Case studies of RCT analyess

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Outline

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The Concorde study: Introduction[2]

In the sequel we will analyze simulated data mimicking the Concorde study (1994)[1].

The Concorde study was a double-blind randomised comparison of two policies of zidovudine (ZDV) treatment in HIV-infected symptom-free individuals:

- immediate ZDV from (Imm)
- deferred ZDV (Def) until the onset of AIDS-related complex (ARC) or AIDS (CDC group IV disease) or the development of persistently low CD4 cell counts if the clinician judged that treatment was indicated.

Between October, 1988, and October, 1991, 1749 HIV-infected individuals were randomized to ZDV 250 mg four times daily (877 Imm) or matching placebo (872 Def) in centers in the UK, Ireland, and France.

Thus, the Concorde study follows the general pattern of the oncology trials we discussed in the previous lecture, where

[1] Concorde Coordinating Committee, Lancet, 1994.

[2] The sequel closely follows a vignette accompanying the `RPSFTM` package in `R` by Simon Bond and Annabel Allison.

Concorde-like simulated data

Bond and Allison simulated data along the trends observed in the Concorde trial.

Their data, which we will analyze looks as follows:

	id	def	imm	censyrs	xo	xoyrs	prog	progyrs	entry
1	1	0	1	3	0	0.000000	0	3.000000	0
2	2	1	0	3	1	2.652797	0	3.000000	0
3	3	0	1	3	0	0.000000	1	1.737838	0
4	4	0	1	3	0	0.000000	1	2.166291	0
5	5	1	0	3	1	2.122100	1	2.884646	0
6	6	1	0	3	1	0.557392	0	3.000000	0

Explanation of variables in the data

- `censyrs` is the period of *potential* censoring (i.e., the maximum time someone has between his/her randomization and the end of the study)
- `imm` and `def` are indicators about whether a subject is in the immediate or deferred ZDV arm
- `xo` and `xoyrs` are an indicator of cross-over (from deferred to immediate treatment) and the number of years from randomization when the cross-over occurred (notice that this variable is zero when no cross-over has occurred and it is universally zero for all immediate ZDV subjects)
- `prog` and `progyrs` are, respectively, the progression or death outcome variable and the year progression occurred (note that `progyrs=censyrs` when no progression has been observed)
- `entry` is the time of entry into the study

Observed progression-free survival in the two arms

The progression-free survival in these two arms is shown in the following Figure:

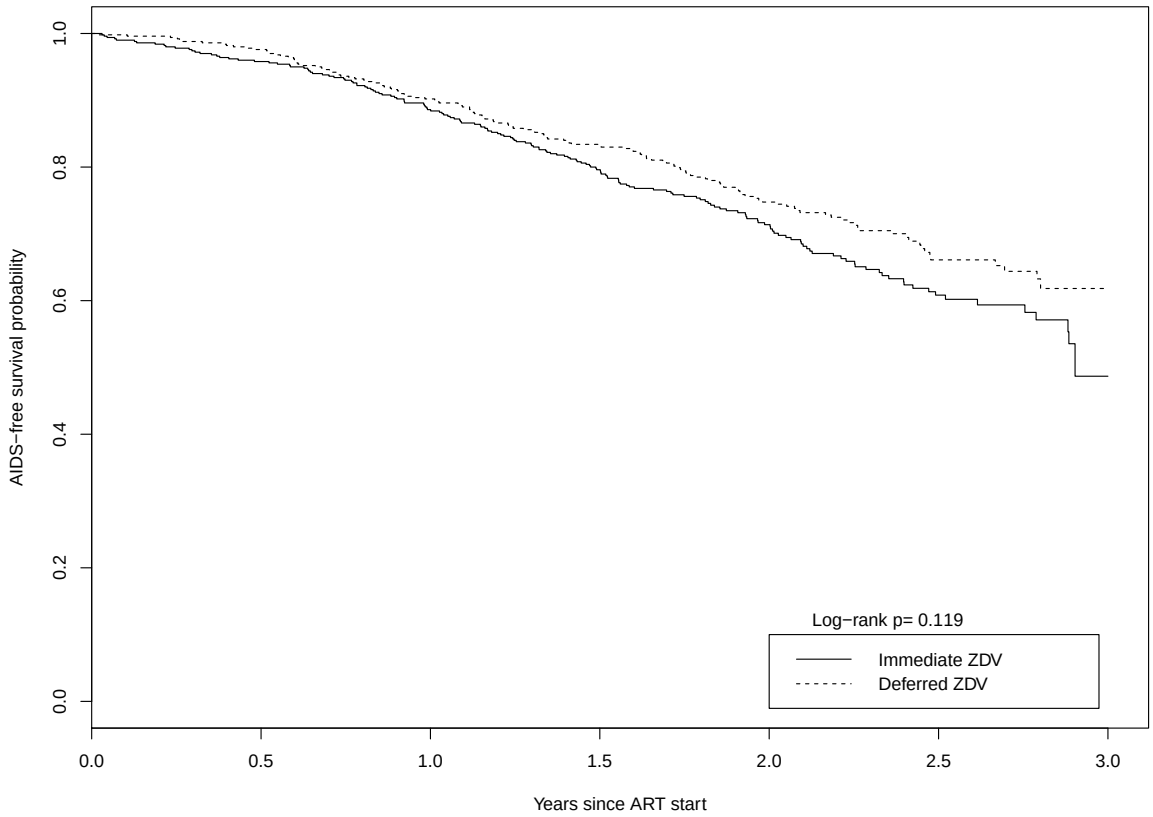

Figure 1: Progression-free survival in the immediate versus deferred arm

Concerns with cross-over

Obviously, the ability of patients to cross over from the deferred treatment arm to, what is essentially the immediate treatment arm, would be expected to lead to an underestimation of any treatment effect of the earlier start of antiretroviral therapy (ART).

