# Sensitivity Analysis for Interval-Censored Discrete Failure Time Data: Application to ACTG 181

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# ACTG 181

- Natural history study of advanced HIV disease.
- 204 participants were scheduled to be monitored for CMV shedding in the urine every 4 weeks and in the blood every 12 weeks.
- Shedding time was discretized into three-month quarters.
- No death during the one year follow-up period.
- At baseline, 69 (135) participants were classified as having high (low) CD4 counts.



# ACTG 181: Research Questions

1. What are the shedding-time distributions for the high and low baseline CD4 groups?
2. What is the effect of baseline CD4 count on the risk of shedding?



# ACTG 181: Challenge

- Participants miss visits
- Missingness may be related to the shedding time

| | High CD4 | Low CD4 |
|---|---|---|
| Left Censored | 23% | 36% |
| Interval Censored | 10% | 12% |
| Right Censored | 57% | 41% |
| Exactly Observed | 10% | 11% |

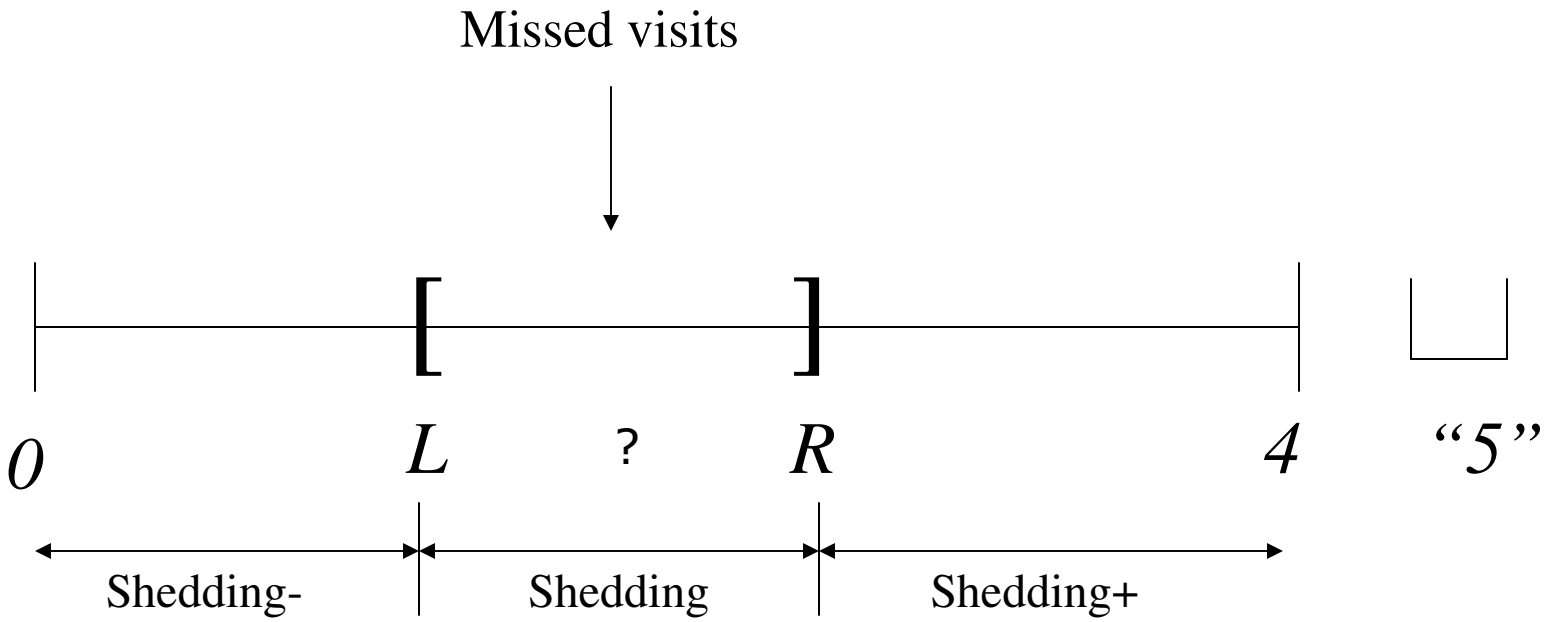


# Data Structure and Notation

- $M=4$
- $T$ = Shedding time (0,1,…,M)
- $T$ = "$M+1$" if no shedding by one year
- Let $p_t = P(T = t)$, $t$ =0,…M+1
- $Z$ = Baseline CD status (1:high; 0:low)



