7.12 Software for Time-varying Covariates

7.12.1 Time-varying covariates in SAS

We have explored multiple types of time-dependent covariates in SAS, and the main issue is that these covariates need to be assigned for every failure time, not just at the failure time for the subject of interest.

As a result, time-dependent covariates are normally created **within** the PROC PHREG code, so that SAS does these calculations for us.

(1) Time-dependent covariates reflecting interactions of covariates with time to check PH assumption

One type of time-dependent covariate is based on the interaction of a **fixed** covariate with time, in order to assess whether the proportional hazards assumption holds for this fixed covariate.

Let's consider an example, first with the fixed covariates and then with time-dependent covariates to assess PH

First we have a model for time to MAC disease with two treatment effects (**clari**=clarithromycin and **rif**=rifabutin), as compared to the reference group (**clari + rif**):

```
proc phreg data=actg196;
  model mactime*macstat(0) =  clari rif;
  title 'Time to MAC by treatment assignment';
```

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
CLARI	1	0.23184	0.25748	0.8107	0.3679
RIF	1	0.82688	0.23601	12.2748	0.0005

Parameter	Hazard Ratio	Label
CLARI	1.261	1=Clarithromycin arm, 0 otherwise
RIF	2.286	1=Rifabutin arm, 0 otherwise

Now we add interactions of time with these fixed covariates within the PROC PHREG code, so that they are created for every subject at every failure time:

```
proc phreg data=actg196;
  model mactime*macstat(0) =  clari rif claritd riftd;
  claritd=clari*mactime;
  riftd=rif*mactime;
  title 'Treatment for Time to MAC with time-dependent indicators';
  title2 'In order to test for PH assumption';
```

We may also want to "center" or rescale the time-dependent interaction to make it easier to interpret the HRs over time. For example, to center the interaction term at one year, and reflect increments of 30 days (1 month), we can rescale as follows:

```
proc phreg data=actg196;
  model mactime*macstat(0) =  clari rif claritd riftd;
  claritd=clari*((mactime-365)/30);
  riftd=rif*((mactime-365)/30);
  title3 'Rescaled time-dependent interactions';
run;
```

An alternative would be to center at approximately the median follow-up time (in this study, that was at about 20 months).

Here is the output from the first version, with TD covars:

Treatment for Time to MAC with time-dependent indicators
In order to test for PH assumption of treatment

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
CLARI	1	0.19252	0.57450	0.1123	0.7375
RIF	1	0.69393	0.52725	1.7322	0.1881
claritd	1	0.0001022	0.00136	0.0057	0.9400
riftd	1	0.0003542	0.00126	0.0797	0.7778

Parameter	Hazard Ratio	Label
CLARI	1.212	1=Clarithromycin arm, 0 otherwise
RIF	2.002	1=Rifabutin arm, 0 otherwise
claritd	1.000	
riftd	1.000	

The time-dependent interactions are not significant, but it is hard to interpret the estimated HRs (even for the CLARI and RIF variables)

Here is the output from the second version, with centered TD covars:

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
CLARI	1	0.22981	0.25809	0.7929	0.3732
RIF	1	0.82323	0.23624	12.1427	0.0005
claritd	1	0.00307	0.04073	0.0057	0.9400
riftd	1	0.01063	0.03765	0.0797	0.7778

Parameter	Hazard Ratio	Label
CLARI	1.258	1=Clarithromycin arm, 0 otherwise
RIF	2.278	1=Rifabutin arm, 0 otherwise
claritd	1.003	
riftd	1.011	

Now we can interpret the CLARI and RIF hazard ratios as being those at 1 year of follow-up. Note that the p-values for `rif` and `clari` have changed, although the p-values for the time-dependent interactions have not!

In cases where the time-dependent covariates are significant, having the HRs for the main covariates at some time during follow-up (in this case, at 1 year) is more helpful.

May alternatively want to estimate the TD covars at some time near the median follow-up time.

(2) Time-dependent covariates reflecting occurrence of an intermediate event

Some of the other examples we have looked at relate to intermediate events, like heart transplant, that we want to evaluate in terms of association with the failure time outcome.

We have seen several different ways of coding these in SAS, but here is one example. In this case, we are using a time dependent indicator to reflect occurrence of MAC disease as a risk factor for death. This time-dependent indicator is 0 up until the time that a subject develops MAC disease, and then stays at a value of 1 until they are censored or die.

```
proc phreg data=actg196;
  model dthtime*dthstat(0) = clari rif mac_event;

  if macstat=1 and (mactime<dthtime) then mac_event=1;
  else mac_event=0;
run;
```

Note that we can't just check whether `mactime` is less than `dthtime`, since the censoring time for MAC may be before the death time, without a subject having developed MAC. So we always need to make sure that the event occurred `macstat=1` and it occurred prior to the failure time.

Counting Process Data Format in SAS

(3) Time-dependent covariates reflecting changing covariates over time

In some cases, there are covariates which change at multiple points during a follow-up study.

For example, we could have measurements of blood pressure or BMI at each study visit in a long-term study of cardiac disease.

In SAS, we can use a "counting process" format to allow one or more covariates to change over time.

Example: The French Three Cities Study

This was a study evaluating time to cardiovascular event in 697 participants, based on systolic and diastolic blood pressure and use of antihypertensive drugs measured at baseline and at two follow-up visits.

Other covariates include age at study entry and sex (baseline covariates which do not change).

Using the counting process format, the data is organized with three rows for each participant:

- The "start" and "end" variables reflect the time periods covered.
- The covariates reflect the values at the beginning of each period (eg., "start" of interval).
- In this particular example, an event only occurs once per subject and there is no further follow-up once it occurs.
- However, the counting process format is flexible and can handle situations where events may be "recurrent" (more to come later in the semester on this topic).

French Three Cities Study Data

id	age	sex	sbp0	dbp0	antihyp0	fuptime	start	end	sysbp	diasbp	antihyp	event
1	65	1	94.0	63.0	0	60.0658	0	853	94.0	63.0	0	0
						60.0658	853	1588	109.0	59.5	0	0
						60.0658	1588	1826	107.5	56.0	0	0
2	79	1	134.0	85.0	1	60.0658	0	841	134.0	85.0	1	0
						60.0658	841	1572	115.5	68.5	1	0
						60.0658	1572	1826	138.5	77.5	1	0
3	75	1	145.5	86.5	1	60.0658	0	828	145.5	86.5	1	0
						60.0658	828	1569	158.5	96.5	1	0
						60.0658	1569	1826	.	.	1	0
.												
.												
.												
17	72	0	140.5	83.5	1	58.8158	0	749	140.5	83.5	1	0
						58.8158	749	1489	121.5	71.5	1	0
						58.8158	1489	1788	130.0	75.0	0	1
18	72	1	112.5	67.5	0	60.0658	0	1239	112.5	67.5	0	0
						60.0658	1239	1539	146.5	74.0	0	0
						60.0658	1539	1826	129.5	70.5	0	0
19	67	1	123.0	70.5	0	58.1908	0	682	123.0	70.5	0	0
						58.1908	682	1430	109.5	65.0	0	0
						58.1908	1430	1769	124.0	68.0	1	0
20	75	1	139.5	77.0	1	60.0658	0	721	139.5	77.0	1	0
						60.0658	721	1492	183.0	88.0	1	0
						60.0658	1492	1826	169.5	75.5	1	0

Fitting the Cox model using counting process format

```
proc phreg data=frtcs_cp;
  model (start,end)*event(0) = age sex diasbp sysbp antihyp  / rl;
  title 'Cox model using counting process data';
run;
```

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
age	1	0.02335	0.02200	1.1268	0.2884
sex	1	-0.99319	0.24032	17.0793	<.0001
sysbp	1	0.01377	0.00728	3.5778	0.0586
diasbp	1	-0.02355	0.01416	2.7682	0.0962
antihyp	1	0.80008	0.26663	9.0044	0.0027

Analysis of Maximum Likelihood Estimates

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
age	1.024	0.980	1.069	Age at entry
sex	0.370	0.231	0.593	Sex (0=male, 1=female)
sysbp	1.014	1.000	1.028	
diasbp	0.977	0.950	1.004	
antihyp	2.226	1.320	3.753	

Note: this gives exactly the same thing as applying statements within the PROC PHREG procedure to update the values of the covariates at each time, like we did with the recidivism and employment example.

In other words, using a dataset with one observation per participant, containing the covariates:

- fixed: `age` and `sex`
- varying
  - Diastolic BP: `dbp0 dbp1 dbp2` at entry, time 1, time 2
  - Systolic BP: `sbp0 sbp1 sbp2`
  - Anti-hypertensive use: `antihyp0 antihyp1 antihyp2`

Then we can use the following code:

```
proc phreg data=frtcs_orig;
  model fuptime*censor(0) = age sex sysbp diasbp antihyp / rl;
  if (0<fuptime<=time1) then do;
    sysbp=sbp0;
    diasbp=dbp0;
    antihyp=antihyp0;
  end;
  else if (time1<fuptime<=time2) then do;
    sysbp=sbp1;
    diasbp=dbp1;
    antihyp=antihyp1;
  end;
  else if (fuptime>time2) then do;
    sysbp=sbp2;
    diasbp=dbp2;
    antihyp=antihyp2;
  end;
  title 'Cox PH model with time-varying covariates - usual data format';
run;
```

7.12.2 Time-varying covariates in Stata

(1) Time-dependent covariates reflecting interactions of covariates with time to check PH assumption

The first types of time-dependent covariates, namely a multiplicative interaction of t and a covariate, can also be created in Stata, using the `tvc` option on the `stcox` command.

