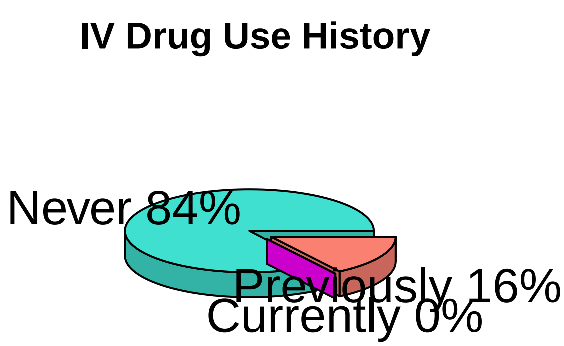
```r
wnh<-sum(aids$raceth==1)
bnh<-sum(aids$raceth==2)
h<-sum(aids$raceth==3)
api<-sum(aids$raceth==4)
aian<-sum(aids$raceth==5)
oth<-sum(aids$raceth==6)
slices <- c(wnh,bnh,h,api,aian,oth)
lbls <- c("White Non-Hispanic", "Black Non-Hispanic", "Hispanic","Asian, Pacific Islander",
          "American Indian, Alaskan Native", "Other/unknown")
pct <- round(slices/sum(slices)*100)
lbls <- paste(lbls, pct)
lbls <- paste(lbls,"%",sep="")
```

```
pie(slices,lbls,col = rainbow(length(lbls)), cex=0.5 )
```



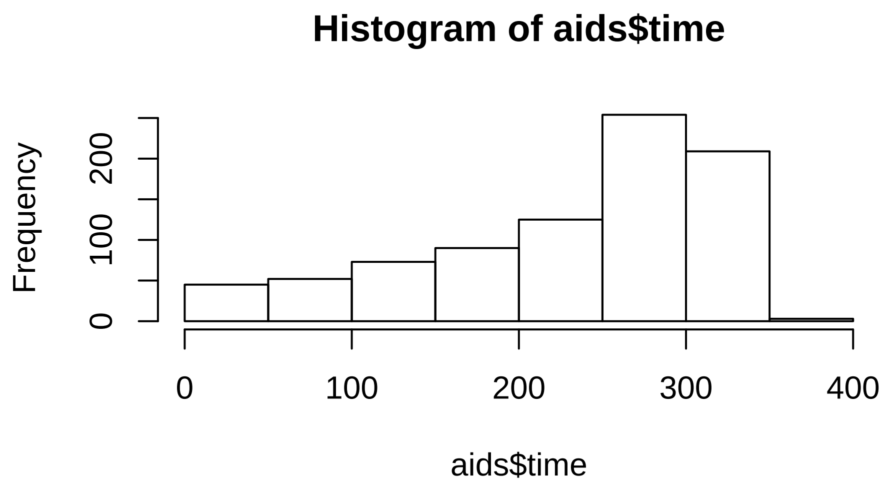
The distribution od race/ethnicity shows that the greatest number of participants consists of white non-hispanic identifying indicideals, with black non-hispanic following and hispanic as the 3rd largest represented group.

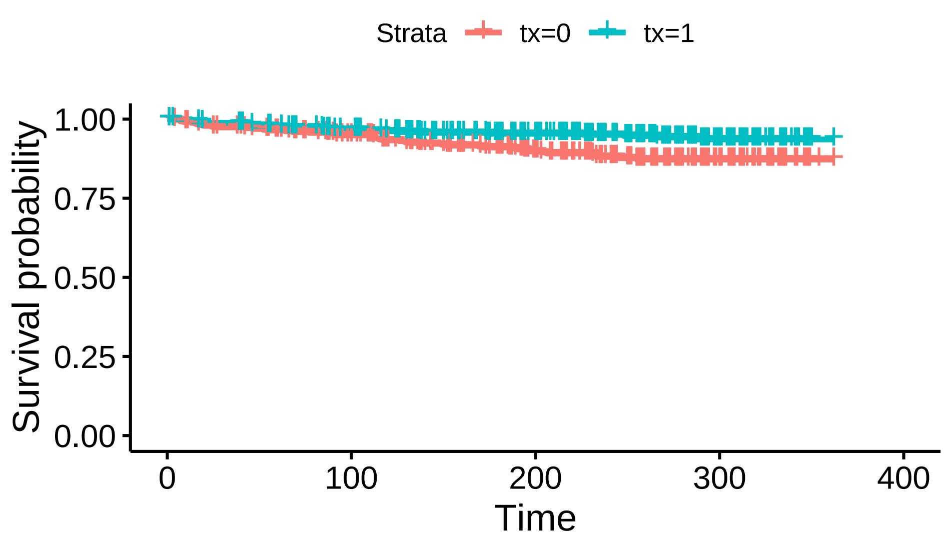
```
never<-sum(aids$ivdrug==1)
cur<-sum(aids$ivdrug==2)
prev<-sum(aids$ivdrug==3)
slices <- c(never,cur,prev)
lbls <- c("Never", "Currently", "Previously")
pct <- round(slices/sum(slices)*100)
lbls <- paste(lbls, pct)
lbls <- paste(lbls,"%",sep="")
pie3D(slices,labels=lbls,explode=0.1,col=c("turquoise","magenta","salmon"),cex.sub=0.5,
   main="IV Drug Use History ")
```



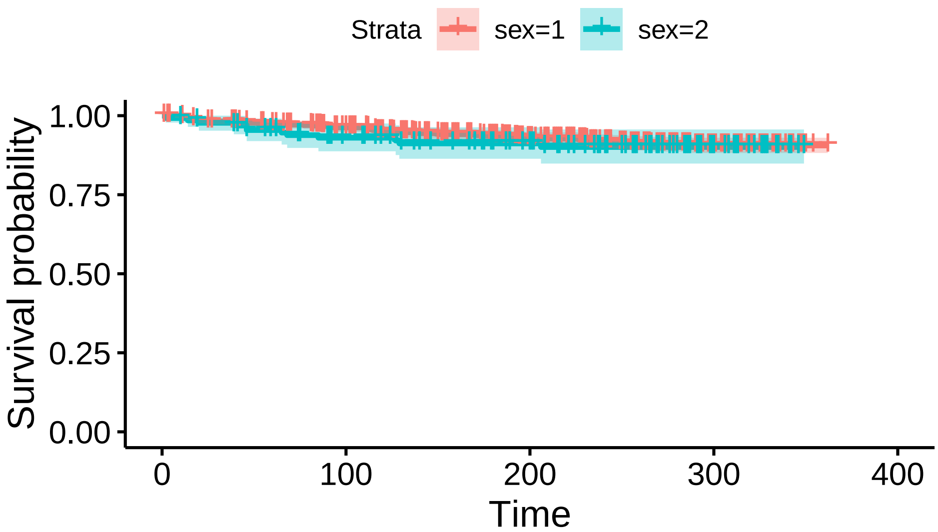
From this chart we see that most of the participants (84%) have never used IV drugs, whereas 16% of participants have some type of history of usage and none of the participants reported to be currently using the drugs.

```r
hist(aids$time)

###Data Plots

fit <- survfit(Surv(time,censor)~tx, data = aids)
ggsurvplot(fit,data = aids,conf.int = FALSE)
```

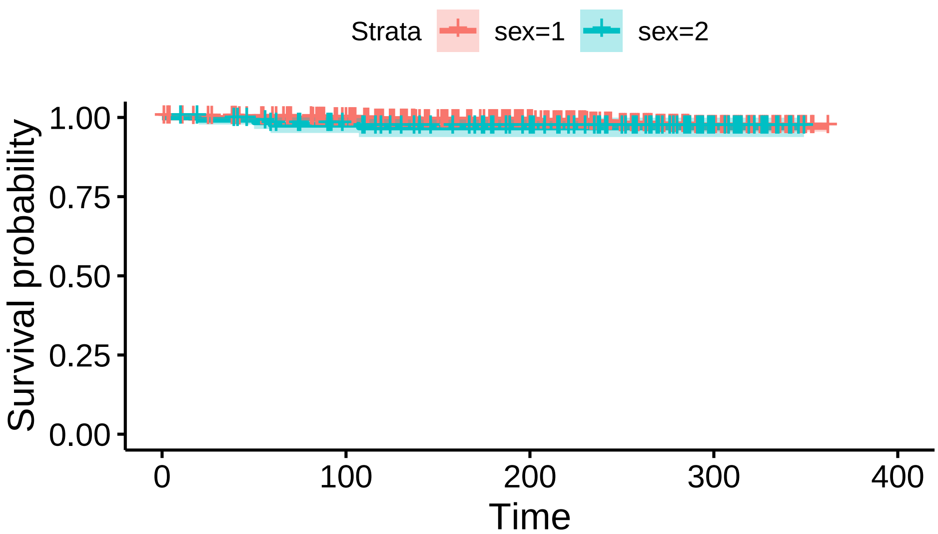





```r
aids_fit_time <- survfit(Surv(time, censor) ~ sex, data=aids)
ggsurvplot(aids_fit_time, data=aids,  conf.int = TRUE)
```




```
aids_fit_time.d <- survfit(Surv(time_d, censor_d) ~ sex, data=aids)
ggsurvplot(aids_fit_time.d, data=aids,  conf.int = TRUE)
```



Survival Analysis

```
#mutation of age
aids <- read.csv( "http://pages.pomona.edu/~jsh04747/courses/math150/AIDSdata.csv")
aids <- aids %>%
  mutate(age = ifelse(age <= 20, "under20",
                           ifelse(age <=30, "20-30",
                                  ifelse(age <= 40, "30-40",
                                         ifelse(age <=50, "40-50",
                                                ifelse(age <=60, "50-60",
                                                       ifelse(age <=70, "60-70",
                                                              "over70"))))))) %>%
  mutate(age = factor(age,
                      levels = c("under20", "20-30", "30-40","40-50", "50-60","60-70","over70")),
```

```
        sex = ifelse(sex == 2, "male","female"))
```

