Applied Survival Analysis
Lab 11: Analysis of competing risks

We analyse data involving treatment interruptions (TI) among HIV-infected patients in the presence of the competing risk of death or loss from follow-up. The data are included in file `TI-data_final.dta`.

The data are as follows:

```
               fail3 |      Freq.     Percent        Cum.
---------------------+-----------------------------------
               Alive |     10,738       75.82       75.82
   TI or new regimen |      1,376        9.72       85.54
Death or lost to fup |      2,048       14.46      100.00
---------------------+-----------------------------------
               Total |     14,162      100.00
```

In other words, there are 1,376 individuals with the event of interest and 2,048 with the competing event. The question is: "What is the cumulative incidence of treatment interruption over time?"

We will perform an analysis of these data in a number of ways. First, we will perform the naïve analysis by considering, as the estimate of the cumulative incidence function, one minus the Kaplan Meier estimate of survival $\hat{S}(t_i)$ at some time point t_i, i.e.,

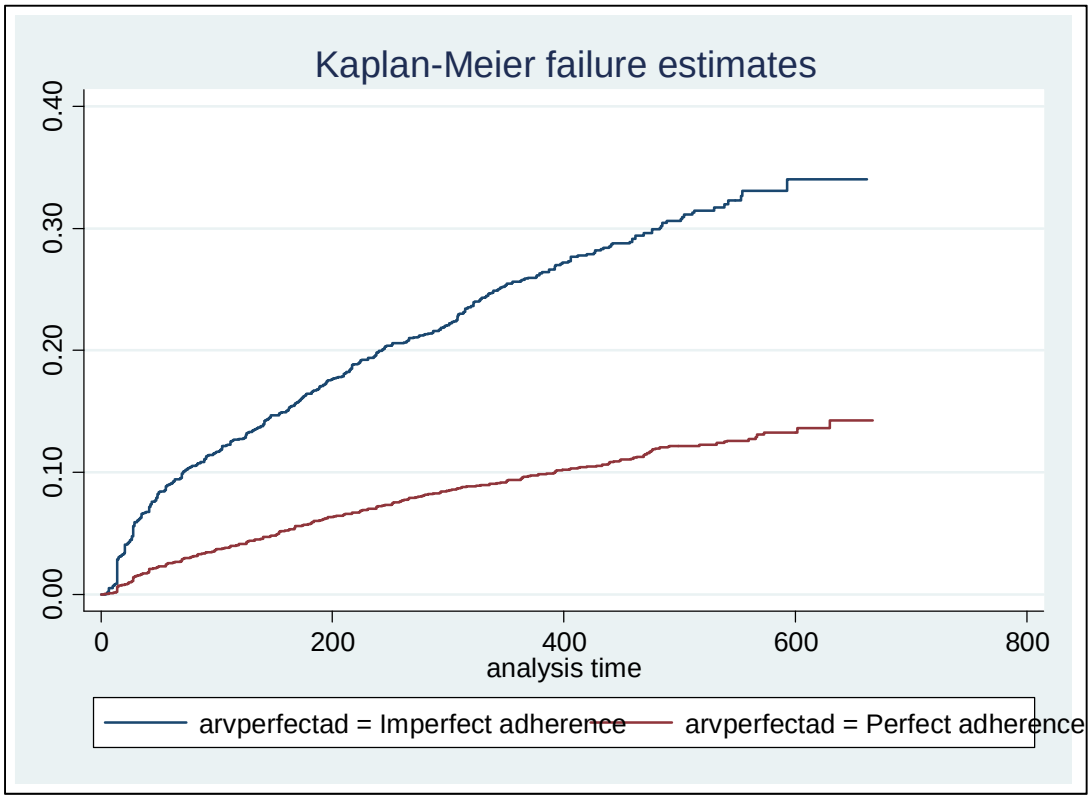
$$\hat{F}_j(t_i) = 1 - \hat{S}(t_i)$$

We will also assess the effect of perfect ARV adherence on the hazard of TI. This is done as follows:

```
. stset time2int , fail(fail3==1)

     failure event:  fail3 == 1
obs. time interval:  (0, time2int]
 exit on or before:  failure

--------------------------------------------------------------------------------
    14162  total obs.
        0  exclusions
--------------------------------------------------------------------------------
    14162  obs. remaining, representing
     1376  failures in single record/single failure data
  3548482  total analysis time at risk, at risk from t =         0
                            earliest observed entry t =         0
                                 last observed exit t =       667
```

```
. sts graph, failure by(arvperfectad) ylab(0 0.1 0.2 0.3 0.4)

         failure _d:  fail3 == 1
   analysis time _t:  time2int
```

The result is as follows:



Now, we are told that this estimate probably overestimates the true cumulative incidence function. So let's see what we can do in order to perform a better estimation.

First of all, we will try performing the following steps:

1. Analyze the data considering any failure other than TI as censored data. This will produce the cause-specific hazard $\hat{h}_1(t)$
2. Analyze the data considering any failure other than death or loss to follow-up as censored data. This will produce the cause-specific hazard $\hat{h}_2(t)$
