BST 222 Final Presentation (F25)

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Outline

Indinavir, HIV treatment

The Treatment

- Human Immunodeficiency Virus (HIV) is an auto-immune condition
- Attacks CD4 white blood cells
- HIV doesn't kill you, it weakens you to other disease
- Most advanced stage is called (Acquired Immune Deficiency Syndrome)
  - Takes ≈10 years without treatment
- Today, many with HIV won't get AIDS, 1990s...
- Old treatments, prevent HIV reproduction
- Indinavir, disrupt HIV reproduction

The Method: Survival Analysis

- Time to event: prolong AIDS development
- KM curves: survival difference
- Cox-PH model, measure immediate risk of getting AIDS
  - PH: risk difference between patients stays the same throughout study

Dataset

- AIDS Clinical Trial Group Study 320 (actg)
  - Measure the effect of IDV on progression to AIDS or Death
  - In conjunction with SoC
  - Highly compromised Immune System
  - 'AIDS-Defining Event or Death' **composite event**
- Demographics
  - 1151 participants from US and Puerto Rico
  - HIV-1 Positive
  - 16 years or older
  - Jan 1996 - Jan 1997
  - mostly sub-200 CD4 level (90%)
  - 60% CD4 level above 50
  - Treated with Zidovudine (ZDV) previously
  - Karnofsky Score of 70 or higher

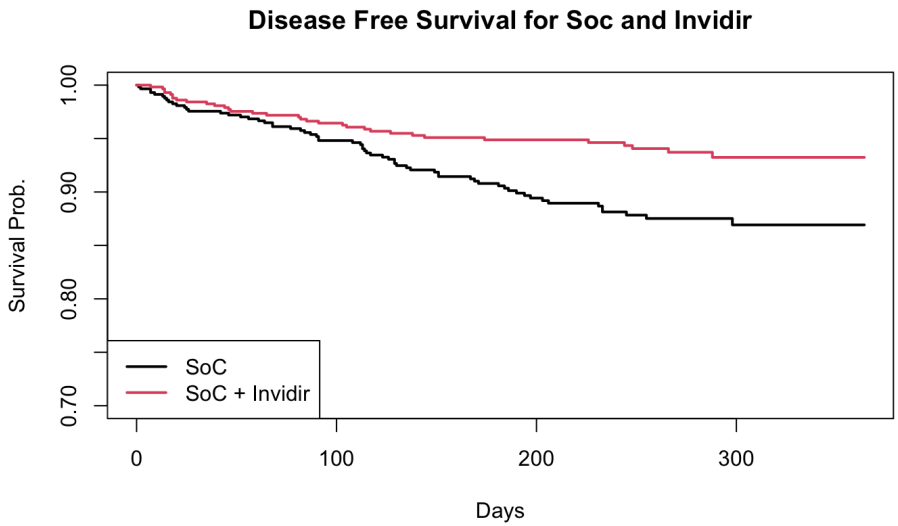
Variables

- `id`: patient id
- `event`: event indicator
- `time_event`: time of the event
- `tx`: IDV indicator
- `txgrp`: (ZDV+3TC, ZDV+3TC+IDV, d4T+3TC, d4T+3TC+IDV)
- `sex`: male or female
- `ivdrug`: use of intravenous drugs (never, previously, currently)
- `hemophil`: hemophilia indicator
- `karnof`: Karnofsky Score (70, 80, 90, 100)
- `priorzdv`: months of prior ZDV
- `age`: age of patient
- `race`: race/ethnicity of patient
- `cd4lvl`: CD4 per mm^3 above 50 indicator
- `base_cd4`: CD4 per mm^3 of patient at induction