Using the same MAC treatment study (to be discussed shortly), we have:

```
. stcox rif clari, tvc(rif clari)

Cox regression -- Breslow method for ties

No. of subjects =         1151                     Number of obs    =      1151
No. of failures =          121
Time at risk    =       489509
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
main         |
         rif |    2.00156   1.055318     1.32   0.188     .7121553     5.62552
       clari |     1.2123   .6964687     0.34   0.738     .3931813    3.737895
-------------+----------------------------------------------------------------
tvc          |
         rif |   1.000354   .0012556     0.28   0.778     .9978964    1.002818
       clari |   1.000102   .0013579     0.08   0.940     .9974443    1.002767
------------------------------------------------------------------------------
Note: variables in tvc equation interacted with _t
```

The hazard ratios and p-values for the tests for time-dependent interaction agree exactly with those obtained in SAS. But just as for the first set of SAS code, they are difficult to interpret.

We can also rescale the interactions with time in Stata using the `texp` option when we have already specified the `tvc` option. The `texp` option allows us to set the function of time. The default is to use just `t`, but you could specify `texp(ln(_t)` to obtain a log transformation.

Note: you have to use `_t` to refer to the time variable.

```
. stcox rif clari, tvc(rif clari) texp((_t-365)/30)

Cox regression -- Breslow method for ties

No. of subjects =         1151                     Number of obs   =      1151
No. of failures =          121
Time at risk    =       489509
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
main         |
         rif |   2.277838   .5381262     3.48   0.000     1.433611    3.619215
       clari |   1.258363   .3247697     0.89   0.373     .7587871    2.086852
-------------+----------------------------------------------------------------
tvc          |
         rif |   1.010684   .0380572     0.28   0.778     .9387793    1.088096
       clari |    1.00307   .0408568     0.08   0.940     .9261049    1.086431
------------------------------------------------------------------------------
Note: variables in tvc equation interacted with (_t-365)/30
```

(2) Time-dependent covariates reflecting occurrence of an intermediate event

For the second type of time-dependent covariate, in which a variable really changes value during a study, this in can be accommodated in Stata again using a counting process format.

The Stata command `stsplit` can be used to split datasets which have one line per subject into multiple observations, so that time dependent covariates can be evaluated.

On the next page I give an example using the ACTG 196 MAC treatment dataset, and evaluating the association of treatment discontinuation due to toxicity as a time-dependent covariate on the risk of developing MAC disease.

```
. use mac

. describe

Contains data from mac.dta
  obs:         1,177
 vars:            20                          16 Aug 1999 12:57
 size:        98,868 (99.1% of memory free)
-------------------------------------------------------------------------------
              storage  display     value
variable name   type   format      label      variable label
-------------------------------------------------------------------------------
patid           float  %9.0g
age             float  %9.0g
agecat          float  %9.0g
sex             float  %9.0g
karnof          float  %9.0g
ivdrug          float  %9.0g
antiret         float  %9.0g
cd4             float  %9.0g
cd4cat          float  %9.0g
ctg             float  %9.0g
dthstat         float  %9.0g
dthtime         float  %9.0g
macstat         float  %9.0g
mactime         float  %9.0g
swdrstat        float  %9.0g
swdrtime        float  %9.0g
rif             float  %9.0g
clari           float  %9.0g
toxstat         float  %9.0g
toxtime         float  %9.0g
-------------------------------------------------------------------------------
```

First I have to assign a very large value for the time to treatment discontinuation due to toxicity for any subjects who never had this intermediate endpoint. The value assigned has to be something beyond the maximum follow-up for the endpoint of interest (time to MAC disease).

Then I use the Stata command to set up the dataset as a failure time dataset, and I have to include the ID variable which identifies unique subjects.

```
. replace toxtime=10000 if toxstat==0
(923 real changes made)

. stset mactime, failure(macstat) id(patid)

                id:  patid
     failure event:  macstat != 0 & macstat < .
obs. time interval:  (mactime[_n-1], mactime]
 exit on or before:  failure

------------------------------------------------------------------------------
     1177  total obs.
       26  obs. end on or before enter()
------------------------------------------------------------------------------
     1151  obs. remaining, representing
     1151  subjects
      121  failures in single failure-per-subject data
   489509  total analysis time at risk, at risk from t =         0
                             earliest observed entry t =         0
                                  last observed exit t =       827
```

Now I invoke the stsplit command to create a new variable, toxicity, as well as a separate observation for those subjects who have a toxicity.

```
. stsplit toxicity, after(toxtime) at(0)
(125 observations (episodes) created)

. replace toxicity=toxicity+1
(1276 real changes made)
```

Now when I list out some of the observations, we will see that there are two records for any subject who had a toxicity before their mactime. For example, see PATID=8 below, who has one observation for time 0 to 422, with toxicity=0, and a second observation from time 422 to 449, with toxicity=1.

```
. list patid toxstat toxtime toxicity macstat mactime in 1/20
```

	patid	toxstat	toxtime	toxicity	macstat	mactime
1.	1	0	10000	0	1	560
2.	2	0	10000	0	0	651
3.	3	0	10000	0	0	26
4.	4	0	10000	0	0	622
5.	5	0	10000	0	0	643
6.	6	1	171	0	0	171
7.	7	0	10000	0	1	174
8.	8	1	422	0	.	422
9.	8	1	422	1	1	449
10.	9	1	28	0	.	28
11.	9	1	28	1	1	377
12.	10	0	10000	0	0	58
13.	11	1	155	0	0	155
14.	12	0	10000	0	0	121
15.	13	0	10000	0	1	308
11.	9	1	28	1	1	377
12.	10	0	10000	0	0	58
13.	11	1	155	0	0	155
14.	12	0	10000	0	0	121
15.	13	0	10000	0	1	308
16.	14	0	10000	0	0	672
17.	15	1	84	0	.	84
18.	15	1	84	1	0	678
19.	16	0	10000	0	1	280
20.	18	0	10000	0	0	785

Now, we use the usual **stcox** command to evaluate the time-dependent covariate **toxicity** on time to MAC disease. Note that the number of observations is larger than the number of subjects.

```
. stcox toxicity

         failure _d:  macstat
   analysis time _t:  mactime
                 id:  patid

Iteration 0:   log likelihood = -770.53218
Iteration 1:   log likelihood = -767.51134
Iteration 2:   log likelihood = -767.20236
Iteration 3:   log likelihood =  -767.2016
Refining estimates:
Iteration 0:   log likelihood =  -767.2016

Cox regression -- Breslow method for ties

No. of subjects =         1151                     Number of obs   =      1276
No. of failures =          121
Time at risk    =       489509
                                                   LR chi2(1)      =      6.66
Log likelihood  =    -767.2016                     Prob > chi2     =    0.0099

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    toxicity |   1.932791   .4605916     2.77   0.006     1.211547    3.083398
------------------------------------------------------------------------------
```

Finally, we can compare this to what we get from the SAS PROC PHREG with a time-dependent indicator of an intermediate event:

```
proc phreg data=mac;
  model mactime*macstat(0) = toxicity;

  if toxstat=1 and (toxtime<mactime) then toxicity=1;
  else toxicity=0;

  title2 'Time-dependent indicator of treatment toxicity';
run;
```

Time-dependent indicator of treatment toxicity

The PHREG Procedure

Model Information

Data Set	WORK.MAC	
Dependent Variable	MACTIME	Time to MAC disease (days)
Censoring Variable	MACSTAT	MAC status (1=yes,0=censored)
Censoring Value(s)	0	
Ties Handling	BRESLOW	

Number of Observations Read	1175
Number of Observations Used	1175

(some results omitted)

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
toxicity	1	0.65899	0.23830	7.6472	0.0057	1.933

(3) Time-dependent covariates reflecting changing covariates over time

The same approach as above can be used to evaluate covariates which change over time, by first putting data in the counting process format.

Often, this is how our data is organized to begin with, if we have a longitudinal follow-up study with multiple study visits at which covariate values are measured.

In this scenario, the key point is to use the `id` option when setting up the survival dataset in Stata, so that observations belonging to the same participant are linked together.

