

Longitudinal AIDS Data Analysis

- **Problem:** Lengthy follow-up times required to evaluate efficacy of a new treatment (e.g., survival time of HIV-infected patients)

Longitudinal AIDS Data Analysis

- **Problem:** Lengthy follow-up times required to evaluate efficacy of a new treatment (e.g., survival time of HIV-infected patients)
- **Solution(?):** Select an easily-measured biological marker, known to be predictive of the clinical outcome, as a **surrogate endpoint**. In AIDS research, typically use **CD4 count** (number of lymphocytes/mm³ blood).

Longitudinal AIDS Data Analysis

- **Problem:** Lengthy follow-up times required to evaluate efficacy of a new treatment (e.g., survival time of HIV-infected patients)
- **Solution(?):** Select an easily-measured biological marker, known to be predictive of the clinical outcome, as a **surrogate endpoint**. In AIDS research, typically use **CD4 count** (number of lymphocytes/mm³ blood).
- **BUT** several studies have cast doubt on this approach...

Longitudinal AIDS Data Analysis

- **Problem:** Lengthy follow-up times required to evaluate efficacy of a new treatment (e.g., survival time of HIV-infected patients)
- **Solution(?):** Select an easily-measured biological marker, known to be predictive of the clinical outcome, as a **surrogate endpoint**. In AIDS research, typically use **CD4 count** (number of lymphocytes/mm³ blood).
- **BUT** several studies have cast doubt on this approach...
- **Example:** Anglo-French “Concorde” trial showed immediate AZT produces consistently higher CD4 counts than deferred, but survival patterns in two groups were nearly identical.

Our data: the ddI/ddC study

- 467 persons randomized to didanosine (ddI) or zalcitabine (ddC)

Our data: the ddI/ddC study

- 467 persons randomized to **didanosine (ddI)** or **zalcitabine (ddC)**
- HIV-infected patients with AIDS or two CD4 counts of 300 or less, and who had failed or could not tolerate zidovudine (AZT)
⇒ **all are very ill**

Our data: the ddI/ddC study

- 467 persons randomized to **didanosine (ddI)** or **zalcitabine (ddC)**
- HIV-infected patients with AIDS or two CD4 counts of 300 or less, and who had failed or could not tolerate zidovudine (AZT)
⇒ **all are very ill**
- CD4 counts recorded at baseline, 2, 6, 12, and 18 months (some **missing**)

Our data: the ddI/ddC study

- 467 persons randomized to **didanosine (ddI)** or **zalcitabine (ddC)**
- HIV-infected patients with AIDS or two CD4 counts of 300 or less, and who had failed or could not tolerate zidovudine (AZT)
⇒ **all are very ill**
- CD4 counts recorded at baseline, 2, 6, 12, and 18 months (some **missing**)
- **covariates:** age, sex, baseline AIDS Dx, baseline Karnofsky score, etc.

Our data: the ddI/ddC study

- 467 persons randomized to **didanosine (ddI)** or **zalcitabine (ddC)**
- HIV-infected patients with AIDS or two CD4 counts of 300 or less, and who had failed or could not tolerate zidovudine (AZT)
⇒ **all are very ill**
- CD4 counts recorded at baseline, 2, 6, 12, and 18 months (some **missing**)
- **covariates**: age, sex, baseline AIDS Dx, baseline Karnofsky score, etc.
- **outcome variables**: clinical disease progression, death

Goal and Subplot of ddI/ddC study

- **Goal:** Analyze the association among CD4 count, survival time, drug group, and AIDS diagnosis at study entry (an indicator of disease progression status). Make recommendations for clinical practice and use of CD4 as surrogate marker for death in end-stage patients.

Goal and Subplot of ddI/ddC study

- **Goal:** Analyze the association among CD4 count, survival time, drug group, and AIDS diagnosis at study entry (an indicator of disease progression status). Make recommendations for clinical practice and use of CD4 as surrogate marker for death in end-stage patients.
- **Subplot:** ddI granted preliminary license in USA based primarily on its ability to “boost” CD4 count at 2 months. ddC makers would like to show a **similar boost** and/or **comparable survival time** (“equivalency trial”).

Modeling of Longitudinal CD4 Counts

- Write vector of CD4 counts for individual i as $Y_i = (Y_{i1}, \dots, Y_{is_i})^T$, and model

$$Y_i = \mathbf{X}_i \boldsymbol{\alpha} + \mathbf{W}_i \boldsymbol{\beta}_i + \boldsymbol{\epsilon}_i ,$$

where

Modeling of Longitudinal CD4 Counts

- Write vector of CD4 counts for individual i as $Y_i = (Y_{i1}, \dots, Y_{is_i})^T$, and model

$$Y_i = \mathbf{X}_i \boldsymbol{\alpha} + \mathbf{W}_i \boldsymbol{\beta}_i + \boldsymbol{\epsilon}_i ,$$

where

- \mathbf{X}_i is a $s_i \times p$ design matrix

Modeling of Longitudinal CD4 Counts

- Write vector of CD4 counts for individual i as $Y_i = (Y_{i1}, \dots, Y_{is_i})^T$, and model

$$Y_i = X_i\alpha + W_i\beta_i + \epsilon_i ,$$

where

- X_i is a $s_i \times p$ design matrix
- α is a $p \times 1$ vector of fixed effects

Modeling of Longitudinal CD4 Counts

- Write vector of CD4 counts for individual i as $Y_i = (Y_{i1}, \dots, Y_{is_i})^T$, and model

$$Y_i = \mathbf{X}_i \boldsymbol{\alpha} + \mathbf{W}_i \boldsymbol{\beta}_i + \boldsymbol{\epsilon}_i ,$$

where

- \mathbf{X}_i is a $s_i \times p$ design matrix
- $\boldsymbol{\alpha}$ is a $p \times 1$ vector of fixed effects
- \mathbf{W}_i is a $s_i \times q$ design matrix ($q < p$), and

Modeling of Longitudinal CD4 Counts

- Write vector of CD4 counts for individual i as $Y_i = (Y_{i1}, \dots, Y_{is_i})^T$, and model

$$Y_i = X_i\alpha + W_i\beta_i + \epsilon_i ,$$

where

- X_i is a $s_i \times p$ design matrix
- α is a $p \times 1$ vector of fixed effects
- W_i is a $s_i \times q$ design matrix ($q < p$), and
- β_i is a $q \times 1$ vector of subject-specific random effects, usually assumed iid $N(0, V)$

Modeling of Longitudinal CD4 Counts

- Write vector of CD4 counts for individual i as $Y_i = (Y_{i1}, \dots, Y_{is_i})^T$, and model

$$Y_i = X_i \alpha + W_i \beta_i + \epsilon_i ,$$

where

- X_i is a $s_i \times p$ design matrix
 - α is a $p \times 1$ vector of fixed effects
 - W_i is a $s_i \times q$ design matrix ($q < p$), and
 - β_i is a $q \times 1$ vector of subject-specific random effects, usually assumed iid $N(0, V)$
-
- W_i has j^{th} row $w_{ij} = (1, t_{ij}, (t_{ij} - 2)^+)$, to accommodate CD4 response at two months.

Modeling of Longitudinal CD4 Counts

- We account for the covariates by letting

$$\mathbf{X}_i = (\mathbf{W}_i \mid d_i \mathbf{W}_i \mid a_i \mathbf{W}_i) , \quad \text{where}$$

Modeling of Longitudinal CD4 Counts

- We account for the covariates by letting

$$\mathbf{X}_i = (\mathbf{W}_i \mid d_i \mathbf{W}_i \mid a_i \mathbf{W}_i) , \quad \text{where}$$

- $d_i = 1$ if i received ddI; $d_i = 0$ if ddC

Modeling of Longitudinal CD4 Counts

- We account for the covariates by letting

$$\mathbf{X}_i = (\mathbf{W}_i \mid d_i \mathbf{W}_i \mid a_i \mathbf{W}_i) , \quad \text{where}$$

- $d_i = 1$ if i received ddI; $d_i = 0$ if ddC
- $a_i = 1$ if i has an AIDS diagnosis at baseline; $a_i = 0$ if not

Modeling of Longitudinal CD4 Counts

- We account for the covariates by letting

$$\mathbf{X}_i = (\mathbf{W}_i \mid d_i \mathbf{W}_i \mid a_i \mathbf{W}_i) , \quad \text{where}$$

- $d_i = 1$ if i received ddl; $d_i = 0$ if ddC
- $a_i = 1$ if i has an AIDS diagnosis at baseline; $a_i = 0$ if not
- **Likelihood:**

$$\prod_{i=1}^n N_{s_i}(Y_i \mid \mathbf{X}_i \boldsymbol{\alpha} + \mathbf{W}_i \boldsymbol{\beta}_i, \sigma^2 \mathbf{I}_{s_i}) \prod_{i=1}^n N_3(\boldsymbol{\beta}_i \mid \mathbf{0}, \mathbf{V}) ,$$

Modeling of Longitudinal CD4 Counts

- We account for the covariates by letting

$$\mathbf{X}_i = (\mathbf{W}_i \mid d_i \mathbf{W}_i \mid a_i \mathbf{W}_i) , \quad \text{where}$$

- $d_i = 1$ if i received ddl; $d_i = 0$ if ddC
- $a_i = 1$ if i has an AIDS diagnosis at baseline; $a_i = 0$ if not

- **Likelihood:**

$$\prod_{i=1}^n N_{s_i}(Y_i | \mathbf{X}_i \boldsymbol{\alpha} + \mathbf{W}_i \boldsymbol{\beta}_i, \sigma^2 \mathbf{I}_{s_i}) \prod_{i=1}^n N_3(\boldsymbol{\beta}_i | \mathbf{0}, \mathbf{V}) ,$$

- **Prior:** $N_9(\boldsymbol{\alpha} | c, \mathbf{D}) \times IG(\sigma^2 | a, b) \times IW(\mathbf{V} | (\rho \mathbf{R})^{-1}, \rho)$

Modeling of Longitudinal CD4 Counts

- We account for the covariates by letting

$$\mathbf{X}_i = (\mathbf{W}_i \mid d_i \mathbf{W}_i \mid a_i \mathbf{W}_i), \quad \text{where}$$

- $d_i = 1$ if i received ddl; $d_i = 0$ if ddC
 - $a_i = 1$ if i has an AIDS diagnosis at baseline; $a_i = 0$ if not
- **Likelihood:**

$$\prod_{i=1}^n N_{s_i}(Y_i \mid \mathbf{X}_i \boldsymbol{\alpha} + \mathbf{W}_i \boldsymbol{\beta}_i, \sigma^2 \mathbf{I}_{s_i}) \prod_{i=1}^n N_3(\boldsymbol{\beta}_i \mid \mathbf{0}, \mathbf{V}),$$

- **Prior:** $N_9(\boldsymbol{\alpha} \mid c, \mathbf{D}) \times IG(\sigma^2 \mid a, b) \times IW(\mathbf{V} \mid (\rho \mathbf{R})^{-1}, \rho)$

⇒ easy full conditional distributions for Gibbs sampling!