# Observed Data




$$T \in [L, R]$$

# Coarsening at Random (CAR)

- Pattern mixture model

$$P(T = t|L = l, R = r) = P(T = t|T \in [l, r]) \text{ for all } t \in [l, r]$$

- HR (1991), GLR (1997)



# Coarsening at Random (CAR)

- Pattern mixture model

$$P(T = t | L = l, R = r) = P(T = t | T \in [l, r]) \text{ for all } t \in [l, r]$$

Failure *and* censoring processes

Failure process only

- HR (1991), GLR (1997)



# Coarsening at Random (CAR)

- Selection model

$$P(L = l, R = r | T = t) \text{ is constant in } t \in [l, r]$$

- HR (1991), GLR (1997)



# Estimation under CAR

- Turnbull (1976, JRSS-B) proposed EM algorithm to estimate the distribution of *T*.
- Tu, Meng, and Pagano (1993) extend Turnbull's method to estimate parameters in a discrete-time Cox model.
- Sun (1997) estimates parameters in a continuation-ratio model using maximum likelihood.



# Coarsening at Random (CAR)

- CAR is untestable without auxiliary information.
- CAR is often considered implausible by scientific experts.
- For example, Sam Bozzette, PI of ACTG 181, believes that the nature of the missed clinic visits relates to shedding time.



# NCAR Models (PM)

$$P(T = t|L = l, R = r) = \frac{P(T = t|T \in [l, r]) \exp\{q(t, l, r)\}}{c(l, r; q)},$$

$$c(l, r; q) = \sum_{s \in [l,r]} P(T = s|T \in [l, r]) \exp\{q(s, l, r)\},$$

$q(t, l, r)$, the model index, is a specified function of $(t, l, r)$

- Exponential tilting (B-N & C, 1989)
- Rotnitzky, Robins, and colleagues



# NCAR Models (S)

$$\log\left\{\frac{P(L=l,R=r|T=t)}{P(L=l,R=r|T\in[l,r])}\right\}=d(l,r;q)+q(t,l,r)\text{ for }t\in[l,r]$$

$$\Downarrow$$

$$\log\left\{\frac{P(L=l,R=r|T=t)}{P(L=l,R=r|T=t')}\right\}=q(t,l,r)-q(t',l,r)\text{ for }t,t'\in[l,r]$$

- WLOG, we assume that $q(l,l,r)=0$.
- $q(t,l,r)$ is interpreted as the log probability ratio of having interval $[l,r]$ comparing a subject with $T=t$ vs. $T=l$.
- $q=0$ iff CAR.



# NCAR Models - Theorems

**Theorem 1:** Suppose Model (PM,S) holds for a specified function $q$. If $P(L=t,R=t)>0$ for all $t$, then the distribution of $T$ is uniquely identified.

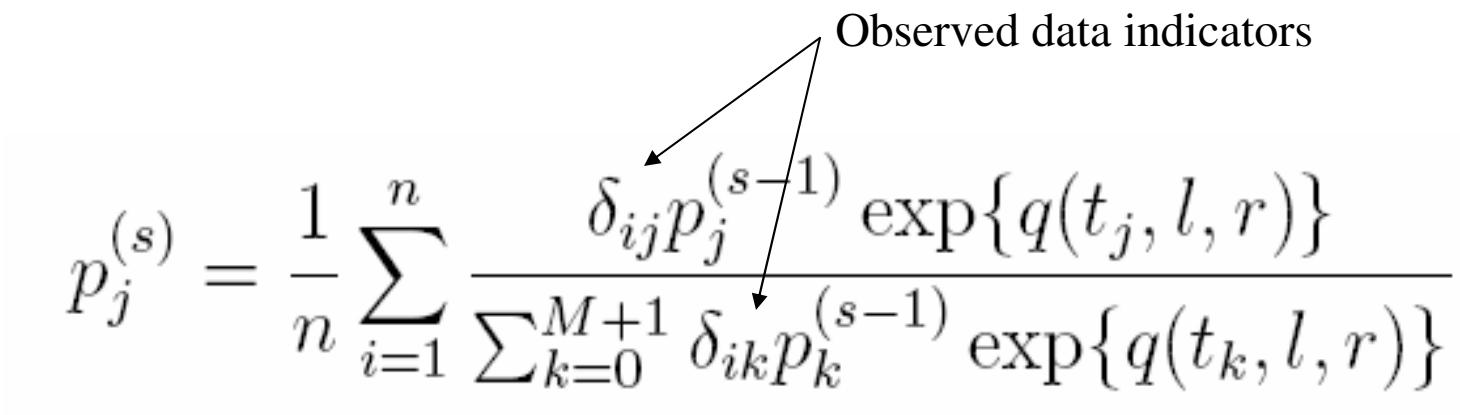
**Theorem 2:** For specified function $q$, the uniquely identified distribution of $T$ (Theorem 1) in conjunction with Model (S) yields a joint distribution for $(L,R,T)$ which marginalizes to the population distribution of $(L,R)$.