Example: French Three Cities Study

For the data as shown previously with 3 rows per subject, we can use the following Stata commands:

```
.use frtcs_cp

.list in 1/10

.stset end, failure(event) id(id)
```

	id	age	sex	start	end	event	sysbp	diasbp	antihyp
1.	1	65	1	0	853	0	94	63	0
2.	1	65	1	853	1588	0	109	59.5	0
3.	1	65	1	1588	1826	0	107.5	56	0
4.	2	79	1	0	841	0	134	85	1
5.	2	79	1	841	1572	0	115.5	68.5	1
6.	2	79	1	1572	1826	0	138.5	77.5	1
7.	3	75	1	0	828	0	145.5	86.5	1
8.	3	75	1	828	1569	0	158.5	96.5	1
9.	3	75	1	1569	1826	0	.	.	1
10.	4	78	1	0	816	0	156	81	1

When we call the Cox model, we don't need to do anything special to indicate that we have repeated observations per subject:

```
. stcox age sex sysbp diasbp antihyp
```

```
         failure _d:  event
   analysis time _t:  end
                 id:  id

Iteration 0:   log likelihood = -463.76699
Iteration 1:   log likelihood = -444.95828
Iteration 2:   log likelihood = -444.69153
Iteration 3:   log likelihood =  -444.6915
Refining estimates:
Iteration 0:   log likelihood =  -444.6915

Cox regression -- Breslow method for ties

No. of subjects =          697                     Number of obs    =      2088
No. of failures =           72
Time at risk    =      1245699
                                                   LR chi2(5)       =     38.15
Log likelihood  =    -444.6915                     Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.023625   .0225161     1.06   0.288     .9804316     1.06872
         sex |   .3703941   .0890144    -4.13   0.000     .2312599    .5932365
       sysbp |   1.013861   .0073786     1.89   0.059     .9995019    1.028426
      diasbp |   .9767205   .0138276    -1.66   0.096     .9499914    1.004202
     antihyp |   2.225714   .5934352     3.00   0.003     1.319824     3.75338
------------------------------------------------------------------------------
```

7.13 Case Study for Time-varying Covariates

Case Study of MAC Disease Trial:

ACTG 196 was a randomized clinical trial to study the effects of combination regimens on prevention of MAC (mycobacterium avium complex) disease, which is one of the most common opportunistic infections in AIDS patients and is associated with high mortality and morbidity.

The **treatment regimens** were:

- clarithromycin (new)
- rifabutin (standard)
- clarithromycin plus rifabutin

The article can be found as:

Benson CA, Williams PL, Cohn D et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of mycobacterium avium complex disease in patients with AIDS: a randomized double-blind controlled trial. *Journal of Infectious Disease* 2000; 181: 1289-97.

CASE STUDY FOR TIME-VARYING COVARIATES

Some history of trial conduct:

- This trial enrolled 1178 patients with AIDS and CD4< 100 cells/mm^3 between April 1993 and February 1994
- The patients were randomized with equal probability to the 3 treatment arms (N=398, 391, 389, respectively to C, R, C+R)
- Patients were followed through August 1995; median follow-up $\approx$ 20 months
- In February of 1994, the dosage of rifabutin was reduced from 3 capsules per day (450mg) to 2 capsules per day (300mg) due to concern over **uveitis**, an adverse experience resulting in inflammation of the uveal tract in the eyes (about 3-4% of patients reported uveitis).
- All patients were told to reduce their dosage by March 8, 1994.
- However, some patients had already discontinued the treatment, died, or discontinued the study.

The main intent-to-treat analysis compared the 3 treatment arms without adjusting for this change in dosage.

Other supporting analyses attempted to untangle the effect of this external decision to change treatment, referred to as a **"study wide dose reduction" (SWDR)**.

Original Logrank test Comparing 3 Treatment Arms

```
 Dependent Variable: MACTIME   Time to MAC disease (days)
 Censoring Variable: MACSTAT   MAC status (1=yes,0=censored)
 Censoring Value(s): 0
 Ties Handling: BRESLOW

                      Summary of the Number of
                      Event and Censored Values
                                              Percent
                 Total       Event    Censored    Censored

                  1178         121        1057       89.73

                 Testing Global Null Hypothesis: BETA=0

               Without        With
Criterion    Covariates    Covariates    Model Chi-Square

-2 LOG L       1541.064      1525.932      15.133 with 2 DF (p=0.0005)
Score                .             .      15.890 with 2 DF (p=0.0004)
Wald                 .             .      15.209 with 2 DF (p=0.0005)

                Analysis of Maximum Likelihood Estimates

                 Parameter    Standard     Wald        Pr >       Hazard
Variable  DF      Estimate      Error   Chi-Square  Chi-Square     Ratio

CLARI      1      0.231842     0.25748     0.81074      0.3679     1.261
RIF        1      0.826883     0.23601    12.27480      0.0005     2.286

Variable  Label

CLARI     1=Clarithromycin arm, 0 otherwise
RIF       1=Rifabutin arm, 0 otherwise
```

Questions:

(1) How do we obtain the overall test statistic for treatment?

(2) How could we obtain pairwise test statistics for:

- Clarithromycin vs (C+R)?
- Rifabutin vs (C+R)?
- Clarithromycin vs Rifabutin (Eg, CLARI vs RIF)?

(3) The original article cites pairwise comparisons with rifabutin rather than the combination C+R - how can we get those estimates?

Answers:

(1) **How do we obtain the overall test statistic for treatment?**

Since there are no other covariates in the model, the overall score, likelihood ratio, and Wald tests with 2df are provided in the overall test of the model ("Testing Global Null Hypothesis: BETA=0")

LR Test: χ^2=15.133 with 2 DF (p=0.0005)

Score: χ^2=15.890 with 2 DF (p=0.0004)

Wald: χ^2=15.209 with 2 DF (p=0.0005)

However, if we had adjusted for other covariates in the model, we could still test the treatment effect using a "test" statement:

```
proc phreg data=weighted;
  model mactime*macstat(0) =  clari rif;
  test_trt: test clari, rif;
  title 'Unadjusted comparison of Treatment for Time to MAC';
run;
```

```
proc phreg data=weighted;
  model mactime*macstat(0) = clari rif ctg cd4cat karnof10;
  test_trt: test clari, rif;
  title 'Adjusted comparison of Treatment for Time to MAC';
run;
```

The "test" statement produces this output:

Unadjusted:

Linear Hypotheses Testing Results

Label	Wald Chi-Square	DF	Pr > ChiSq
test_trt	15.2094	2	0.0005

Adjusted:

Linear Hypotheses Testing Results

Label	Wald Chi-Square	DF	Pr > ChiSq
test_trt	17.8594	2	0.0001

The treatment differences are even larger when adjusted for clinical trials group (ACTG or CPCRA), CD4 and Karnofsky score, but the intent to treat analysis relies on the unadjusted model.

Question:

(2) **How could we obtain pairwise test statistics for:**

- Clarithromycin vs (C+R)?
- Rifabutin vs (C+R)?
- Clarithromycin vs Rifabutin (Eg, CLARI vs RIF)?

Answer:

Since we only have terms for CLARI and RIF in the model, that means that the combination treatment CLARI+RIF must be the reference (comparison) group.

So the estimate for CLARI is the log(HR) for comparing Clarithromycin vs the combination (C+R): log(HR)=0.232, HR=1.26

And the estimate for RIF is the log(HR) for comparing Rifabutin vs the combination (C+R): log(HR)=0.827, HR=2.29

That means that, compared to the combination, clarithromycin is associated with 26% increase in risk of MAC disease (not significant) and rifabutin is associated with more than a 2-fold higher risk of MAC disease (significant).

However, we still need to get the estimated HR for Clari vs Rif.

We can do this via a "contrast" statement added to our PHREG code:

```
proc phreg data=weighted;
  model mactime*macstat(0) =  clari rif;
  test_trt: test clari, rif;
  contrast 'c_vs_r' clari 1 rif -1 / estimate=both;
  title 'Unadjusted comparison of Treatment for Time to MAC';
run;
```

[Note: The ESTIMATE=BOTH option requests both the parameter estimate and the exponentiated form (HR).]

The "contrast" statement produces the following output:

Contrast Rows Estimation and Testing Results

Contrast	Type	Row	Estimate	Standard Error	Alpha	Confidence Limits	
c_vs_r	PARM	1	-0.5950	0.2118	0.05	-1.0101	-0.1800
c_vs_r	EXP	1	0.5515	0.1168	0.05	0.3642	0.8353

Contrast Rows Estimation and Testing Results

Contrast	Type	Row	Wald Chi-Square	Pr > ChiSq
c_vs_r	PARM	1	7.8952	0.0050
c_vs_r	EXP	1	7.8952	0.0050

We can also easily calculate the estimated HR for C vs R ourselves:

$$\begin{aligned} \log(HR) &= 0.2318 - 0.8269 \\ &= -0.595 \\ \\ \text{so} \quad \text{HR} &= \exp(-0.595) \\ &= 0.552 \end{aligned}$$

However, while calculating the log(HR) and exponentiating it to get the HR is relatively easy, it doesn't provide us with an estimated standard error or a test statistic for $H_0 : HR = 1$.

So using the contrast statement in PROC PHREG is a good way to obtain estimates and test statistics for other quantities, as long as they are linear combinations of the parameters.

Question:

(3) The original article cites pairwise comparisons with rifabutin rather than the combination C+R - **how can we get those estimates?**

Answer: there are multiple options...