Prior Selection

- We would prefer a **vague** (low-information) prior, but must take care with variance components, since if both have improper priors, the posterior will be **improper**!
Possible solutions:

Prior Selection

- We would prefer a **vague** (low-information) prior, but must take care with variance components, since if both have improper priors, the posterior will be **improper!**
Possible solutions:
 - Add **constraints** to reduce parameter count, or

Prior Selection

- We would prefer a **vague** (low-information) prior, but must take care with variance components, since if both have improper priors, the posterior will be **improper!**
Possible solutions:
 - Add **constraints** to reduce parameter count, or
 - Use vague but proper priors in a **hierarchically centered** parametrization (reduce correlations)

Prior Selection

- We would prefer a **vague** (low-information) prior, but must take care with variance components, since if both have improper priors, the posterior will be **improper!**
Possible solutions:
 - Add **constraints** to reduce parameter count, or
 - Use vague but proper priors in a **hierarchically centered** parametrization (reduce correlations)
- **Our rule of thumb:** Take $\rho = n/20$ and $\mathbf{R} = E(\mathbf{V}) = \text{Diag}((r_1/8)^2, (r_2/8)^2, (r_3/8)^2)$, where r_i is total range of plausible parameter values across individuals

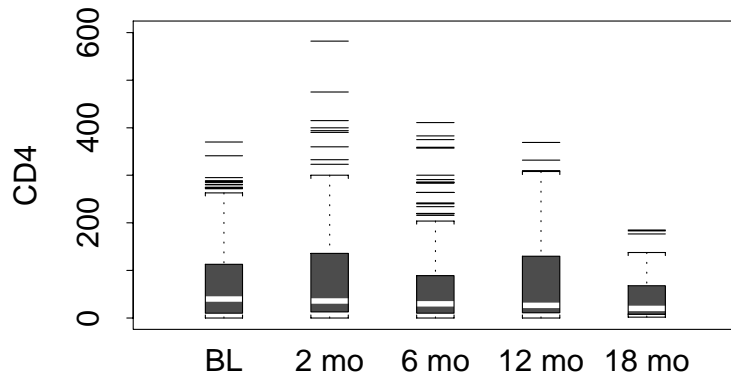
Prior Selection

- We would prefer a **vague** (low-information) prior, but must take care with variance components, since if both have improper priors, the posterior will be **improper!**
Possible solutions:
 - Add **constraints** to reduce parameter count, or
 - Use vague but proper priors in a **hierarchically centered** parametrization (reduce correlations)
 - **Our rule of thumb:** Take $\rho = n/20$ and $\mathbf{R} = E(\mathbf{V}) = \text{Diag}((r_1/8)^2, (r_2/8)^2, (r_3/8)^2)$, where r_i is total range of plausible parameter values across individuals
- ⇒ ± 2 prior standard deviations covers **half** the plausible range (since \mathbf{R} is roughly the prior mean of \mathbf{V})

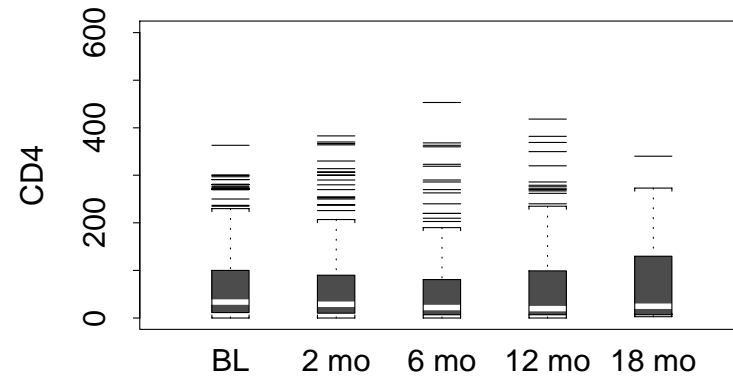
Prior Selection

- We would prefer a **vague** (low-information) prior, but must take care with variance components, since if both have improper priors, the posterior will be **improper!**
Possible solutions:
 - Add **constraints** to reduce parameter count, or
 - Use vague but proper priors in a **hierarchically centered** parametrization (reduce correlations)
 - **Our rule of thumb:** Take $\rho = n/20$ and $\mathbf{R} = E(\mathbf{V}) = \text{Diag}((r_1/8)^2, (r_2/8)^2, (r_3/8)^2)$, where r_i is total range of plausible parameter values across individuals
- ⇒ ± 2 prior standard deviations covers **half** the plausible range (since \mathbf{R} is roughly the prior mean of \mathbf{V})
- Other priors can be vague **except** for “placeholder” α_4 (drug intercept): insist it be close to 0 since patients are **randomized** to drug

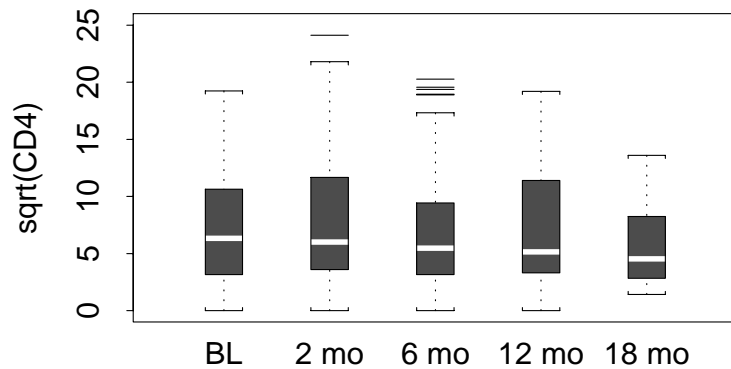
Exploratory plots of CD4 count



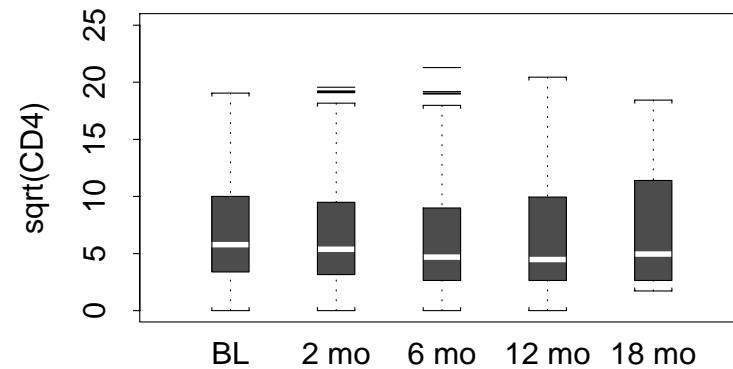
a) CD4 count over time, ddl treatment group



b) CD4 count over time, ddC treatment group



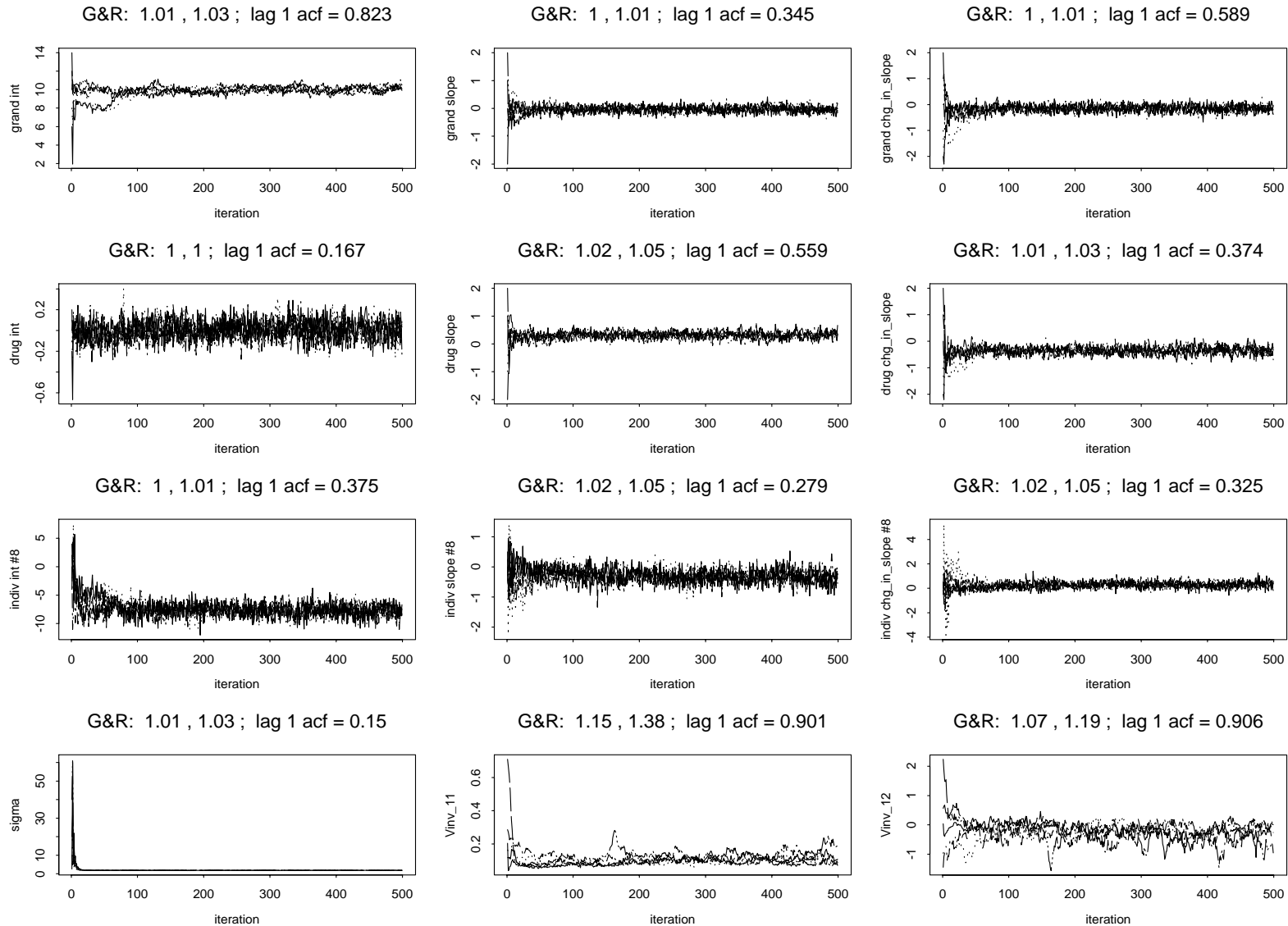
c) square root CD4 count over time, ddl group