- So, the NCAR models (i.e., $q$) are untestable.
- Sensitivity analysis



# Inference for Survival Curves

- Estimation proceeds via EM algorithm.




- Re-weighted version of Turnbull's self-consistency equation.
- Standard errors via Louis' method.



# Inference for Subgroup Effects

- Continuation Ratio Model

$$\rho_{ij} = P(T_i = t_j | T_i \geq t_j)$$

$$\log\left(\frac{\rho_{ij}}{1-\rho_{ij}}\right) = \theta_j + \beta Z_i$$

- Estimation via EM algorithm.
- Standard errors using Louis' method



# Simulation Study

- $M=4$
- $n$ = 100/arm
- Z = 0,1
- $\beta$ = 0 or 0.75

$$q(\phi, t, l, r, z) = \phi^z \frac{(t-l)}{(r-l)}, \; z = 0, 1$$

- For each treatment group, exp{$\phi^z$} is the probability ratio of having interval [$l$, $r$] comparing those with $T=r$ to those with $T=l$.
- $\phi^z$ = -log(2), 0, or log(2)



# Simulation Results: $\beta = 0$

CAR Analysis

| True $\phi^0$ | True $\phi^1$ | Bias | Coverage |
|---|---|---|---|
| -log(2) | -log(2) | 0.02 | 0.93 |
| -log(2) | 0 | 0.16 | 0.87 |
| -log(2) | log(2) | 0.29 | 0.74 |



# Simulation Results: $\beta = 0.75$

Truth

| True $\phi^0$ | True $\phi^1$ | Bias | Coverage |
|---|---|---|---|
| -log(2) | -log(2) | -0.01 | 0.95 |
| -log(2) | 0 | 0.00 | 0.96 |
| -log(2) | log(2) | -0.04 | 0.94 |



# ACTG 181 – Censoring Bias Function

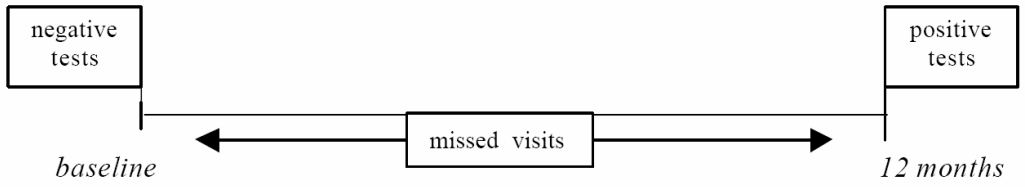
$$q(\boldsymbol{\phi}, t, l, r, z) = \phi_1^z \mathrm{I}(r < M+1)\frac{(t-l)}{(M-1)} + \phi_2^z \mathrm{I}(r = M+1)\frac{(t-l)}{M},\ z = 0, 1$$

- $\exp\{\phi_1^z\}$ is the CD4-specific probability ratio of having interval [3 mos., 12 mos.] comparing those who begin shedding at 12 mos. to those who begin shedding at 3 mos.
- $\exp\{\phi_2^z\}$ is the CD4-specific probability ratio of dropping out just after baseline comparing those who do not begin within 12 mos. to those who begin shedding within 3 mos. from baseline.