The Direction

	Censor	Event
No IDV	514	63
IDV	541	33

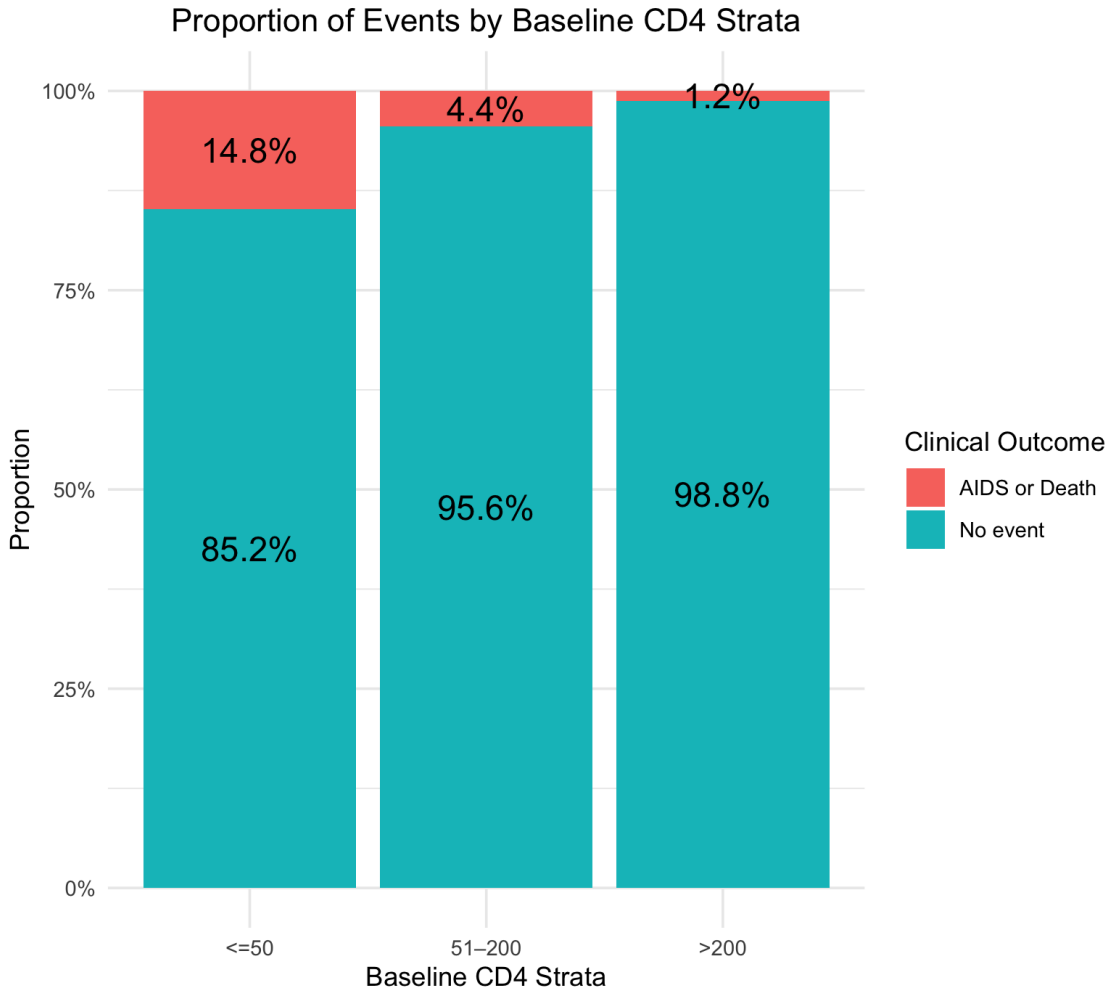
Table: Treatment Against Event



Fails Log-rank Test (Mantel–Haenszel): p=0.001.

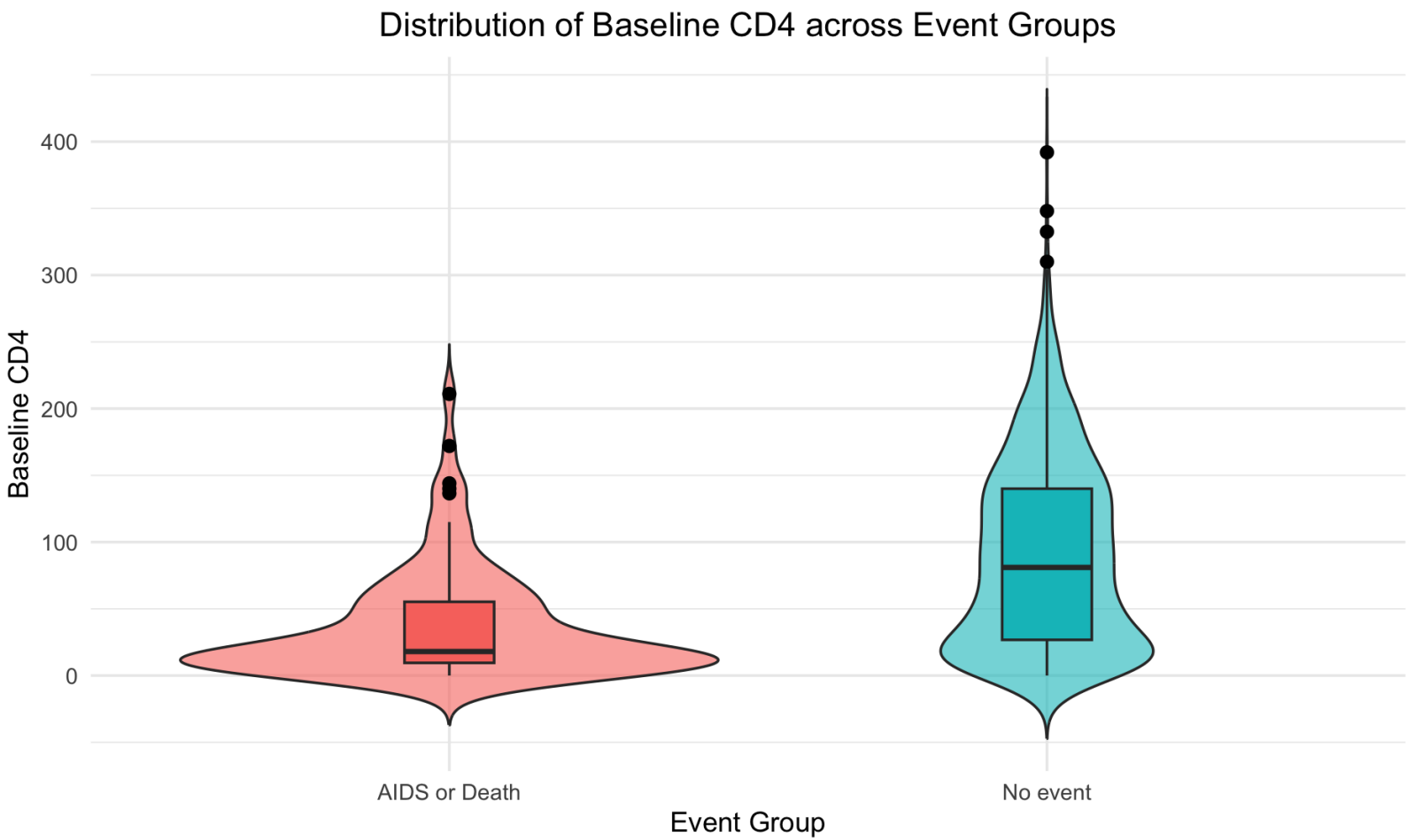
Exploratory Data Analysis: Baseline CD4 and Clinical Outcomes

- **Key Observation:** Strong separation across CD4 strata.