d) square root CD4 count over time, ddC group

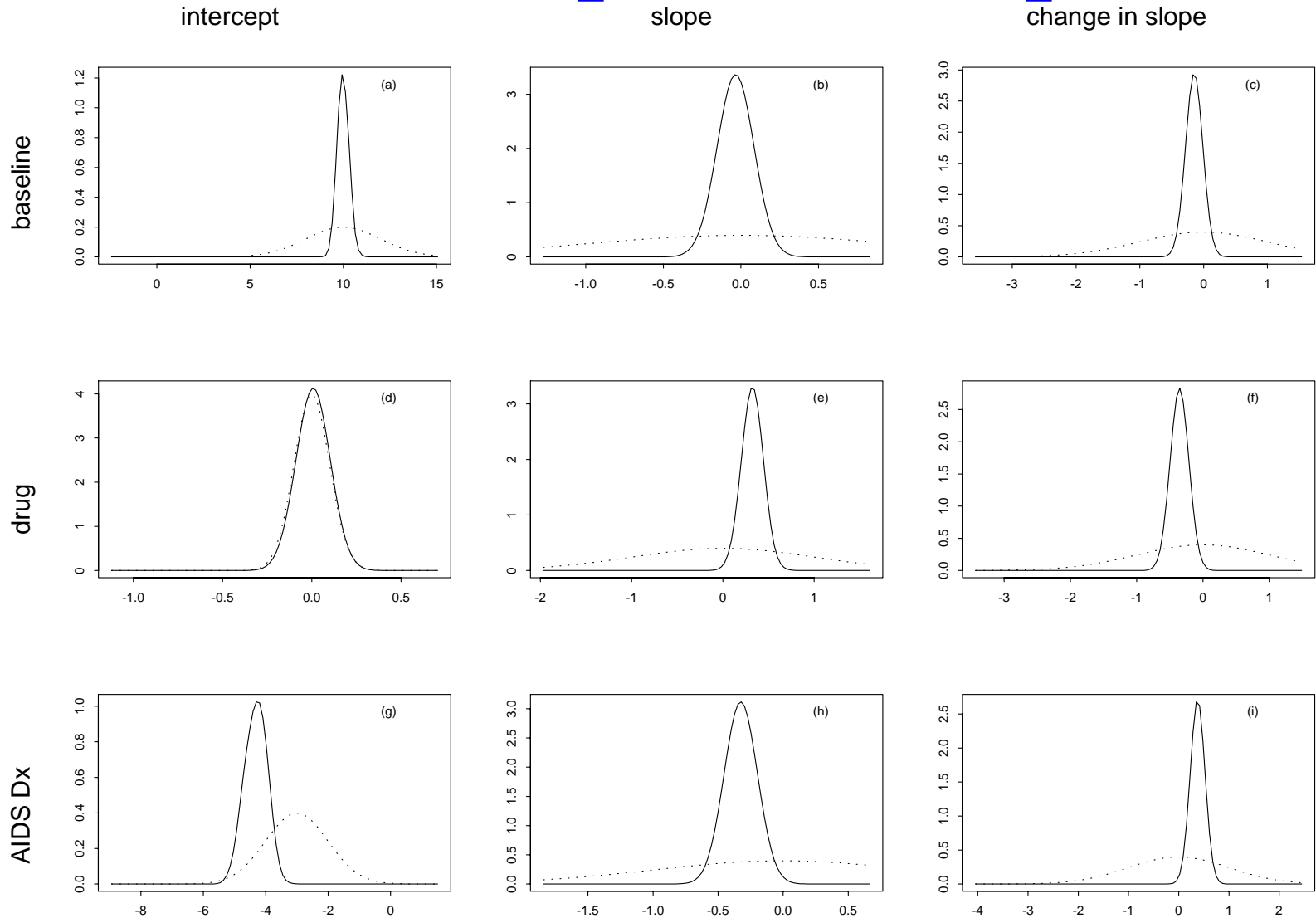
Sample sizes show **increasing missingness** over time –
ddl: (230, 182, 153, 102, 22); **ddC**: (236, 186, 157, 123, 14)

MCMC convergence monitoring plots



Note: horizontal axis is iteration number; vertical axes are $\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6, \beta_{8,1}, \beta_{8,2}, \beta_{8,3}, \sigma, (\mathbf{V}^{-1})_{11},$ and $(\mathbf{V}^{-1})_{12}.$

Fixed effect (α) priors and posteriors



Priors (dashed lines) and estimated posteriors (solid lines) for the α parameters; note no “learning” for α_4 (placeholder).

Point and interval estimates

			mode	95% interval	
Baseline	intercept	α_1	9.938	9.319	10.733
	slope	α_2	-0.041	-0.285	0.204
	change in slope	α_3	-0.166	-0.450	0.118
Drug	intercept	α_4	0.004	-0.190	0.198
	slope	α_5	0.309	0.074	0.580
	change in slope	α_6	-0.348	-0.671	-0.074
AIDS Dx	intercept	α_7	-4.295	-5.087	-3.609
	slope	α_8	-0.322	-0.588	-0.056
	change in slope	α_9	0.351	0.056	0.711

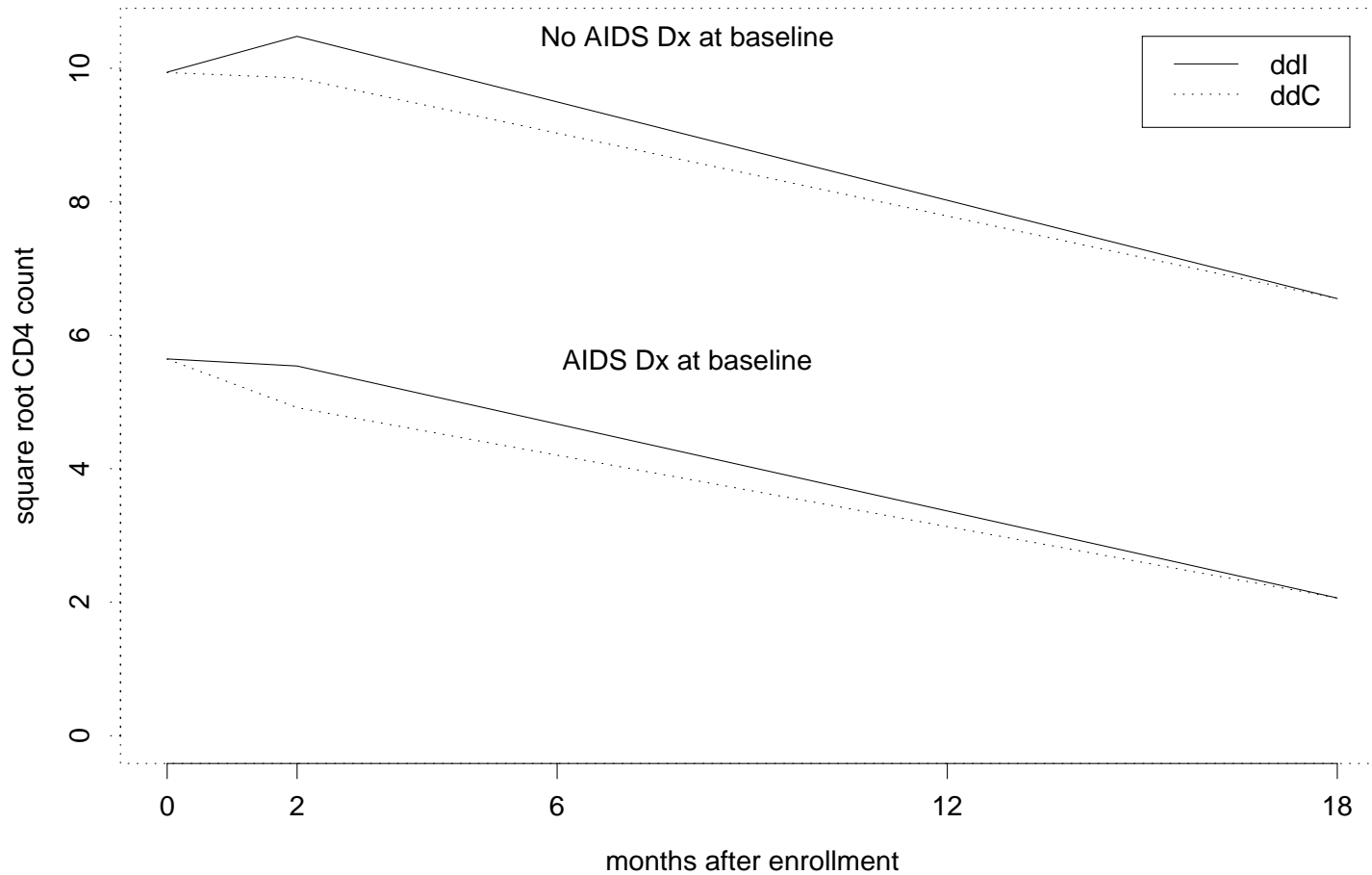
- ddl trajectories significantly different both before and after the changepoint