Since there are many vuales of the explanatory variable "age" in the original data, we've decided to mutate the variable into age categories from under 20 to over 70 in incriments of 10 years.

```
library(survival)
library (survminer)
library(ggplot2)
library(broom)

##### backwards selection ######


#full model
cph_full<- coxph(Surv(time,censor)~., data = aids)
cph_full$loglik
```

```
## [1] -452.6325 -380.7368
```

```
cph_full
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ ., data = aids)
##
##                  coef  exp(coef)   se(coef)      z        p
## id          2.136e-05  1.000e+00  3.956e-04  0.054  0.95695
## time_d      1.362e-03  1.001e+00  2.139e-03  0.637  0.52432
## censor_d    2.887e+00  1.795e+01  3.990e-01  7.237 4.59e-13
## tx         -3.917e-01  6.759e-01  2.757e-01 -1.421  0.15540
## txgrp              NA         NA  0.000e+00     NA       NA
## strat2      3.418e-01  1.408e+00  4.397e-01  0.777  0.43690
## sexmale     3.152e-01  1.371e+00  3.518e-01  0.896  0.37024
## raceth     -8.821e-02  9.156e-01  1.543e-01 -0.572  0.56759
## ivdrug     -3.625e-01  6.959e-01  1.942e-01 -1.867  0.06197
## hemophil   -1.247e-01  8.828e-01  7.136e-01 -0.175  0.86132
## karnof     -4.400e-02  9.569e-01  1.555e-02 -2.829  0.00467
## cd4        -1.592e-02  9.842e-01  4.988e-03 -3.191  0.00142
## priorzdv   -1.722e-04  9.998e-01  5.076e-03 -0.034  0.97293
## age20-30   -8.852e-01  4.126e-01  1.249e+00 -0.709  0.47862
## age30-40   -8.065e-01  4.464e-01  1.216e+00 -0.663  0.50706
## age40-50   -7.004e-01  4.964e-01  1.207e+00 -0.580  0.56174
## age50-60   -3.926e-01  6.753e-01  1.252e+00 -0.314  0.75384
## age60-70   -1.054e+00  3.485e-01  1.617e+00 -0.652  0.51443
## ageover70 -1.362e+01  1.214e-06  2.189e+03 -0.006  0.99503
##
## Likelihood ratio test=143.8  on 18 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```
#reduced model 1
cph_r1 <- coxph(Surv(time,censor)~.-priorzdv, data = aids)
cph_r1$loglik
```

```
## [1] -452.6325 -380.7374
```

```
cph_r1
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv, data = aids)
##
```

```
##                 coef  exp(coef)   se(coef)      z        p
## id          2.138e-05  1.000e+00  3.956e-04  0.054  0.95690
## time_d      1.364e-03  1.001e+00  2.137e-03  0.638  0.52338
## censor_d    2.889e+00  1.797e+01  3.977e-01  7.263 3.78e-13
## tx         -3.918e-01  6.758e-01  2.756e-01 -1.422  0.15513
## txgrp              NA         NA  0.000e+00     NA       NA
## strat2      3.417e-01  1.407e+00  4.398e-01  0.777  0.43720
## sexmale     3.150e-01  1.370e+00  3.517e-01  0.896  0.37046
## raceth     -8.808e-02  9.157e-01  1.543e-01 -0.571  0.56802
## ivdrug     -3.630e-01  6.956e-01  1.936e-01 -1.875  0.06080
## hemophil   -1.251e-01  8.824e-01  7.137e-01 -0.175  0.86086
## karnof     -4.397e-02  9.570e-01  1.551e-02 -2.835  0.00459
## cd4        -1.592e-02  9.842e-01  4.987e-03 -3.193  0.00141
## age20-30   -8.791e-01  4.151e-01  1.237e+00 -0.711  0.47738
## age30-40   -8.014e-01  4.487e-01  1.207e+00 -0.664  0.50669
## age40-50   -6.951e-01  4.990e-01  1.198e+00 -0.580  0.56163
## age50-60   -3.881e-01  6.783e-01  1.246e+00 -0.312  0.75539
## age60-70   -1.048e+00  3.508e-01  1.606e+00 -0.652  0.51426
## ageover70 -1.362e+01  1.216e-06  2.190e+03 -0.006  0.99504
##
## Likelihood ratio test=143.8  on 17 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```
#likelihood ratio test
stat1<- 2*(cph_full$loglik[2]-cph_r1$loglik[2])
1-pchisq(stat1,1)
```

```
## [1] 0.9728893
```

```
#reduced model 2
cph_r2 <- coxph(Surv(time,censor)~.-priorzdv -id, data = aids)
cph_r2$loglik
```

```
## [1] -452.6325 -380.7389
```

```
cph_r2
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id, data = aids)
##
##                 coef  exp(coef)   se(coef)      z        p
## time_d      1.382e-03  1.001e+00  2.111e-03  0.654  0.51285
## censor_d    2.894e+00  1.807e+01  3.831e-01  7.555 4.18e-14
## tx         -3.910e-01  6.764e-01  2.752e-01 -1.421  0.15535
## txgrp              NA         NA  0.000e+00     NA       NA
## strat2      3.434e-01  1.410e+00  4.388e-01  0.783  0.43391
## sexmale     3.145e-01  1.370e+00  3.516e-01  0.895  0.37103
## raceth     -8.832e-02  9.155e-01  1.542e-01 -0.573  0.56676
## ivdrug     -3.621e-01  6.962e-01  1.928e-01 -1.878  0.06041
## hemophil   -1.282e-01  8.797e-01  7.115e-01 -0.180  0.85705
## karnof     -4.404e-02  9.569e-01  1.546e-02 -2.849  0.00439
## cd4        -1.592e-02  9.842e-01  4.987e-03 -3.193  0.00141
## age20-30   -8.819e-01  4.140e-01  1.236e+00 -0.713  0.47563
## age30-40   -8.049e-01  4.472e-01  1.205e+00 -0.668  0.50419
## age40-50   -6.981e-01  4.975e-01  1.196e+00 -0.584  0.55950
## age50-60   -3.908e-01  6.765e-01  1.245e+00 -0.314  0.75354
## age60-70   -1.053e+00  3.488e-01  1.603e+00 -0.657  0.51119
## ageover70 -1.362e+01  1.218e-06  2.188e+03 -0.006  0.99503
##
```

```
## Likelihood ratio test=143.8  on 16 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```r
#likelihood ratio test
stat2 <- 2*(cph_r1$loglik[2]-cph_r2$loglik[2])
1-pchisq(stat2,1)
```

```
## [1] 0.9569002
```

```r
#reduced model 3
cph_r3 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil, data = aids)
cph_r3$loglik
```

```
## [1] -452.6325 -380.7555
```

```r
cph_r3
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil,
##     data = aids)
##
##                 coef  exp(coef)   se(coef)      z        p
## time_d     1.359e-03  1.001e+00  2.108e-03  0.645  0.51912
## censor_d   2.882e+00  1.785e+01  3.765e-01  7.654 1.94e-14
## tx        -3.895e-01  6.774e-01  2.752e-01 -1.415  0.15692
## txgrp             NA         NA  0.000e+00     NA       NA
## strat2     3.381e-01  1.402e+00  4.387e-01  0.771  0.44085
## sexmale    3.186e-01  1.375e+00  3.509e-01  0.908  0.36394
## raceth    -8.537e-02  9.182e-01  1.530e-01 -0.558  0.57691
## ivdrug    -3.605e-01  6.973e-01  1.927e-01 -1.871  0.06135
## karnof    -4.402e-02  9.569e-01  1.546e-02 -2.847  0.00441
## cd4       -1.600e-02  9.841e-01  4.990e-03 -3.206  0.00134
## age20-30  -7.754e-01  4.605e-01  1.089e+00 -0.712  0.47650
## age30-40  -6.919e-01  5.006e-01  1.032e+00 -0.670  0.50275
## age40-50  -5.925e-01  5.529e-01  1.045e+00 -0.567  0.57085
## age50-60  -2.756e-01  7.591e-01  1.071e+00 -0.257  0.79702
## age60-70  -9.293e-01  3.948e-01  1.451e+00 -0.640  0.52190
## ageover70 -1.350e+01  1.374e-06  2.187e+03 -0.006  0.99508
##
## Likelihood ratio test=143.8  on 15 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```r
#likelihood ratio test
stat3 <- 2*(cph_r3$loglik[2]-cph_r2$loglik[2])
1-pchisq(stat3,1)
```

```
## [1] 1
```

```r
#reduced model 4
cph_r4 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil -raceth, data = aids)
cph_r4$loglik
```

```
## [1] -452.6325 -380.9154
```

```r
cph_r4
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil -
##     raceth, data = aids)
##
##                 coef  exp(coef)   se(coef)      z        p
```

```
## time_d      1.282e-03  1.001e+00  2.093e-03  0.612  0.54042
## censor_d    2.861e+00  1.748e+01  3.737e-01  7.657 1.91e-14
## tx         -3.907e-01  6.766e-01  2.752e-01 -1.419  0.15576
## txgrp              NA         NA  0.000e+00     NA       NA
## strat2      3.386e-01  1.403e+00  4.373e-01  0.774  0.43871
## sexmale     3.215e-01  1.379e+00  3.487e-01  0.922  0.35665
## ivdrug     -3.823e-01  6.823e-01  1.886e-01 -2.027  0.04265
## karnof     -4.462e-02  9.564e-01  1.549e-02 -2.880  0.00397
## cd4        -1.588e-02  9.842e-01  4.961e-03 -3.202  0.00137
## age20-30   -7.510e-01  4.719e-01  1.087e+00 -0.691  0.48974
## age30-40   -6.587e-01  5.175e-01  1.030e+00 -0.639  0.52254
## age40-50   -5.503e-01  5.768e-01  1.042e+00 -0.528  0.59749
## age50-60   -2.362e-01  7.896e-01  1.069e+00 -0.221  0.82503
## age60-70   -8.498e-01  4.275e-01  1.444e+00 -0.589  0.55611
## ageover70 -1.347e+01  1.418e-06  2.181e+03 -0.006  0.99507
##
## Likelihood ratio test=143.4  on 14 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```r
#likelihood ratio test
stat4 <- 2*(cph_r3$loglik[2]-cph_r4$loglik[2])
1-pchisq(stat4,1)
```

```
## [1] 0.5718012
```

```r
#reduced model 5
cph_r5 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil -raceth -time_d, data = aids)
cph_r5$loglik
```

```
## [1] -452.6325 -381.1059
```

```r
cph_r5
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil -
##     raceth - time_d, data = aids)
##
##                 coef  exp(coef)   se(coef)      z       p
## censor_d    2.741e+00  1.550e+01  3.178e-01  8.625 < 2e-16
## tx         -4.008e-01  6.698e-01  2.738e-01 -1.464 0.14321
## txgrp              NA         NA  0.000e+00     NA      NA
## strat2      3.581e-01  1.431e+00  4.351e-01  0.823 0.41051
## sexmale     2.735e-01  1.315e+00  3.409e-01  0.802 0.42232
## ivdrug     -3.773e-01  6.857e-01  1.881e-01 -2.006 0.04487
## karnof     -4.545e-02  9.556e-01  1.539e-02 -2.953 0.00315
## cd4        -1.602e-02  9.841e-01  4.953e-03 -3.234 0.00122
## age20-30   -6.860e-01  5.036e-01  1.082e+00 -0.634 0.52598
## age30-40   -5.895e-01  5.546e-01  1.024e+00 -0.576 0.56483
## age40-50   -4.787e-01  6.196e-01  1.036e+00 -0.462 0.64393
## age50-60   -1.506e-01  8.602e-01  1.059e+00 -0.142 0.88700
## age60-70   -8.000e-01  4.493e-01  1.443e+00 -0.554 0.57945
## ageover70 -1.342e+01  1.481e-06  2.176e+03 -0.006 0.99508
##
## Likelihood ratio test=143.1  on 13 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```r
#likelihood ratio test
stat5 <- 2*(cph_r5$loglik[2]-cph_r4$loglik[2])
1-pchisq(stat5,1)
```

```
## [1] 1
```

```r
#reduced model 6
cph_r6 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil -raceth -time_d -strat2, data = aids)
cph_r6$loglik
```

```
## [1] -452.6325 -381.4390
```

```r
cph_r6
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil -
##     raceth - time_d - strat2, data = aids)
##
##                 coef  exp(coef)   se(coef)      z       p
## censor_d   2.727e+00  1.529e+01  3.159e-01  8.635 < 2e-16
## tx        -4.203e-01  6.568e-01  2.726e-01 -1.542 0.12303
## txgrp             NA         NA  0.000e+00     NA      NA
## sexmale    2.625e-01  1.300e+00  3.415e-01  0.769 0.44201
## ivdrug    -3.941e-01  6.743e-01  1.873e-01 -2.104 0.03542
## karnof    -4.573e-02  9.553e-01  1.541e-02 -2.967 0.00301
## cd4       -1.295e-02  9.871e-01  3.012e-03 -4.301 1.7e-05
## age20-30  -6.334e-01  5.308e-01  1.079e+00 -0.587 0.55725
## age30-40  -5.580e-01  5.723e-01  1.023e+00 -0.546 0.58539
## age40-50  -4.327e-01  6.487e-01  1.033e+00 -0.419 0.67536
## age50-60  -7.496e-02  9.278e-01  1.054e+00 -0.071 0.94333
## age60-70  -6.578e-01  5.180e-01  1.430e+00 -0.460 0.64555
## ageover70 -1.329e+01  1.691e-06  2.197e+03 -0.006 0.99517
##
## Likelihood ratio test=142.4  on 12 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```r
#likelihood ratio test
stat6 <- 2*(cph_r5$loglik[2]-cph_r6$loglik[2])
1-pchisq(stat6,1)
```

```
## [1] 0.4144233
```

```r
#reduced model 7
cph_r7 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil -raceth -time_d -strat2 -sex,
                data = aids)
cph_r7$loglik
```

```
## [1] -452.6325 -381.7212
```

```r
cph_r7
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil -
##     raceth - time_d - strat2 - sex, data = aids)
##
##                 coef  exp(coef)   se(coef)      z        p
## censor_d   2.723e+00  1.523e+01  3.140e-01  8.672  < 2e-16
## tx        -4.284e-01  6.516e-01  2.723e-01 -1.573  0.11567
## txgrp             NA         NA  0.000e+00     NA       NA
## ivdrug    -4.023e-01  6.688e-01  1.875e-01 -2.146  0.03189
## karnof    -4.622e-02  9.548e-01  1.530e-02 -3.020  0.00253
## cd4       -1.301e-02  9.871e-01  3.012e-03 -4.319 1.57e-05
## age20-30  -5.567e-01  5.731e-01  1.074e+00 -0.518  0.60438
## age30-40  -5.760e-01  5.621e-01  1.023e+00 -0.563  0.57333
## age40-50  -4.452e-01  6.407e-01  1.034e+00 -0.431  0.66667
```

```
## age50-60  -4.385e-02  9.571e-01  1.054e+00 -0.042  0.96680
## age60-70  -6.931e-01  5.000e-01  1.429e+00 -0.485  0.62774
## ageover70 -1.332e+01  1.642e-06  2.195e+03 -0.006  0.99516
##
## Likelihood ratio test=141.8  on 11 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```r
#likelihood ratio test
stat7 <- 2*(cph_r6$loglik[2]-cph_r7$loglik[2])
1-pchisq(stat7,1)
```

```
## [1] 0.45249
```

```r
#reduced model 8
cph_r8 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil -raceth -time_d -strat2
                -sex -txgrp -age, data = aids)
cph_r8$loglik
```

```
## [1] -452.6325 -383.0225
```

```r
cph_r8
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil -
##     raceth - time_d - strat2 - sex - txgrp - age, data = aids)
##
##                coef exp(coef)  se(coef)      z        p
## censor_d  2.801853 16.475139  0.303119  9.243  < 2e-16
## tx       -0.406626  0.665893  0.267694 -1.519  0.12876
## ivdrug   -0.401503  0.669313  0.187580 -2.140  0.03232
## karnof   -0.045366  0.955648  0.015162 -2.992  0.00277
## cd4      -0.012959  0.987125  0.003004 -4.314 1.61e-05
##
## Likelihood ratio test=139.2  on 5 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```r
#likelihood ratio test
stat8 <- 2*(cph_r7$loglik[2]-cph_r8$loglik[2])
1-pchisq(stat8,1)
```

```
## [1] 0.1066782
```

```r
#reduced model 9
cph_r9 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil -raceth -time_d -strat2 -sex
                -txgrp -age -tx, data = aids)
cph_r9$loglik
```

```
## [1] -452.6325 -384.2077
```

```r
cph_r9
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil -
##     raceth - time_d - strat2 - sex - txgrp - age - tx, data = aids)
##
##                coef exp(coef)  se(coef)      z        p
## censor_d  2.919993 18.541150  0.293976  9.933  < 2e-16
## ivdrug   -0.379834  0.683975  0.186804 -2.033  0.04202
## karnof   -0.045797  0.955235  0.015201 -3.013  0.00259
## cd4      -0.013233  0.986854  0.002997 -4.415 1.01e-05
##
```

```
## Likelihood ratio test=136.8  on 4 df, p=< 2.2e-16
## n= 851, number of events= 69
```

```
###best model using backwards selection?
#likelihood ratio test
stat9 <- 2*(cph_r8$loglik[2]-cph_r9$loglik[2])
1-pchisq(stat9,1)
```

```
## [1] 0.1236681
```

```
#reduced model 10
cph_r10 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil -raceth -time_d -strat2 -sex
                 -txgrp -age -tx -censor_d, data = aids)
cph_r10$loglik
```

```
## [1] -452.6325 -417.9688
```

```
cph_r10
```

```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil -
##     raceth - time_d - strat2 - sex - txgrp - age - tx - censor_d,
##     data = aids)
##
##             coef exp(coef)  se(coef)      z        p
## ivdrug -0.216832  0.805065  0.180491 -1.201     0.23
## karnof -0.061043  0.940783  0.014157 -4.312 1.62e-05
## cd4    -0.015127  0.984987  0.003076 -4.917 8.77e-07
##
## Likelihood ratio test=69.33  on 3 df, p=5.947e-15
## n= 851, number of events= 69
```

```
#NOTE: should we take out censor_d anyways since its related to censor or keep it?
#likelihood ratio test
stat10 <- 2*(cph_r9$loglik[2]-cph_r10$loglik[2])
1-pchisq(stat10,1)
```

```
## [1] 2.220446e-16
```

```
coxph(Surv(time_d,censor_d) ~ sex , data=aids)  %>% tidy()
```

```
## # A tibble: 1 x 7
##   term    estimate std.error statistic p.value conf.low conf.high
##   <chr>      <dbl>     <dbl>     <dbl>   <dbl>    <dbl>     <dbl>
## 1 sexmale    0.390     0.559     0.697   0.486   -0.706      1.49
```

```
coxph(Surv(time,censor) ~ sex, data=aids) %>% tidy()
```

```
## # A tibble: 1 x 7
##   term    estimate std.error statistic p.value conf.low conf.high
##   <chr>      <dbl>     <dbl>     <dbl>   <dbl>    <dbl>     <dbl>
## 1 sexmale    0.199     0.318     0.625   0.532   -0.424     0.821
```

```
coxph(Surv(time,censor) ~ age+ txgrp+ karnof, data=aids) %>% tidy()
```

```
## # A tibble: 8 x 7
##   term      estimate std.error statistic       p.value conf.low conf.high
##   <chr>        <dbl>     <dbl>     <dbl>         <dbl>    <dbl>     <dbl>
## 1 age20-30   -0.438      1.07     -0.409   0.682          -2.53      1.66
## 2 age30-40   -0.442      1.02     -0.434   0.665          -2.44      1.55
## 3 age40-50   -0.361      1.03     -0.352   0.725          -2.37      1.65
## 4 age50-60    0.460      1.04      0.442   0.659          -1.58      2.50
```

```
## 5 age60-70   -0.780      1.42    -0.551   0.582           -3.55     2.00
## 6 ageover70 -14.1    2688.      -0.00525 0.996          -Inf      Inf
## 7 txgrp      -0.844      0.257   -3.28    0.00103          -1.35    -0.340
## 8 karnof     -0.0814     0.0138  -5.89    0.00000000385   -0.109   -0.0543
```

```
cox.zph(coxph(Surv(time,censor) ~ age + txgrp+karnof, data=aids))
```

```
##                rho    chisq     p
## age20-30   0.09054 5.70e-01 0.450
## age30-40   0.19294 2.53e+00 0.112
## age40-50   0.14871 1.50e+00 0.220
## age50-60   0.19861 2.69e+00 0.101
## age60-70   0.16251 1.81e+00 0.179
## ageover70  0.16355 2.57e-07 1.000
## txgrp     -0.10779 8.34e-01 0.361
## karnof     0.00121 1.03e-04 0.992
## GLOBAL          NA 7.98e+00 0.435
```

```
coxph(Surv(time,censor) ~ age *txgrp*karnof, data=aids) %>% tidy()
```