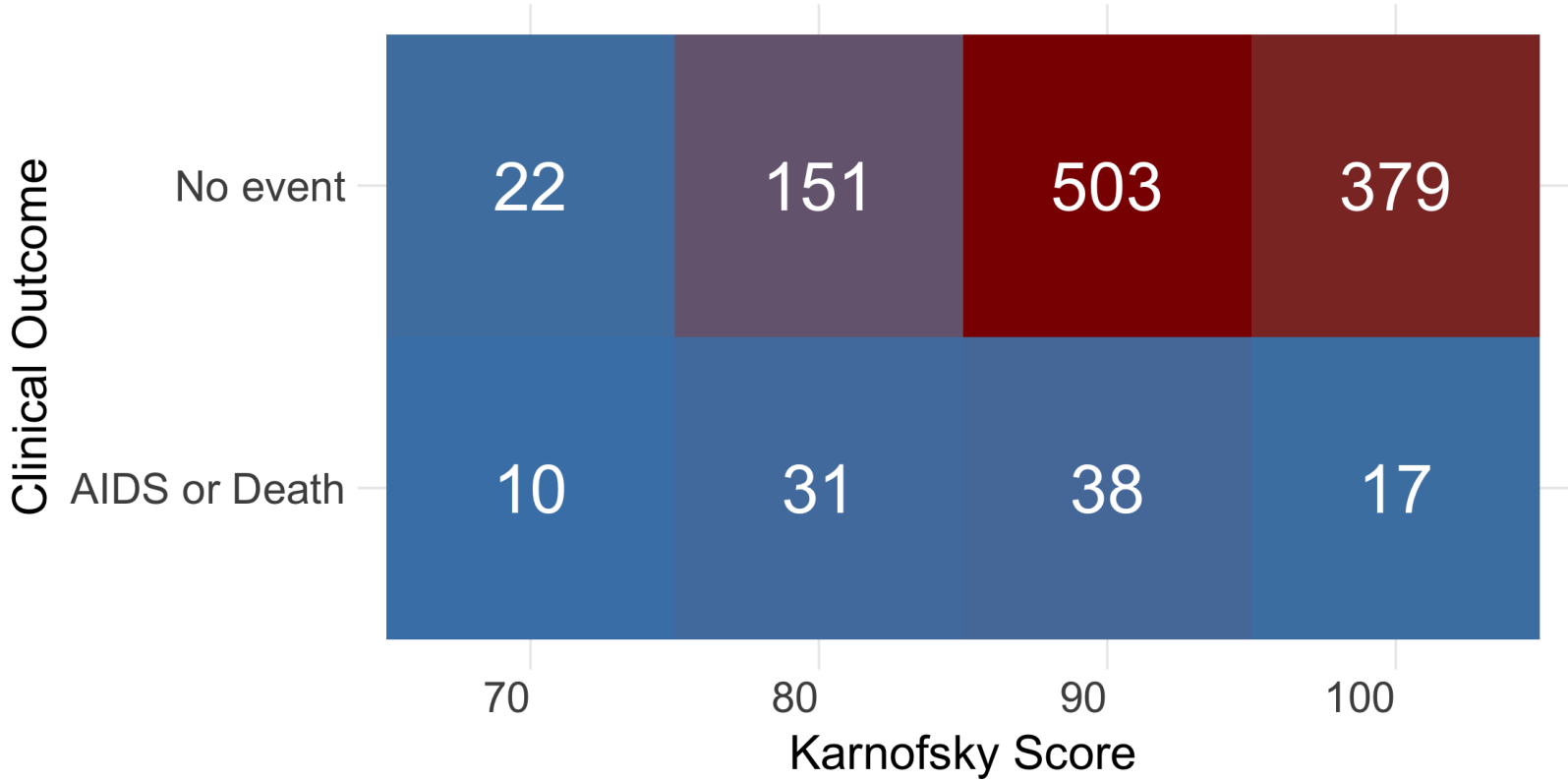
Exploratory Data Analysis: Baseline CD4 by Outcome

- Baseline CD4 distributions differ markedly across outcome groups.



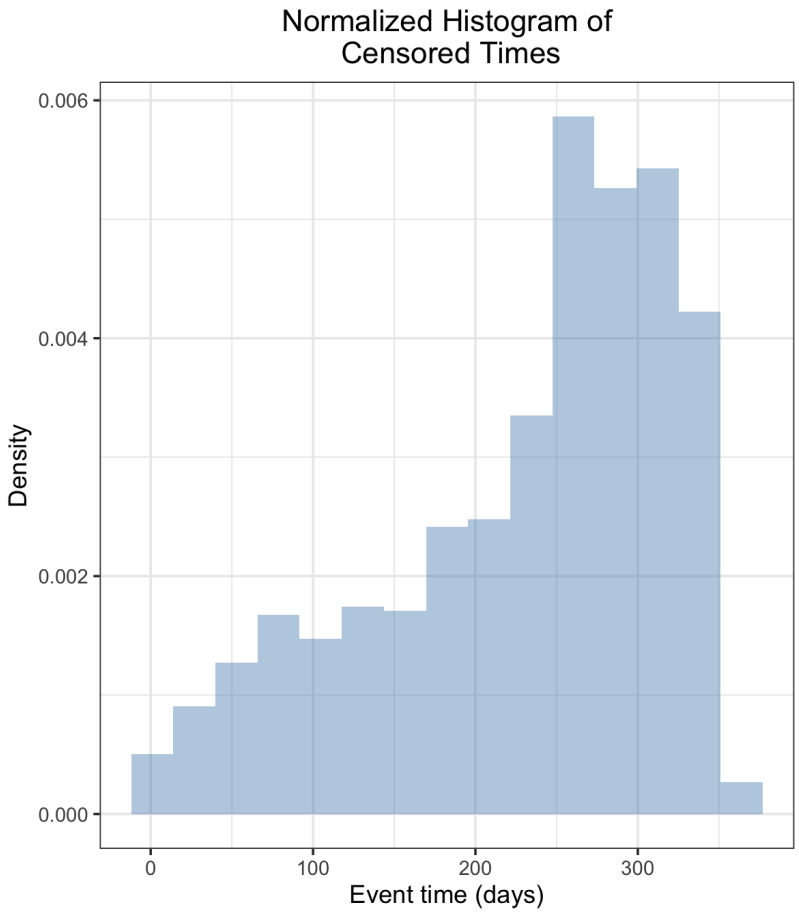
Exploratory Data Analysis: Karnofsky & Outcomes