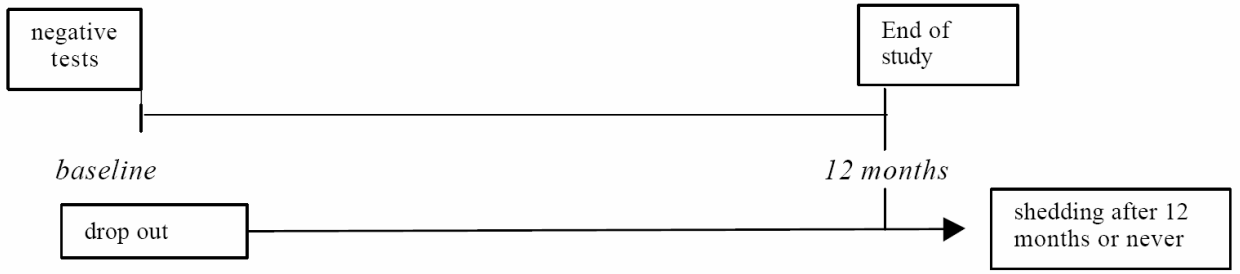


# ACTG 181: Elicitation Schematic

a.




b.



# ACTG 181: Bozzette's Responses

- Among participants with low baseline CD4, those who begin shedding within 3 months of testing negative at baseline are less likely to drop out (be interval-censored) than those who begin shedding after (at) 12 months.
- Sam believes that those with low baseline CD4 have probably not managed their HIV well, and the least healthy of this group have the greatest motivation to make visits. The most healthy of this group are likely to shed later and may feel less motivated to comply with the visit schedule.
- $\exp\{\phi_1^0\}$ and $\exp\{\phi_2^0\}$ are between 1 and 3.