3. Estimate the discrete survival function $\hat{S}(t) = \prod_{i:t_i<t}\{1 - \hat{h}_1(t) - \hat{h}_2(t)\}$
4. Estimate the cumulative incidence function as $\hat{F}_{TI}(t) = \sum_{i:t_i<t} \hat{h}_1(t_i)\hat{S}(t_{i-1})$

Let's follow this approach.

STEP 1. Analyze the data considering any failure other than TI as censored data. This will produce the cause-specific hazard $\hat{h}_1(t)$[1]

```
. quietly stcox arvperfectad
```

[1] Note that we have already set up the data to consider all failures other than TI as censored data (from the Kaplan-Meier analysis previously.

Predict the baseline hazard of TI (this is the same as the hazard for TI among those with imperfect ARV adherence:

```
. predict h_TI_0, basehc
(12790 missing values generated)
```

Now we sort the data in ascending order by time and descending order by event. This will ensure that the censored times tied with event times will be placed after the event times:

```
. gsort _t  - _d

. by _t: replace h_TI_0 = . if _n > 1
(994 real changes made, 994 to missing)
```

Note that, because we had 994 ties in the data with death or loss to follow-up as the event, we needed to remove any duplicate contributions of the hazards during all but the first of these tied event times. Now predict the hazard for TI among those with perfect adherence:

```
. gen h_TI_1 = h_TI_0*exp(_b[arvperfectad ])
(13784 missing values generated)
```

STEP 2. Analyze the data considering any failure other than death or loss to follow-up as censored data. This will produce the cause-specific hazard $\hat{h}_2(t)$

```
. stset time2int , fail(fail3==2)

     failure event:  fail3 == 2
obs. time interval:  (0, time2int]
 exit on or before:  failure

------------------------------------------------------------------------------
    14162  total obs.
        0  exclusions
------------------------------------------------------------------------------
    14162  obs. remaining, representing
     2048  failures in single record/single failure data
  3548482  total analysis time at risk, at risk from t =         0
                            earliest observed entry t =         0
                                 last observed exit t =       667
```

```
. quietly stcox arvperfectad
```

Predict the baseline hazard of death or loss to follow-up (DL) (this is the same as the hazard for TI among those with imperfect ARV adherence):

```
. predict h_DL_0, basehc
(12266 missing values generated)
```

Now we sort the data in ascending order by time and descending order by event. This will ensure that the censored times tied with event times will be placed after the event times:

```
. gsort _t  - _d

. by _t: replace h_DL_0 = . if _n > 1
(1537 real changes made, 1537 to missing)
```