Point and interval estimates

			mode	95% interval	
Baseline	intercept	α_1	9.938	9.319	10.733
	slope	α_2	-0.041	-0.285	0.204
	change in slope	α_3	-0.166	-0.450	0.118
Drug	intercept	α_4	0.004	-0.190	0.198
	slope	α_5	0.309	0.074	0.580
	change in slope	α_6	-0.348	-0.671	-0.074
AIDS Dx	intercept	α_7	-4.295	-5.087	-3.609
	slope	α_8	-0.322	-0.588	-0.056
	change in slope	α_9	0.351	0.056	0.711

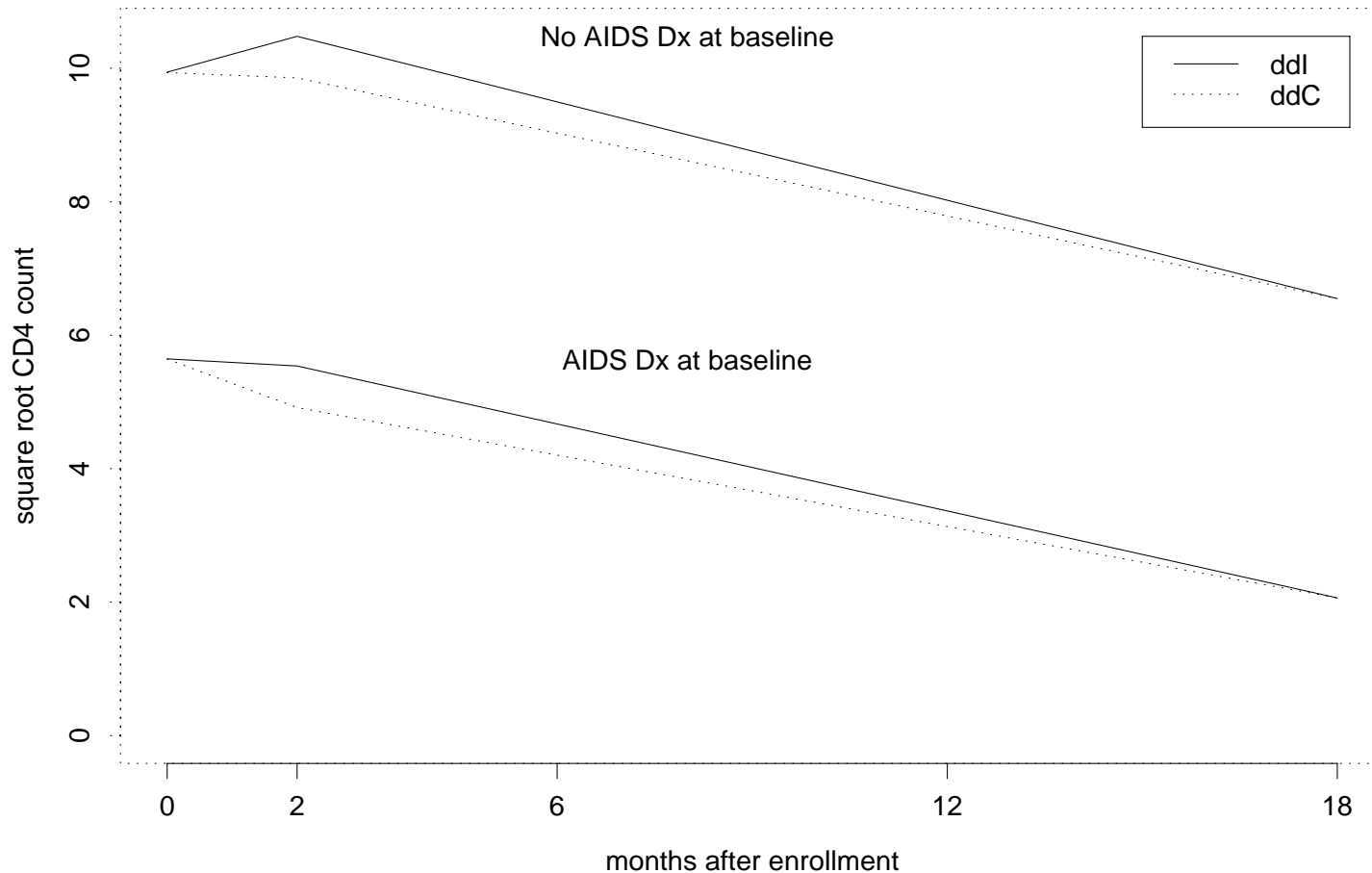
- ddl trajectories significantly different both before and after the changepoint
- AIDS Dx main effects also all significant

Fitted population model by drug and Dx



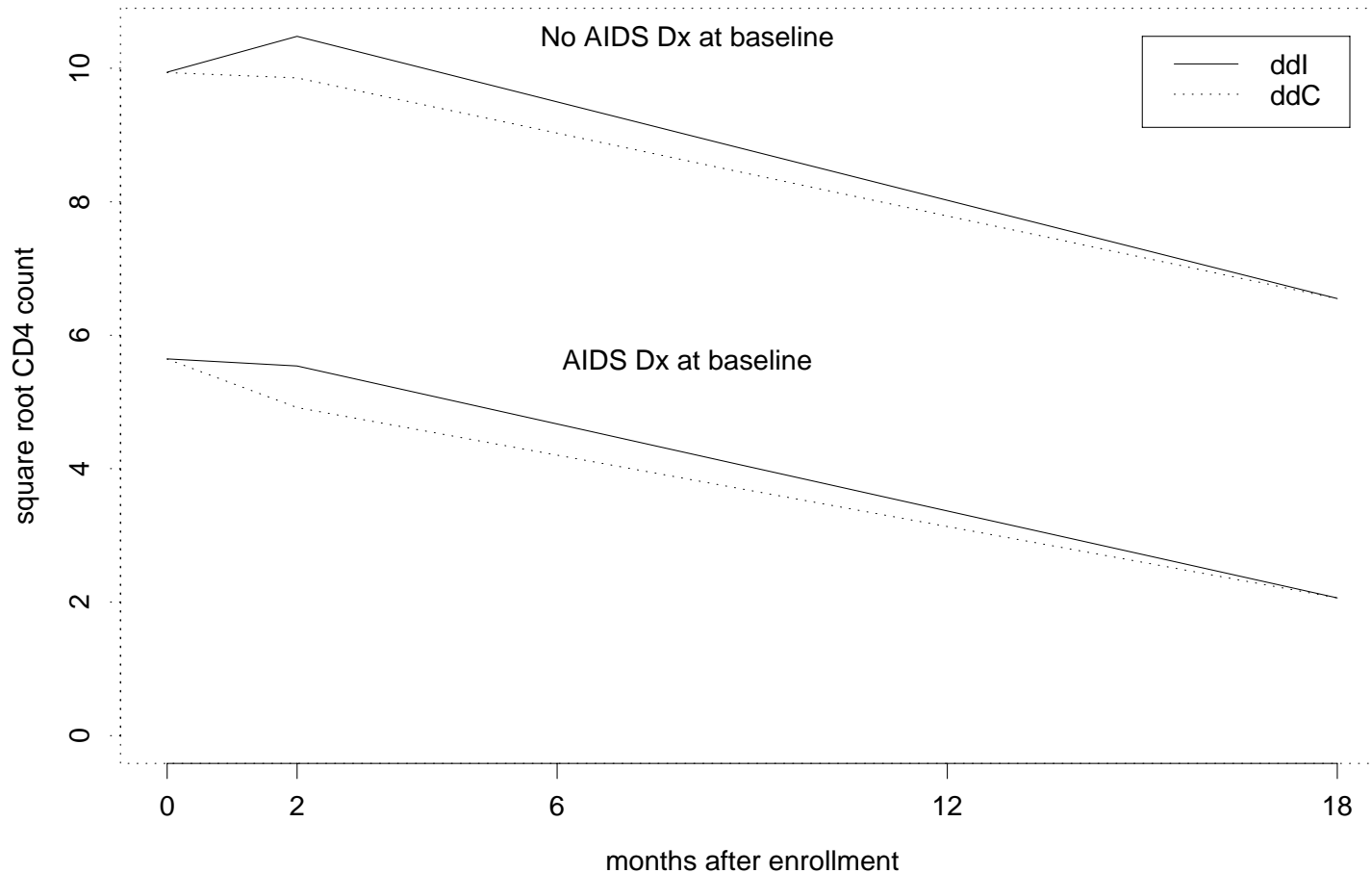
- Obtained by setting $\beta_i = \epsilon_i = 0$, $\alpha = \text{posterior mode}$

Fitted population model by drug and Dx



- Obtained by setting $\beta_i = \epsilon_i = 0$, $\alpha =$ posterior mode
- On average, only **AIDS-free ddl** patients get a “boost”...

Fitted population model by drug and Dx

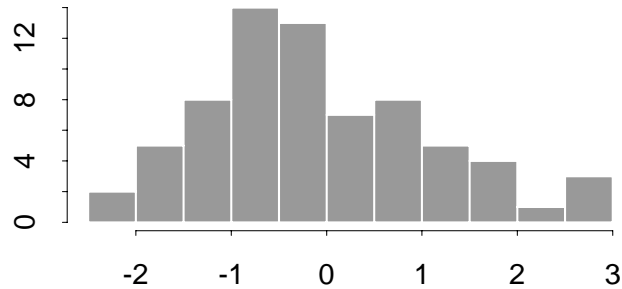


- Obtained by setting $\beta_i = \epsilon_i = 0$, $\alpha =$ posterior mode
- On average, only **AIDS-free ddl** patients get a “boost”...
- **But** ddC patients “catch up” by the end of the period!

