Appendix A: Non-proportional hazards models

Introduction

We review the statistical evidence for using non-proportional hazards when modelling the association between exposure and outcome. We report results for the joint model when we used three and six months rather than one month to separate early events from later events.

Non-proportional hazards

One of the simplest ways to detect non-proportional hazards is to plot a Kaplan Meier survival distribution for each level of exposure [1]. That plot suggests that the association between exposure and outcome varies with time (Figure 2). In the log-minus-log plot of AIDS event free survival against log survival time, the line for two pills crosses the line for one pill in the first few months of treatment. If a proportional hazards model were appropriate for these data, these lines would not cross.

As a first non-proportional hazard model, we then fitted a model with a time dependent interaction between each exposure and log treatment time. This model is often used as a non-proportional hazards model [1,2] – the model assumes a gradual change in hazards with (in this example) time on ART. We can assess the statistical evidence for non-proportional hazards by calculating a likelihood ratio statistic for both this model and for a standard proportional hazards Cox model. The likelihood ratio statistic is a measure of how well each model fits these data.

Concern over the high frequency of early AIDs events led us to fit a standard Cox model to data excluding follow up during the first month on ART. Alternatively, we could include this follow up but fit a second non-proportional hazards model with a different hazard ratio for each exposure before and after one month. We can then assess how well this second model fits the data by comparing likelihood ratio statistics.

Our use of one month to separate early events from later events is somewhat arbitrary. While many IRIS events will be reported within weeks of starting ART [3], such events can occur up to three months after starting ART or even later [4]. We therefore also estimated hazard ratios for each exposure before and after either three or six months on ART.

Results

The two non-proportional hazards models were both a better fit to these data than a standard proportional Cox model; both had higher likelihood ratio statistics (Table A1). There was no real difference in model fit between a non-proportional hazards model that assumed a constant rate of change in hazard ratio with log time on ART and a clinically more plausible non-proportional hazards model with different hazards ratios before and after one month on ART. When patients with early events were excluded, there was no evidence of further non-proportionality – a standard Cox model then fitted the remaining data just as well as a non-proportional hazards model that assumed a constant rate of change in hazard ratio with log time on ART.

When early events were defined as those within the first three or six months on ART, rather than in the first month, estimates varied predictably compared to those seen in the main analysis (Table A2). There was a shift in the two early HRs toward the two later HRs, consistent with a change in HRs within the first few months on ART. In all models, later HRs implied that after the change, two pills rather than one was associated with an increase in the risk of AIDS or death but three pills rather than two did not appreciably add to that increase.

An advantage of defining early events as those within the first month on ART is that it is then reasonable to assume no difference in the future between regimens in the risk of AIDS events or death during this short period. That assumption becomes more questionable if early events are defined as those within the first three or six months. It is possible that adherence might influence events within the first three or six months on ART.

2

Summary

Model fit statistics suggest that a model with early and late hazard ratios accounts for the non-proportionality seen in exposure hazard ratios. Estimates of early and late hazard ratios changed predictably if early events were defined as events within the first three or six months on ART, instead of within the first month. In all models, later HRs implied that after the first few months on ART, two pills rather than one was associated with an increase in the risk of AIDS or death but three pills rather than two did not appreciably add to that increase.

References

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Table A1. Proportional and non-proportional Cox models for the analysis of the primary outcome: time from starting antiretroviral therapy to a first new or recurrent AIDS event or death (n=11739). Models include a standard proportional Cox model and two non-proportional Cox models, one with interactions between exposures and log time on ART and the other with different estimates for exposure before and after one month on antiretroviral therapy (ART).

Data and model [1]		Exposure hazard ratios (95% confidence interval)				Likelihood ratio statistic
		Two pills versus one pill		Three pills versus two pills		(degrees of freedom)
All						
Proportional	Standard Cox [2]	1.04	(0.80 to 1.35)	1.32	(0.98 to 1.79)	403.0 (10)
Non-proportional	Interaction with log time on ART [3]	1.65	(1.12 to 2.43)	1.06	(0.71 to 1.58)	413.8 (12)
	Different before and after one month [4]	1.39	(1.01 to 1.91)	1.19	(0.84 to 1.68)	413.3 (12)
Early events excluded [5]						
Proportional	Standard Cox [2]	1.29	(0.92 to 1.82)	1.04	(0.71 to 1.52)	208.2 (10)
Non-proportional	Interaction with log time on ART [6]	1.29	(0.84 to 1.98)	0.95	(0.60 to 1.51)	208.9 (12)

[1] All models are adjusted for the covariates in Table 2 (including calendar year).

[2] Note that when fit to all data, the standard Cox model suggests that three and two pill regimens were associated with different risks while two and one pill regimens were not. This situation reversed when the standard Cox model was fit to data with early events excluded.

[3] The exposure hazard ratios shown apply at one year on ART. Estimates of interaction suggest that the hazard ratio for two pill regimens versus one pill regimens increases with time on ART.

[4] This is the main joint model shown in Table 2. For each exposure, only the hazard ratios after one month are shown in this table.

[5] Follow up begins 30 days after starting ART. This was then an analysis of 10,587 patients with 298 events (rather than of 11,739 patients with 473 events).

[6] The hazard ratios shown apply at one year on ART. The estimates of interaction suggest that both hazard ratios do not change with time on ART.

Table A2. Cox model estimates for the analysis of the primary outcome: time from starting antiretroviral therapy to a first new or recurrent AIDS event or death (n=11739). The association between this outcome and two or one pill regimens or three or two pill regimens is estimated before (early effects) and after (later effects) either one, three or six months on antiretroviral therapy and both with and without calendar year as a covariate.

Hazard ratio (95% confidence interval) per pill		Two pills versus one pill				Three pills versus two pills			
Covariates [1]	Exposures	Early effect		Later effect		Early effect		Later effect	
With calendar year	Before and after 1 month	0.65	(0.44 - 0.95)	1.39	(1.01 - 1.91)	1.64	(1.05 - 2.55)	1.19	(0.84 - 1.68)
	Before and after 3 months	0.88	(0.64 - 1.21)	1.35	(0.91 – 1.99)	1.44	(1.00 - 2.06)	1.17	(0.76 - 1.76)
	Before and after 6 months	0.94	(0.70 - 1.26)	1.45	(0.91 – 2.33)	1.49	(1.06 - 2.07)	0.94	(0.55 - 1.56)
Without calendar year	Before and after 1 month	0.67	(0.46 – 0.98)	1.45	(1.09 - 1.95)	1.76	(1.18 - 2.61)	1.27	(0.94 - 1.71)
	Before and after 3 months	0.92	(0.69 - 1.24)	1.42	(0.99 - 2.05)	1.55	(1.14 - 2.10)	1.24	(0.84 - 1.81)
	Before and after 6 months	0.98	(0.75 - 1.28)	1.53	(0.98 - 2.40)	1.60	(1.21 - 2.09)	0.99	(0.60 - 1.61)

[1] All models include additional covariates as in Table 2.