Note that, because we had 1,537 ties in the data with death or loss to follow-up as the event, we needed to remove any duplicate contributions of the hazards during all but the first of these tied event times. Now predict the hazard for death or loss to follow-up among those with perfect adherence:

```
. gen h_DL_1 = h_DL_0*exp(_b[arvperfectad ])
(13803 missing values generated)
```

Before going further, note that there are 513 observations with missing adherence measures:

```
. tab arvperfectad fail3, missing

        arv perfect |              fail3
          adherence |     Alive  TI or new  Death or  |     Total
--------------------+---------------------------------+----------
Imperfect adherence |     1,563        577        330 |     2,470
  Perfect adherence |     8,818        795      1,566 |    11,179
                  . |       357          4        152 |       513
--------------------+---------------------------------+----------
              Total |    10,738      1,376      2,048 |    14,162
```

STEP 2a. Generate an indicator to exclude observation without failure from any kind and replace missing hazards with zeros in cases where one or the other failure was observed.

```
. gen exclude=(missing(h_TI_0) & missing(h_DL_0))
```

Note that the following observations will be excluded:

```
. tab exclude fail3

           |              fail3
   exclude |     Alive  TI or new  Death or  |     Total
-----------+---------------------------------+----------
         0 |         0        378        359 |       737
         1 |    10,738        998      1,689 |    13,425
-----------+---------------------------------+----------
     Total |    10,738      1,376      2,048 |    14,162
```

In addition to the 10,738 observations which are censored (since they have not experienced either type of failure) there are 994 ties and 4 observations with missing adherence measures among subjects with a TI and 1537 ties and 152 observations with missing adherence measures among patients who died or were lost to follow-up. These will also be excluded.

Now replace the remaining observations with missing only one of the two types of failure with zero hazard.

```
. replace h_TI_0 =0 if h_TI_0 ==. & h_DL_0 ~=.
(359 real changes made)

. replace h_TI_1 =0 if h_TI_1 ==. & h_DL_1 ~=.
(359 real changes made)

. replace h_DL_0 =0 if h_DL_0 ==. & h_TI_0 ~=.
(378 real changes made)
```

```
. replace h_DL_1 =0 if h_DL_1 ==. & h_TI_1 ~=.
(378 real changes made)
```

Note that there were 359 changes made among those experiencing a TI and 378 changes among those experiencing death or loss to follow-up.

STEP 3. Estimate the discrete survival function $\hat{S}(t) = \prod_{i:t_i<t}\{1 - \hat{h}_1(t) - \hat{h}_2(t)\}$[2]

```
. gsort -exclude _t
```

Note that we sorted the excluded variables first and the non-excluded last, so we can produce a running sum over them[3]:

```
. gen S_0 = exp(sum(log(1- h_DL_0 - h_TI_0))) if exclude==0
(13425 missing values generated)

. gen S_1 = exp(sum(log(1- h_DL_1 - h_TI_1))) if exclude ==0
(13425 missing values generated)
```

Note the trick where, instead of performing the product we sum the log survival and exponentiate, i.e., we use the property that,

$$\hat{S}(t) = \prod_{i:t_i<t}\{1 - \hat{h}_1(t) - \hat{h}_2(t)\} = \exp\left\{\sum_{i:t_i<t}\log\left(1 - \hat{h}_1(t) - \hat{h}_2(t)\right)\right\}$$