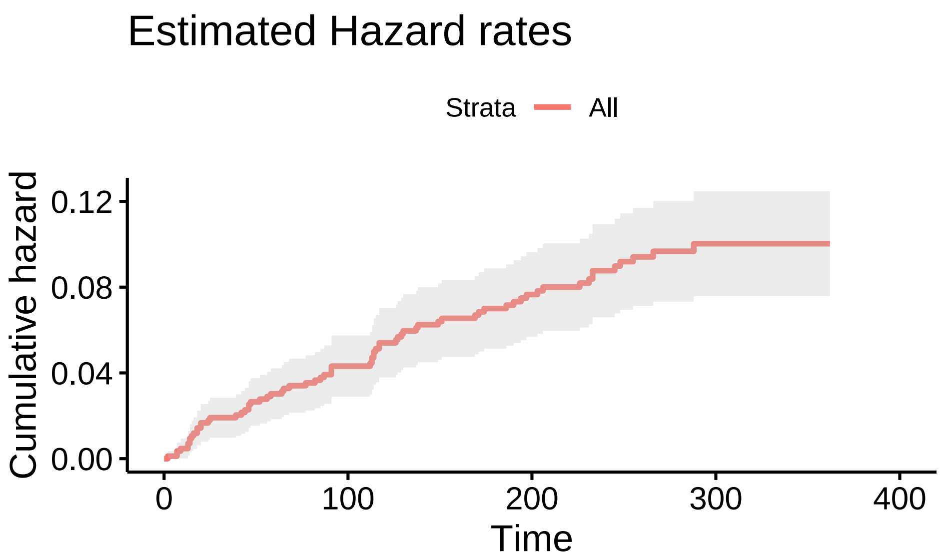
```
## # A tibble: 27 x 7
##    term           estimate std.error  statistic p.value conf.low conf.high
##    <chr>             <dbl>     <dbl>      <dbl>   <dbl>    <dbl>     <dbl>
##  1 age20-30         307.     138277.  0.00222     0.998     -Inf       Inf
##  2 age30-40         319.     138277.  0.00231     0.998     -Inf       Inf
##  3 age40-50         327.     138277.  0.00237     0.998     -Inf       Inf
##  4 age50-60         343.     138277.  0.00248     0.998     -Inf       Inf
##  5 age60-70         287.     176491.  0.00163     0.999     -Inf       Inf
##  6 ageover70         -1.66    29414. -0.0000565   1.000     -Inf       Inf
##  7 txgrp            150.      92392.  0.00163     0.999     -Inf       Inf
##  8 karnof             3.36     1424.  0.00236     0.998     -Inf       Inf
##  9 age20-30:txgrp  -144.      92392. -0.00156     0.999     -Inf       Inf
## 10 age30-40:txgrp  -146.      92392. -0.00158     0.999     -Inf       Inf
## # ... with 17 more rows
```

```
cox.zph(coxph(Surv(time,censor) ~ age *txgrp*karnof, data=aids))
```

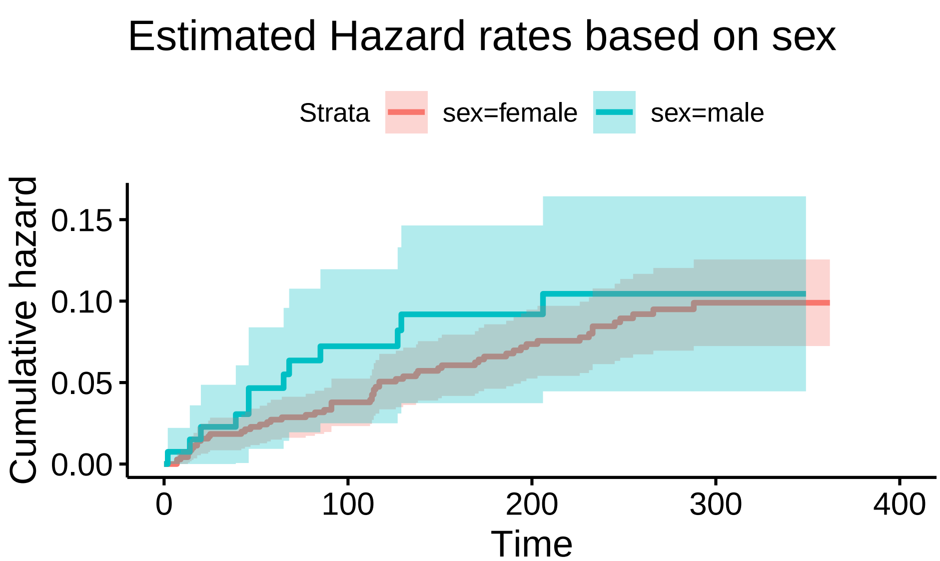
```
##                          rho    chisq     p
## age20-30             -0.1008 4.31e-08 1.000
## age30-40             -0.1583 3.15e-08 1.000
## age40-50             -0.0965 1.25e-08 1.000
## age50-60             -0.2071 6.53e-08 1.000
## age60-70             -0.2062 3.04e-08 1.000
## ageover70            -0.2493 7.81e-11 1.000
## txgrp                -0.2032 2.68e-08 1.000
## karnof               -0.1974 5.24e-08 1.000
## age20-30:txgrp        0.0921 2.14e-08 1.000
## age30-40:txgrp        0.1142 1.08e-08 1.000
## age40-50:txgrp        0.0826 5.64e-09 1.000
## age50-60:txgrp        0.1851 3.47e-08 1.000
## age60-70:txgrp        0.2102 2.15e-08 1.000
## ageover70:txgrp       0.1967 3.96e-11 1.000
## age20-30:karnof       0.0984 4.53e-08 1.000
## age30-40:karnof       0.1524 3.44e-08 1.000
## age40-50:karnof       0.0938 1.40e-08 1.000
## age50-60:karnof       0.2053 7.78e-08 1.000
## age60-70:karnof       0.1978 3.00e-08 1.000
## ageover70:karnof          NA      NaN   NaN
## txgrp:karnof          0.1996 2.81e-08 1.000
```

```
## age20-30:txgrp:karnof  -0.0910 2.15e-08 1.000
## age30-40:txgrp:karnof  -0.1020 9.71e-09 1.000
## age40-50:txgrp:karnof  -0.0823 6.23e-09 1.000
## age50-60:txgrp:karnof  -0.1796 3.72e-08 1.000
## age60-70:txgrp:karnof  -0.1981 1.98e-08 1.000
## ageover70:txgrp:karnof      NA      NaN   NaN
## GLOBAL                      NA 1.84e+01 0.891
```

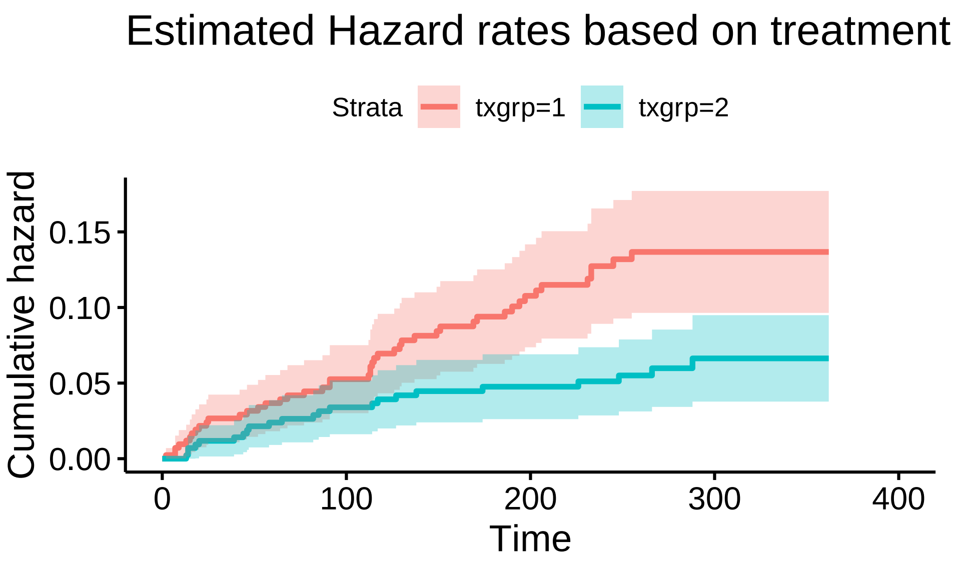
```r
ggsurvplot(survfit(Surv(time,censor) ~ 1, data=aids),
           censor=F, conf.int=T, fun="cumhaz") + ggtitle("Estimated Hazard rates")
```



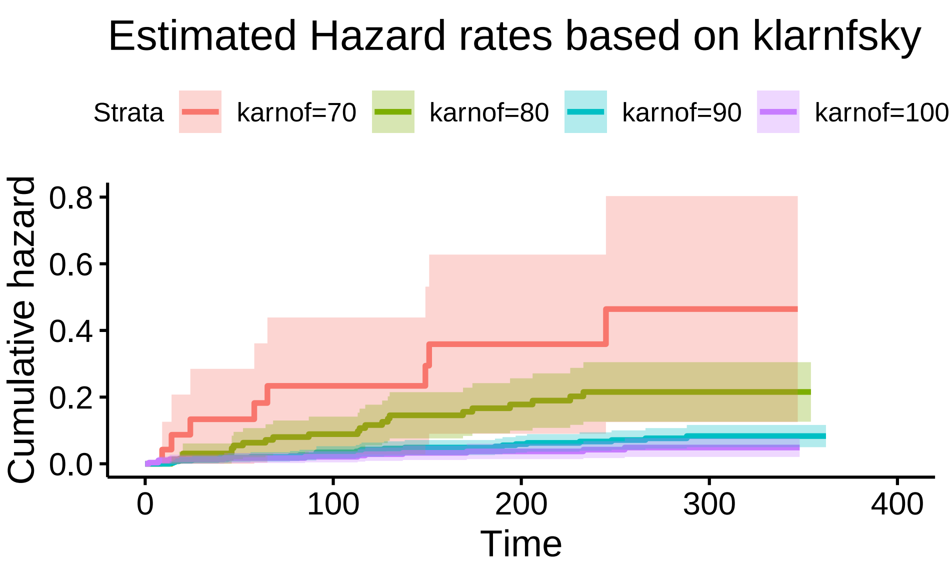

```r
ggsurvplot(survfit(Surv(time,censor) ~ sex, data=aids),
           censor=F, conf.int=T, fun="cumhaz") +
  ggtitle("Estimated Hazard rates based on sex")
```



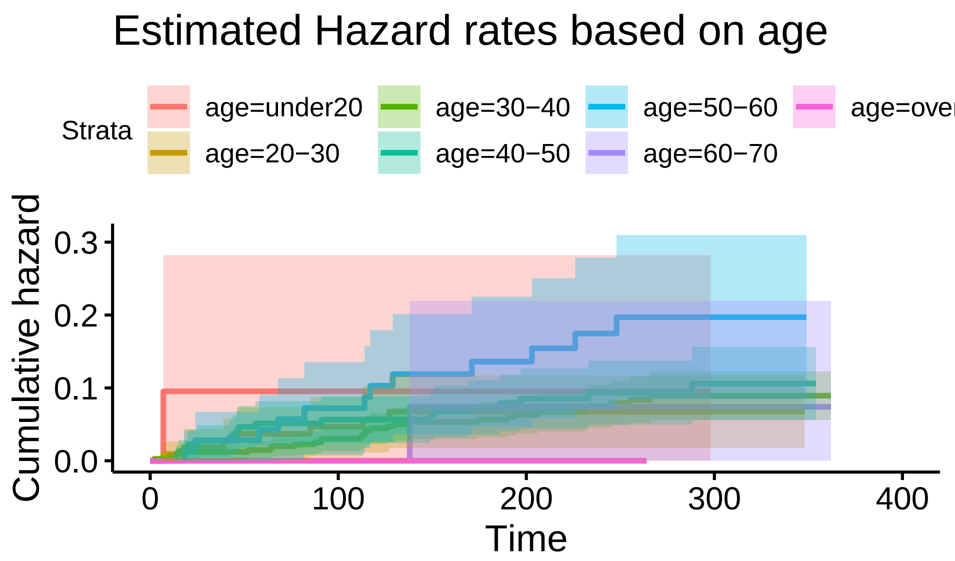

```r
ggsurvplot(survfit(Surv(time,censor) ~ txgrp, data=aids),
           censor=F, conf.int=T, fun="cumhaz") +
  ggtitle("Estimated Hazard rates based on treatment group")
```



