BST 222 Final Presentation (F25)

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Outline

1 Introduction

2 Analysis

3 Conclusions

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

Disease Free Survival for Soc and Invidir

Survival Prob.

— SoC
— SoC + Invidir

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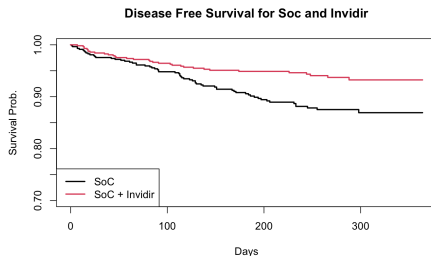
Fails Log-rank Test (Mantel–Haenszel): p=0.001.

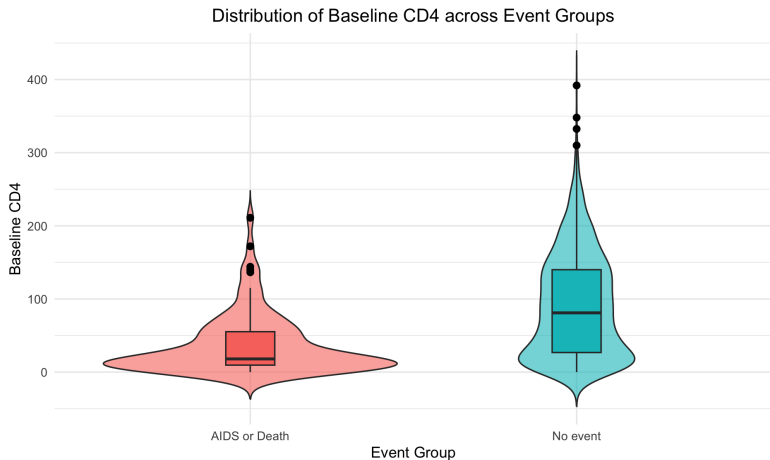# Exploratory Data Analysis: Baseline CD4 and Clinical Outcomes

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

Proportion of Events by Baseline CD4 Strata
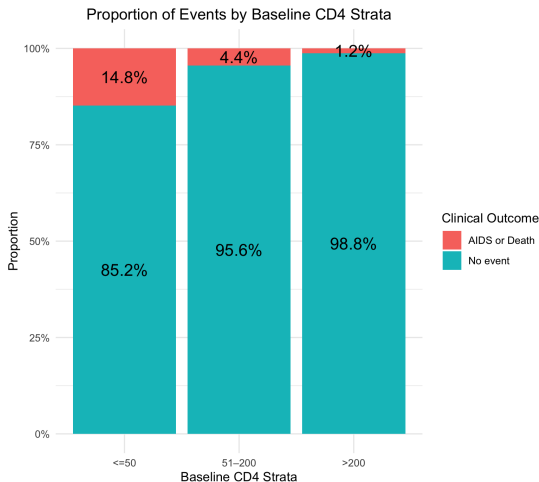
Exploratory Data Analysis: Baseline CD4 by Outcome

- Baseline CD4 distributions differ markedly across outcome groups.