(a) Use the parameter estimates provided in the original output to obtain the HRs of interest (although this wouldn't give us se's or tests)

(b) Use a contrast statement similar to that shown above

(c) Refit the cox model with CLARI and COMBO as terms

The contrast statement would look like this:

```
proc phreg data=weighted;
  model mactime*macstat(0) =  clari rif;
  contrast 'c_vs_r' clari 1 rif -1 / estimate=both;
  contrast 'combo_vs_r' rif -1 / estimate=both;
  title 'Unadjusted comparison of Treatment for Time to MAC';
run;
```

Contrast Rows Estimation and Testing Results

Contrast	Type	Row	Estimate	Standard Error	Alpha	Confidence Limits	
c_vs_r	PARM	1	-0.5950	0.2118	0.05	-1.0101	-0.1800
c_vs_r	EXP	1	0.5515	0.1168	0.05	0.3642	0.8353
combo_vs_r	PARM	1	-0.8269	0.2360	0.05	-1.2895	-0.3643
combo_vs_r	EXP	1	0.4374	0.1032	0.05	0.2754	0.6947

Contrast Rows Estimation and Testing Results

Contrast	Type	Row	Wald Chi-Square	Pr > ChiSq
c_vs_r	PARM	1	7.8952	0.0050
c_vs_r	EXP	1	7.8952	0.0050
combo_vs_r	PARM	1	12.2748	0.0005
combo_vs_r	EXP	1	12.2748	0.0005

These are the same as the refit model with COMBO and CLARI:

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
combo	1	-0.82688	0.23601	12.2748	0.0005
CLARI	1	-0.59504	0.21177	7.8952	0.0050

Analysis of Maximum Likelihood Estimates

Parameter	Hazard Ratio	Label
combo	0.437	
CLARI	0.552	1=Clarithromycin arm, 0 otherwise

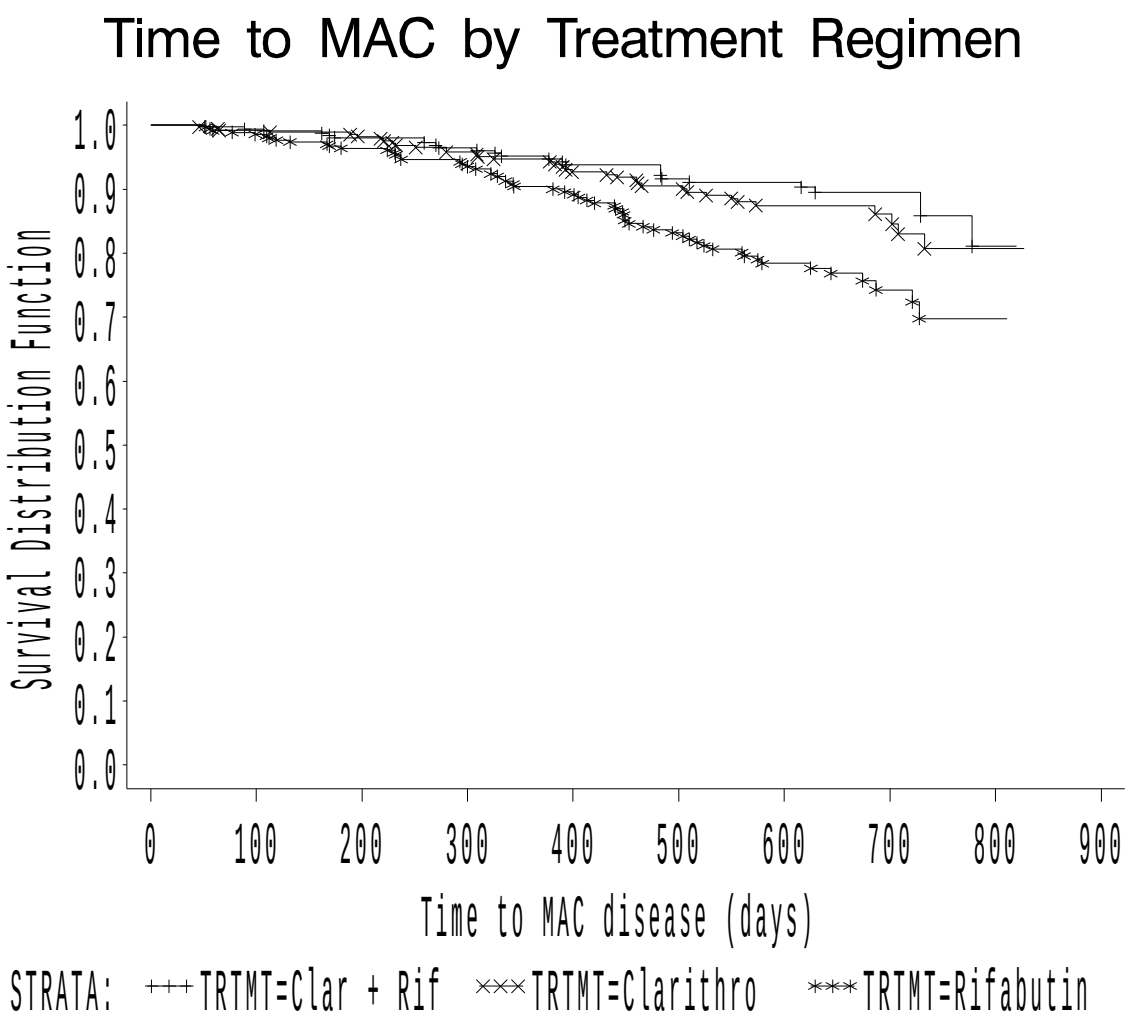
Clarithromycin or Rifabutin Alone or in Combination for Primary Prophylaxis of *Mycobacterium avium* Complex Disease in Patients with AIDS: A Randomized, Double-Blind, Placebo-Controlled Trial

Constance A. Benson,[1,a] Paige L. Williams,[3] David L. Cohn,[5] Simone Becker,[4,a] Peter Hojczyk,[7] Thomas Nevin,[9] Joyce A. Korvick,[10,a] Leonid Heifets,[6] Carroll C. Child,[11] Michael M. Lederman,[12] Richard C. Reichman,[8] William G. Powderly,[14] Gerard F. Notario,[2] Beverly A. Wynne,[13,a] Richard Hafner,[10] and the AIDS Clinical Trials Group 196/Terry Beirn Community Programs for Clinical Research on AIDS 009 Protocol Team[b]

[1]Rush Medical College/Rush-Presbyterian–St. Luke's Medical Center, Chicago, and [2]Abbott Laboratories—Macrolide Venture, Abbott Park, Illinois; [3]Department of Biostatistics and [4]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, Massachusetts; [5]Denver Public Health and University of Colorado Health Sciences Center and [6]National Jewish Medical and Research Center, Denver, Colorado; [7]Frontier Science and Technology Research Foundation, Amherst, and [8]Division of Infectious Diseases, University of Rochester School of Medicine, Rochester, New York; [9]Adult AIDS Clinical Trials Group Operations Center, Social and Scientific Systems, Rockville, and [10]Opportunistic Infection Research Branch/Treatment Research Programs/Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; [11]University of California, San Francisco, and San Francisco General Hospital; [12]Division of Infectious Diseases, Case Western Reserve University School of Medicine, Cleveland, and [13]Adria Laboratories, Division of Erbamont, Inc., Dublin, Ohio; [14]Division of Infectious Diseases, Washington University School of Medicine, St. Louis, Missouri

The efficacy and safety of clarithromycin and rifabutin alone and in combination for prevention of *Mycobacterium avium* complex (MAC) disease were compared in 1178 patients with AIDS who had ≤100 CD4 T cells/μL in a randomized, double-blind, placebo-controlled trial. MAC disease occurred in 9%, 15%, and 7% of those randomized to clarithromycin or rifabutin alone or in combination, respectively; time-adjusted event rates per 100 patient-years (95% confidence interval [CI]) were 6.3 (4.2–8.3), 10.5 (7.8–13.2), and 4.7 (2.9–6.5). Risk of MAC disease was reduced by 44% with clarithromycin (risk ratio [RR], 0.56; 95% CI, 0.37–0.84; $P = .005$) and by 57% with combination therapy (RR, 0.43; 95% CI, 0.27–0.69; $P = .0003$), versus rifabutin. Combination therapy was not more effective than clarithromycin (RR, 0.79; 95% CI, 0.48–1.31; $P = .36$). Of those in whom clarithromycin or combination therapy failed, 29% and 27% of MAC isolates, respectively, were resistant to clarithromycin. There were no survival differences. Clarithromycin and combination therapy were more effective than rifabutin for prevention of MAC disease, but combination therapy was associated with more adverse effects (31%; $P < .001$).