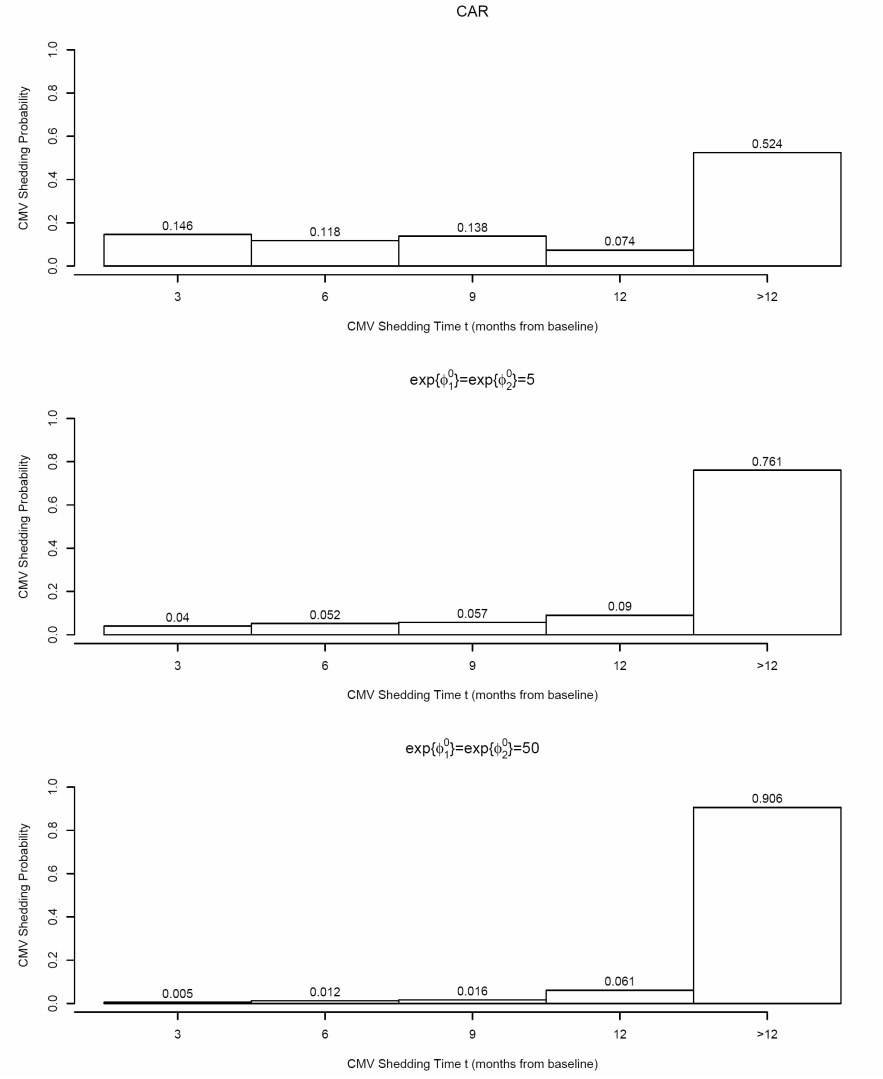


# ACTG 181: Bozzette's Responses

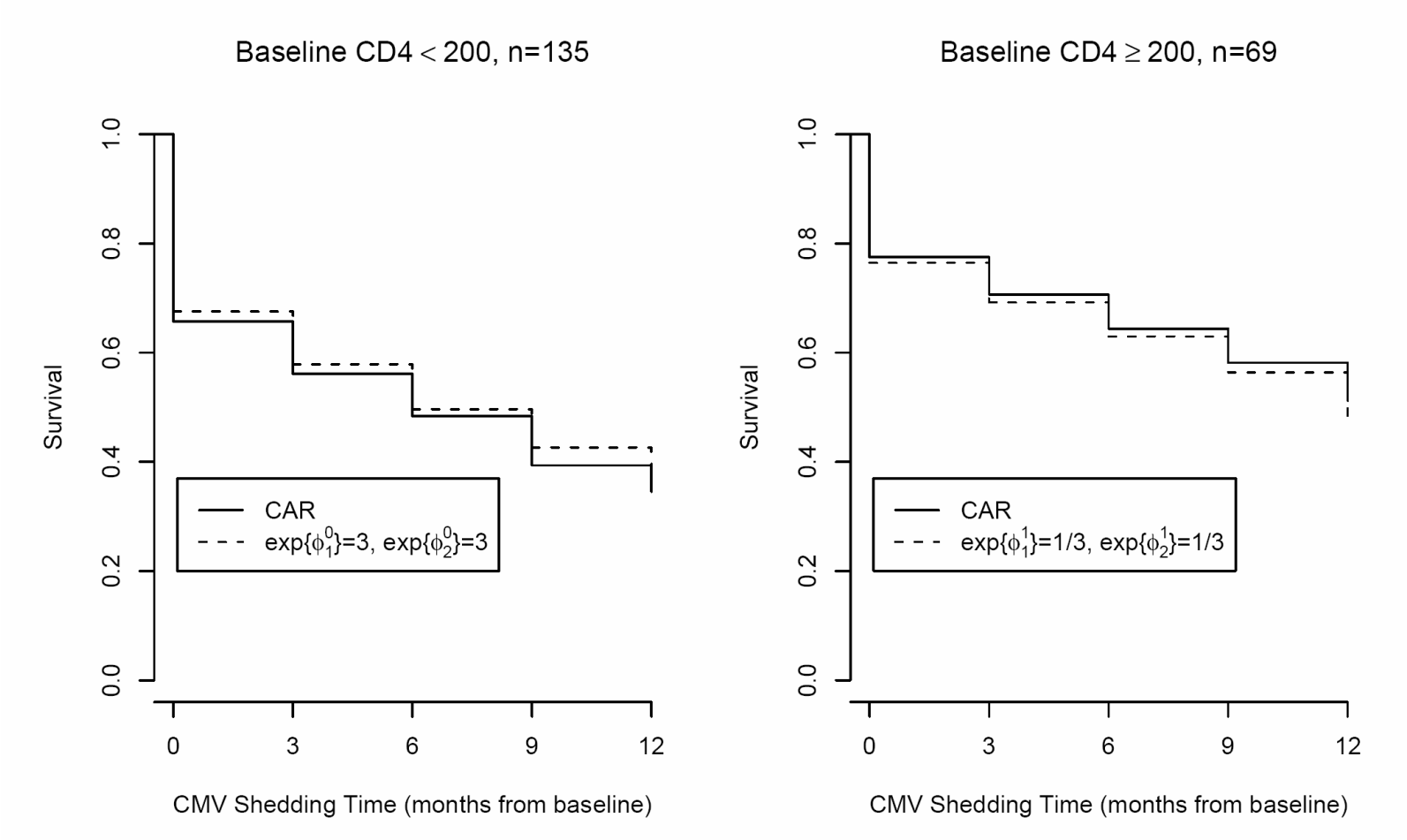
- Among participants with high baseline CD4, those who begin shedding within 3 months of testing negative at baseline are more likely to drop out (be interval-censored) than those who begin shedding after (at) 12 months.
- Sam believes that those with high baseline CD4 have likely managed their HIV well, and the most healthy of this group will continue to do so. However, he believes that the least healthy of this group are more likely to miss visits and shed earlier.
- $\exp\{\phi_1^1\}$ and $\exp\{\phi_2^1\}$ are between 1/3 and 1