We will use a rank-preserving structure failure-time model (RPSFT) to address this. First we must create a new variable of the proportion of time someone spends in the immediate arm.

```
rx <- with(immdef, 1 - xoyrs/progyrs)
```

Notice that all patients who are in the immediate arm (and do not cross over) will be 100% of the time in that arm (will be receiving ZDV).

Fitting the model

Fitting the RPSFT model through the R package RPSFTM generates the following output:

```
rpsftm(formula = Surv(progyrs, prog) ~ rand(imm, rx), data = immdef,
    censor_time = censyrs, test = coxph)
       coef exp(coef) se(coef)    z    p
arm 0.00354   1.00354  0.11849 0.03 0.98

Likelihood ratio test=0  on 1 df, p=0.976
n= 1000, number of events= 285

psi: -0.1812637
exp(psi): 0.8342153
```

This means that $\hat{\psi} = -0.1811$ corresponding to a $1 - \exp(\hat{\psi}) \approx 17\%$ reduction in survival if one is in the deferred arm.

Revised survival curves

The revised survival curves are shown in Figure **??** below:

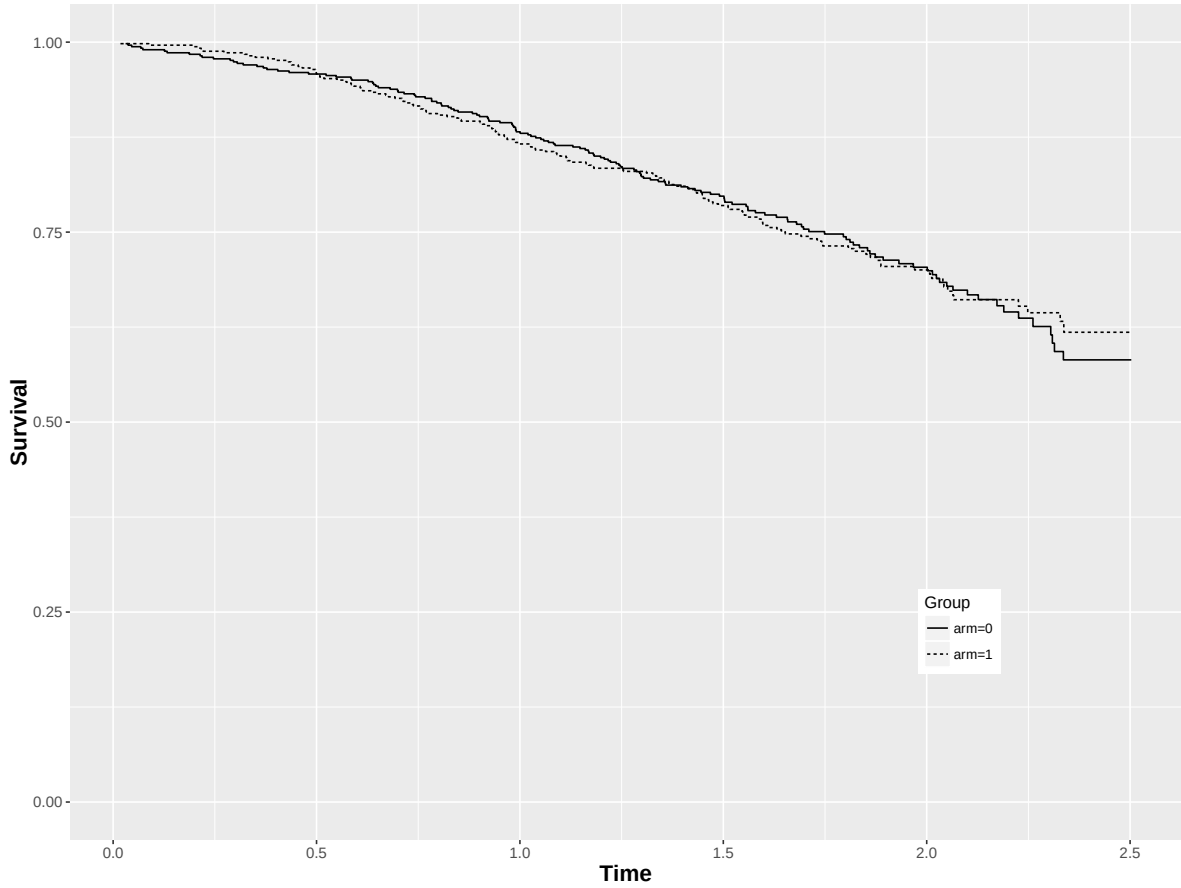

Figure 2: Revised survival curves in the two arms generated by the RPSFT model

From ψ to hazard ratios

To estimate the revised hazard ratio, we take the revised (re-censored) observations and perform a survival analysis on them as usual. Doing this in the current example produces the following results:

```
rpsftm(formula = Surv(progyrs, prog) ~ rand(imm, rx), data = immdef,
    censor_time = censyrs, test = coxph)
       coef exp(coef) se(coef)    z    p
arm 0.00354   1.00354  0.11849 0.03 0.98

Likelihood ratio test=0  on 1 df, p=0.976
n= 1000, number of events= 285

psi: -0.1812637
exp(psi): 0.8342153
```

Thus, the (revised) hazard ratio is $\theta = 1.00354$.