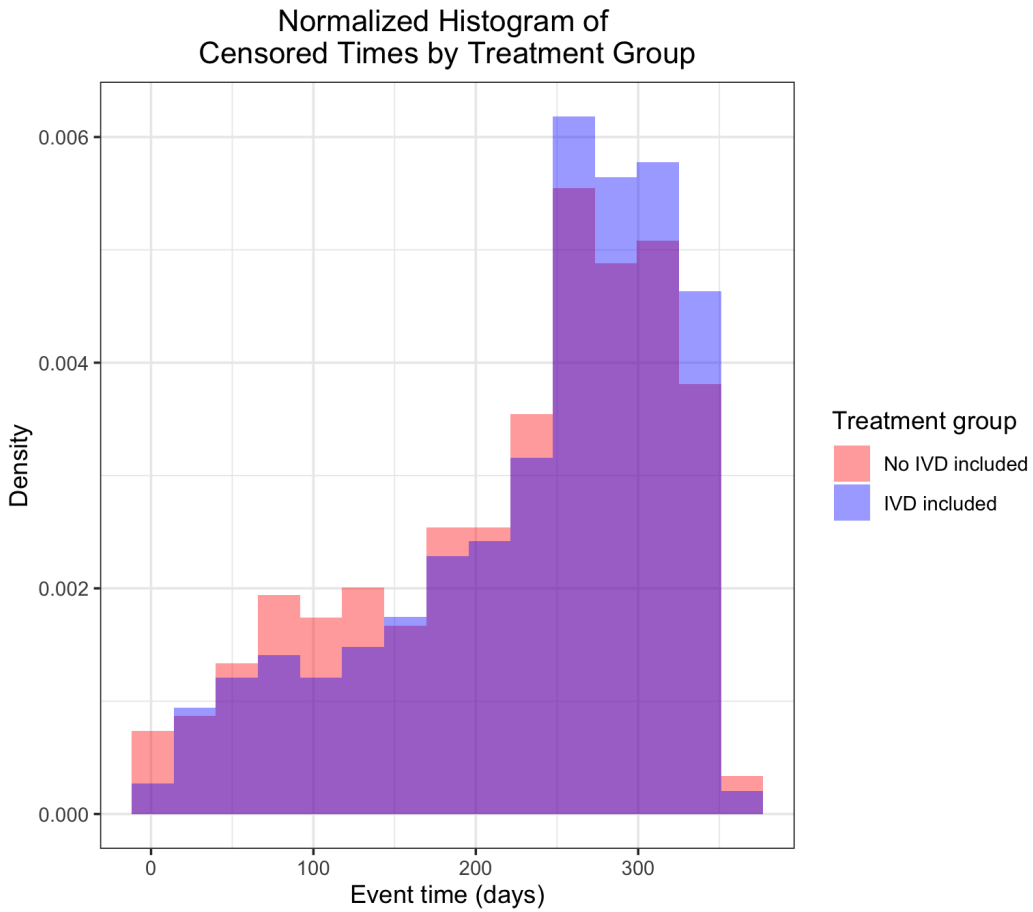
- Strong association between Karnofsky score and clinical outcomes.
- This supports including Karnofsky as a major prognostic covariate in our survival models.



Exploratory Data Analysis: Follow-up & Censoring Pattern

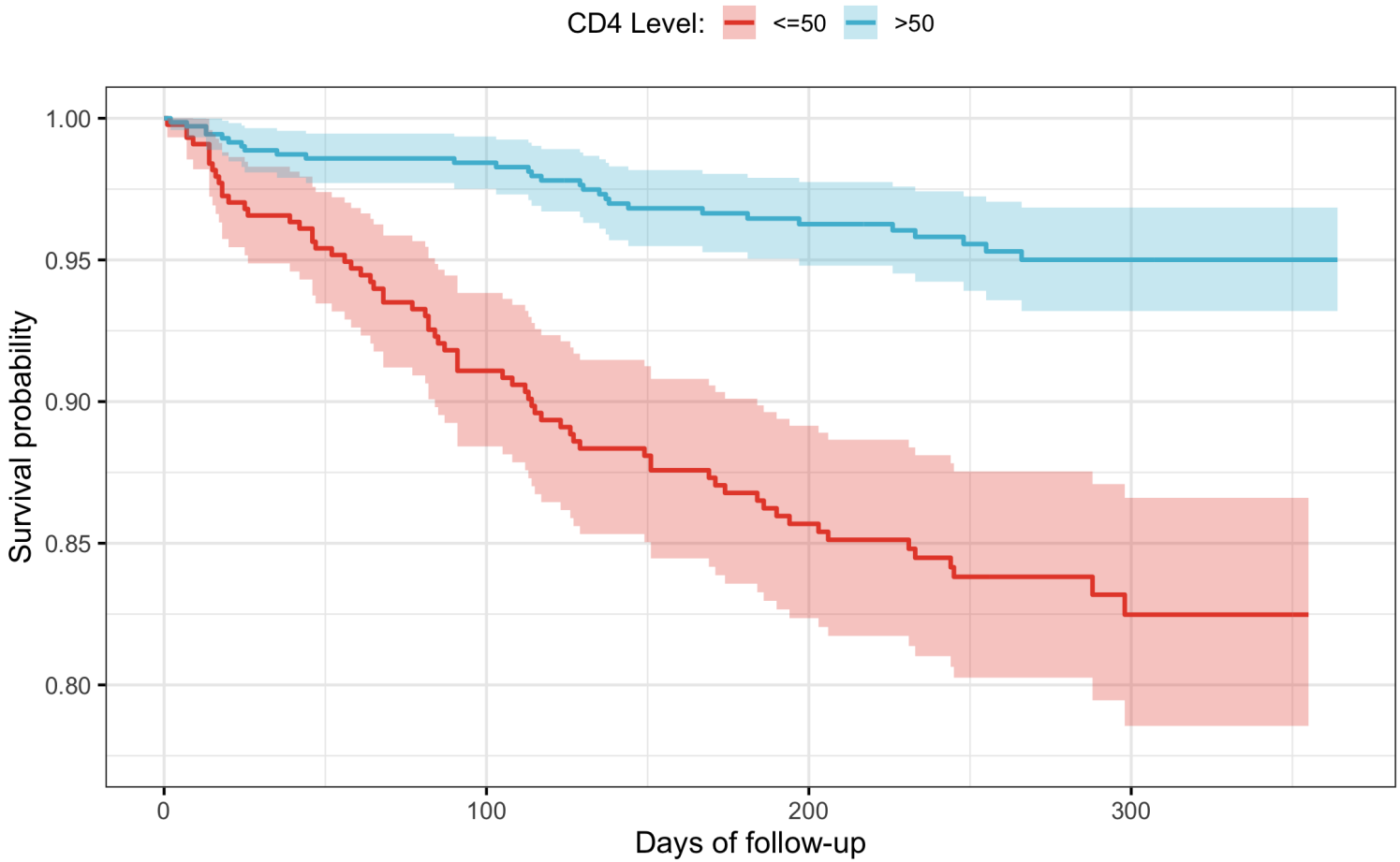
- Censoring patterns are similar across treatment groups, suggesting limited informative censoring.