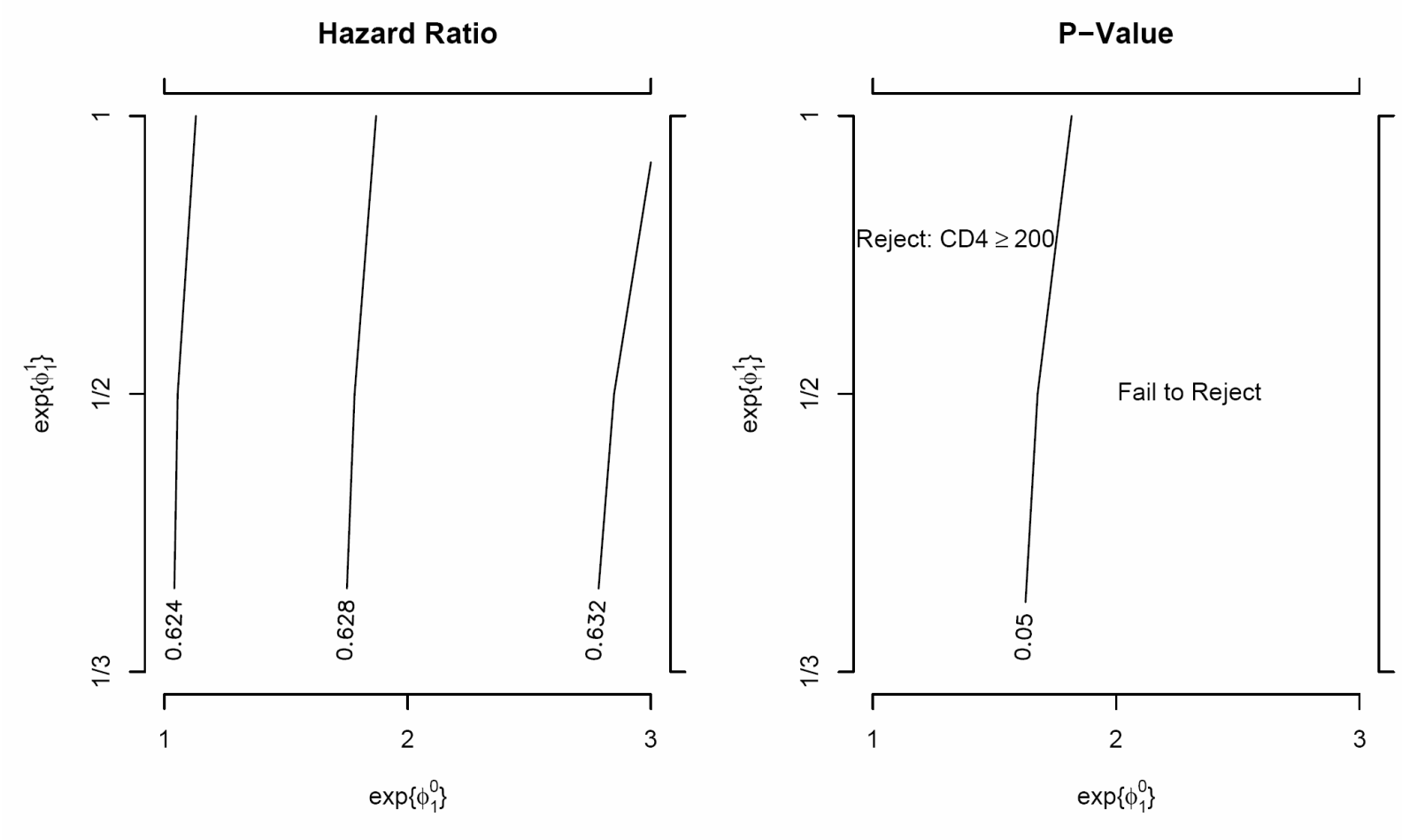
# Redistribution under CAR and NCAR



# ACTG 181: Results



# ACTG 181 Results



# Summary

- We have presented a formal sensitivity analysis approach for analyzing informative interval-censored, discrete time-to-event data.

# Future Directions

- Formal Bayesian approach
- Asymptotic theory for continuous time.
- High dimensional covariates
- Elicitation from experts