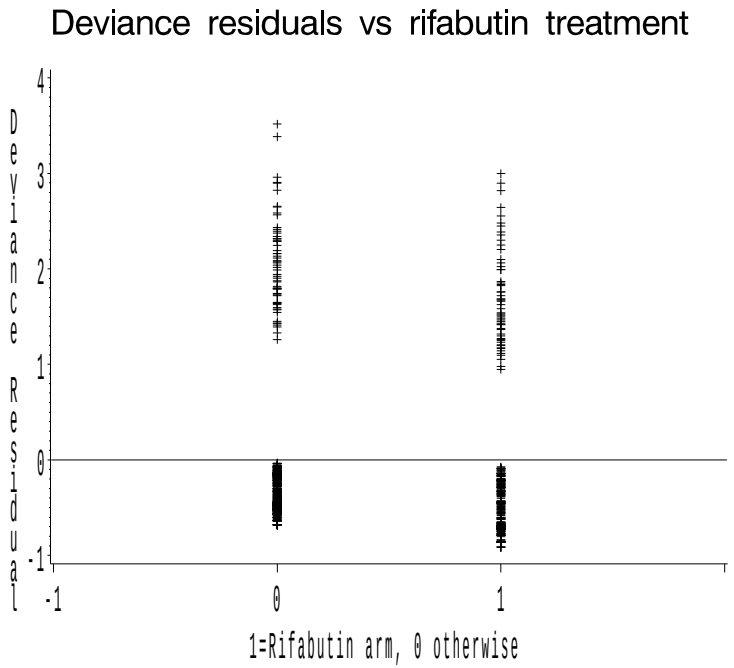
Kaplan-Meier Survival Plot
Estimated Probabilities of Remaining MAC-free

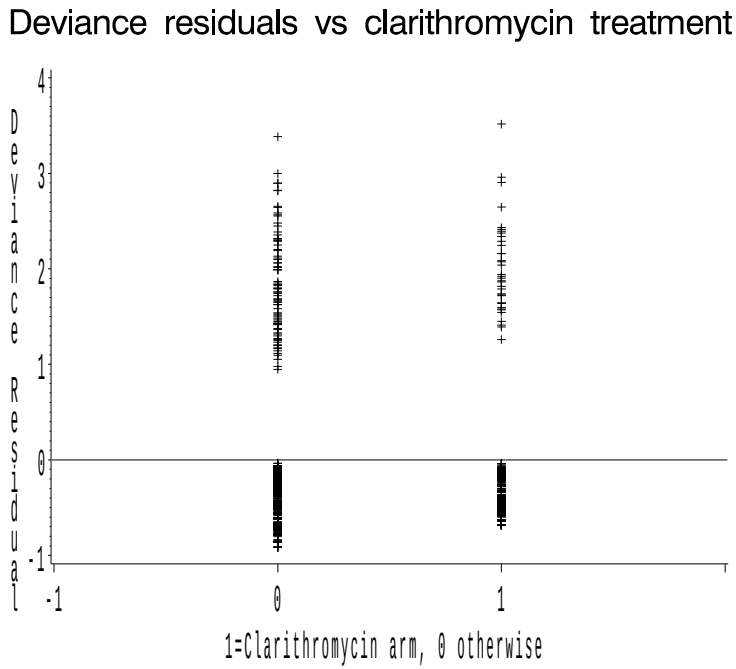


How well does the original model fit?

Let's take a look at the residual plots...

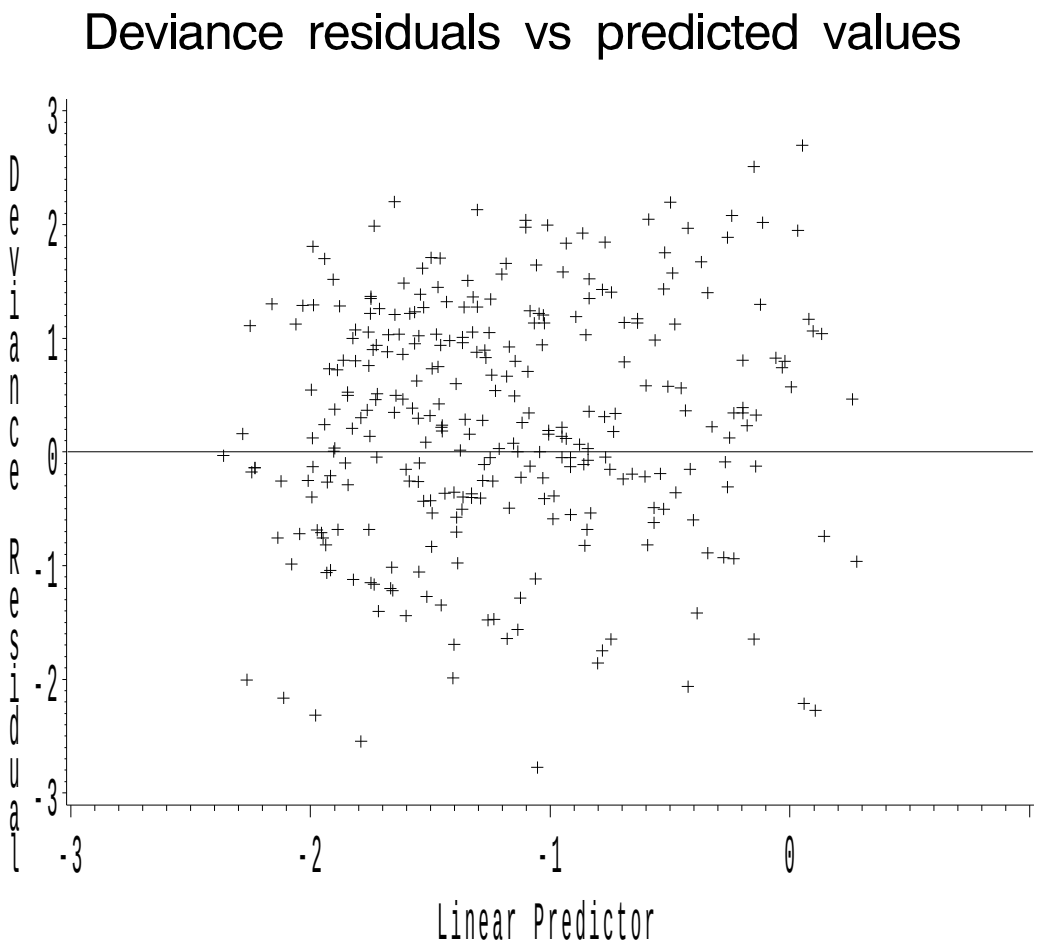
First, the deviance residuals:





Plotting deviance residuals vs binary covariates is not very useful.

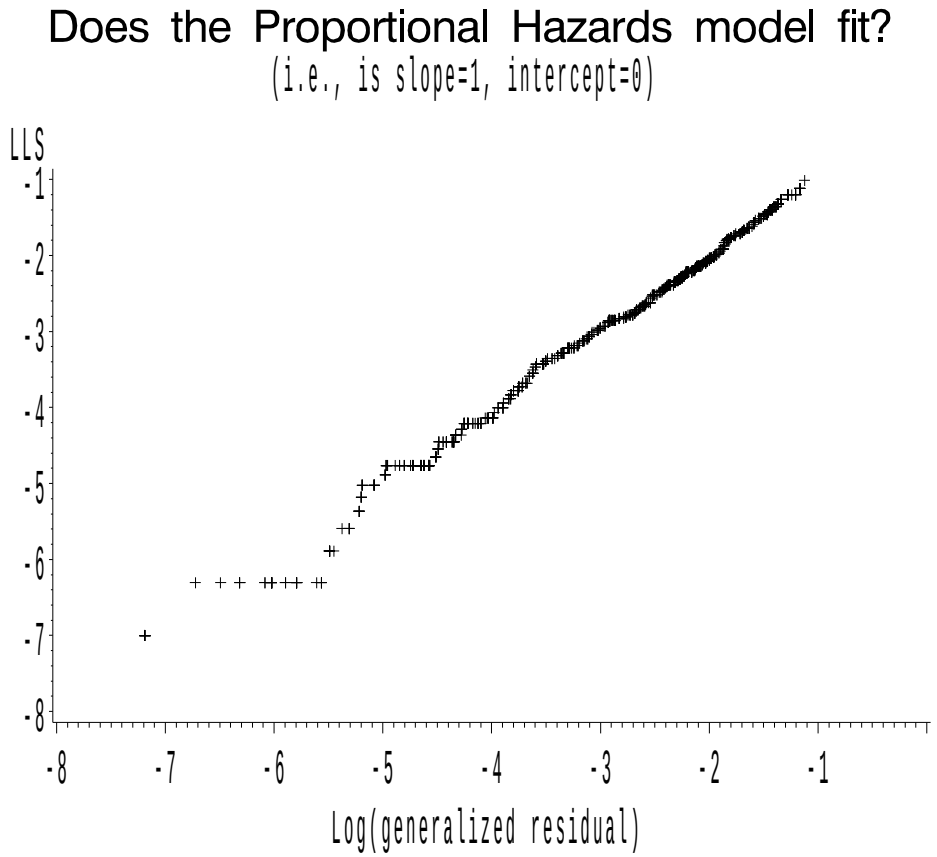
But plotting the residuals vs the predicted values may be useful:



This plot doesn't indicate any particular outliers or pattern with the predicted values.

How about the generalized residuals?