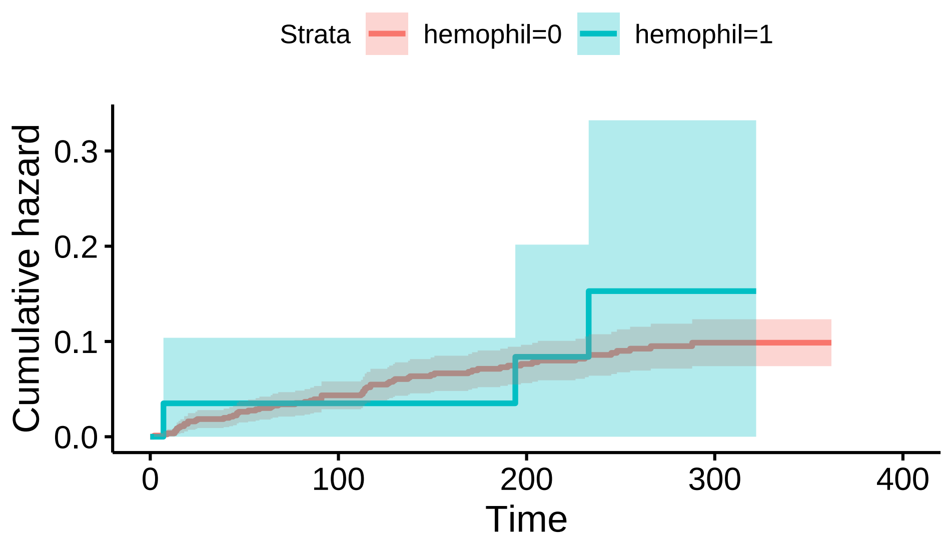

```r
ggsurvplot(survfit(Surv(time,censor) ~ karnof, data=aids),
           censor=F, conf.int=T, fun="cumhaz") +
  ggtitle("Estimated Hazard rates based on klarnfsky")
```



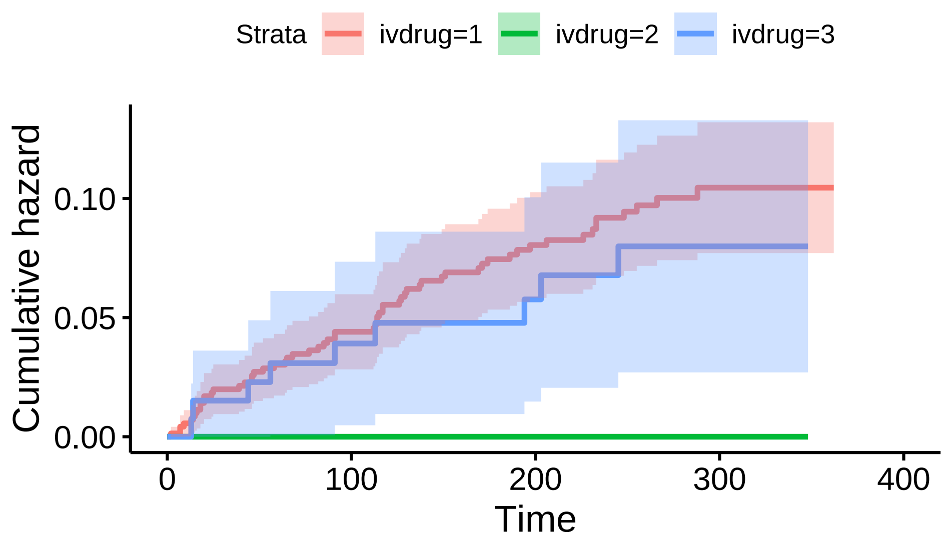

```r
ggsurvplot(survfit(Surv(time,censor) ~ age, data=aids),
           censor=F, conf.int=T, fun="cumhaz") +
  ggtitle("Estimated Hazard rates based on age")
```




```
ggsurvplot(survfit(Surv(time, censor)~hemophil, data = aids),
          censor=F, conf.int = T, fun = "cumhaz")
```




```
ggsurvplot(survfit(Surv(time, censor)~ivdrug, data = aids),
          censor=F, conf.int = T, fun = "cumhaz")
```




```
coxph(Surv(time,censor) ~ ivdrug, data=aids) %>% tidy()
```

```
## # A tibble: 1 x 7
##   term   estimate std.error statistic p.value conf.low conf.high
##   <chr>     <dbl>     <dbl>     <dbl>   <dbl>    <dbl>     <dbl>
## 1 ivdrug   -0.130     0.179    -0.723   0.470   -0.481     0.222
```

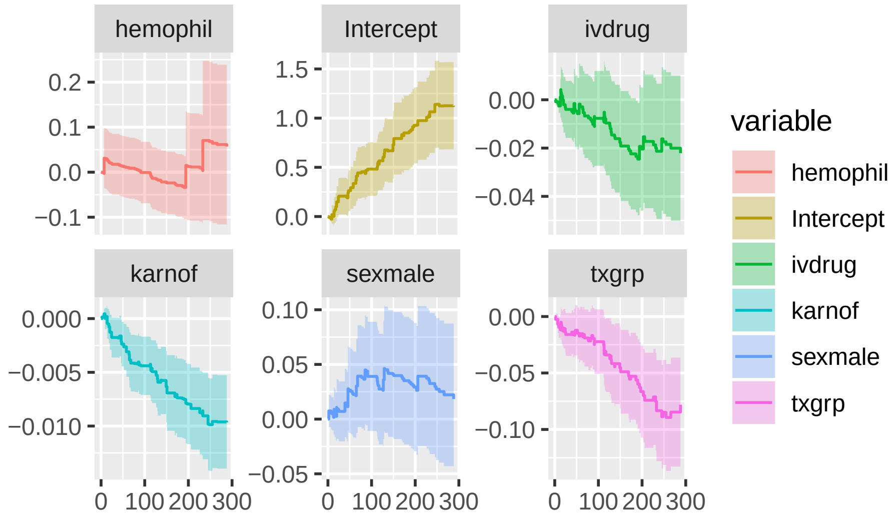
```
coxph(Surv(time,censor) ~ ivdrug*karnof, data=aids) %>% tidy()
```

```
## # A tibble: 3 x 7
##   term          estimate std.error statistic p.value conf.low conf.high
##   <chr>            <dbl>     <dbl>     <dbl>   <dbl>    <dbl>     <dbl>
## 1 ivdrug        -0.711      1.71      -0.416 0.678   -4.07       2.64
## 2 karnof        -0.0903     0.0294    -3.07  0.00214 -0.148     -0.0326
## 3 ivdrug:karnof  0.00573    0.0201     0.285 0.775   -0.0336     0.0451
```

```
coxph(Surv(time,censor)~sex+tx+age+txgrp, data = aids) %>% tidy()
```

```
## # A tibble: 9 x 7
##   term      estimate std.error statistic  p.value conf.low conf.high
##   <chr>        <dbl>     <dbl>     <dbl>    <dbl>    <dbl>     <dbl>
## 1 sexmale     0.302      0.324   0.931    0.352     -0.333     0.937
## 2 tx         -0.790      0.256  -3.08     0.00205   -1.29     -0.288
## 3 age20-30   -0.424      1.07   -0.396    0.692     -2.52      1.67
## 4 age30-40   -0.214      1.02   -0.209    0.834     -2.21      1.79
## 5 age40-50   -0.0490     1.03   -0.0475   0.962     -2.07      1.97
## 6 age50-60    0.639      1.05    0.611    0.541     -1.41      2.69
## 7 age60-70   -0.328      1.42   -0.231    0.817     -3.11      2.46
## 8 ageover70 -14.1     2672.     -0.00528  0.996   -Inf       Inf
## 9 txgrp       NA         0      NA       NA         NA        NA
```

```
library(ggfortify)

aa_fit <-aareg(Surv(time, censor) ~ txgrp + sex + ivdrug + hemophil + karnof,
                 data = aids)
autoplot(aa_fit)
```



The Aalen model assumes that the cumulative hazard $H(t)$ for a subject can be expressed as $a(t)$ + X $B(t)$, where $a(t)$ is a time-dependent intercept term, X is the vector of covariates for the subject possibly time-dependent, and $B(t)$ is a time-dependent matrix of coefficients.

The plots show how the effects of the covariates change over time.

Patricia's "Something New"

I will be doing a power analysis by simulating survival analysis curves

1. What is the topic?

The topic is using sim.survdata in R to simulate survival data. Using that simulated data, we will make that the alternative and control for the coefficient beta by setting it equal to some value. Then using power analysis, we will see how many times we reject H_0.

2. How it is relevant? How it relates to survival analysis/analysis at hand?

Power analysis relates to survival analysis because if power is large after comparing our data to the simulated survival data, this tells us that there is a high chance that we would reject the null in favor of the alternative (control versus treatment?)

3. Resources to learn about the topic.

Below are some of the resources I have begun to use to learn about creating simulations of survival curves and performing power analysis:

a). https://cran.r-project.org/web/packages/coxed/vignettes/simulating_survival_data.html b). http://www.icssc.org/documents/advbiosgoa/tab%2026.00_survss.pdf

4. What will be challenging about learning something new?

Learning something new will be challenging because in this case, the concept of power analysis is something I just recently learned in Intro to Statistics. So learning to apply this concept in the context of survival analysis curves will be a challenge for me to learn. Learning how to simulate survival curves will also be challenging because I will have to learn how to use and interpret new functions in R.

Power Analysis code and simulation

```
simdata <- sim.survdata(N=1000, T=100, num.data.frames=1, beta = c(0.01,0.07,0.3))
head(simdata$data,10)
```

```
##             X1         X2          X3   y failed
## 1   0.1390272  2.2018658 -0.61603972  64   TRUE
## 2   0.2989827 -2.0487913  0.72235599  57   TRUE
## 3   0.9431141  0.0143370 -0.34850719  23   TRUE
## 4   0.1173749  0.1154529  1.23296541  93  FALSE
## 5  -1.3184045 -0.3076940  1.24192379 100   TRUE
## 6   0.3886520 -0.3847928  0.16304862   1   TRUE
## 7  -1.2892947  1.4026664 -0.23776499   1   TRUE
## 8   1.0974116  0.9735271 -0.79900969  59   TRUE
## 9   1.1071629 -0.5285643 -1.02885821  99   TRUE
## 10 -0.8741064  0.2450979 -0.06074939 100  FALSE
```

```
simdata$betas
```

```
##      [,1]
## [1,] 0.01
## [2,] 0.07
## [3,] 0.30
```

```
head(simdata$baseline,10)
```

```
##    time  failure.PDF failure.CDF  survivor       hazard
## 1     1 0.2243766478   0.2243766 0.7756234 0.2243766478
## 2     2 0.1198731707   0.3442498 0.6557502 0.1545507498
## 3     3 0.0033308083   0.3475806 0.6524194 0.0050793860
## 4     4 0.0027770719   0.3503577 0.6496423 0.0042565749
## 5     5 0.0022736752   0.3526314 0.6473686 0.0034998879
## 6     6 0.0018206182   0.3544520 0.6455480 0.0028123361
## 7     7 0.0014179008   0.3558699 0.6441301 0.0021964296
## 8     8 0.0010655231   0.3569354 0.6430646 0.0016542047
## 9     9 0.0007634850   0.3576989 0.6423011 0.0011872603
## 10   10 0.0005117867   0.3582107 0.6417893 0.0007968018
```

```
#ggsurvplot(survfit(Surv(y,failed) ~ X1 + X2 + X3, data = simdata$data))
model <- coxph(Surv(y, failed) ~ X1 + X2 + X3, data = simdata$data)

library(dplyr)
library(broom)
model %>% tidy()
```

```
## # A tibble: 3 x 7
##   term  estimate std.error statistic p.value conf.low conf.high
##   <chr>    <dbl>     <dbl>     <dbl>   <dbl>    <dbl>     <dbl>
## 1 X1      0.0187     0.0344     0.543  0.587   -0.0488   0.0861
## 2 X2     -0.00992    0.0333    -0.298  0.766   -0.0753   0.0554
## 3 X3     -0.0595     0.0328    -1.81   0.0699  -0.124    0.00484
```

```
n.reps <- 100
simoutput <- c()
for(i in 1:n.reps){
```

```r
  simdata <- sim.survdata(N=1000, T=100, num.data.frames=1, xvars=4,beta = c(0,0.01,0.07,0.3))
  model <- coxph(Surv(y, failed) ~ X1 + X2 + X3 + X4, data = simdata$data)
  simoutput <- rbind(simoutput, cbind(rep = rep(i, 4), model %>% tidy()))

}

simoutput
```

```
##     rep term      estimate  std.error    statistic      p.value
## 1     1   X1 -2.942375e-03 0.03280299 -0.089698384 9.285269e-01
## 2     1   X2 -4.341808e-03 0.03307349 -0.131277577 8.955557e-01
## 3     1   X3  5.204506e-02 0.03444830  1.510816718 1.308352e-01
## 4     1   X4  2.894434e-01 0.03562147  8.125531261 4.454072e-16
## 5     2   X1 -5.158064e-02 0.03340164 -1.544254896 1.225266e-01
## 6     2   X2  3.197743e-02 0.03289656  0.972059791 3.310208e-01
## 7     2   X3  5.009229e-02 0.03210825  1.560106304 1.187348e-01
## 8     2   X4  1.160173e-02 0.03316143  0.349856095 7.264467e-01
## 9     3   X1 -5.201846e-03 0.03353868 -0.155099912 8.767426e-01
## 10    3   X2 -1.501617e-02 0.03298510 -0.455241117 6.489358e-01
## 11    3   X3  2.190895e-02 0.03229475  0.678406079 4.975143e-01
## 12    3   X4  1.522862e-01 0.03268185  4.659655302 3.167393e-06
## 13    4   X1  4.953353e-02 0.03360603  1.473947498 1.404957e-01
## 14    4   X2 -2.984262e-02 0.03442505 -0.866886575 3.860042e-01
## 15    4   X3  7.383681e-02 0.03275996  2.253873755 2.420411e-02
## 16    4   X4  3.384017e-01 0.03524821  9.600536936 7.952904e-22
## 17    5   X1 -1.278007e-02 0.03555141 -0.359481407 7.192350e-01
## 18    5   X2  1.001004e-02 0.03345003  0.299253461 7.647467e-01
## 19    5   X3  8.177433e-02 0.03327416  2.457592669 1.398717e-02
## 20    5   X4  2.960095e-01 0.03612804  8.193346307 2.540618e-16
## 21    6   X1 -1.272116e-02 0.03442776 -0.369503095 7.117528e-01
## 22    6   X2 -1.112505e-02 0.03377103 -0.329425949 7.418338e-01
## 23    6   X3  8.122775e-02 0.03342231  2.430345423 1.508444e-02
## 24    6   X4  2.729298e-01 0.03614649  7.550658214 4.330640e-14
## 25    7   X1  5.857933e-02 0.03391508  1.727235605 8.412536e-02
## 26    7   X2 -5.873707e-03 0.03403403 -0.172583332 8.629790e-01
## 27    7   X3 -1.472681e-02 0.03633756 -0.405278072 6.852731e-01
## 28    7   X4  1.059988e-01 0.03318951  3.193743932 1.404406e-03
## 29    8   X1 -9.640695e-03 0.03296757 -0.292429684 7.699581e-01
## 30    8   X2 -4.379905e-02 0.03236760 -1.353175649 1.759995e-01
## 31    8   X3  5.121126e-02 0.03451233  1.483853828 1.378477e-01
## 32    8   X4  2.621929e-01 0.03510162  7.469536412 8.047784e-14
## 33    9   X1  7.042053e-02 0.03427516  2.054564430 3.992109e-02
## 34    9   X2  1.430208e-02 0.03269872  0.437389575 6.618288e-01
## 35    9   X3  4.900188e-02 0.03510057  1.396042160 1.627018e-01
## 36    9   X4  1.682008e-01 0.03394202  4.955533511 7.213209e-07
## 37   10   X1 -2.359897e-03 0.03255529 -0.072488893 9.422128e-01
## 38   10   X2  8.726394e-03 0.03337186  0.261489589 7.937150e-01
## 39   10   X3  5.626856e-02 0.03366107  1.671621268 9.459903e-02
## 40   10   X4  3.046236e-01 0.03535263  8.616716460 6.890148e-18
## 41   11   X1 -4.009897e-02 0.03208430 -1.249800525 2.113724e-01
## 42   11   X2 -2.023304e-03 0.03308808 -0.061149030 9.512405e-01
## 43   11   X3 -1.097379e-04 0.03396241 -0.003231158 9.974219e-01
## 44   11   X4  1.369901e-01 0.03292644  4.160487504 3.175690e-05
## 45   12   X1  1.897598e-02 0.03268213  0.580622497 5.614949e-01
## 46   12   X2  9.361520e-02 0.03388709  2.762562217 5.734963e-03
## 47   12   X3  4.961232e-02 0.03324738  1.492217468 1.356421e-01
```