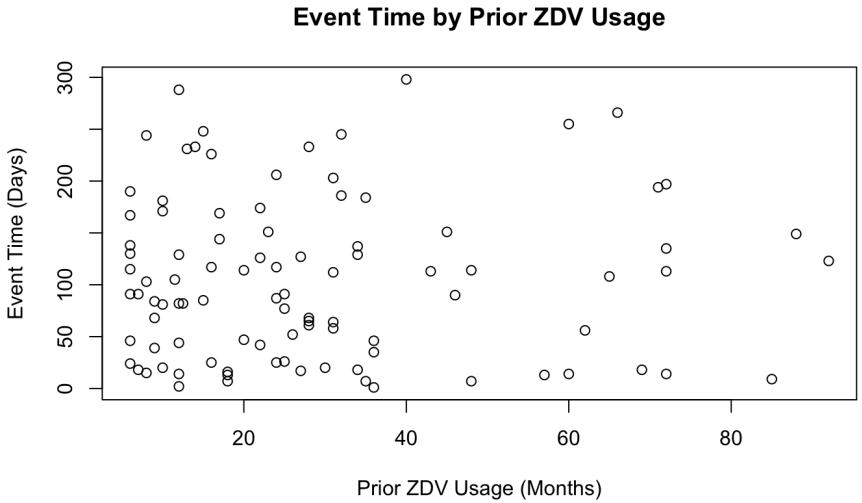
Survival by CD4 Level

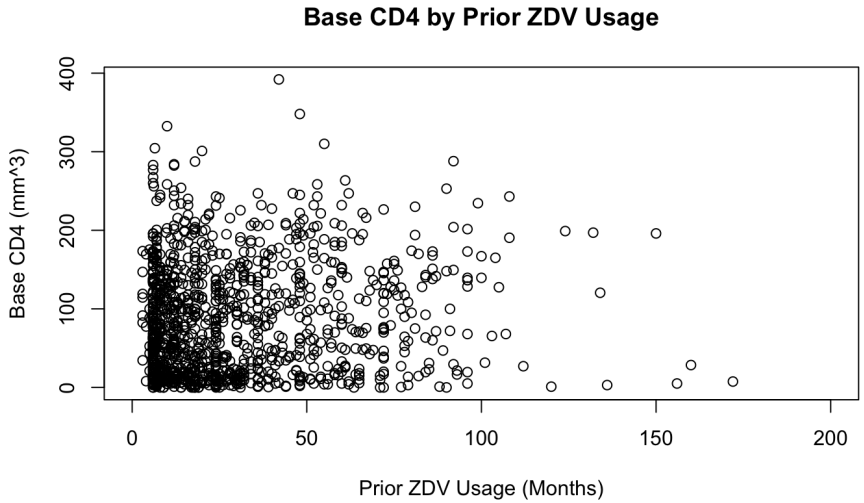
- Patients with CD4 ≤ 50 have substantially lower survival throughout follow-up.
- Clear early and persistent separation supports CD4 level as a strong prognostic factor.



Note on ZDV

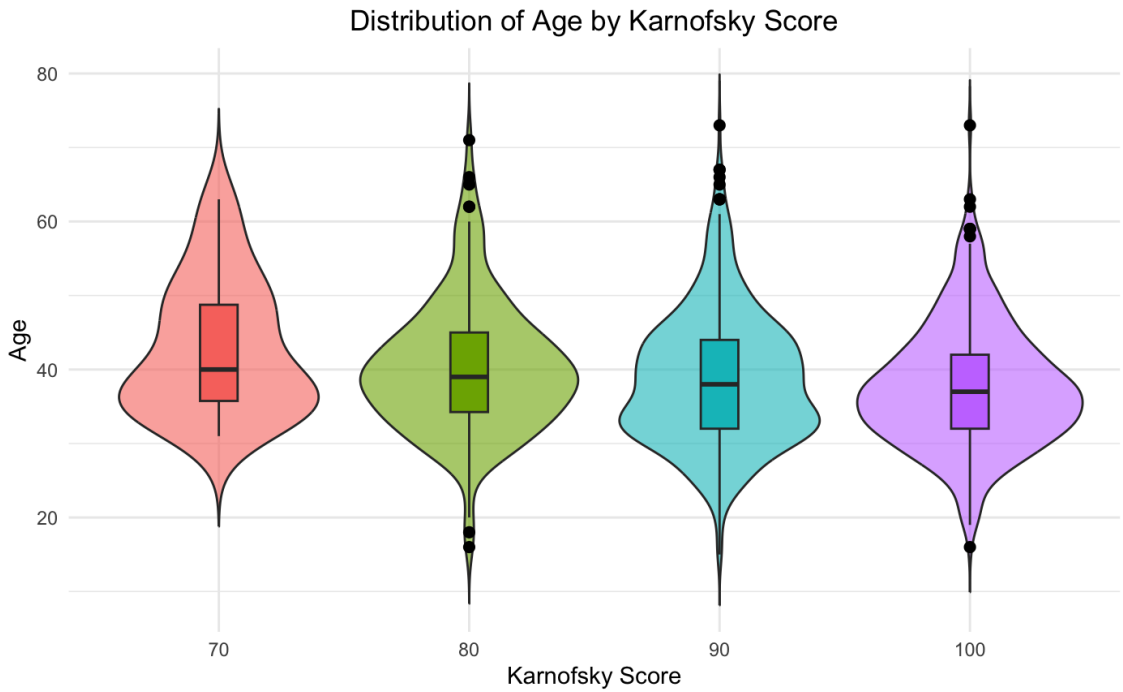
- Prior ZDV usage is clinically relevant
  - Signal for time with HIV
  - Effect may dull over time, part of SoC
- Hurt preliminary model fit, and statistically insignificant
  - Interaction with CD4 tested; ZDV may keep CD4 high, but HIV has other effects: **No transform helpful**
  - **Dropped from consideration**