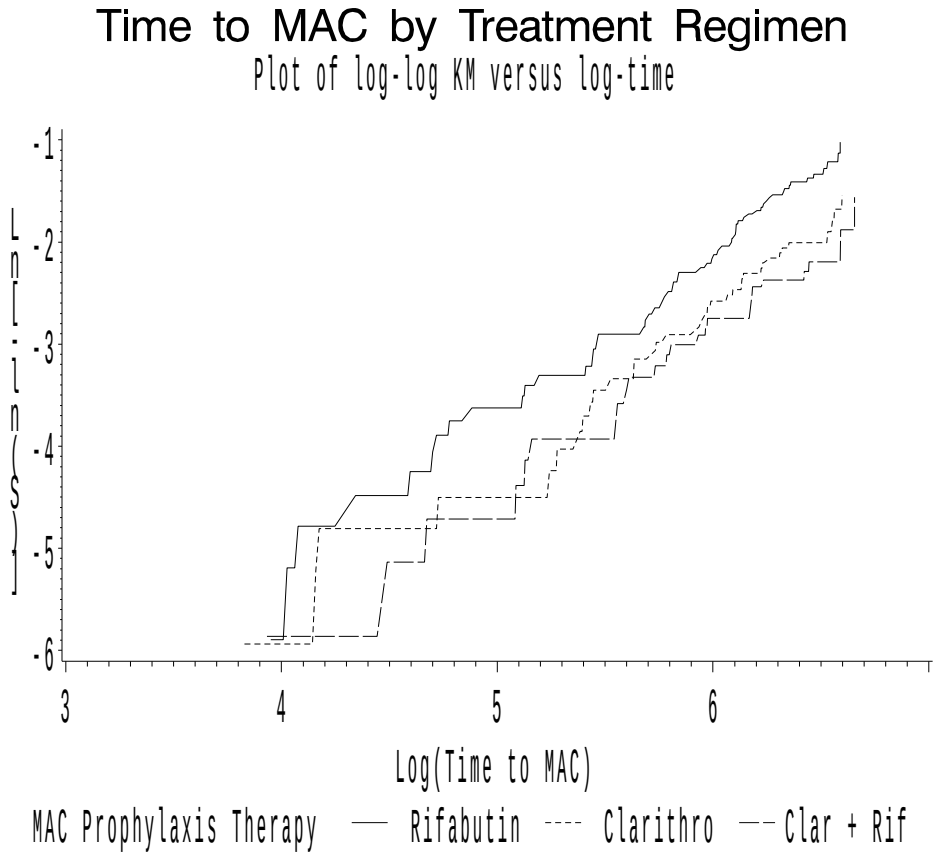
(Are they like a sample from a censored unit exponential?)



Based on fitting a regression line to residuals, I obtained:

$$intercept = 0.056, slope = 1.028 \quad \text{(looks pretty close to 1!)}$$

We can also look at the log cumulative hazard plots (i.e., $\log[-\log(\hat{S})]$) versus log time to see whether the lines are parallel for the three treatment groups.



The line for rifabutin looks fairly parallel to the other two treatment arms. The CLARI and C+R arms cross, but that is partly because they are not different from each other.

Shouldn't we adjust for Baseline CD4 count?

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1541.064	1488.737	52.328 with 3 DF (p=0.0001)
Score	.	.	43.477 with 3 DF (p=0.0001)
Wald	.	.	43.680 with 3 DF (p=0.0001)

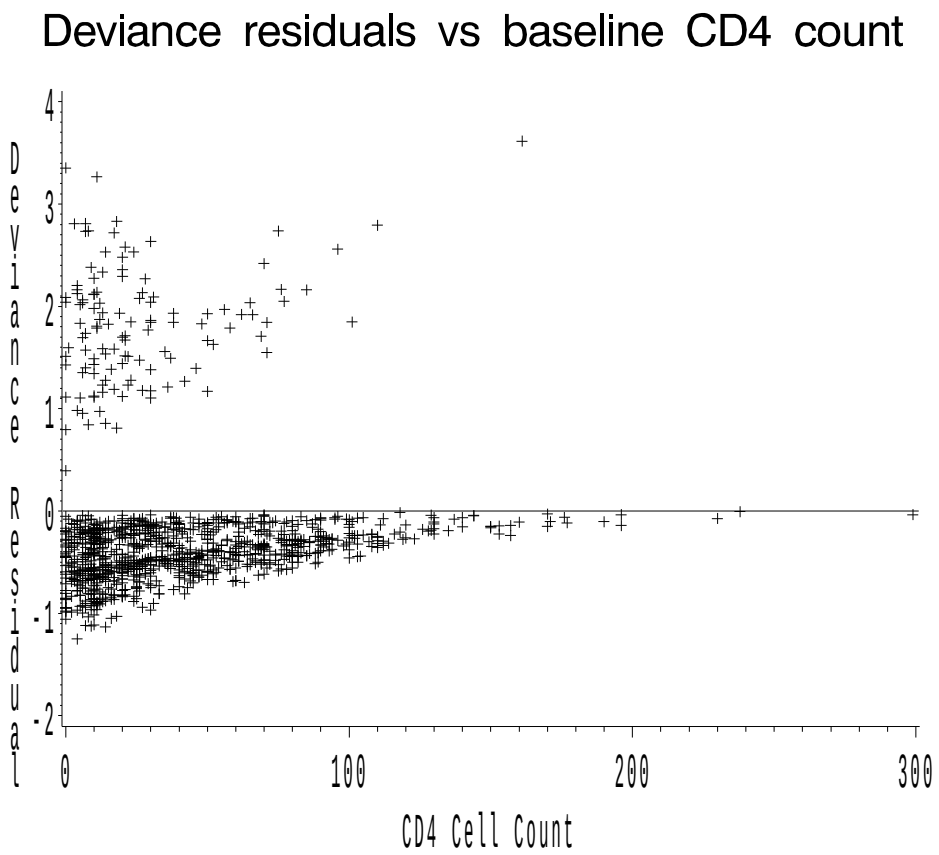
Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Hazard Ratio
CLARI	1	0.198798	0.25747	0.59619	0.4400	1.220
RIF	1	0.837240	0.23598	12.58738	0.0004	2.310
CD4	1	-0.019641	0.00367	28.59491	0.0001	0.981

Is CD4 count a confounder?

(Other important covariates included CTG (clinical trials group) and Karnofsky status. However, all of these should be balanced across treatment arms given the randomization, so none should be confounders since they should not be associated with treatment.).

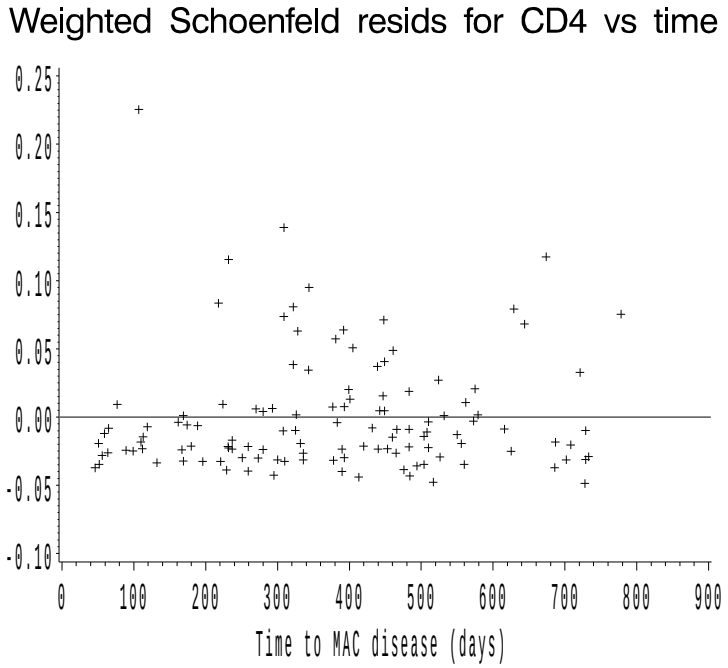
What do the deviance residuals look like versus a continuous covariate, like CD4?



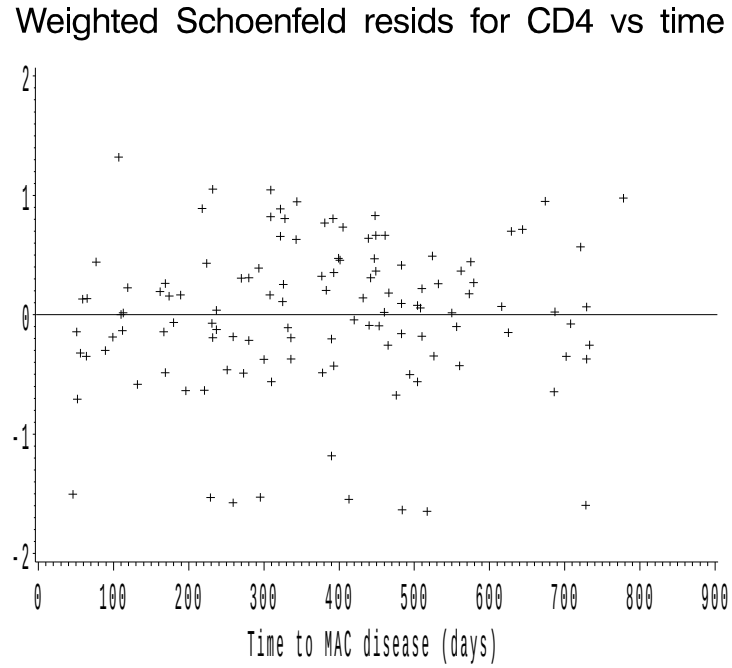
We might want to consider some kind of transformation of CD4 count (like log or square root). If we don't feel comfortable with the linearity of CD4 count, we can also dichotomize it (CD4CAT).