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## 48   12   X4  3.085376e-01 0.03382345  9.122003333 7.374826e-20
## 49   13   X1  5.553288e-02 0.03153764  1.760844698 7.826469e-02
## 50   13   X2 -1.555896e-02 0.03267357 -0.476194063 6.339361e-01
## 51   13   X3  1.134710e-01 0.03234010  3.508678503 4.503389e-04
## 52   13   X4  2.913628e-01 0.03485391  8.359543814 6.296124e-17
## 53   14   X1 -2.874956e-02 0.03512822 -0.818417682 4.131187e-01
## 54   14   X2  4.512509e-02 0.03428363  1.316228430 1.880974e-01
## 55   14   X3  8.548869e-02 0.03176486  2.691297462 7.117470e-03
## 56   14   X4  1.368406e-01 0.03338518  4.098841775 4.152228e-05
## 57   15   X1 -1.441500e-02 0.03336081 -0.432093795 6.656732e-01
## 58   15   X2  8.567007e-03 0.03436935  0.249262995 8.031574e-01
## 59   15   X3  7.537933e-02 0.03331200  2.262828109 2.364629e-02
## 60   15   X4  2.622307e-01 0.03637812  7.208472711 5.658291e-13
## 61   16   X1  2.239479e-03 0.03413475  0.065607013 9.476907e-01
## 62   16   X2  4.587118e-02 0.03215380  1.426617771 1.536901e-01
## 63   16   X3  2.741006e-02 0.03252814  0.842656779 3.994204e-01
## 64   16   X4  3.466934e-01 0.03475005  9.976773145 1.926296e-23
## 65   17   X1 -1.005876e-01 0.03501322 -2.872845186 4.067934e-03
## 66   17   X2  1.752665e-02 0.03468651  0.505287274 6.133571e-01
## 67   17   X3  4.241196e-02 0.03353194  1.264822794 2.059349e-01
## 68   17   X4  2.434752e-01 0.03593854  6.774766858 1.246070e-11
## 69   18   X1 -2.153129e-02 0.03212092 -0.670320001 5.026538e-01
## 70   18   X2  3.024077e-02 0.03349452  0.902857439 3.666016e-01
## 71   18   X3  1.598158e-02 0.03238006  0.493562318 6.216153e-01
## 72   18   X4  1.986424e-01 0.03423023  5.803129020 6.508867e-09
## 73   19   X1  4.260758e-02 0.03293410  1.293722226 1.957614e-01
## 74   19   X2  1.004401e-02 0.03417492  0.293899910 7.688344e-01
## 75   19   X3  2.824325e-02 0.03423134  0.825069922 4.093319e-01
## 76   19   X4  2.084557e-01 0.03212868  6.488147954 8.689793e-11
## 77   20   X1 -1.012963e-03 0.03445606 -0.029398706 9.765466e-01
## 78   20   X2 -2.624491e-03 0.03428500 -0.076549248 9.389821e-01
## 79   20   X3  9.412167e-02 0.03383980  2.781390053 5.412666e-03
## 80   20   X4  2.391264e-01 0.03234851  7.392191067 1.444288e-13
## 81   21   X1 -2.703129e-02 0.03501859 -0.771912578 4.401662e-01
## 82   21   X2 -1.695473e-02 0.03168590 -0.535087571 5.925893e-01
## 83   21   X3  5.986037e-03 0.03152753  0.189866996 8.494134e-01
## 84   21   X4  2.188586e-01 0.03454073  6.336246007 2.354308e-10
## 85   22   X1  5.328262e-02 0.03260545  1.634163051 1.022246e-01
## 86   22   X2 -2.008125e-02 0.03398095 -0.590956078 5.545499e-01
## 87   22   X3  6.167153e-02 0.03540773  1.741753430 8.155160e-02
## 88   22   X4  1.769714e-01 0.03522848  5.023532697 5.072958e-07
## 89   23   X1 -4.354270e-02 0.03506424 -1.241797960 2.143111e-01
## 90   23   X2 -4.610575e-02 0.03428726 -1.344690608 1.787252e-01
## 91   23   X3  5.751532e-02 0.03480952  1.652286858 9.847609e-02
## 92   23   X4  2.217008e-02 0.03502852  0.632915098 5.267891e-01
## 93   24   X1 -3.777205e-02 0.03531320 -1.069629865 2.847859e-01
## 94   24   X2  3.435317e-02 0.03565401  0.963514745 3.352893e-01
## 95   24   X3 -1.305561e-02 0.03419319 -0.381818944 7.025957e-01
## 96   24   X4  2.863849e-01 0.03767535  7.601386277 2.929752e-14
## 97   25   X1 -8.466420e-03 0.03219986 -0.262933444 7.926019e-01
## 98   25   X2  5.639743e-03 0.03384184  0.166650013 8.676454e-01
## 99   25   X3  4.863435e-02 0.03545621  1.371673877 1.701650e-01
## 100  25   X4  3.048354e-01 0.03535462  8.622222600 6.566690e-18
## 101  26   X1  8.095773e-03 0.03196031  0.253307076 8.000309e-01
## 102  26   X2 -1.592221e-02 0.03200477 -0.497494958 6.188401e-01
## 103  26   X3  4.235576e-02 0.03341435  1.267592135 2.049436e-01
```

```
## 104  26   X4  1.894526e-01 0.03382589  5.600817689 2.133430e-08
## 105  27   X1 -1.824187e-02 0.03384945 -0.538911958 5.899476e-01
## 106  27   X2  1.333063e-02 0.03358236  0.396953287 6.914019e-01
## 107  27   X3  1.027667e-01 0.03279192  3.133902290 1.724983e-03
## 108  27   X4  3.747933e-01 0.03569026 10.501275824 8.522044e-26
## 109  28   X1 -2.737909e-02 0.03370558 -0.812301196 4.166188e-01
## 110  28   X2 -1.415477e-02 0.03327001 -0.425451430 6.705076e-01
## 111  28   X3  9.904894e-02 0.03450658  2.870436769 4.099052e-03
## 112  28   X4  1.470291e-01 0.03629352  4.051110373 5.097515e-05
## 113  29   X1  8.569083e-03 0.03357629  0.255212299 7.985591e-01
## 114  29   X2  5.436153e-02 0.03243721  1.675900212 9.375774e-02
## 115  29   X3  7.137181e-02 0.03355515  2.127000169 3.342007e-02
## 116  29   X4  2.809085e-01 0.03453441  8.134162396 4.147962e-16
## 117  30   X1 -1.990298e-02 0.03240225 -0.614246706 5.390523e-01
## 118  30   X2 -1.128787e-02 0.03254888 -0.346797658 7.287433e-01
## 119  30   X3  1.095390e-01 0.03342791  3.276872832 1.049636e-03
## 120  30   X4  2.269321e-01 0.03366000  6.741891455 1.563379e-11
## 121  31   X1  5.785619e-02 0.03375991  1.713754499 8.657382e-02
## 122  31   X2 -1.872523e-02 0.03160131 -0.592546049 5.534850e-01
## 123  31   X3  1.018464e-01 0.03286570  3.098867307 1.942620e-03
## 124  31   X4  2.992125e-01 0.03446567  8.681463272 3.907092e-18
## 125  32   X1 -4.235542e-02 0.03412684 -1.241117494 2.145623e-01
## 126  32   X2  3.712511e-02 0.03334019  1.113524219 2.654834e-01
## 127  32   X3  4.381289e-03 0.03320797  0.131934856 8.950358e-01
## 128  32   X4  2.093635e-02 0.03307812  0.632936509 5.267751e-01
## 129  33   X1 -5.246364e-02 0.03422890 -1.532729287 1.253426e-01
## 130  33   X2 -3.308923e-02 0.03378120 -0.979515979 3.273251e-01
## 131  33   X3  1.035507e-01 0.03293227  3.144352461 1.664548e-03
## 132  33   X4  2.390171e-01 0.03366821  7.099192264 1.254881e-12
## 133  34   X1  3.010674e-02 0.03513828  0.856807383 3.915513e-01
## 134  34   X2 -8.204749e-04 0.03445902 -0.023810165 9.810040e-01
## 135  34   X3  4.208679e-02 0.03411478  1.233682139 2.173214e-01
## 136  34   X4  2.370527e-01 0.03439411  6.892246011 5.491829e-12
## 137  35   X1  2.147200e-02 0.03365577  0.637988564 5.234811e-01
## 138  35   X2 -2.876981e-02 0.03335861 -0.862440377 3.884452e-01
## 139  35   X3  7.070044e-02 0.03432486  2.059744485 3.942297e-02
## 140  35   X4  3.277280e-01 0.03464607  9.459313027 3.099729e-21
## 141  36   X1 -9.313057e-04 0.03230382 -0.028829586 9.770005e-01
## 142  36   X2 -2.343826e-04 0.03426159 -0.006840973 9.945417e-01
## 143  36   X3  2.947623e-02 0.03222456  0.914713417 3.603421e-01
## 144  36   X4  2.813087e-01 0.03355813  8.382728837 5.171452e-17
## 145  37   X1 -3.875559e-02 0.03413389 -1.135399083 2.562081e-01
## 146  37   X2 -2.845373e-02 0.03386850 -0.840123643 4.008391e-01
## 147  37   X3  2.294456e-03 0.03496339  0.065624521 9.476768e-01
## 148  37   X4  5.317012e-02 0.03496632  1.520609435 1.283579e-01
## 149  38   X1 -3.087677e-02 0.03368009 -0.916766082 3.592652e-01
## 150  38   X2 -3.176692e-02 0.03320218 -0.956772225 3.386822e-01
## 151  38   X3  5.500942e-02 0.03385518  1.624844760 1.041956e-01
## 152  38   X4  2.042186e-01 0.03401024  6.004623120 1.917768e-09
## 153  39   X1 -2.687831e-02 0.03433742 -0.782770084 4.337621e-01
## 154  39   X2 -4.364375e-02 0.03195816 -1.365652808 1.720480e-01
## 155  39   X3  7.381026e-02 0.03281953  2.248974038 2.451415e-02
## 156  39   X4  3.276968e-01 0.03547414  9.237626357 2.520258e-20
## 157  40   X1  1.463456e-02 0.03322974  0.440405513 6.596434e-01
## 158  40   X2  5.603734e-02 0.03466247  1.616657682 1.059522e-01
## 159  40   X3  4.147747e-02 0.03248167  1.276950001 2.016199e-01
```