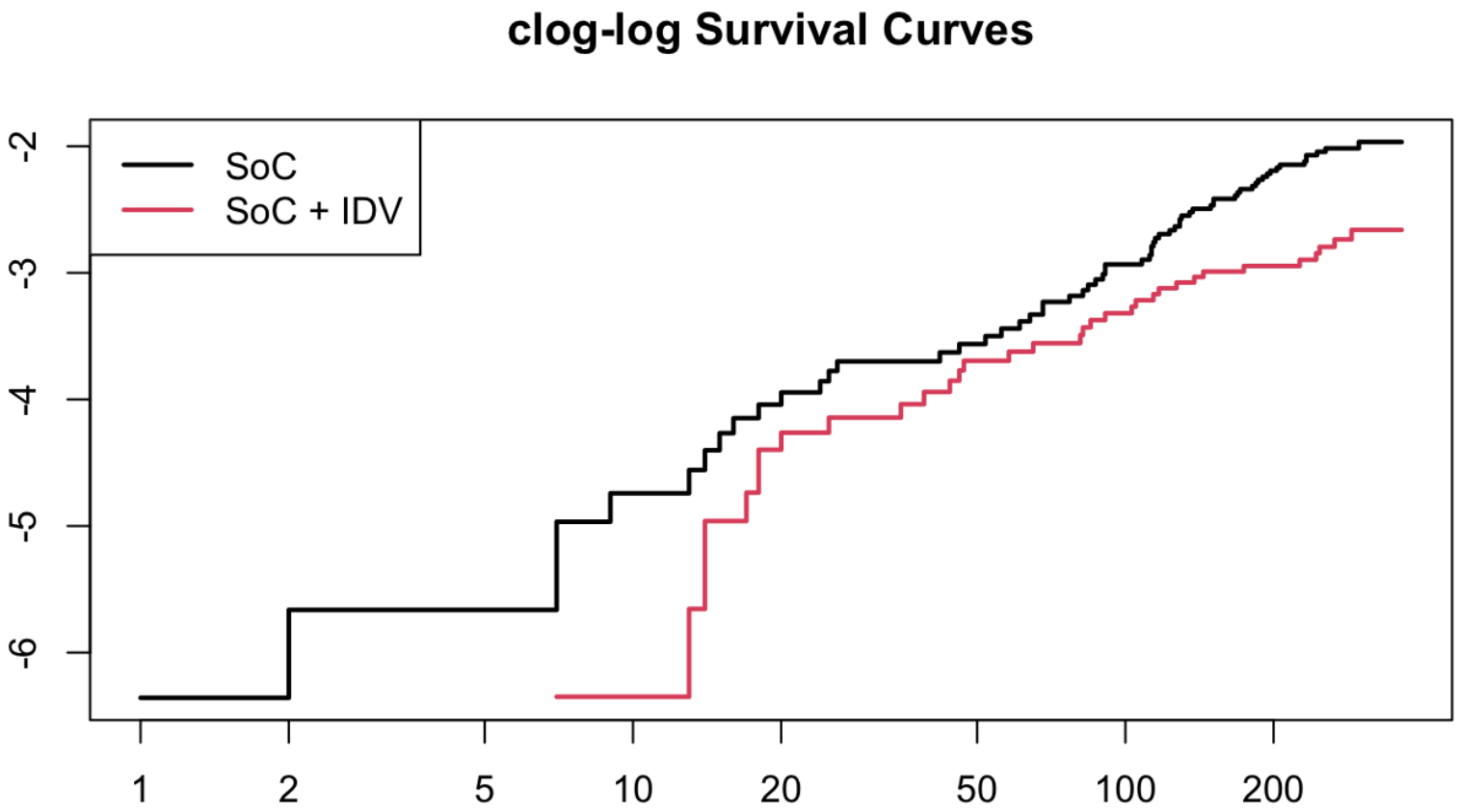
Note on Age and Karnofsky Score

- Age and Karnofsky Score intuitively correlated
  - Sampling Difficulties
  - Interaction: 30 y/o with 100 healthier than 70 y/o with 100
- Scores evenly distributed (no masking)
- Interaction tested: **Not significant**; no transformation helpful
- **Both variables kept**



PH Assumption: cloglog

Parallel?



Final Cox Model Results

- Final Cox model from 'add1', clinical thinking, and covariate analysis:

$$\text{surv\_actg} \sim tx + ivdrug\_bin + karnof + age + base\_cd4$$

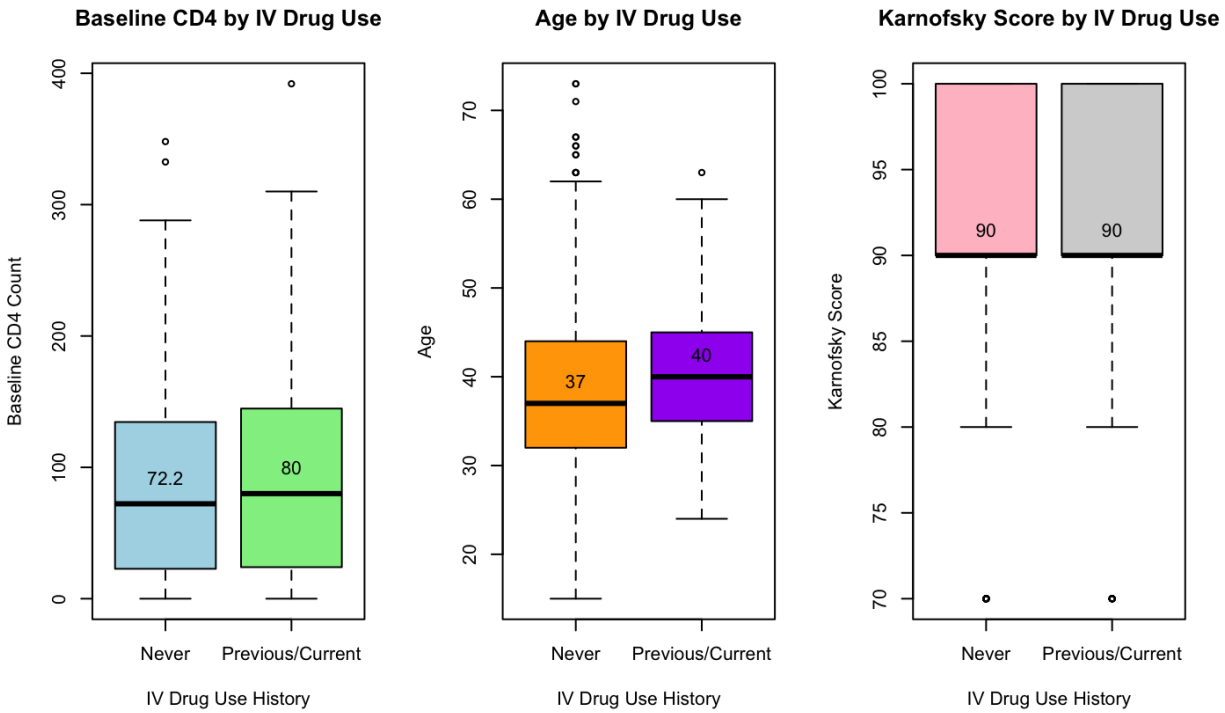
Variable	Coef	exp(Coef)	SE(Coef)	p-value	Sig.
tx	-0.6685	0.5125	0.2154	0.0019	**
ivdrug_bin(*)	-0.5520	0.5758	0.3225	0.0870	.
karnof80	-0.4433	0.6419	0.3662	0.2261	
karnof90	-1.1355	0.3213	0.3652	0.0019	**
karnof100	-1.5633	0.2094	0.4090	0.0001	***
age	0.0220	1.0223	0.0112	0.0503	.
base_cd4	-0.0144	0.9857	0.0025	1.06e-08	***