Distribution of Baseline CD4 across Event 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.
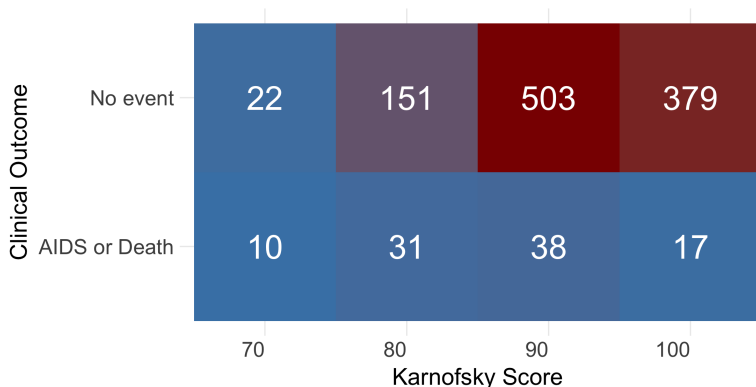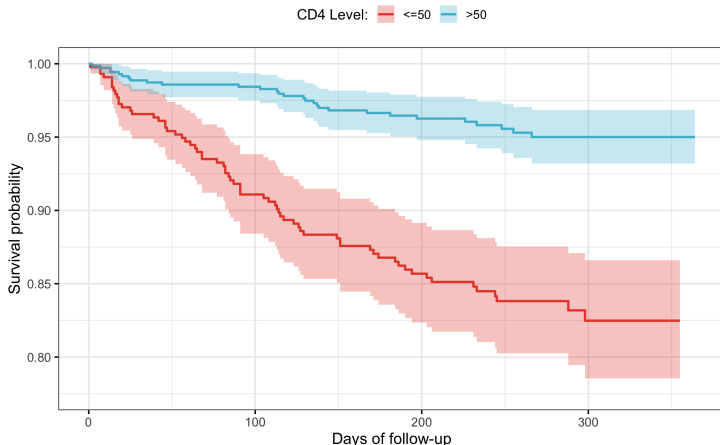
Exploratory Data Analysis: Follow-up & Censoring Pattern

- Censoring patterns are similar across treatment groups, suggesting limited informative censoring.
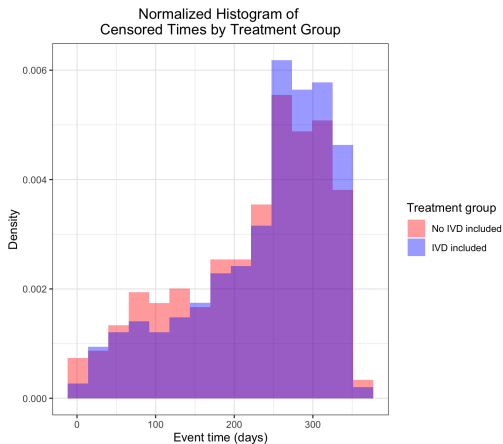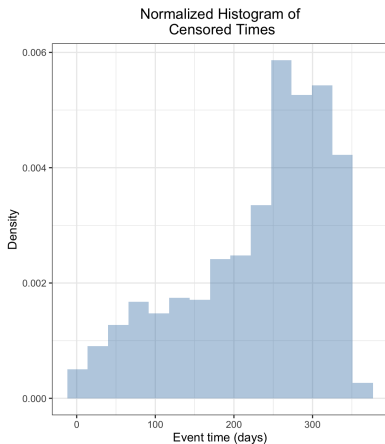
Survival by CD4 Level

- Patients with CD4 $\leq$ 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**

Event Time by Prior ZDV Usage

Base CD4 by Prior ZDV Usage
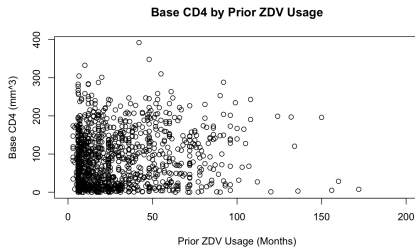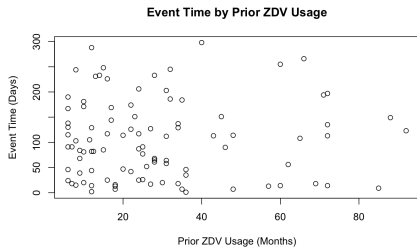
Note on Age and Karnofsky Score