```
## 160  40   X4  2.735820e-01 0.03461835  7.902802427 2.727017e-15
## 161  41   X1 -2.841173e-02 0.03325607 -0.854332300 3.929209e-01
## 162  41   X2  2.348130e-02 0.03407624  0.689081247 4.907721e-01
## 163  41   X3  2.666475e-02 0.03115491  0.855876354 3.920662e-01
## 164  41   X4  3.546157e-02 0.03160266  1.122107041 2.618169e-01
## 165  42   X1 -3.841942e-02 0.03312155 -1.159952483 2.460682e-01
## 166  42   X2 -3.431501e-02 0.03312559 -1.035906350 3.002458e-01
## 167  42   X3  5.575775e-02 0.03253254  1.713907106 8.654579e-02
## 168  42   X4  2.218091e-01 0.03362044  6.597448262 4.182946e-11
## 169  43   X1  4.150710e-02 0.03355802  1.236875641 2.161333e-01
## 170  43   X2 -3.363367e-03 0.03129476 -0.107473785 9.144131e-01
## 171  43   X3  1.620468e-02 0.03322353  0.487747088 6.257290e-01
## 172  43   X4  1.174852e-01 0.03233086  3.633839096 2.792350e-04
## 173  44   X1  3.006563e-02 0.03485896  0.862493763 3.884159e-01
## 174  44   X2  5.612645e-02 0.03440675  1.631262447 1.028350e-01
## 175  44   X3  2.358197e-02 0.03331310  0.707888711 4.790144e-01
## 176  44   X4  1.860959e-01 0.03532090  5.268719516 1.373787e-07
## 177  45   X1  4.990570e-02 0.03289865  1.516952792 1.292786e-01
## 178  45   X2 -2.835655e-02 0.03383895 -0.837985419 4.020389e-01
## 179  45   X3  8.354431e-02 0.03274927  2.551028447 1.074056e-02
## 180  45   X4  2.222337e-01 0.03534012  6.288425680 3.207015e-10
## 181  46   X1  1.188751e-02 0.03369692  0.352777249 7.242554e-01
## 182  46   X2  2.197037e-02 0.03240266  0.678042045 4.977450e-01
## 183  46   X3  1.001409e-01 0.03462518  2.892141468 3.826256e-03
## 184  46   X4  2.769402e-01 0.03501762  7.908598221 2.603032e-15
## 185  47   X1 -3.346525e-02 0.03314681 -1.009606791 3.126837e-01
## 186  47   X2 -1.434724e-03 0.03375581 -0.042503029 9.660977e-01
## 187  47   X3  1.531653e-02 0.03360060  0.455841023 6.485043e-01
## 188  47   X4 -4.587290e-02 0.03371623 -1.360558493 1.736533e-01
## 189  48   X1  1.442626e-02 0.03530500  0.408618026 6.828200e-01
## 190  48   X2  2.427122e-02 0.03430502  0.707512010 4.792484e-01
## 191  48   X3  6.424467e-02 0.03356776  1.913879939 5.563550e-02
## 192  48   X4  1.484379e-01 0.03522167  4.214391571 2.504524e-05
## 193  49   X1  6.270038e-02 0.03376774  1.856812936 6.333777e-02
## 194  49   X2 -5.592047e-05 0.03248438 -0.001721457 9.986265e-01
## 195  49   X3  5.469215e-02 0.03414793  1.601624103 1.092388e-01
## 196  49   X4  2.128810e-01 0.03244451  6.561385918 5.330995e-11
## 197  50   X1  5.946816e-02 0.03312070  1.795498086 7.257438e-02
## 198  50   X2 -6.265913e-03 0.03346156 -0.187257076 8.514591e-01
## 199  50   X3 -2.537159e-02 0.03262835 -0.777593519 4.368087e-01
## 200  50   X4  1.349431e-01 0.03374901  3.998430673 6.376385e-05
## 201  51   X1 -5.845197e-02 0.03134290 -1.864919041 6.219275e-02
## 202  51   X2  3.414400e-02 0.03482853  0.980345895 3.269154e-01
## 203  51   X3  7.244738e-02 0.03126421  2.317262320 2.048945e-02
## 204  51   X4  3.375380e-01 0.03362419 10.038548785 1.031809e-23
## 205  52   X1  4.959085e-03 0.03252983  0.152447309 8.788341e-01
## 206  52   X2 -3.790573e-02 0.03483306 -1.088211160 2.765019e-01
## 207  52   X3  6.582901e-02 0.03504119  1.878617940 6.029668e-02
## 208  52   X4  2.631186e-01 0.03441203  7.646123993 2.071279e-14
## 209  53   X1 -1.566442e-02 0.03424806 -0.457381249 6.473970e-01
## 210  53   X2  2.525773e-02 0.03483076  0.725155750 4.683565e-01
## 211  53   X3  2.025461e-02 0.03262112  0.620904702 5.346623e-01
## 212  53   X4  1.963734e-01 0.03445830  5.698869346 1.206046e-08
## 213  54   X1 -1.084067e-03 0.03325080 -0.032602723 9.739914e-01
## 214  54   X2  3.914441e-02 0.03280295  1.193319635 2.327442e-01
## 215  54   X3  3.297167e-02 0.03132769  1.052476928 2.925808e-01
```

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## 216  54   X4  2.115446e-01 0.03505951  6.033872635 1.600762e-09
## 217  55   X1  1.347382e-02 0.03319005  0.405959650 6.847722e-01
## 218  55   X2  3.665326e-02 0.03343581  1.096227679 2.729791e-01
## 219  55   X3  4.448275e-02 0.03300034  1.347948346 1.776750e-01
## 220  55   X4  2.818621e-01 0.03438972  8.196115414 2.482800e-16
## 221  56   X1 -2.325012e-02 0.03422742 -0.679283614 4.969582e-01
## 222  56   X2  5.549962e-02 0.03311773  1.675828113 9.377187e-02
## 223  56   X3 -8.334309e-03 0.03387934 -0.245999764 8.056824e-01
## 224  56   X4  1.461933e-01 0.03478643  4.202596638 2.638705e-05
## 225  57   X1  7.328166e-02 0.03252554  2.253049976 2.425600e-02
## 226  57   X2 -6.266939e-03 0.03467941 -0.180710671 8.565947e-01
## 227  57   X3 -1.694368e-02 0.03364262 -0.503637443 6.145162e-01
## 228  57   X4  5.369228e-02 0.03231404  1.661577555 9.659751e-02
## 229  58   X1  1.231562e-02 0.03345264  0.368150901 7.127607e-01
## 230  58   X2  5.976734e-02 0.03361382  1.778058542 7.539424e-02
## 231  58   X3  8.588573e-02 0.03369833  2.548664444 1.081363e-02
## 232  58   X4  2.305254e-01 0.03529833  6.530773912 6.543071e-11
## 233  59   X1 -7.036701e-02 0.03299517 -2.132645582 3.295381e-02
## 234  59   X2 -1.012107e-02 0.03461281 -0.292408118 7.699746e-01
## 235  59   X3 -7.138345e-03 0.03414069 -0.209086147 8.343810e-01
## 236  59   X4  6.860452e-02 0.03242828  2.115576853 3.438081e-02
## 237  60   X1  2.134177e-02 0.03339636  0.639044859 5.227937e-01
## 238  60   X2  1.426739e-02 0.03366007  0.423867035 6.716628e-01
## 239  60   X3  7.471042e-02 0.03321525  2.249280641 2.449465e-02
## 240  60   X4  3.151222e-01 0.03488643  9.032801099 1.673326e-19
## 241  61   X1 -5.223472e-02 0.03236230 -1.614060856 1.065142e-01
## 242  61   X2  4.644161e-02 0.03332803  1.393470050 1.634777e-01
## 243  61   X3  7.911858e-02 0.03200410  2.472139124 1.343072e-02
## 244  61   X4  2.358183e-01 0.03454769  6.825877926 8.738922e-12
## 245  62   X1 -1.428354e-02 0.03318983 -0.430359113 6.669344e-01
## 246  62   X2  1.094555e-02 0.03324815  0.329207841 7.419986e-01
## 247  62   X3  1.047741e-03 0.03295263  0.031795375 9.746352e-01
## 248  62   X4  2.888000e-01 0.03297703  8.757609395 1.994349e-18
## 249  63   X1  2.886358e-02 0.03512250  0.821797444 4.111922e-01
## 250  63   X2 -7.222087e-03 0.03453069 -0.209149797 8.343313e-01
## 251  63   X3  1.131008e-01 0.03390260  3.336051430 8.497744e-04
## 252  63   X4  1.809742e-01 0.03284611  5.509762722 3.593177e-08
## 253  64   X1  1.342023e-02 0.03476062  0.386075727 6.994406e-01
## 254  64   X2  4.587802e-02 0.03345047  1.371520749 1.702127e-01
## 255  64   X3 -1.074865e-02 0.03352602 -0.320606097 7.485089e-01
## 256  64   X4  1.287664e-01 0.03302818  3.898682710 9.671741e-05
## 257  65   X1  5.764653e-03 0.03126417  0.184385264 8.537112e-01
## 258  65   X2 -4.960458e-02 0.03434254 -1.444406271 1.486247e-01
## 259  65   X3  6.380880e-02 0.03487061  1.829873380 6.726887e-02
## 260  65   X4  1.970329e-01 0.03509725  5.613913014 1.978017e-08
## 261  66   X1  7.469593e-03 0.03246265  0.230098066 8.180156e-01
## 262  66   X2  8.518968e-02 0.03304016  2.578367653 9.926832e-03
## 263  66   X3  6.696575e-03 0.03430222  0.195222819 8.452185e-01
## 264  66   X4  3.370085e-01 0.03593182  9.379111534 6.653097e-21
## 265  67   X1 -3.738888e-02 0.03397472 -1.100490930 2.711183e-01
## 266  67   X2 -9.118275e-03 0.03109720 -0.293218493 7.693551e-01
## 267  67   X3  5.760707e-02 0.03057242  1.884282269 5.952680e-02
## 268  67   X4  2.492939e-01 0.03330243  7.485759001 7.113482e-14
## 269  68   X1  2.947461e-02 0.03504365  0.841082856 4.003015e-01
## 270  68   X2 -4.703696e-02 0.03314086 -1.419304313 1.558103e-01
## 271  68   X3  5.311918e-02 0.03158679  1.681689579 9.262905e-02
```

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## 272  68   X4  3.530541e-01 0.03428584 10.297372851 7.241188e-25
## 273  69   X1  2.613546e-02 0.03392894  0.770299939 4.411220e-01
## 274  69   X2 -1.486994e-02 0.03322174 -0.447596776 6.544442e-01
## 275  69   X3  2.960194e-02 0.03261746  0.907549050 3.641165e-01
## 276  69   X4  2.059053e-01 0.03467442  5.938248050 2.880839e-09
## 277  70   X1  8.513941e-03 0.03211156  0.265136317 7.909045e-01
## 278  70   X2 -4.019987e-02 0.03336245 -1.204943669 2.282250e-01
## 279  70   X3  2.543675e-02 0.03266492  0.778717567 4.361461e-01
## 280  70   X4  3.900577e-02 0.03367483  1.158306430 2.467390e-01
## 281  71   X1 -7.693492e-03 0.03360344 -0.228949546 8.189081e-01
## 282  71   X2 -3.054785e-02 0.03393724 -0.900127714 3.680523e-01
## 283  71   X3 -4.758840e-02 0.03530891 -1.347772877 1.777314e-01
## 284  71   X4  1.394694e-01 0.03372073  4.136012906 3.533923e-05
## 285  72   X1 -1.497760e-02 0.03325581 -0.450375510 6.524397e-01
## 286  72   X2  1.736625e-02 0.03487213  0.497998048 6.184854e-01
## 287  72   X3  8.937743e-02 0.03302629  2.706250990 6.804759e-03
## 288  72   X4  3.152468e-01 0.03559909  8.855473562 8.332927e-19
## 289  73   X1 -1.967423e-03 0.03482241 -0.056498758 9.549445e-01
## 290  73   X2 -2.510619e-02 0.03243024 -0.774159908 4.388362e-01
## 291  73   X3  7.572253e-02 0.03404029  2.224497209 2.611501e-02
## 292  73   X4  2.200275e-01 0.03437055  6.401629580 1.537273e-10
## 293  74   X1 -5.079143e-02 0.03375666 -1.504634147 1.324182e-01
## 294  74   X2  1.840316e-02 0.03376144  0.545093992 5.856889e-01
## 295  74   X3  5.274042e-02 0.03426291  1.539286032 1.237345e-01
## 296  74   X4  2.257929e-01 0.03295712  6.851110184 7.327904e-12
## 297  75   X1 -3.612296e-02 0.03414769 -1.057845131 2.901261e-01
## 298  75   X2 -2.497991e-02 0.03218855 -0.776049453 4.377198e-01
## 299  75   X3  4.785515e-02 0.03390166  1.411587058 1.580716e-01
## 300  75   X4  2.463614e-01 0.03659906  6.731360236 1.680842e-11
## 301  76   X1  7.458724e-03 0.03236313  0.230469792 8.177267e-01
## 302  76   X2 -3.091735e-02 0.03382613 -0.914008052 3.607126e-01
## 303  76   X3 -3.113884e-03 0.03436095 -0.090622772 9.277923e-01
## 304  76   X4  1.226418e-01 0.03248922  3.774845279 1.601070e-04
## 305  77   X1  5.032948e-02 0.03351003  1.501922830 1.331170e-01
## 306  77   X2 -2.952622e-02 0.03471632 -0.850499746 3.950473e-01
## 307  77   X3  2.189109e-02 0.03403187  0.643252620 5.200602e-01
## 308  77   X4  2.924730e-01 0.03518932  8.311414082 9.456831e-17
## 309  78   X1  4.225085e-03 0.03296308  0.128176255 8.980095e-01
## 310  78   X2  2.782812e-02 0.03434881  0.810162437 4.178468e-01
## 311  78   X3  9.270956e-02 0.03393084  2.732309873 6.289196e-03
## 312  78   X4  2.706544e-01 0.03630596  7.454821139 8.998983e-14
## 313  79   X1 -5.013012e-02 0.03327547 -1.506518849 1.319340e-01
## 314  79   X2  5.151859e-02 0.03414829  1.508672751 1.313824e-01
## 315  79   X3  2.692936e-02 0.03298267  0.816470057 4.142313e-01
## 316  79   X4  3.222589e-01 0.03612092  8.921669125 4.593127e-19
## 317  80   X1  4.036318e-02 0.03244356  1.244104445 2.134611e-01
## 318  80   X2  2.516829e-02 0.03364530  0.748047671 4.544314e-01
## 319  80   X3  1.207759e-01 0.03598843  3.355965288 7.908849e-04
## 320  80   X4  3.706696e-01 0.03539592 10.472099469 1.160404e-25
## 321  81   X1  5.239391e-02 0.03630534  1.443146157 1.489793e-01
## 322  81   X2  4.074054e-02 0.03150099  1.293309508 1.959040e-01
## 323  81   X3  7.848190e-02 0.03341295  2.348846430 1.883167e-02
## 324  81   X4  2.884923e-01 0.03456740  8.345792711 7.073779e-17
## 325  82   X1  5.546863e-02 0.03459523  1.603360897 1.088550e-01
## 326  82   X2  5.653877e-02 0.03285762  1.720719989 8.530165e-02
## 327  82   X3  7.304612e-02 0.03235399  2.257715713 2.396339e-02
```