Table: Cox Proportional Hazards Model Estimates

- Drug use history (ivdrug_ bin): HR < 1 but not statistically significant.
- IDV treatment reduces the hazard by 48.75%.
- A Karnofsky score of 100 (vs. 70) reduces the hazard by 79.06%.
- Each additional 100 mm^3 increase in CD4 substantially reduces the hazard by 75%; for example, $1 - HR = 1 - 0.986^{100} \approx 75\%$.

Why does the "previous/current" group appear healthier?

- The group is dominated by **previous users** (179/183).
- Individuals with past IV drug use who enroll in trials are typically:
  - already detoxified and medically stable
  - diagnosed earlier and monitored more frequently
  - started on treatment earlier
- Resulting in **higher baseline CD4** (strongest covariate).



PH Assumption: Schoenfeld Tests

- Results from `cox.zph(cox_reduced)`:
  - No covariate violates PH at 0.05 level.
  - base_cd4 borderline ($p = 0.057$) but acceptable.
  - GLOBAL test $p = 0.180 \rightarrow$ PH assumption holds.

Covariate	Chi-square	df	p-value
tx	1.90464	1	0.168
ivdrug_bin	0.00709	1	0.933
karnof	2.08425	3	0.555
age	2.54416	1	0.111
base_cd4	3.61645	1	0.057
Global	**10.15317**	**7**	**0.180**

Table: Schoenfeld Residual Tests for Proportional Hazards Assumption

Test	Statistic	p-value
Likelihood Ratio Test	102.8	$< 2 \times 10^{-16}$
Wald Test	85.66	1×10^{-15}
Score (Log-rank) Test	102.8	$< 2 \times 10^{-16}$
Concordance (C-index)	0.783	SE = 0.023

Table: Overall Tests for the Cox Proportional Hazards Model

Attempted Stratification by CD4

- CD4 manually stratified:

$$\text{cd4 strata} = \begin{cases} \leq 50, \\ 51\text{–}200, \\ > 200 \end{cases}$$

- Stratified model:

$$\text{surv\_actg} \sim tx + ivdrug\_bin + karnof + age + \text{strata}(\text{cd4\_strata3})$$

- Stratified model **concordance** dropped from **0.783 to 0.674**.
- CD4 loses quantitative interpretation because stratification removes its coefficient.

Conclusion: Do not need to stratify CD4.

Summary of Potentially Influential Observations

Table: Influence Diagnostics: dfbeta Values and Deviance Residuals

	dfbeta (influence on each coefficient)							Dev.Res
ID	tx	ivdrug_bin	karnof80	karnof90	karnof100	age	base_cd4	dev.res
610	0.0322	-0.0080	0.0028	0.0070	0.0687	0.0006	-0.00027	**2.584**
633	0.0292	-0.0167	-0.0944	-0.0978	-0.0964	-0.0012	0.00001	1.686
638	0.0203	0.0268	0.1213	0.1167	0.1156	-0.0024	0.00017	-1.595
671	0.0317	-0.0173	-0.1018	-0.1043	-0.1025	-0.0015	-0.00004	2.266
680	-0.0137	-0.0192	-0.0995	-0.1013	-0.1020	-0.0009	0.00005	2.246
996	-0.0190	-0.0106	0.0025	0.0255	-0.0010	0.0030	0.00049	2.073

- None of these observations have extremely large `dfbeta` values $\Rightarrow$ **limited influence on regression coefficients**.
- Deviance residuals identify observation **610** as the largest (2.58), suggesting it may moderately affect model fit.

Influential Observations: Interpretation

Six observations were flagged (610, 633, 638, 671, 680, 996). :

Obs	txgrp	ivdrug	Karnofsky	Age	Baseline CD4	Time to Event
610	idv_zdv	never	100	43	5.5	18
633	idv_zdv	never	70	33	18.0	65
638	zdv	never	70	58	6.0	290
671	idv_zdv	never	70	31	8.0	14
680	zdv	never	70	36	23.0	9
996	zdv	never	90	67	136.5	129

- **Very poor baseline health:** (CD4 $\leq$ 50 and Karnofsky mostly 70) These patients naturally have high event risk.
- **Early occurrence of events:** Short time-to-event is exactly what we expect from severely ill patients.
- **No unusually large dfbeta values:** Their inclusion does not meaningfully shift estimated coefficients.

Conclusion: Model is robust; no observation needs removal.

Final Conclusions

- **IDV treatment significantly improves survival.**
- Higher CD4 and better Karnofsky score strongly improve outcomes.
- Age increases risk.
- Proportional hazards assumption holds; model is robust.

Advanced Models

CD4 count is at the borderline of violating PH assumption, to correct it:

- Time-Varying Coefficient (TVC) Cox Models
  - **Clinical Priors:** CD4 naturally drops with disease progression, or go up with treatment

Part A: Time-Varying Coefficient Cox Model (TVC)

Model with (base_cd4) * log(t) term:

surv_actg $\sim$ *tx* + *ivdrug_bin* + *karnof* + *age* + *base_cd4* + *(base_cd4)* * *log(t)*

Variable	Coef	exp(Coef)	SE(Coef)	z	p-value
tx	-0.667969	0.512749	0.215396	-3.101	0.00193
ivdrug_bin	-0.549405	0.577293	0.322564	-1.703	0.08852
karnof80	-0.432216	0.649069	0.366318	-1.180	0.23804
karnof90	-1.121711	0.325722	0.365450	-3.069	0.00214
karnof100	-1.545351	0.213237	0.409443	-3.774	0.00016
age	0.021931	1.022173	0.011238	1.951	0.05101
base_cd4	-0.031306	0.969179	0.012170	-2.572	0.01010
(base_cd4) * log(t)	0.003836	1.003844	0.002626	1.461	0.14400

The p-value of time-varying term is **0.144**, not sufficient.