- 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**

Distribution of Age by Karnofsky Score
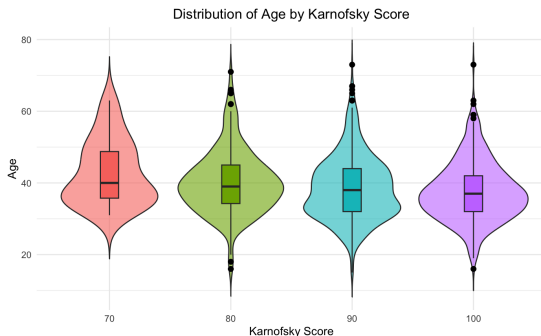
PH Assumption: cloglog

Parallel?

clog-log Survival Curves

Final Cox Model Results

- Final Cox model from 'add1', clinical thinking, and covariate analysis:
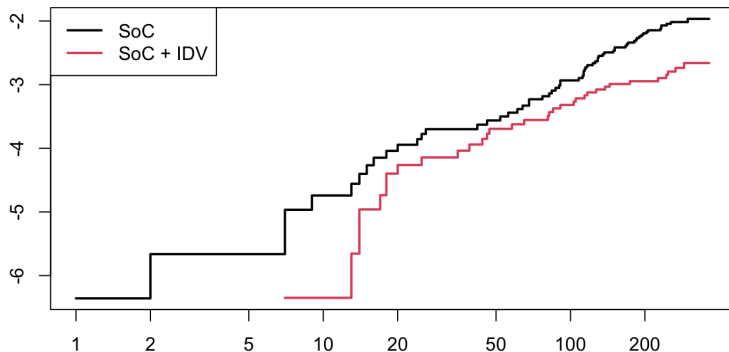
$$surv\_actg \sim tx + ivdrug\_bin + karnof + age + base\_cd4$$

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).
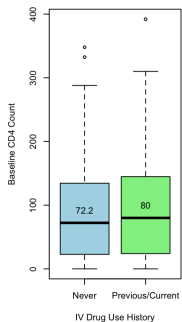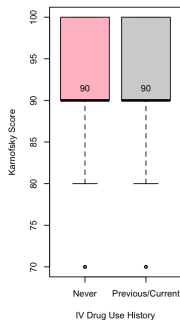
PH Assumption: Schoenfeld Tests

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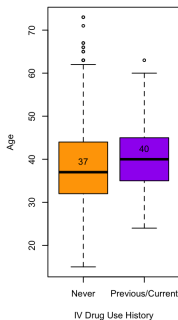 - base_cd4 borderline ($p = 0.057$) but acceptable.
  - GLOBAL test $p = 0.180 \rightarrow$ PH assumption holds.

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:

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

- 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 ⇒ **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 in Cox Model

- **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

Time-varying Hazard Ratio for base_cd4 under TVC model
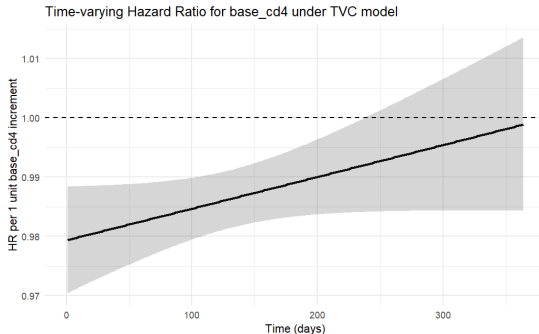
Key Interpretation

- $HR(t) < 1$ 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

📄 Hammer, S., Squires, K., Hughes, M., Grimes, J., Demeter, L., Currier, J., Eron, J. J., Feinberg, J., Balfour, H. J., Deyton, L., Chodakewitz, J., Fischl, M., and Team, A. C. T. G. . S. (1997).
A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and cd4 cell counts of 200 per cubic millimeter or less.
New England Journal of Medicine, 337(11):725–733.

📄 Stanford University / HIV Drug Resistance Database (2025).
Actg 320 clinical study data.
Accessed: 2025-11-19.

📄 Su, S. and Core Team, R. (2025).
GLDreg: Fit GLD Regression/Quantile/AFT Model to Data.
R package version 1.1.2.

Thank you

Questions?