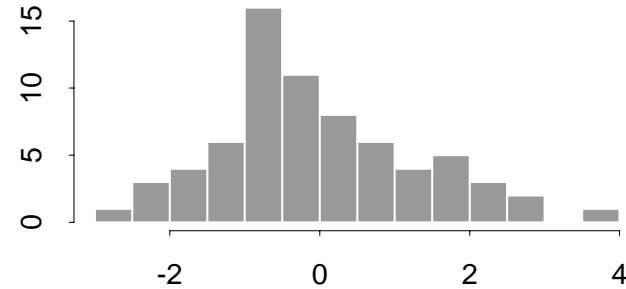
Changepoint vs. linear decay model

Model 1: $V_{inv} \sim W(\rho = 24, R = \text{Diag}(4, 0.0625, 0.0625))$

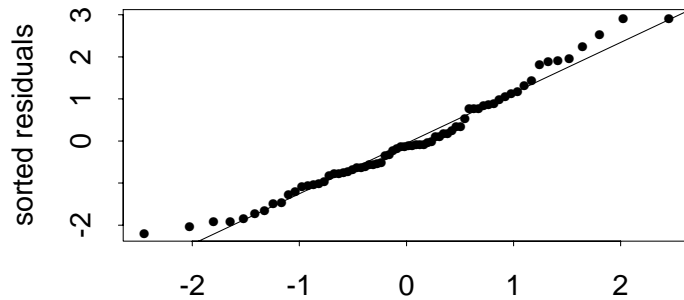
Model 2: $V_{inv} \sim W(\rho = 24, R = \text{Diag}(4, 0.0625))$



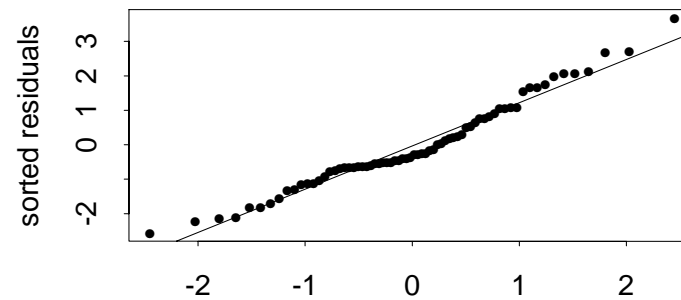
residuals, Model 1



residuals, Model 2



quantiles of standard normal, Model 1



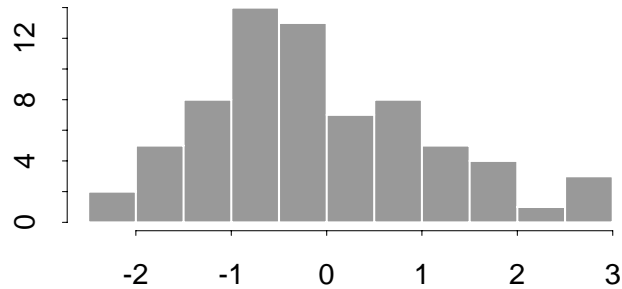
quantiles of standard normal, Model 2

- q-q plots indicate a reasonable degree of normality in these **cross validation** residuals, $r_{ij} = y_{ij} - E(Y_{ij} | \mathbf{y}_{(ij)})$

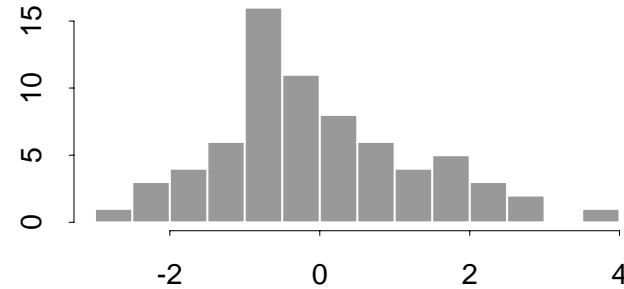
Changepoint vs. linear decay model

Model 1: $V_{inv} \sim W(\rho = 24, R = \text{Diag}(4 \ 0.0625 \ 0.0625))$

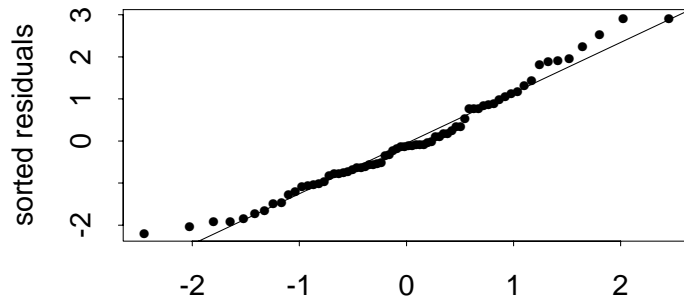
Model 2: $V_{inv} \sim W(\rho = 24, R = \text{Diag}(4 \ 0.0625))$



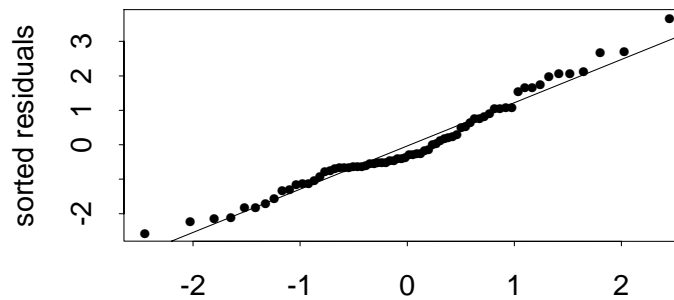
residuals, Model 1



residuals, Model 2



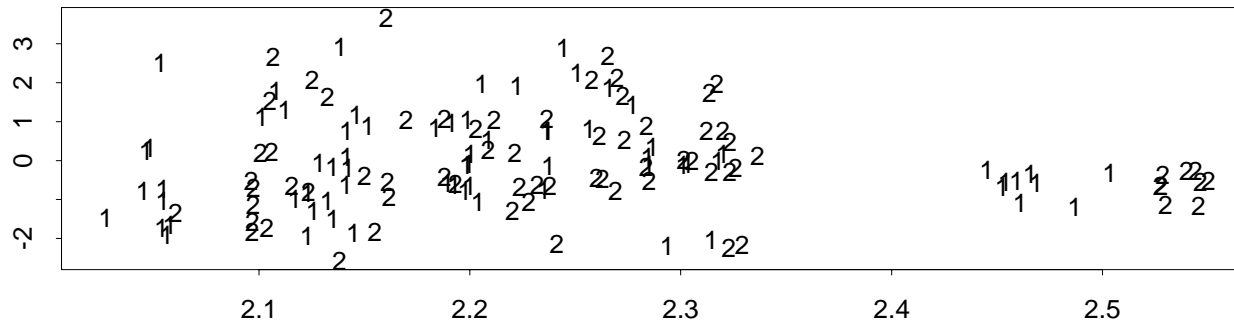
quantiles of standard normal, Model 1



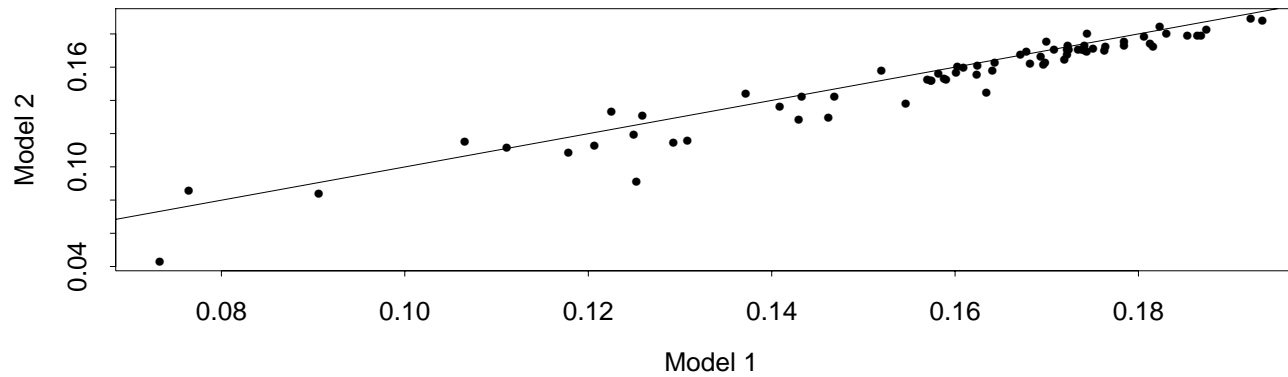
quantiles of standard normal, Model 2

- q-q plots indicate a reasonable degree of normality in these **cross validation** residuals, $r_{ij} = y_{ij} - E(Y_{ij} | \mathbf{y}_{(ij)})$
- $\sum_{ij} |r_{ij}| = 66.37$ and 70.82 , respectively \Rightarrow **similar fits!**

Residual and CPO comparison



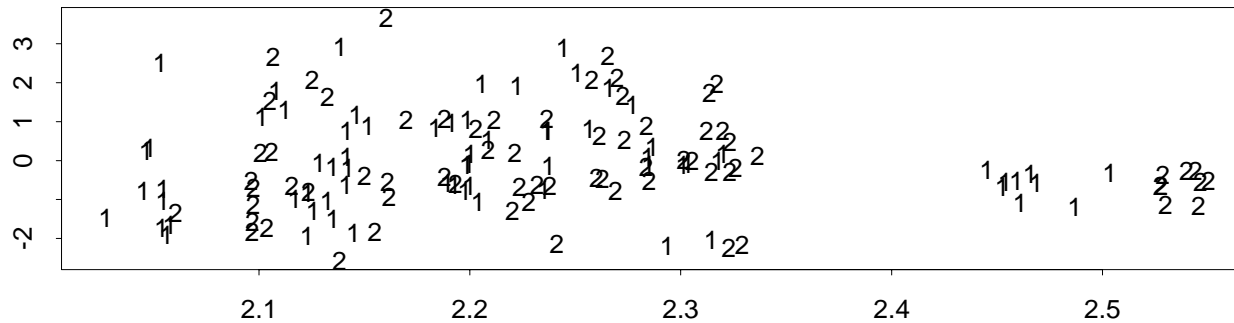
a) $y_r - E(y_r)$ versus $sd(y_r)$; plotting character indicates model number