```
## 328  82   X4  2.826928e-01 0.03378573  8.367226698 5.899014e-17
## 329  83   X1 -1.536186e-02 0.03235266 -0.474825217 6.349116e-01
## 330  83   X2 -1.691366e-02 0.03301460 -0.512308406 6.084352e-01
## 331  83   X3  4.602831e-02 0.03434378  1.340222421 1.801730e-01
## 332  83   X4  2.796547e-01 0.03448816  8.108716835 5.115711e-16
## 333  84   X1 -9.204563e-02 0.03267344 -2.817139332 4.845350e-03
## 334  84   X2 -4.642166e-02 0.03221107 -1.441171039 1.495364e-01
## 335  84   X3  4.283950e-02 0.03305308  1.296081964 1.949472e-01
## 336  84   X4  2.450675e-01 0.03392648  7.223488475 5.067060e-13
## 337  85   X1 -2.173282e-02 0.03307573 -0.657062509 5.111407e-01
## 338  85   X2  1.554076e-02 0.03048861  0.509723516 6.102452e-01
## 339  85   X3  4.617025e-03 0.03343550  0.138087514 8.901713e-01
## 340  85   X4 -5.751054e-02 0.03256348 -1.766105458 7.737816e-02
## 341  86   X1  5.465058e-02 0.03336003  1.638205397 1.013789e-01
## 342  86   X2  3.315058e-02 0.03320858  0.998253368 3.181565e-01
## 343  86   X3  9.692767e-02 0.03506369  2.764331878 5.703949e-03
## 344  86   X4  2.835047e-01 0.03871077  7.323666718 2.412855e-13
## 345  87   X1 -4.384124e-02 0.03527251 -1.242929404 2.138938e-01
## 346  87   X2  2.151020e-02 0.03399985  0.632655671 5.269585e-01
## 347  87   X3  6.882446e-02 0.03208230  2.145246972 3.193311e-02
## 348  87   X4  3.870674e-01 0.03475519 11.136965263 8.289610e-29
## 349  88   X1  7.600160e-03 0.03448919  0.220363546 8.255880e-01
## 350  88   X2  1.740389e-02 0.03434359  0.506757934 6.123247e-01
## 351  88   X3  3.140490e-02 0.03515821  0.893245204 3.717259e-01
## 352  88   X4  6.467945e-02 0.03291546  1.965017110 4.941226e-02
## 353  89   X1  1.036688e-02 0.03315136  0.312713635 7.544982e-01
## 354  89   X2 -3.454672e-02 0.03281962 -1.052623952 2.925134e-01
## 355  89   X3  3.400926e-02 0.03312680  1.026638788 3.045906e-01
## 356  89   X4  4.186194e-02 0.03380710  1.238258756 2.156201e-01
## 357  90   X1  3.575505e-02 0.03391328  1.054308151 2.917419e-01
## 358  90   X2 -3.583262e-02 0.03336660 -1.073907069 2.828643e-01
## 359  90   X3  7.135431e-02 0.03374711  2.114383055 3.448256e-02
## 360  90   X4  3.125650e-01 0.03484351  8.970538744 2.950676e-19
## 361  91   X1 -1.065532e-02 0.03228530 -0.330036154 7.413726e-01
## 362  91   X2  3.145756e-02 0.03394373  0.926756009 3.540532e-01
## 363  91   X3  1.512188e-02 0.03373024  0.448318191 6.539236e-01
## 364  91   X4  3.301935e-01 0.03435358  9.611617846 7.141788e-22
## 365  92   X1 -6.948612e-02 0.03294147 -2.109381550 3.491166e-02
## 366  92   X2 -1.293863e-02 0.03123425 -0.414244990 6.786947e-01
## 367  92   X3 -4.191962e-02 0.03344638 -1.253337808 2.100828e-01
## 368  92   X4  9.057743e-02 0.03388997  2.672691735 7.524536e-03
## 369  93   X1  4.079022e-02 0.03415279  1.194345249 2.323429e-01
## 370  93   X2 -1.652138e-02 0.03472235 -0.475813955 6.342069e-01
## 371  93   X3  4.627906e-02 0.03198707  1.446805074 1.479515e-01
## 372  93   X4  2.027673e-01 0.03479796  5.826987243 5.643692e-09
## 373  94   X1  3.698127e-02 0.03281526  1.126953392 2.597622e-01
## 374  94   X2 -1.318634e-02 0.03433079 -0.384096694 7.009068e-01
## 375  94   X3  6.396709e-02 0.03479522  1.838387011 6.600540e-02
## 376  94   X4  2.142899e-01 0.03520441  6.087016997 1.150338e-09
## 377  95   X1 -1.050808e-02 0.03426119 -0.306705102 7.590678e-01
## 378  95   X2  1.957859e-02 0.03335512  0.586974079 5.572211e-01
## 379  95   X3  1.070691e-01 0.03381558  3.166265962 1.544095e-03
## 380  95   X4  3.379633e-01 0.03469319  9.741487203 2.005968e-22
## 381  96   X1  2.997712e-02 0.03485143  0.860140201 3.897118e-01
## 382  96   X2  1.789653e-02 0.03348160  0.534518526 5.929828e-01
## 383  96   X3  4.542387e-02 0.03389207  1.340250642 1.801639e-01
```

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## 384  96   X4  2.936252e-01 0.03701853  7.931844492 2.159147e-15
## 385  97   X1  1.287701e-02 0.03388646  0.380004658 7.039420e-01
## 386  97   X2 -3.014094e-03 0.03484587 -0.086497886 9.310706e-01
## 387  97   X3  4.354489e-02 0.03429667  1.269653565 2.042081e-01
## 388  97   X4  1.131764e-01 0.03512295  3.222291154 1.271698e-03
## 389  98   X1  1.687233e-02 0.03293156  0.512345311 6.084094e-01
## 390  98   X2 -2.865331e-02 0.03445685 -0.831570744 4.056513e-01
## 391  98   X3  2.664582e-02 0.03427548  0.777401920 4.369217e-01
## 392  98   X4  7.650937e-02 0.03171793  2.412180507 1.585743e-02
## 393  99   X1  2.381387e-02 0.03359568  0.708837421 4.784254e-01
## 394  99   X2 -9.311286e-03 0.03334445 -0.279245482 7.800564e-01
## 395  99   X3  1.145219e-01 0.03309145  3.460770857 5.386311e-04
## 396  99   X4  1.151180e-01 0.03482557  3.305560486 9.478664e-04
## 397 100   X1  7.211333e-03 0.03372500  0.213827495 8.306816e-01
## 398 100   X2 -2.436007e-02 0.03374014 -0.721990880 4.703001e-01
## 399 100   X3  7.079161e-02 0.03384917  2.091384118 3.649364e-02
## 400 100   X4  1.809244e-01 0.03256998  5.554944848 2.776994e-08
##         conf.low    conf.high
## 1   -0.067235052  0.061350301
## 2   -0.069164665  0.060481048
## 3   -0.015472359  0.119562487
## 4    0.219626585  0.359260190
## 5   -0.117046651  0.013885365
## 6   -0.032498652  0.096453505
## 7   -0.012838732  0.113023314
## 8   -0.053393482  0.076596940
## 9   -0.070936442  0.060532750
## 10  -0.079665773  0.049633429
## 11  -0.041387590  0.085205498
## 12   0.088230919  0.216341434
## 13  -0.016333085  0.115400138
## 14  -0.097314479  0.037629247
## 15   0.009628472  0.138045150
## 16   0.269316525  0.407486972
## 17  -0.082459549  0.056899409
## 18  -0.055550823  0.075570900
## 19   0.016558175  0.146990477
## 20   0.225199872  0.366819177
## 21  -0.080198325  0.054756000
## 22  -0.077315049  0.055064943
## 23   0.015721233  0.146734268
## 24   0.202083999  0.343775654
## 25  -0.007893001  0.125051666
## 26  -0.072579186  0.060831772
## 27  -0.085947114  0.056493485
## 28   0.040948556  0.171049057
## 29  -0.074255935  0.054974546
## 30  -0.107238381  0.019640283
## 31  -0.016431673  0.118854193
## 32   0.193394943  0.330990783
## 33   0.003242446  0.137598618
## 34  -0.049786240  0.078390402
## 35  -0.019793980  0.117797743
## 36   0.101675682  0.234725958
## 37  -0.066167095  0.061447301
## 38  -0.056681251  0.074134039
```

```
## 39  -0.009705924  0.122243044
## 40   0.235333690  0.373913443
## 41  -0.102983047  0.022785097
## 42  -0.066874748  0.062828140
## 43  -0.066674845  0.066455369
## 44   0.072455412  0.201524696
## 45  -0.045079821  0.083031783
## 46   0.027197721  0.160032683
## 47  -0.015551347  0.114775993
## 48   0.242244898  0.374830395
## 49  -0.006279752  0.117345510
## 50  -0.079597979  0.048480060
## 51   0.050085577  0.176856426
## 52   0.223050355  0.359675157
## 53  -0.097599606  0.040100491
## 54  -0.022069592  0.112319769
## 55   0.023230705  0.147746668
## 56   0.071406821  0.202274323
## 57  -0.079800984  0.050970986
## 58  -0.058795681  0.075929695
## 59   0.010089010  0.140669653
## 60   0.190930855  0.333530446
## 61  -0.064663402  0.069142360
## 62  -0.017149106  0.108891460
## 63  -0.036343929  0.091164049
## 64   0.278584508  0.414802196
## 65  -0.169212217 -0.031962912
## 66  -0.050457656  0.085510959
## 67  -0.023309430  0.108133346
## 68   0.173036981  0.313913465
## 69  -0.084487136  0.041424549
## 70  -0.035407272  0.095888819
## 71  -0.047482171  0.079445324
## 72   0.131552417  0.265732447
## 73  -0.021942074  0.107157233
## 74  -0.056937609  0.077025621
## 75  -0.038848940  0.095335430
## 76   0.145484596  0.271426726
## 77  -0.068545590  0.066519664
## 78  -0.069821861  0.064572879
## 79   0.027796891  0.160446457
## 80   0.175724475  0.302528321
## 81  -0.095666463  0.041603884
## 82  -0.079057964  0.045148497
## 83  -0.055806779  0.067778853
## 84   0.151159967  0.286557134
## 85  -0.010622887  0.117188135
## 86  -0.086682688  0.046520190
## 87  -0.007726340  0.131069408
## 88   0.107924866  0.246017967
## 89  -0.112267336  0.025181943
## 90  -0.113307539  0.021096036
## 91  -0.010710094  0.125740734
## 92  -0.046484562  0.090824723
## 93  -0.106984642  0.031440543
## 94  -0.035527414  0.104233748
```

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## 95  -0.080073019  0.053961807
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## 102 -0.078650401  0.046805981
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## 105 -0.084585565  0.048101823
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## 117 -0.083410229  0.043604273
## 118 -0.075082505  0.052506755
## 119  0.044021513  0.175056520
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## 121 -0.008312010  0.124024399
## 122 -0.080662667  0.043212201
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## 129 -0.119551053  0.014623774
## 130 -0.099299170  0.033120713
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## 133 -0.038763029  0.098976510
## 134 -0.068358907  0.066717957
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## 140  0.259822948  0.395633034
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## 142 -0.067385868  0.066917103
## 143 -0.033682735  0.092635202
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## 145 -0.105656780  0.028145607
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## 150 -0.096841988  0.033308149
```

```
## 151 -0.011345523  0.121364359
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## 161 -0.093592424  0.036768961
## 162 -0.043306908  0.090269508
## 163 -0.034397755  0.087727262
## 164 -0.026478509  0.097401648
## 165 -0.103336470  0.026497621
## 166 -0.099239969  0.030609953
## 167 -0.008004855  0.119520353
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## 169 -0.024265416  0.107279620
## 170 -0.064699978  0.057973245
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## 172  0.054117827  0.180852481
## 173 -0.038256665  0.098387928
## 174 -0.011309553  0.123562443
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## 177 -0.014574471  0.114385877
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## 193 -0.003483178  0.128883930
## 194 -0.063724129  0.063612288
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## 202 -0.034118654  0.102406658
## 203  0.011170651  0.133724117
## 204  0.271635848  0.403440240
## 205 -0.058798209  0.068716378
## 206 -0.106177282  0.030365822
```

```
## 207 -0.002850462  0.134508489
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## 210 -0.043009315  0.093524774
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## 216  0.142829227  0.280259967
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## 218 -0.028879725  0.102186252
## 219 -0.020196721  0.109162216
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## 221 -0.090334633  0.043834383
## 222 -0.009409934  0.120409171
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## 256  0.064032352  0.193500441
## 257 -0.055512003  0.067041310
## 258 -0.116914719  0.017705561
## 259 -0.004536339  0.132153947
## 260  0.128243553  0.265822236
## 261 -0.056156030  0.071095216
## 262  0.020432156  0.149947202
```