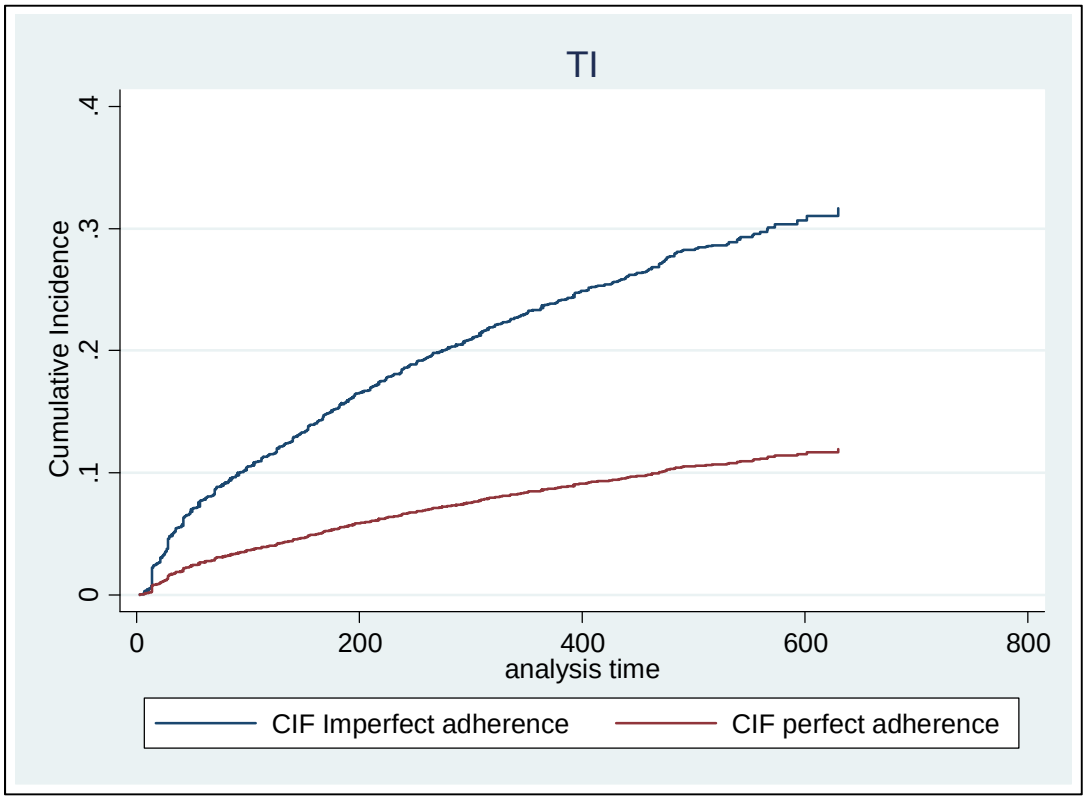
Finally, we calculate the estimated CIFs and graph:

```
. gen cif_TI_0 = sum(S_0[_n-1]*h_TI_0) if exclude==0
(13425 missing values generated)

. label var cif_TI_0 "CIF Imperfect adherence"

. gen cif_TI_1 = sum(S_1[_n-1]*h_TI_1) if exclude==0
(13425 missing values generated)

. label var cif_TI_1 "CIF perfect adherence"

. twoway line cif_TI* _t , connect(J J) sort ylab(0 0.1 0.2 0.3 0.4) title(TI)
> ytitle(Cumulative Incidence) xtitle(analysis time)
```

[2] Note that 1,753 missing values will be generated for the observations with neither of the two failures (which will be excluded from the analysis as censored observations and thus observations providing no information).

[3] If we did not do this, only values with successively available observations would be summed resulting in a virtually zero result!

This results in the following graph:



Now we will generate the Aalen-Johansen estimator of the cumulative incidence function. First we will perform the analysis of the effect of ARV adherence on TI in the presence of death or loss to follow-up.

```
. stset time2int , fail(fail3==1)

     failure event:  fail3 == 1
obs. time interval:  (0, time2int]
 exit on or before:  failure

--------------------------------------------------------------------------------
    14162  total obs.
        0  exclusions
--------------------------------------------------------------------------------
    14162  obs. remaining, representing
     1376  failures in single record/single failure data
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                              earliest observed entry t =         0
                                   last observed exit t =       667
```
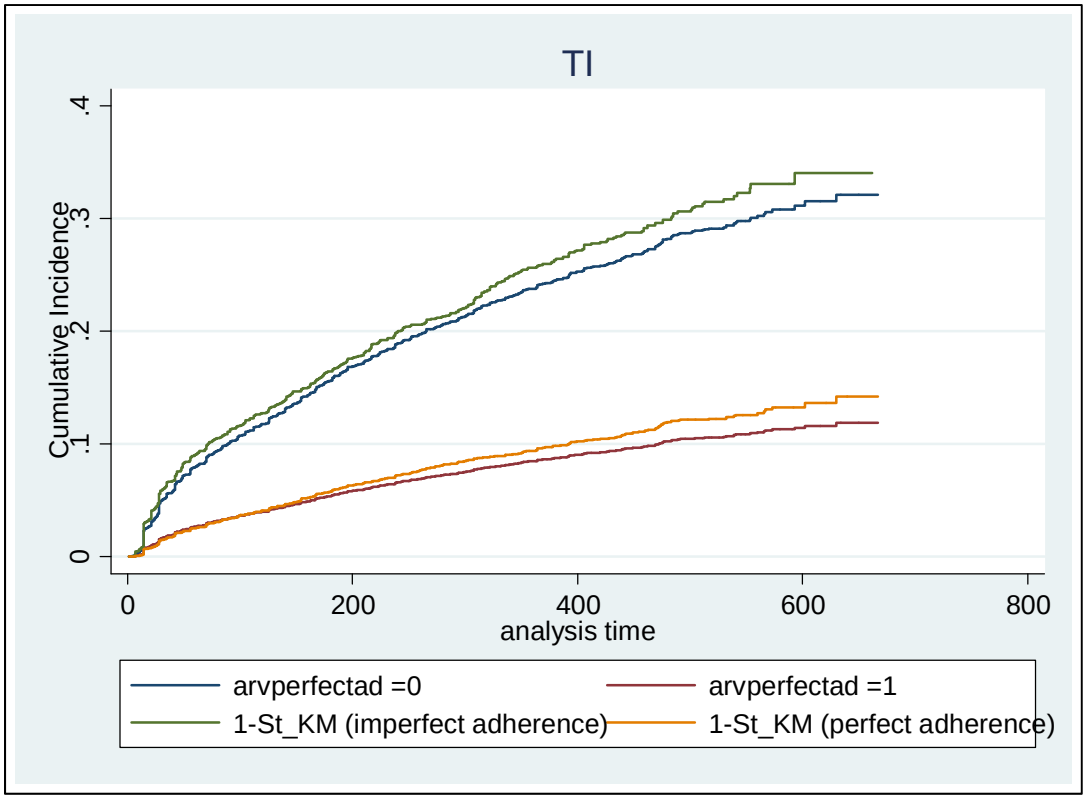

```
. stcrreg arvperfectad , compete(fail3 == 2)

         failure _d:  fail3 == 1
   analysis time _t:  time2int

Iteration 0:   log pseudolikelihood = -12326.422
Iteration 1:   log pseudolikelihood = -12326.263
Iteration 2:   log pseudolikelihood = -12326.263

Competing-risks regression                          No. of obs       =     13649
                                                    No. of subjects  =     13649
Failure event  : fail3 == 1                         No. failed       =      1372
Competing event: fail3 == 2                         No. competing    =      1896
                                                    No. censored     =     10381

                                                    Wald chi2(1)     =    418.43
Log pseudolikelihood = -12326.263                   Prob > chi2      =    0.0000

------------------------------------------------------------------------------
             |               Robust
          _t |        SHR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
arvperfectad |   .3258656   .0178622   -20.46   0.000     .2926713    .3628248
------------------------------------------------------------------------------
```

We note that perfect adherence is associated with an almost 2/3 reduction of the sub-hazard for TI adjusted for the effect of death and loss to follow-up. The CIF estimate based on the Aalen-Johansen estimator is produced as follows:

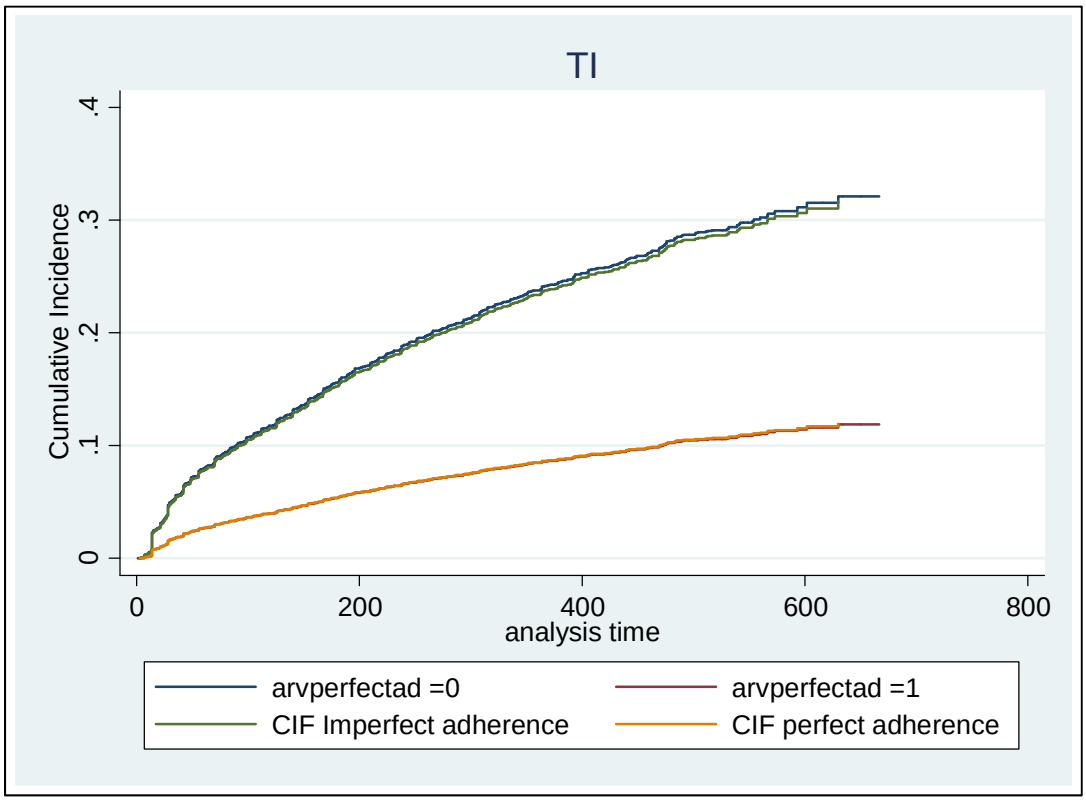
```
. sts gen St_KM=s, by(arvperfectad )

gen CIF_KM_0=1-St_KM if arvperfectad ==0
(11692 missing values generated)

. gen CIF_KM_1=1-St_KM if arvperfectad ==1
(2983 missing values generated)

. label var CIF_KM_1 "1-St_KM (perfect adherence)"

. label var CIF_KM_0 "1-St_KM (imperfect adherence)"

. stcurve, cif at1(arvperfectad =0) at2(arvperfectad =1) title(TI)  ylab(0 0.1 0.2 0.3
> 0.4) addplot( line CIF_KM_0 _t , connect(J)||line CIF_KM_1 _t, connect(J))
```



We see how the Kaplan Meier estimate of the CIF for TI overestimates the true CIF (adjusted for death or loss to follow-up).

On the other hand, plotting the Aalen-Johansen estimator and the one manually produced by the Cox model produces the following graph:

```
. stcurve, cif at1(arvperfectad =0) at2(arvperfectad =1) title(TI)  ylab(0 0.1 0.2 0.3
> 0.4) addplot(  line cif_TI_0 _t , connect(J)||line cif_TI_1 _t, connect(J))
```



The agreement is remarkable!