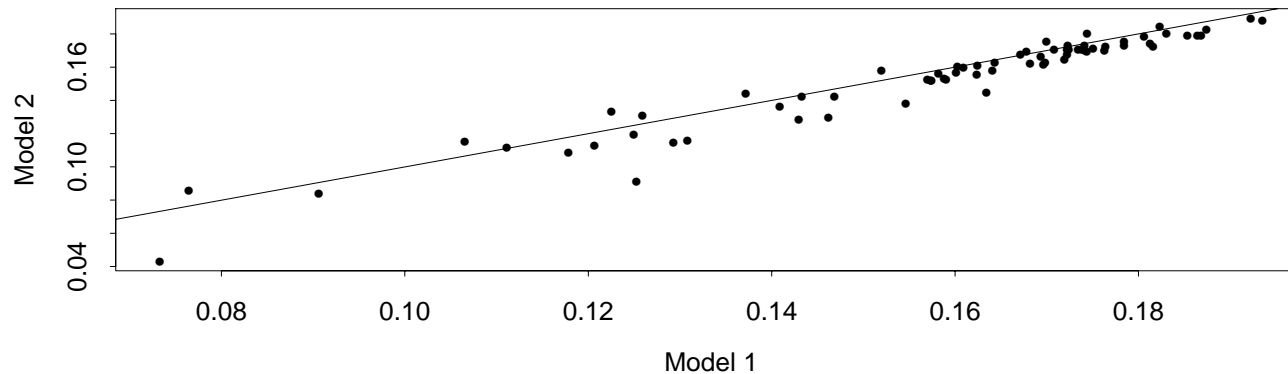
b) Comparison of CPO values

- reduction in r_{ij} from Model 2 (linear) to Model 1 (changepoint) is negligible

Residual and CPO comparison



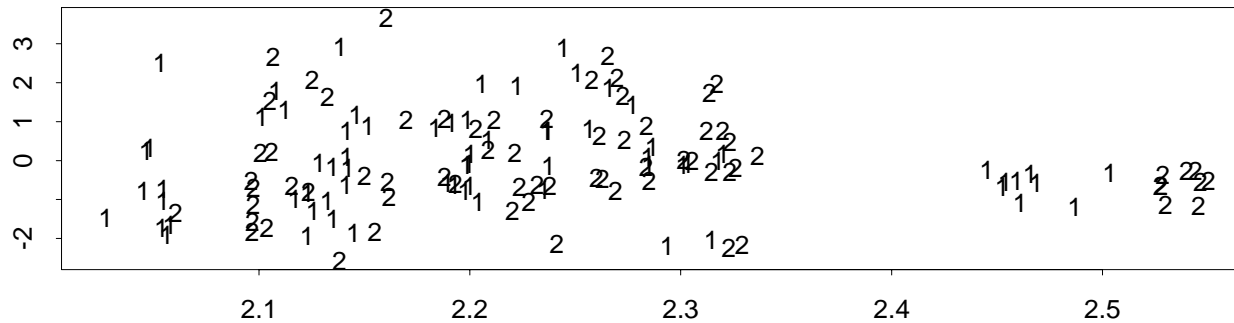
a) $y_r - E(y_r)$ versus $sd(y_r)$; plotting character indicates model number



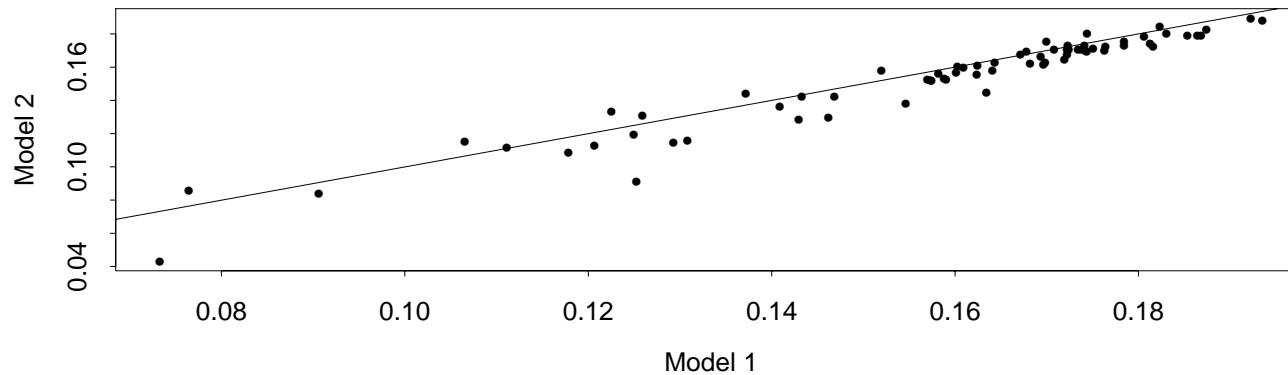
b) Comparison of CPO values

- reduction in r_{ij} from Model 2 (linear) to Model 1 (changepoint) is negligible
- CPO's are usually larger for Model 1, but not much

Residual and CPO comparison



a) $y_r - E(y_r)$ versus $sd(y_r)$; plotting character indicates model number



b) Comparison of CPO values

- reduction in r_{ij} from Model 2 (linear) to Model 1 (changepoint) is negligible
 - CPO's are usually larger for Model 1, but not much
- ⇒ CD4 counts adequately explained by the linear model!

CD4 “Boost” at Two Months

- Direct way of capturing the chance of a CD4 response:
Define $R_i = 1$ if $Y_{i2} - Y_{i1} \geq 0$, and $R_i = 0$ otherwise, for $i = 1, \dots, m = 367$.

CD4 “Boost” at Two Months

- Direct way of capturing the chance of a CD4 response: Define $R_i = 1$ if $Y_{i2} - Y_{i1} \geq 0$, and $R_i = 0$ otherwise, for $i = 1, \dots, m = 367$.
- Fit the **probit** regression model:

$$p_i \equiv P(R_i = 1|\gamma) = \Phi(\gamma_0 + \gamma_1 d_i + \gamma_2 a_i) ,$$

since calculations easy under a flat prior on γ

CD4 “Boost” at Two Months

- Direct way of capturing the chance of a CD4 response: Define $R_i = 1$ if $Y_{i2} - Y_{i1} \geq 0$, and $R_i = 0$ otherwise, for $i = 1, \dots, m = 367$.
- Fit the **probit** regression model:

$$p_i \equiv P(R_i = 1 | \gamma) = \Phi(\gamma_0 + \gamma_1 d_i + \gamma_2 a_i),$$

since calculations easy under a flat prior on γ

- **Results:**

	mode	95% LL	95% UL
γ_0 (intercept)	.120	-.135	.378
γ_1 (treatment)	.226	-.040	.485
γ_2 (AIDS Dx)	-.339	-.610	-.068

CD4 “Boost” at Two Months

- Direct way of capturing the chance of a CD4 response: Define $R_i = 1$ if $Y_{i2} - Y_{i1} \geq 0$, and $R_i = 0$ otherwise, for $i = 1, \dots, m = 367$.
- Fit the **probit** regression model:

$$p_i \equiv P(R_i = 1 | \gamma) = \Phi(\gamma_0 + \gamma_1 d_i + \gamma_2 a_i),$$

since calculations easy under a flat prior on γ

- **Results:**

	mode	95% LL	95% UL
γ_0 (intercept)	.120	-.135	.378
γ_1 (treatment)	.226	-.040	.485
γ_2 (AIDS Dx)	-.339	-.610	-.068

⇒ Boost more likely for patients without an AIDS Dx and (to a lesser extent) taking ddl

CD4 “Boost” at Two Months

- We can use the fitted probit model to transform our $\gamma^{(g)}$ Gibbs samples to the probability-of-response scale for a typical patient in each drug-diagnosis group

CD4 “Boost” at Two Months

- We can use the fitted probit model to transform our $\gamma^{(g)}$ Gibbs samples to the probability-of-response scale for a typical patient in each drug-diagnosis group
- **Results:**

	ddl	ddC
AIDS diagnosis at baseline	.502	.413
No AIDS diagnosis at baseline	.637	.550

CD4 “Boost” at Two Months

- We can use the fitted probit model to transform our $\gamma^{(g)}$ Gibbs samples to the probability-of-response scale for a typical patient in each drug-diagnosis group

- **Results:**

	ddl	ddC
AIDS diagnosis at baseline	.502	.413
No AIDS diagnosis at baseline	.637	.550

- Posterior median probability of a response is almost .09 larger for ddl

CD4 “Boost” at Two Months

- We can use the fitted probit model to transform our $\gamma^{(g)}$ Gibbs samples to the probability-of-response scale for a typical patient in each drug-diagnosis group

- **Results:**

	ddl	ddC
AIDS diagnosis at baseline	.502	.413
No AIDS diagnosis at baseline	.637	.550

- Posterior median probability of a response is almost .09 larger for ddl
- AIDS-negative patients have a .135 larger chance of responding than an AIDS-positive patient

CD4 “Boost” at Two Months

- We can use the fitted probit model to transform our $\gamma^{(g)}$ Gibbs samples to the probability-of-response scale for a typical patient in each drug-diagnosis group

- **Results:**

	ddl	ddC
AIDS diagnosis at baseline	.502	.413
No AIDS diagnosis at baseline	.637	.550

- Posterior median probability of a response is almost .09 larger for ddl
- AIDS-negative patients have a .135 larger chance of responding than an AIDS-positive patient
- **But** for even the best response group (AIDS-free ddl patients), there is a substantial estimated probability of **not** experiencing a boost

Survival Analysis

- Does the CD4 “boost” translate into an improvement in survival?