```
## 263 -0.060534534  0.073927685
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## 267 -0.002313773  0.117527909
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## 271 -0.008789796  0.115028156
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## 274 -0.079983354  0.050243468
## 275 -0.034327101  0.093530988
## 276  0.137944698  0.273865933
## 277 -0.054423564  0.071451447
## 278 -0.105589072  0.025189327
## 279 -0.038585325  0.089458825
## 280 -0.026995680  0.105007218
## 281 -0.073555024  0.058168039
## 282 -0.097063612  0.035967915
## 283 -0.116792593  0.021615803
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## 286 -0.050981869  0.085714376
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```

```
## 319  0.050239900  0.191311966
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## 328  0.216474026  0.348911640
## 329 -0.078771915  0.048048195
## 330 -0.081621085  0.047793770
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## 334 -0.109554192  0.016710875
## 335 -0.021943344  0.107622341
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## 354 -0.098871990  0.029778555
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## 358 -0.101229953  0.029564704
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## 360  0.244273013  0.380857051
## 361 -0.073933333  0.052622703
## 362 -0.035070935  0.097986051
## 363 -0.050988175  0.081231934
## 364  0.262861712  0.397525276
## 365 -0.134050213 -0.004922034
## 366 -0.074156632  0.048279370
## 367 -0.107473325  0.023634090
## 368  0.024154319  0.157000543
## 369 -0.026148016  0.107728462
## 370 -0.084575927  0.051533173
## 371 -0.016414452  0.108972572
## 372  0.134564509  0.270969993
## 373 -0.027335458  0.101297992
## 374 -0.080473448  0.054100764
```

```
## 375 -0.004230298  0.132164477
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## 383 -0.021003371  0.111851119
## 384  0.221070241  0.366180214
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## 389 -0.047672347  0.081417012
## 390 -0.096187488  0.038880874
## 391 -0.040532882  0.093824530
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## 394 -0.074665201  0.056042629
## 395  0.049663876  0.179379977
## 396  0.046861162  0.183374880
## 397 -0.058888459  0.073311124
## 398 -0.090489527  0.041769383
## 399  0.004448462  0.137134763
## 400  0.117088442  0.244760404
```

```r
#sum(which(simoutput$p.value < 0.05))
sum(simoutput$p.value <0.05)
```

```
## [1] 132
```

```r
#simoutput%>%filter(term=="X1")%>%summarize(sum(p.value<0.05))

simoutput%>%dplyr::filter(term=="X1")%>%dplyr::summarize(sum(p.value<0.05))
```

```
##   sum(p.value < 0.05)
## 1                   6
```

```r
simoutput%>%dplyr::filter(term=="X2")%>%dplyr::summarize(sum(p.value<0.05))
```

```
##   sum(p.value < 0.05)
## 1                   2
```

```r
simoutput%>%dplyr::filter(term=="X3")%>%dplyr::summarize(sum(p.value<0.05))
```

```
##   sum(p.value < 0.05)
## 1                  34
```

```r
simoutput%>%dplyr::filter(term=="X4")%>%dplyr::summarize(sum(p.value<0.05))
```

```
##   sum(p.value < 0.05)
## 1                  90
```

Juste's "Something New"

I will be analyzing the Shoenfeld residuals for the Cox PH model.

1. What is goign on? What is the topic? 2. How it is relevant? How it relates to survival analysis/analysis at hand?

Cox proportional hazards (PH) model is considered a great way to identify combined effects of several covariates on the relative risk (hazard). This model assumes that the hazards of the different strata formed by the levels of the covariates are proportional. This proportional hazards assumption is particularly important and can be tested via three different clases of tests. The first class is focused on the piecewise estimation of models for subsets of data defined by stratification of time. The second one considers the interactions between covariates and some function of time. Final, third one is based on examinations of regression residuals. The Schoenfeld Residuals are a part of the third class of proportional hazard assumption testing and I will be exploring it in order to be able to eradicate a method for testing for the PH assumption in the current and future data set analyses. This topic is particularly important in relation to survival analysis since it provides an idea of whether the model is appropriate for the data set at hand and whether some covariates should be considered as variants of time in order to supply the best model for prediction of proportional hazards.

3. Resources to learn about the topic.

I have been researching articles and scientific journals that provide insights into tthe Schoenfeld residuals and their use in the Cox PH model. Sources include:

1. https://onlinelibrary.wiley.com/doi/full/10.1111/ajps.12176
2. https://rstudio-pubs-static.s3.amazonaws.com/39354_34153ff19e624116bd2fbdec7d2534aa.html

4. What will be challenging about learning something new?

Taking a completely new model of analyzing survival data is particulalrly difficult since the mathematical derivations and notations are also very varied from what we have seen in class. Although, I do remember some of the ideas behind parametric functions, their applications to statistical models are much more challenging than I have expected. Therefore, it will require me a lot of time and extensive research to be able to understand and learn how to apply this model to our data and other instances of survival analysis.

Explanation of the Theory Behind Schoenfeld Residuals

Let $z_{ij}(t)$ be the j^{th} covariate of the i^{th} unit, where $i = 1, 2, ..., n$ and $j = 1, 2..., p$

This notation indicates that z_{ij} is allowed to vary as a function of the time scale.

1) As we know from lecture, the Cox PH model assumes that $h(t)$ of the i^{th} individual satisfies:

- $h_i(t) = h_0(t)e^{z_i(t)\beta}$ where:
- h_0 -> baseline hazard
- $z_i(t)$ -> 1 x p vector of covariates for unit i each of which can be time fixed or time-varying.

2) However, another possibility has been presented by Therneau and Granbsh in 2000, where they proposed an idea that there ciuyld be an alternative to the current Cox model, where the coefficient of the estimate could also be varying as a function of time.

   The new hazard function would look like this: $h_i(t) = h_0(t)e^{z_i(t)\beta(t)}$

Therefore, in order to examine thee two models in a case when $\beta = \beta(t)$ requires a residual analysis that could indicate whether a model should consider a covariate as a variable with time.

Due to the fact that that some observations might be censored and in particular, regarding the Cox PH model, the baseline hazard is not estimated, in oprder to analyse the residuals a particular score process. The risk score for unit i at time t is thought to be $r_i(t) = e^{z_i(t)\beta}$, where $Y_i(t)$ is the indicator function and $Y_i(t) = 1$ indicates a point in which i is under risk and thus observation and it is equal to 0 in other occasions.

The Schoenfeld residuals are given by the equations:

1. $s_k = Z_{(k)} - \frac{\sum_i Y_i(t_k) r_i(t_k) Z_i(t_k)}{\sum_i Y_i(t_k) r_i(t_k)}$
2. $s_k = Z_{(k)} - \bar{z}(\hat{\beta}, t_k)$

In this case, the $Z(k)$ is the covariate vector of the particular unit that is experiencing the evnt at time k; $\hat{\beta}$ is the estimate of β and $\bar{z}(\hat{\beta}, t_k)$ is the wighted mean of covariate values.

Furthermore, the weighted variance can be represented by the derived equation at the k^{th} time as

$V(\beta, t_k) = \sum_i Y_i(t_k) r_i(t_k) Z_i(t_k) - \bar{z}(\hat{\beta}, t_k)' Z_i(t_k) - \frac{\bar{z}(\hat{\beta}, t_k)}{\sum_i Y_i(t_k) r_i(t_k)}$

From this, we can scale the Schoenfeld residuals by $V(\beta, t_k)$ of X at t_k via the equation:

$s_k^* = V^{-1}(\hat{\beta}, t_k) s_k$

The scaled Schoenfeld residuals can also be defined as follows:

$s_k^* = m \sum_{k=1}^{d} V(\hat{\beta}, t_k) s_k$

here, m is the total number of deaths in the data set.

Following the calculations, the residuals are plotted against time in order to test the prportional hazards assumption. If the assumption is correct, the residuals should be fiting around the line centered at zero (y=0). The further away this predicted line is form the horizontal of (y=0) the more likely one is to call the PH assumption to question and determine whether it is met through the model.

> To go a little deeper into the analysis of the resiaul calculation, one can look at the calculations of the test statistic for this residual mdoel.

By producing a least squares slope of regression and assuming a relationship between s_{kj}^* and t_{kj} or some function $g(t_k)$ allows to derive a test statistic for the proportional hazards assumption in regards to the j^{th} covariate, which is given by:

$T_j = \frac{[\sum_{k=1}^{d} (g(t_k) - \hat{g}) s_{kj}^8]^2}{dI^{jj} \sum_{k=1}^{d} (g(t_k) - \hat{g})^2}$

Here, the distribution is asymptotical as $X^2(1)$ stating the null hypothesis that the relationship between the covariate, in this case j and the evnt time follows the assumption of PH.

> Interpretation of Schoenfeld Residuals from plots in R and the p-values presented.

The y-axis of the Schoenfeld residuals graph can be interpreted as the log of the hazard ratio for the explanatory variable– the coefficient in Cox's model if it were allow to vary over time. If the graph is flat, then the PH assumption is adequate. Furthermore, the Schoenfeld residuals are independent of time. A plot that shows a non-random pattern against time is evidence of violation of the PH assumption. The PH assumption is supported when there's a non-significan relationship between residuals and time. ### HIV Data Cox PH model analysis using Schoenfeld Residuals

Schoenfeld Residuals applied to our best Cox PH model for AIDS data where, we have an additive model of explanatory variables: baseline cd4 count, iv drug use history, and karnofsky performance scale score:

```
cph_r10 <- coxph(Surv(time,censor)~.-priorzdv -id -hemophil -raceth -time_d -strat2
                 -sex -txgrp -age -tx -censor_d, data = aids)
cph_r10
```

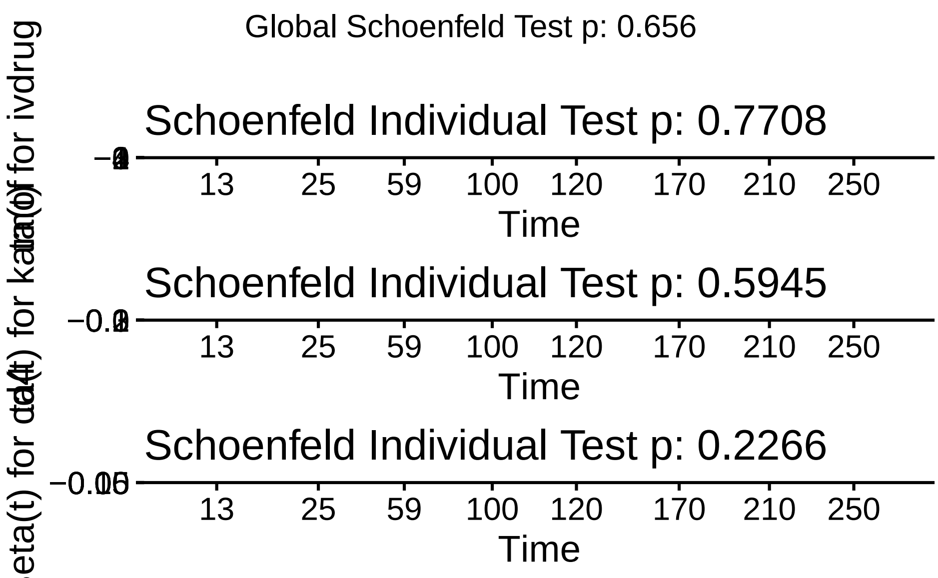
```
## Call:
## coxph(formula = Surv(time, censor) ~ . - priorzdv - id - hemophil -
##     raceth - time_d - strat2 - sex - txgrp - age - tx - censor_d,
```

```
##     data = aids)
##
##              coef exp(coef)  se(coef)      z        p
## ivdrug -0.216832  0.805065  0.180491 -1.201     0.23
## karnof -0.061043  0.940783  0.014157 -4.312 1.62e-05
## cd4    -0.015127  0.984987  0.003076 -4.917 8.77e-07
##
## Likelihood ratio test=69.33  on 3 df, p=5.947e-15
## n= 851, number of events= 69
```

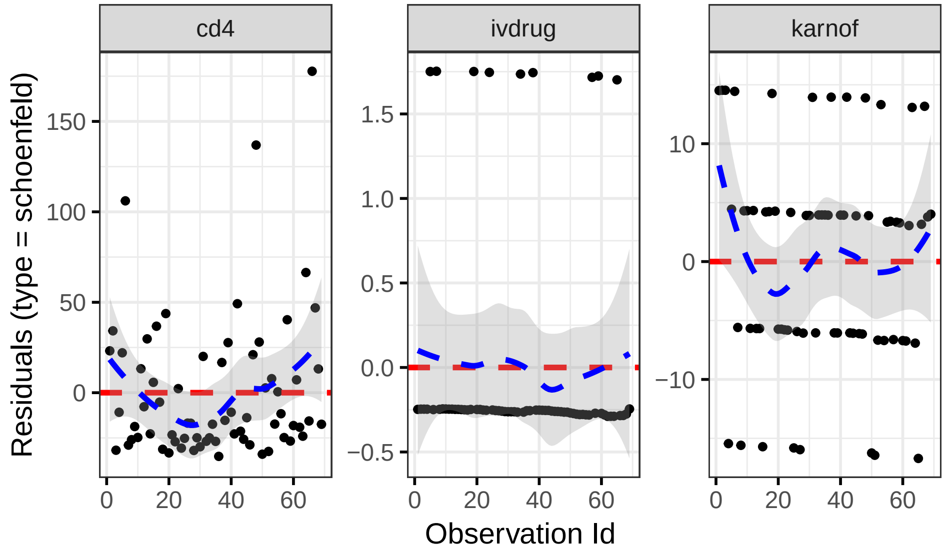
```
zph_r10 <- cox.zph(cph_r10)
zph_r10
```

```
##            rho  chisq     p
## ivdrug -0.0348 0.0849 0.771
## karnof -0.0630 0.2834 0.595
## cd4     0.1524 1.4618 0.227
## GLOBAL      NA 1.6150 0.656
```

```
ggcoxzph(zph_r10)
```




```
ggcoxdiagnostics(cph_r10, type="schoenfeld")
```



Using the best determined Cox PH model for our data, we can look at the Schoenfeld residuals to determine if the PH assumption is met. Via the function "ggcoxzph()"", which produces, for each covariate, graphs of the scaled Schoenfeld residuals against the transformed time. Here, the solid line is a smoothing spline fit to the plot, with the dashed lines representing a +/- 2-standard-error. from these graphs, we don't see any patterns or significance of the residual fit regarding the graphs of the covariates with time. Therefore, the assumption of proportional hazrads seems to be supported for the covariates: baseline cd4 count, iv drug use history, and karnofsky performance scale score.

Using the ggcoxdiagnostics() function we can provide another graphic representation of the residual distribution in regards to the covariates with time. Here, we also see that there's no particular pattern of the residuals around the line of fit, threfore again, we can state that the PH assumption has been met.