Part A: Time-Varying Coefficient Cox Model (TVC)

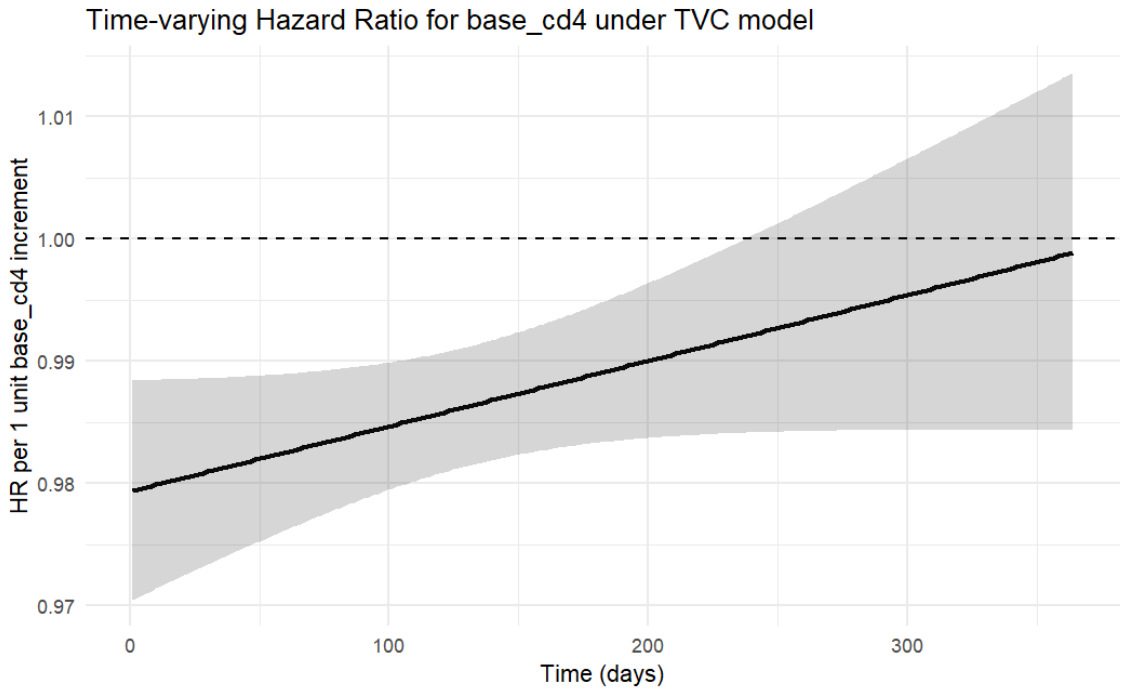
Model with (base_cd4) * t term:

surv_actg ~ *tx + ivdrug_bin + karnof + age + base_cd4 + (base_cd4) * t*

Variable	Coef	exp(Coef)	SE(Coef)	z	p-value	Si
tx	-6.668e-01	5.133e-01	2.154e-01	-3.096	0.001963	**
ivdrug_bin	-5.493e-01	5.773e-01	3.226e-01	-1.703	0.088556	.
karnof80	-4.295e-01	6.509e-01	3.663e-01	-1.172	0.241043	
karnof90	-1.117e+00	3.272e-01	3.655e-01	-3.057	0.002235	**
karnof100	-1.541e+00	2.142e-01	4.094e-01	-3.764	0.000167	**
age	2.190e-02	1.022e+00	1.124e-02	1.949	0.051344	.
base_cd4	-2.085e-02	9.794e-01	4.697e-03	-4.439	9.03e-06	**
(base_cd4) * t	5.416e-05	1.000e+00	3.018e-05	1.795	0.072688	.

The p-value of time-varying term becomes **0.0727**. We proceed with this model with (base_cd4) * t term.

Time-varying Effect of Baseline CD4



Key Interpretation

- $HR(t) < 1$ at time 0 initially $\rightarrow$ higher baseline CD4 **reduces the risk** of disease progression.
- $HR(t)$ gradually approaches 1 $\rightarrow$ this protective effect **declines** over time.

Advanced Models

Large sample, low event probability, guaranteed event with infinite time

- Accelerated Failure Time (AFT) Model
  - **Set Up:** Study similar to Engineering Failure Time Model
  - Every patient (hard drive) experiences Death/AIDS (drive failure)
  - **Models survival time, not hazard rate**

Part B: AFT (Accelerated Failure Time) Models

We fit four commonly used AFT models (Gumbel Extreme/ Weibull / log-normal / log-logistic) and compare their AIC's:

Model	df	AIC
aft_gumbel	9	1735.003
aft_weib	9	1621.059
aft_lognorm	9	1622.750
aft_loglog	9	1619.771

Table: AIC comparison of AFT models

According to the AIC's, the log-logistic model has the smallest AIC, thus fits the best.

The final AFT model: log-logistic

$$\log(T) = \beta_0 + \beta_1 tx + \beta_2 ivdrug\_bin + \beta_3 karnof + \beta_4 age + \beta_5 base\_cd4 + \sigma\varepsilon,$$

where $\varepsilon \sim \text{Logistic}(0, 1)$.

Part B: AFT (Accelerated Failure Time) Models

Variable	Coef
Intercept	6.42521
tx	0.87228
ivdrug_bin	0.75411
karnof80	0.70487
karnof90	1.62012
karnof100	2.11731
age	-0.02822
base_cd4	0.01830
Log(scale)	0.16933

Notes: Fitting the AFT log-logistic model gives us almost the **same results** as the reduced Cox model, while requiring **additional assumptions** and having **higher AIC**. Thus we prefer the reduced Cox model.

Final Thoughts

- The **TVC model** for CD4 is our preference
  - Most logical + strong fit
- Actual study went ahead with a stratified CD4 model at 50
- Drug deemed effective after a year of study, still used today
- Today, AIDS is determined by $<$200 CD4 per mm^3 of blood
  - Almost all patients would be considered to have AIDS already
- Use the Fine-Gray Model to analyze the endpoints split-up

References

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Thank you

Questions?