Survival Analysis

- Does the CD4 “boost” translate into an improvement in survival?
- To check, fit a **proportional hazards** model:

$$h(t|\mathbf{z}, \boldsymbol{\beta}) = h_0(t) \exp(\mathbf{z}'\boldsymbol{\beta})$$

where we employ the covariates

Survival Analysis

- Does the CD4 “boost” translate into an improvement in survival?
- To check, fit a **proportional hazards** model:

$$h(t|\mathbf{z}, \boldsymbol{\beta}) = h_0(t) \exp(\mathbf{z}'\boldsymbol{\beta})$$

where we employ the covariates

- $z_0 = 1$ for all patients

Survival Analysis

- Does the CD4 “boost” translate into an improvement in survival?
- To check, fit a **proportional hazards** model:

$$h(t|\mathbf{z}, \boldsymbol{\beta}) = h_0(t) \exp(\mathbf{z}'\boldsymbol{\beta})$$

where we employ the covariates

- $z_0 = 1$ for all patients
- $z_1 = 1$ for ddl patients with a CD4 response, and 0 otherwise

Survival Analysis

- Does the CD4 “boost” translate into an improvement in survival?
- To check, fit a **proportional hazards** model:

$$h(t|\mathbf{z}, \boldsymbol{\beta}) = h_0(t) \exp(\mathbf{z}'\boldsymbol{\beta})$$

where we employ the covariates

- $z_0 = 1$ for all patients
- $z_1 = 1$ for ddl patients with a CD4 response, and 0 otherwise
- $z_2 = 1$ for ddC patients without a CD4 response, and 0 otherwise

Survival Analysis

- Does the CD4 “boost” translate into an improvement in survival?
- To check, fit a **proportional hazards** model:

$$h(t|\mathbf{z}, \boldsymbol{\beta}) = h_0(t) \exp(\mathbf{z}'\boldsymbol{\beta})$$

where we employ the covariates

- $z_0 = 1$ for all patients
- $z_1 = 1$ for ddl patients with a CD4 response, and 0 otherwise
- $z_2 = 1$ for ddC patients without a CD4 response, and 0 otherwise
- $z_3 = 1$ for ddC patients with a CD4 response, and 0 otherwise

Survival Analysis

- Loglikelihood (Cox and Oakes, 1984):

$$\log L(\boldsymbol{\beta}) = \sum_{i \in \mathcal{U}} \log h(t_i | \mathbf{z}_i, \boldsymbol{\beta}) + \sum_{i=1}^m \log S(t_i | \mathbf{z}_i, \boldsymbol{\beta}) ,$$

where

Survival Analysis

- Loglikelihood (Cox and Oakes, 1984):

$$\log L(\boldsymbol{\beta}) = \sum_{i \in \mathcal{U}} \log h(t_i | \mathbf{z}_i, \boldsymbol{\beta}) + \sum_{i=1}^m \log S(t_i | \mathbf{z}_i, \boldsymbol{\beta}) ,$$

where

- h denotes the **hazard** function

Survival Analysis

- Loglikelihood (Cox and Oakes, 1984):

$$\log L(\boldsymbol{\beta}) = \sum_{i \in \mathcal{U}} \log h(t_i | \mathbf{z}_i, \boldsymbol{\beta}) + \sum_{i=1}^m \log S(t_i | \mathbf{z}_i, \boldsymbol{\beta}) ,$$

where

- h denotes the **hazard** function
- S denotes the **survival** function

Survival Analysis

- Loglikelihood (Cox and Oakes, 1984):

$$\log L(\boldsymbol{\beta}) = \sum_{i \in \mathcal{U}} \log h(t_i | \mathbf{z}_i, \boldsymbol{\beta}) + \sum_{i=1}^m \log S(t_i | \mathbf{z}_i, \boldsymbol{\beta}) ,$$

where

- h denotes the **hazard** function
- S denotes the **survival** function
- \mathcal{U} the collection of **uncensored** failure times (**observed deaths**), and

Survival Analysis

- Loglikelihood (Cox and Oakes, 1984):

$$\log L(\boldsymbol{\beta}) = \sum_{i \in \mathcal{U}} \log h(t_i | \mathbf{z}_i, \boldsymbol{\beta}) + \sum_{i=1}^m \log S(t_i | \mathbf{z}_i, \boldsymbol{\beta}) ,$$

where

- h denotes the **hazard** function
- S denotes the **survival** function
- \mathcal{U} the collection of **uncensored** failure times (**observed deaths**), and
- $\mathbf{z}_i = (z_{0i}, z_{1i}, z_{2i}, z_{3i})'$

Survival Analysis

- Loglikelihood (Cox and Oakes, 1984):

$$\log L(\boldsymbol{\beta}) = \sum_{i \in \mathcal{U}} \log h(t_i | \mathbf{z}_i, \boldsymbol{\beta}) + \sum_{i=1}^m \log S(t_i | \mathbf{z}_i, \boldsymbol{\beta}) ,$$

where

- h denotes the **hazard** function
 - S denotes the **survival** function
 - \mathcal{U} the collection of **uncensored** failure times (**observed deaths**), and
 - $\mathbf{z}_i = (z_{0i}, z_{1i}, z_{2i}, z_{3i})'$
- Our parametrization uses nonresponding ddl patients as a reference group; β_1, β_2 , and β_3 capture the effect of being in one of the other 3 drug-response groups.

Survival Analysis

- Begin with a parametric baseline hazard, say **Weibull**:

$$h_0(t) = \rho t^{\rho-1}$$

Survival Analysis

- Begin with a parametric baseline hazard, say **Weibull**:

$$h_0(t) = \rho t^{\rho-1}$$

- **Result:** extremely high posterior correlation between ρ and β_0 ! So **fix $\rho = 1$** (return to constant baseline hazard, i.e., an **exponential** survival model).

Survival Analysis

- Begin with a parametric baseline hazard, say **Weibull**:

$$h_0(t) = \rho t^{\rho-1}$$

- **Result:** extremely high posterior correlation between ρ and β_0 ! So **fix** $\rho = 1$ (return to constant baseline hazard, i.e., an **exponential** survival model).
- Resulting posterior quantiles:

	median	95% LL	95% UL
β_0 (baseline)	-7.00	-7.34	-6.67
β_1 (ddl resp)	-.07	-.54	.38
β_2 (ddC nonresp)	.06	-.39	.53
β_2 (ddC resp)	-.53	-1.10	.02

Survival Analysis

- Begin with a parametric baseline hazard, say **Weibull**:

$$h_0(t) = \rho t^{\rho-1}$$

- **Result:** extremely high posterior correlation between ρ and β_0 ! So **fix** $\rho = 1$ (return to constant baseline hazard, i.e., an **exponential** survival model).
- Resulting posterior quantiles:

	median	95% LL	95% UL
β_0 (baseline)	-7.00	-7.34	-6.67
β_1 (ddl resp)	-.07	-.54	.38
β_2 (ddC nonresp)	.06	-.39	.53
β_2 (ddC resp)	-.53	-1.10	.02

⇒ only the **ddC responders** seem different!

Survival Analysis

- Typical nice feature of parametric MCMC analysis:
Our posterior $\gamma^{(g)}$ samples may be easily transformed to investigate:

Survival Analysis

- Typical nice feature of parametric MCMC analysis:
Our posterior $\gamma^{(g)}$ samples may be easily transformed to investigate:
 - the survival function at time t :

$$S(t|\mathbf{z}, \boldsymbol{\beta}) = \exp\{-t \exp(\mathbf{z}'\boldsymbol{\beta})\} ,$$

or

Survival Analysis

- Typical nice feature of parametric MCMC analysis:
Our posterior $\gamma^{(g)}$ samples may be easily transformed to investigate:

- the survival function at time t :

$$S(t|\mathbf{z}, \boldsymbol{\beta}) = \exp\{-t \exp(\mathbf{z}'\boldsymbol{\beta})\} ,$$

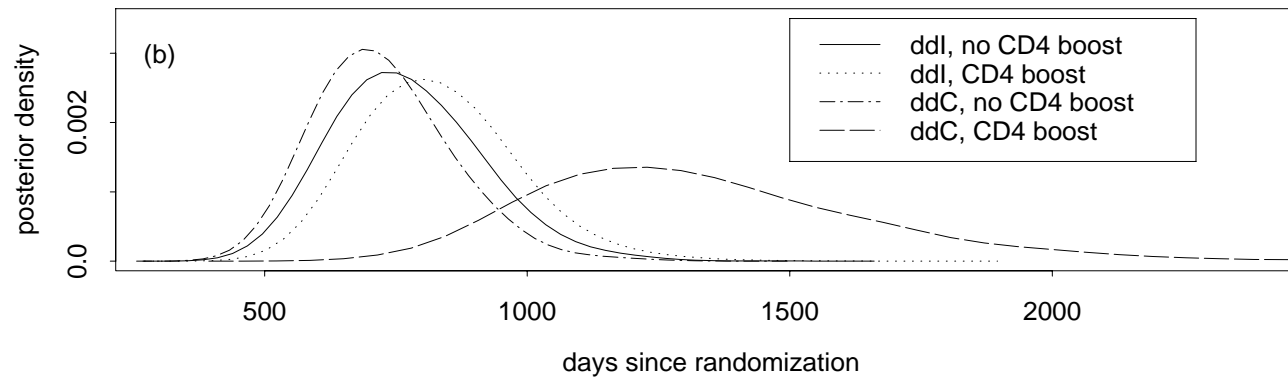
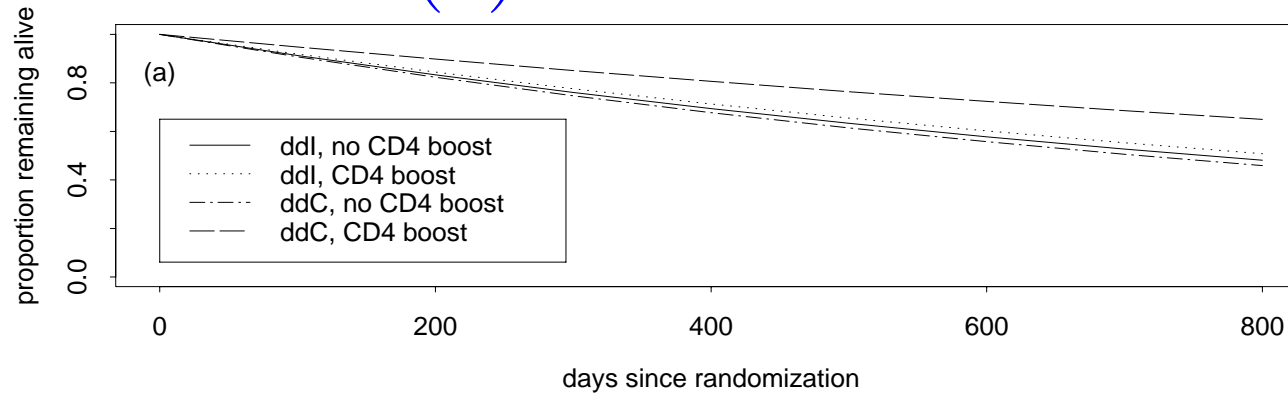
or

- the median survival time:

$$\theta(\mathbf{z}, \boldsymbol{\beta}) = (\log 2) \exp(-\mathbf{z}'\boldsymbol{\beta})$$