The Weighted Schoenfeld residual plots can be used as another way of checking the proportionality assumption, versus each covariate or "candidate" covariate

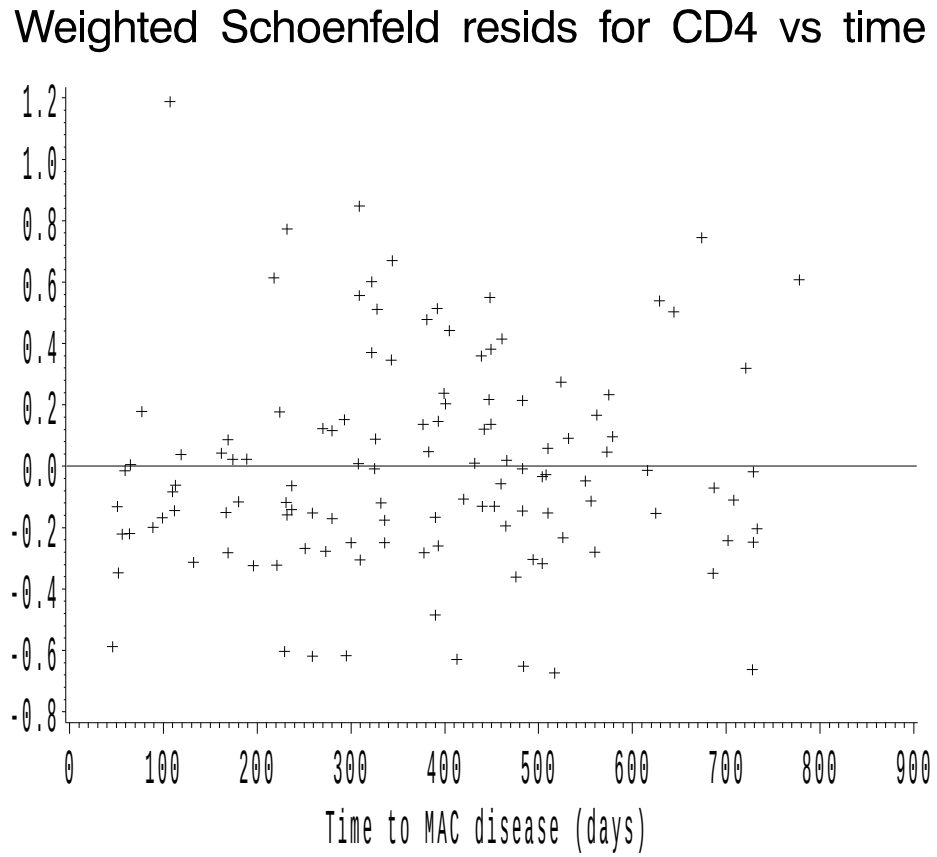
Raw CD4 count



log CD4 count



and Square root CD4 count



This one looks the best, so may suggest this as a possible transformation.

Creation of Time-Dependent Covariates (for assessing PH)

So far, the graphical techniques have not indicated any major departure from proportional hazards. However, we can test this formally by creating time dependent covariates for rifabutin and clarithromycin:

```
riftd=rif*((mactime-365)/30);

claritd=clari*((mactime-365)/30);
```

Even though the dose reduction was only for rifabutin, patients on all 3 arms had to have the dose reduction ... they just took 2 capsules of their placebo, and didn't know whether it was placebo or active drug.

I have centered the time-dependent covariates at 365 days (one year), so that the HR for rif alone and clari alone will apply at one year. Then I have divided by 30, so that the resulting HR can be interpreted as the change for each month away from 365 days.

Question: Can we do this within a data step using the above statements, or do these statements need to be given in the PROC PHREG procedure?

Time-dependent covariates for clari and rif

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1541.064	1525.837	15.227 with 4 DF (p=0.0043)
Score	.	.	16.033 with 4 DF (p=0.0030)
Wald	.	.	15.327 with 4 DF (p=0.0041)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Hazard Ratio
CLARI	1	0.229811	0.25809	0.79287	0.3732	1.258
RIF	1	0.823227	0.23624	12.14274	0.0005	2.278
CLARITD	1	0.003065	0.04073	0.00566	0.9400	1.003
RIFTD	1	0.010627	0.03765	0.07965	0.7778	1.011

Analysis of Maximum Likelihood Estimates

Variable	Label
CLARI	1=Clarithromycin arm, 0 otherwise
RIF	1=Rifabutin arm, 0 otherwise

Neither time-dependent covariate was significant.

Creation of Time-Dependent Covariates (for assessing SWDR)

This analysis also indicated that there are no major departures from proportional hazards for the three treatment arms.

However, it may still be the case that having the study-wide dose reduction had some relationship with MAC disease.

We can assess this by creating a time-dependent variable for the SWDR.

We'll look at the following models:

(1) SWDRSTAT as a simple indicator (naive approach, using indicator of whether a subject EVER had the dose reduction as a baseline indicator)

(2) SWDRSTAT and SWDRTD, with

```
swdrtd = swdrstat*((mactime-365)/30)
```

(3) SWDR as time dependent covariate, reflecting when during follow-up a subject had the dose reduction

Proportion on each treatment arm with SWDR

Treatment by study wide dose reduction

TABLE OF TRTMT BY SWDRSTAT

TRTMT	SWDRSTAT(Study Wide Dose Reduction Status)		
Frequency|			
Row Pct |	No	Yes	Total
R	125	266	391
	31.97	68.03	
C+R	170	219	389
	43.70	56.30	
C	124	274	398
	31.16	68.84	
Total	419	759	1178

STATISTICS FOR TABLE OF TRTMT BY SWDRSTAT

Statistic	DF	Value	Prob
Chi-Square	2	16.820	0.001
Likelihood Ratio Chi-Square	2	16.610	0.001
Mantel-Haenszel Chi-Square	1	0.067	0.795

Patients on the combination arm (C+R) were less likely to have the study wide dose reduction than those on either of the single drug arms.

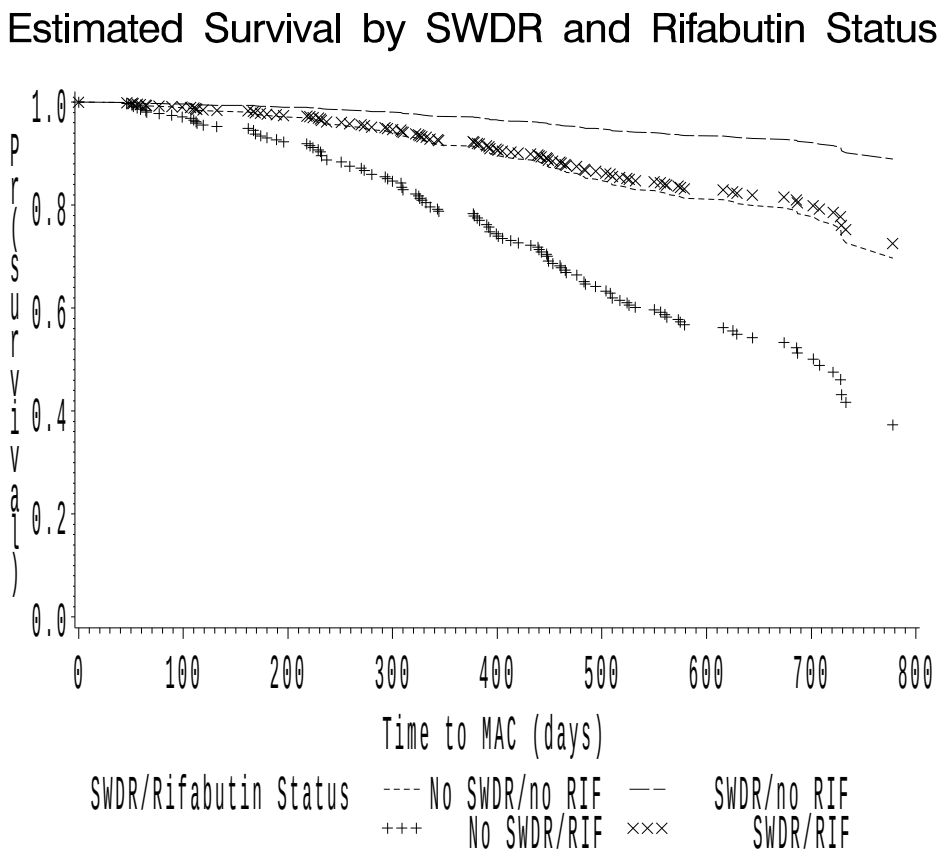
Naive model with fixed SWDR indicator (SWDRSTAT):

```
 Dependent Variable: MACTIME   Time to MAC disease (days)
 Censoring Variable: MACSTAT   MAC status (1=yes,0=censored)

                 Testing Global Null Hypothesis: BETA=0

               Without        With
Criterion    Covariates    Covariates    Model Chi-Square

-2 LOG L       1541.064      1495.857      45.208 with 3 DF (p=0.0001)
Score                .             .      51.497 with 3 DF (p=0.0001)
Wald                 .             .      48.749 with 3 DF (p=0.0001)

                Analysis of Maximum Likelihood Estimates

                 Parameter    Standard     Wald        Pr >       Hazard
Variable  DF      Estimate      Error   Chi-Square  Chi-Square     Ratio

CLARI      1      0.449936     0.26142     2.96236      0.0852     1.568
RIF        1      1.006639     0.23852    17.81114      0.0001     2.736
SWDRSTAT   1     -1.125032     0.19283    34.04055      0.0001     0.325

Variable  Label

CLARI     1=Clarithromycin arm, 0 otherwise
RIF       1=Rifabutin arm, 0 otherwise
SWDRSTAT  Study Wide Dose Reduction Status
```

Reduction of dosage from 450mg to 300mg appears to be protective, which seems counter-intuitive

Predicted Baseline Survival Curves:

Another way to see this is through the predicted baseline survival curves. The two lines are for those not on rifabutin, while the x's and +'s are for those on rifabutin. In each case, the higher line (better prognosis) of the pair is for those who did have the SWDR.