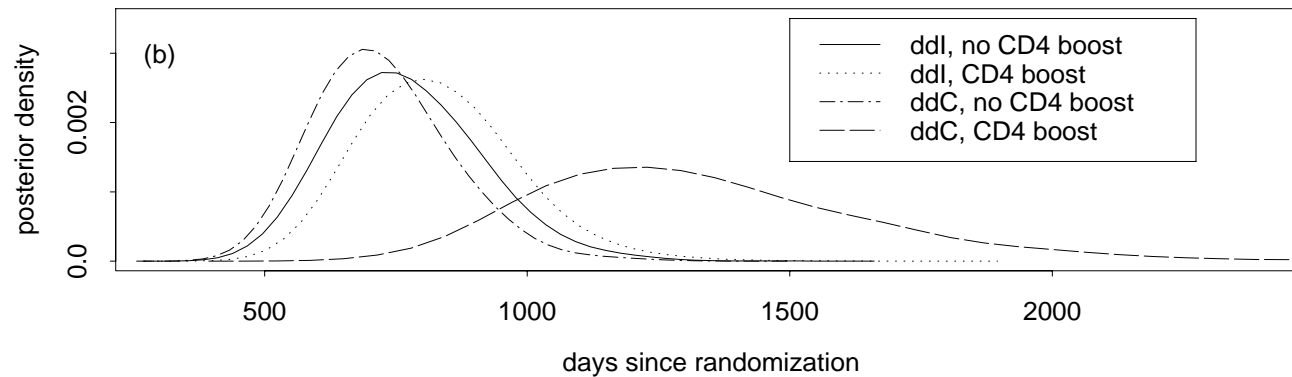
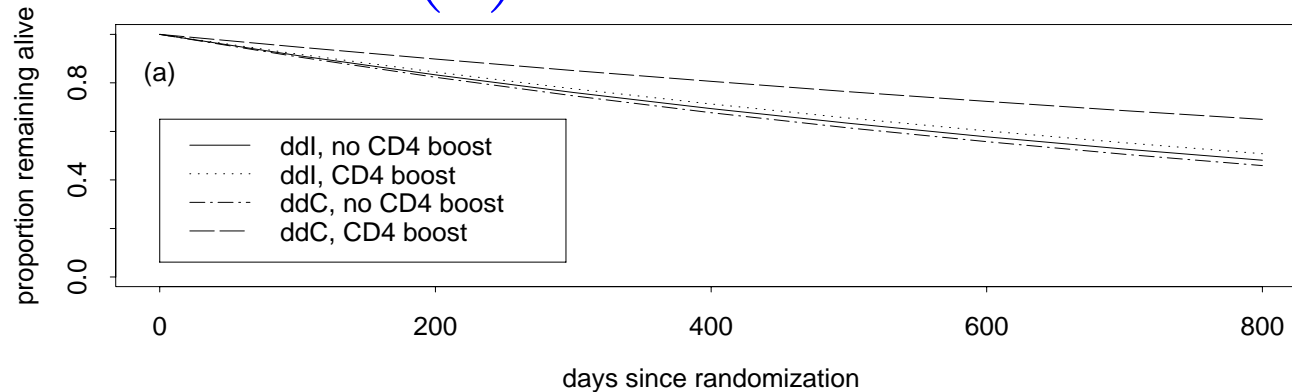
(set $S(t|\mathbf{z}, \boldsymbol{\beta}) = 1/2$ and solve for t)

Estimated $S(t)$ and median survival



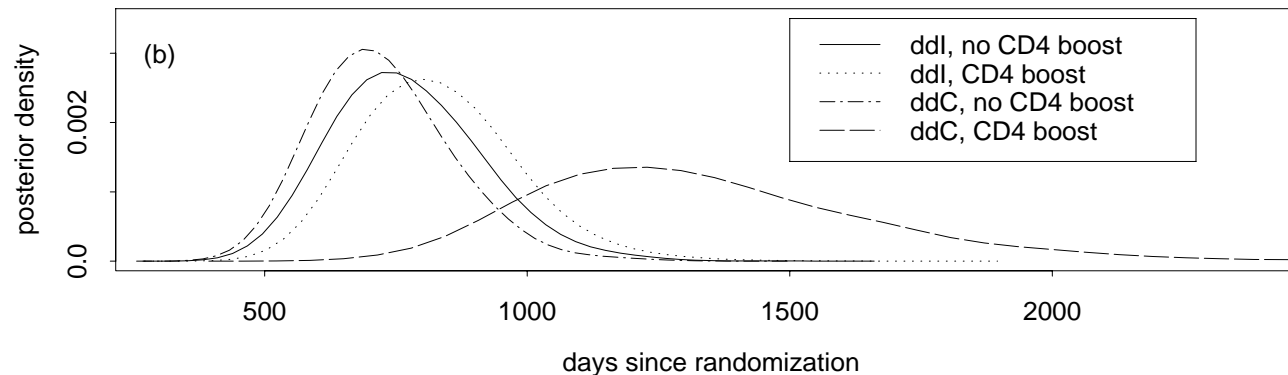
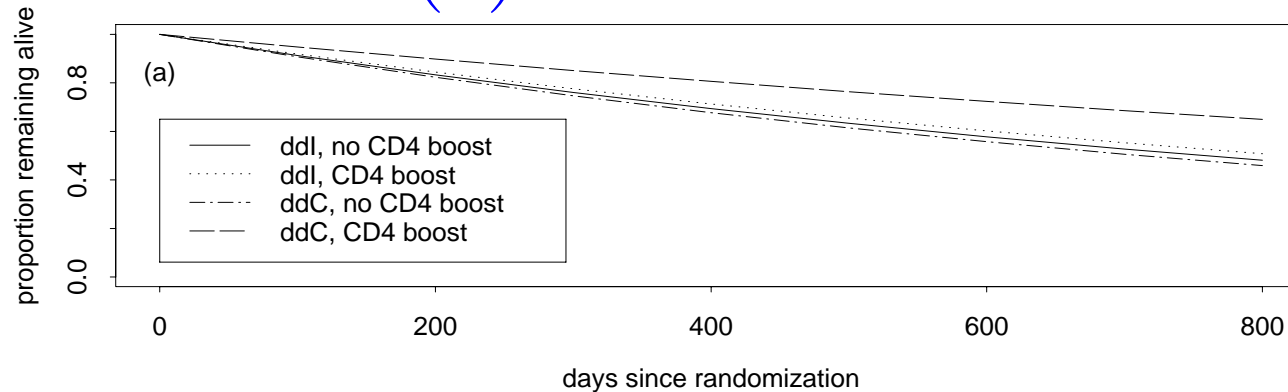
● Fitted survival for **ddC responders** stands out

Estimated $S(t)$ and median survival



- Fitted survival for **ddC responders** stands out
- Difference is even more dramatic on the median survival time scale (lower panel)

Estimated $S(t)$ and median survival



- Fitted survival for **ddC responders** stands out
 - Difference is even more dramatic on the median survival time scale (lower panel)
- ⇒ Clinically significant improvement in survival **only** for **ddC** patients experiencing a boost!

Conclusions

- ddC is less successful than ddI in producing a CD4 boost in patients with advanced HIV infection, **BUT...**

Conclusions

- ddC is less successful than ddI in producing a CD4 boost in patients with advanced HIV infection, **BUT...**
- This superior CD4 performance does **not** seem to translate into improved survival.

Conclusions

- ddC is less successful than ddI in producing a CD4 boost in patients with advanced HIV infection, **BUT...**
- This superior CD4 performance does **not** seem to translate into improved survival.
- That is, CD4 is **prognostic**, but **not a surrogate endpoint**.

Conclusions

- ddC is less successful than ddI in producing a CD4 boost in patients with advanced HIV infection, **BUT...**
- This superior CD4 performance does **not** seem to translate into improved survival.
- That is, CD4 is **prognostic**, but **not** a **surrogate endpoint**.
- **Recommendations**

Conclusions

- ddC is less successful than ddI in producing a CD4 boost in patients with advanced HIV infection, **BUT...**
- This superior CD4 performance does **not** seem to translate into improved survival.
- That is, CD4 is **prognostic**, but **not a surrogate endpoint**.
- **Recommendations**
 - Rethink the practice of licensing drugs based primarily on an increase in CD4 count.

Conclusions

- ddC is less successful than ddI in producing a CD4 boost in patients with advanced HIV infection, **BUT...**
- This superior CD4 performance does **not** seem to translate into improved survival.
- That is, CD4 is **prognostic**, but **not** a **surrogate endpoint**.
- **Recommendations**
 - Rethink the practice of licensing drugs based primarily on an increase in CD4 count.
 - Review the use of these drugs with end-stage patients (**low efficacy, unpleasant side effects**)

Conclusions

- ddC is less successful than ddI in producing a CD4 boost in patients with advanced HIV infection, **BUT...**
- This superior CD4 performance does **not** seem to translate into improved survival.
- That is, CD4 is **prognostic**, but **not a surrogate endpoint**.
- **Recommendations**
 - Rethink the practice of licensing drugs based primarily on an increase in CD4 count.
 - Review the use of these drugs with end-stage patients (**low efficacy, unpleasant side effects**)
 - Reconsider placebo trials?!?

Medical journal references:

- **“Main paper”**: ABRAMS, D.I., GOLDMAN, A.I., ET AL. (1994). Comparative trial of didanosine and zalcitabine in patients with human immunodeficiency virus infection who are intolerant of or have failed zidovudine therapy. *New England Journal of Medicine*, **330**, 657–662.

Medical journal references:

- **“Main paper”**: ABRAMS, D.I., GOLDMAN, A.I., ET AL. (1994). Comparative trial of didanosine and zalcitabine in patients with human immunodeficiency virus infection who are intolerant of or have failed zidovudine therapy. *New England Journal of Medicine*, **330**, 657–662.
- **Bayesian followup paper**: GOLDMAN, A.I., CARLIN, B.P., CRANE, L.R., LAUNER, C., KORVICK, J.A., DEYTON, L., AND ABRAMS, D.I. (1996). Response of CD4 lymphocytes and clinical consequences of treatment using ddl or ddC in patients with advanced HIV infection. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, **11**, 161–169.