Test for proportionality: This is testing whether the effect of SWDR on risk of MAC disease remains constant over follow-up time.

```
proc phreg data=weighted;
  model mactime*macstat(0) = clari rif swdrstat swdrtd;

  *** create time by covariate interaction for swdr status;
  swdrtd=swdrstat*((mactime-365)/30);

  test_trt: test clari, rif;
  title 'Test of treatment Differences';
  title2 'and test of proportionality at t=365 days';
run;
```

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1541.064	1492.692	48.372 with 4 DF (p=0.0001)
Score	.	.	55.174 with 4 DF (p=0.0001)
Wald	.	.	50.719 with 4 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Hazard Ratio
CLARI	1	0.430051	0.26126	2.70947	0.0998	1.537
RIF	1	1.005416	0.23845	17.77884	0.0001	2.733
SWDRSTAT	1	-1.126498	0.19752	32.52551	0.0001	0.324
SWDRTD	1	0.055550	0.03201	3.01112	0.0827	1.057

Interpretation of Hazard Ratios

$$HR = \exp[\beta_{\text{swdrstat}} + \beta_{\text{swdrtd}} \left(\frac{\text{mactime} - 365)}{30} \right)]$$

$$\beta_{\text{swdrstat}} = -1.1265, \quad \beta_{\text{swdrtd}} = 0.0556$$

Time (months)	Time (days)	calculation	Hazard Ratio
6	182.5	$\exp[-1.1265 + (0.0556)(-6.08)]$	0.231
12	**365**	$\exp[-1.1265 + (0.0556)(0)]$	0.324
18	547.5	$\exp[-1.1265 + (0.0556)(6.08)]$	0.454
24	730	$\exp[-1.1265 + (0.0556)(12.17)]$	0.637
30	912.5	$\exp[-1.1265 + (0.0556)(18.25)]$	0.893
36	1095	$\exp[-1.1265 + (0.0556)(24.33)]$	1.253

- In the early period after randomization to treatment, reduction of randomized dosage from 450mg to 300mg is associated with a decreased risk of MAC disease.
- After taking the higher dosage for about 32 months, dropping to the lower dosage has no impact
- As the treatment time increases beyond 32 months, a lower dosage tends to be associated with increased risk of MAC.

3 different ways to code SWDR as time-dependent covariate

```
proc phreg data=weighted;
  model mactime*macstat(0) = clari rif swdr;

  if (swdrtime>=mactime) then swdr=0;
  else do;
    if swdrstat=1 then swdr=1;
    else swdr=0;
  end;

  test_trt: test clari, rif;
  title2 'I. Time-dependent indicator of dose reduction';

proc phreg data=weighted;
  model mactime*macstat(0) = clari rif swdr;

  if swdrstat=0 or (swdrtime>=mactime) then swdr=0;
  else swdr=1;

  test_trt: test clari, rif;
  title2 'II. Time-dependent indicator of dose reduction';

proc phreg data=weighted;
  model mactime*macstat(0) = clari rif swdr;

  if swdrstat=1 and (swdrtime<mactime) then swdr=1;
  else swdr=0;

  test_trt: test clari, rif;
  title2 'III. Time-dependent indicator of dose reduction';
```

The resulting output from model-fitting is the same for all 3 cases:

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1178	121	1057	89.73

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1541.064	1517.426	23.639 with 3 DF (p=0.0001)
Score	.	.	24.844 with 3 DF (p=0.0001)
Wald	.	.	24.142 with 3 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
CLARI	1	0.328849	0.26017	1.59762	0.2062	1.389
RIF	1	0.905299	0.23775	14.49956	0.0001	2.473
SWDR	1	-0.648887	0.21518	9.09389	0.0026	0.523

SWDR is still protective? Does this make sense intuitively?

What other methods can we use to account for change in dosage?

Weighted adjusted dose (WAD) analyses

To try to get a better idea of the effect of changing doses of rifabutin on the hazard for MAC disease, I created the following weighted dose of randomized rifabutin:

- Between randomization date and SWDR date
  $\Longrightarrow$ # Days at 450mg
- Between SWDR date and off-study date
  $\Longrightarrow$ # Days at 300mg
- Between randomization date and Off-study date
  $\Longrightarrow$ # Total Days
- Weighted randomized dose

```
rifwadr = (days450 + days300)/totdays
```

- Transformed to number of capsules per day;

```
rifwadr=rifwadr/150;
```

- Also calculated weighted dose *while on treatment* by starting with on treatment date, stopping with off-treatment date, and dividing by the total days on study.

Weighted adjusted dose (WAD) analyses:

Randomized assignment to rifabutin

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1178	121	1057	89.73

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1541.064	1493.476	47.588 with 3 DF (p=0.0001)
Score	.	.	52.770 with 3 DF (p=0.0001)
Wald	.	.	50.295 with 3 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
CLARI	1	0.453283	0.26119	3.01179	0.0827	1.573
RIF	1	1.004846	0.23826	17.78681	0.0001	2.731
RIFWADR	1	1.530462	0.25681	35.51502	0.0001	4.620

For each additional capsule of rifabutin specified as randomized treatment, the HR for MAC increased by 4.6 times

Weighted adjusted dose (WAD) analyses:

Actual dosage of rifabutin during the study

Dependent Variable: MACTIME Time to MAC disease (days)
Censoring Variable: MACSTAT MAC status (1=yes,0=censored)

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1541.064	1489.993	51.071 with 3 DF (p=0.0001)
Score	.	.	55.942 with 3 DF (p=0.0001)
Wald	.	.	53.477 with 3 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
CLARI	1	0.489583	0.26256	3.47693	0.0622	1.632
RIF	1	1.019675	0.23873	18.24291	0.0001	2.772
RIFWAD	1	-0.664689	0.10686	38.69332	0.0001	0.514

Here, higher values of RIFWAD probably reflect that the patient was able to stay on treatment longer, which was protective. The SWDR variable is also capturing whether a patient had been able to tolerate the treatment long enough to have the chance to have the protocol-mandated dose reduction.

What happens if we add treatment discontinuation as a time dependent covariate?

Dependent Variable: MACTIME Time to MAC disease (days)
Censoring Variable: MACSTAT MAC status (1=yes,0=censored)

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1541.064	1501.595	39.469 with 4 DF (p=0.0001)
Score	.	.	42.817 with 4 DF (p=0.0001)
Wald	.	.	41.027 with 4 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
CLARI	1	0.420447	0.26111	2.59284	0.1073	1.523
RIF	1	0.984114	0.23847	17.02975	0.0001	2.675
SWDR	1	-0.139245	0.23909	0.33919	0.5603	0.870
RXSTOP	1	0.902592	0.21792	17.15473	0.0001	2.466

SWDR is no longer significant!

Last of all, a comparison of some of these models:

Model terms	q	$-2\log L$	AIC Criterion
Clari, Rif	2	1525.93	1531.93
Clari, Rif, Cd4cat	3	1497.57	1506.57
Clari, Rif, Cd4	3	1488.74	1497.74
Clari, Rif, Cd4cat, Ctg, Karnof	5	1482.67	1497.67
Clari, Rif, Swdrstat	3	1495.86	1504.86
Clari, Rif, Rifwadr	3	1493.48	1502.48
Clari, Rif, Swdrstat, Rifwadr	4	1493.44	1505.44
Clari, Rif, Rifwad	3	1489.99	1498.99
Models with time-dependent covariates			
Clari, Rif, Claritd, Riftd	4	1525.84	1537.84
Clari, Rif, Swdrstat, Swdrtd	4	1492.69	1504.69
Clari, Rif, Swdr	3	1517.43	1526.43
Clari, Rif, Swdr, Rxstop	4	1501.60	1513.60
Clari, Rif, Cd4cat, Karnof, Rxstop	5	1461.90	1476.90
Clari, Rif, Cd4cat, Karnof, Rifwad	5	1448.14	1463.14

Sometimes, the model with the lowest AIC may be best in terms of prediction, but may not be the most appropriate model for addressing your scientific questions.

Contents