Estimation of natural HIV disease progression incorporating unknown infection dates

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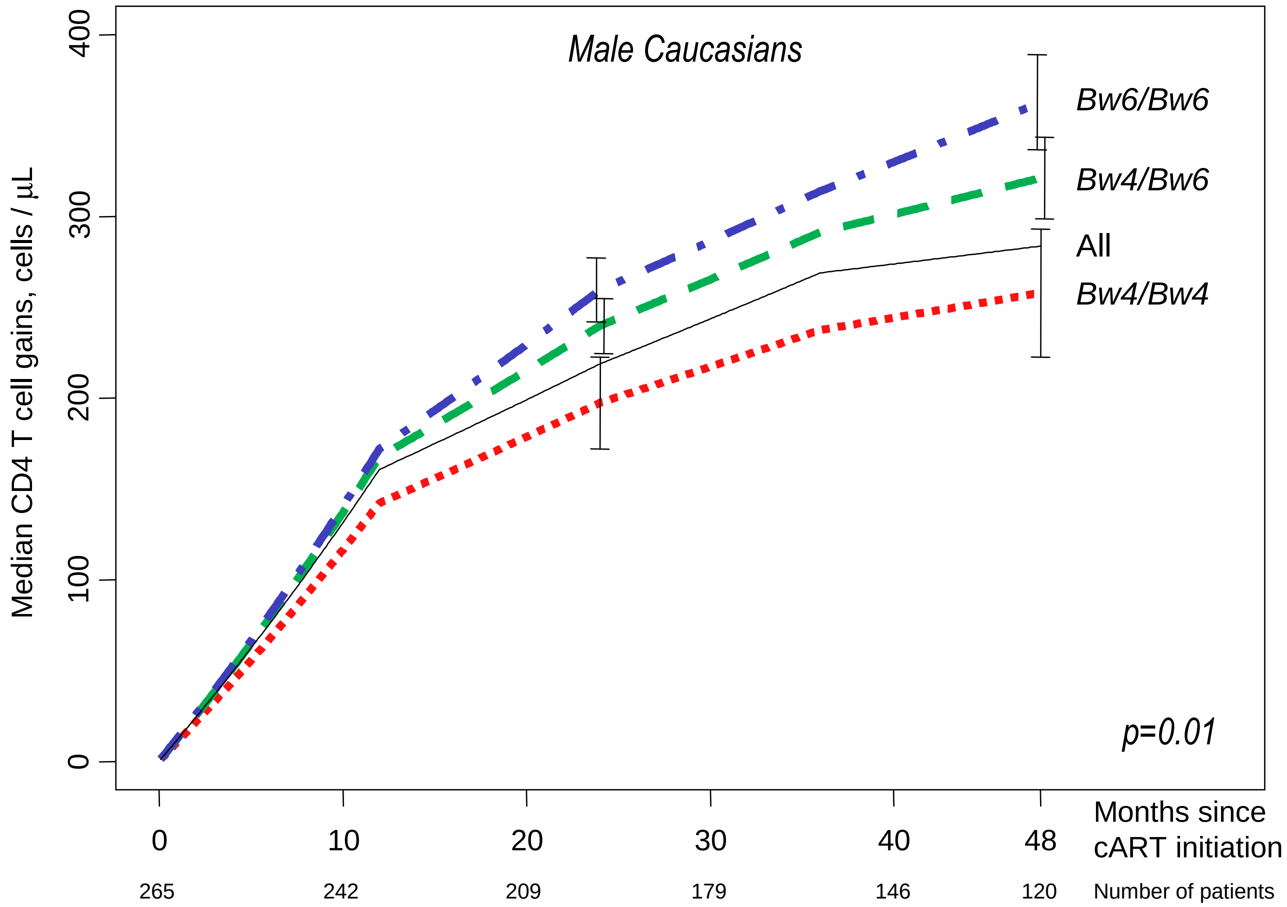
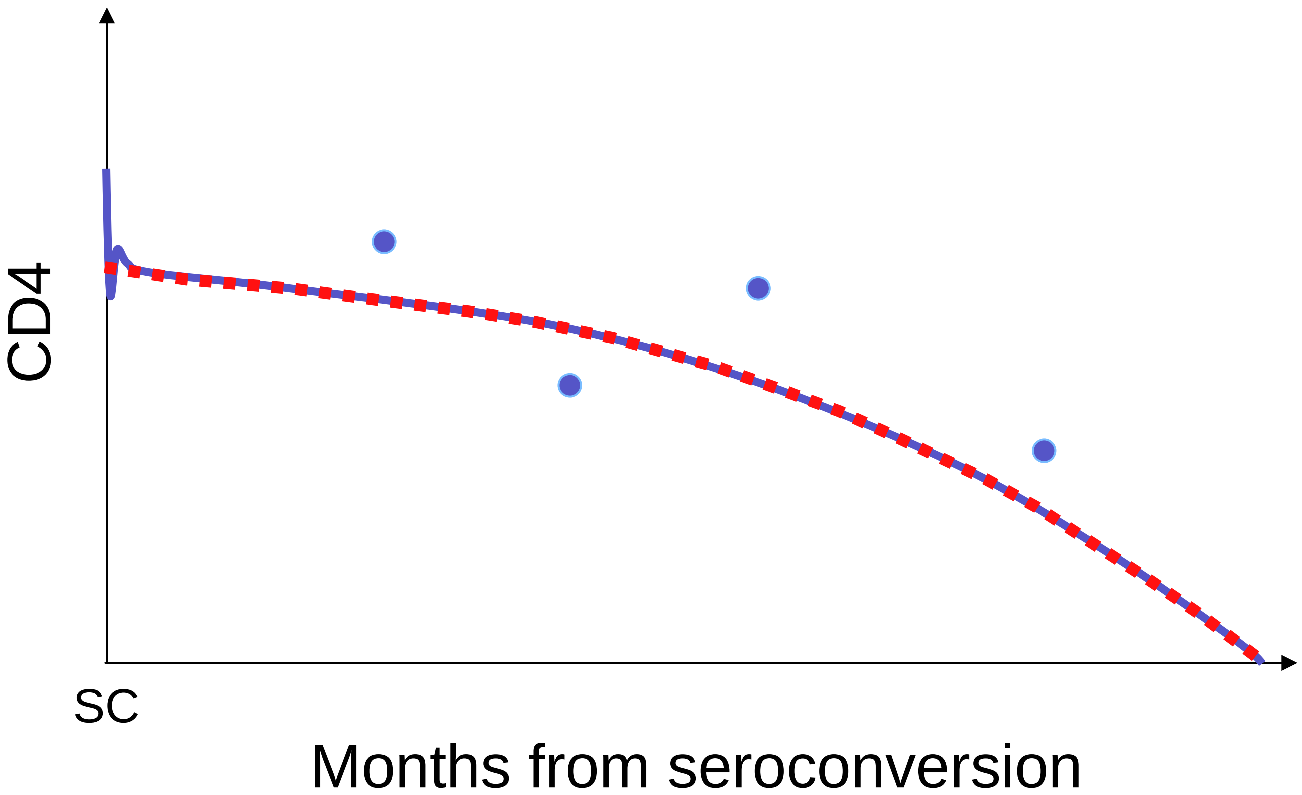
Carriage of HLA-Bw4 alleles is associated with inferior post-ART recovery despite apparently better natural progression



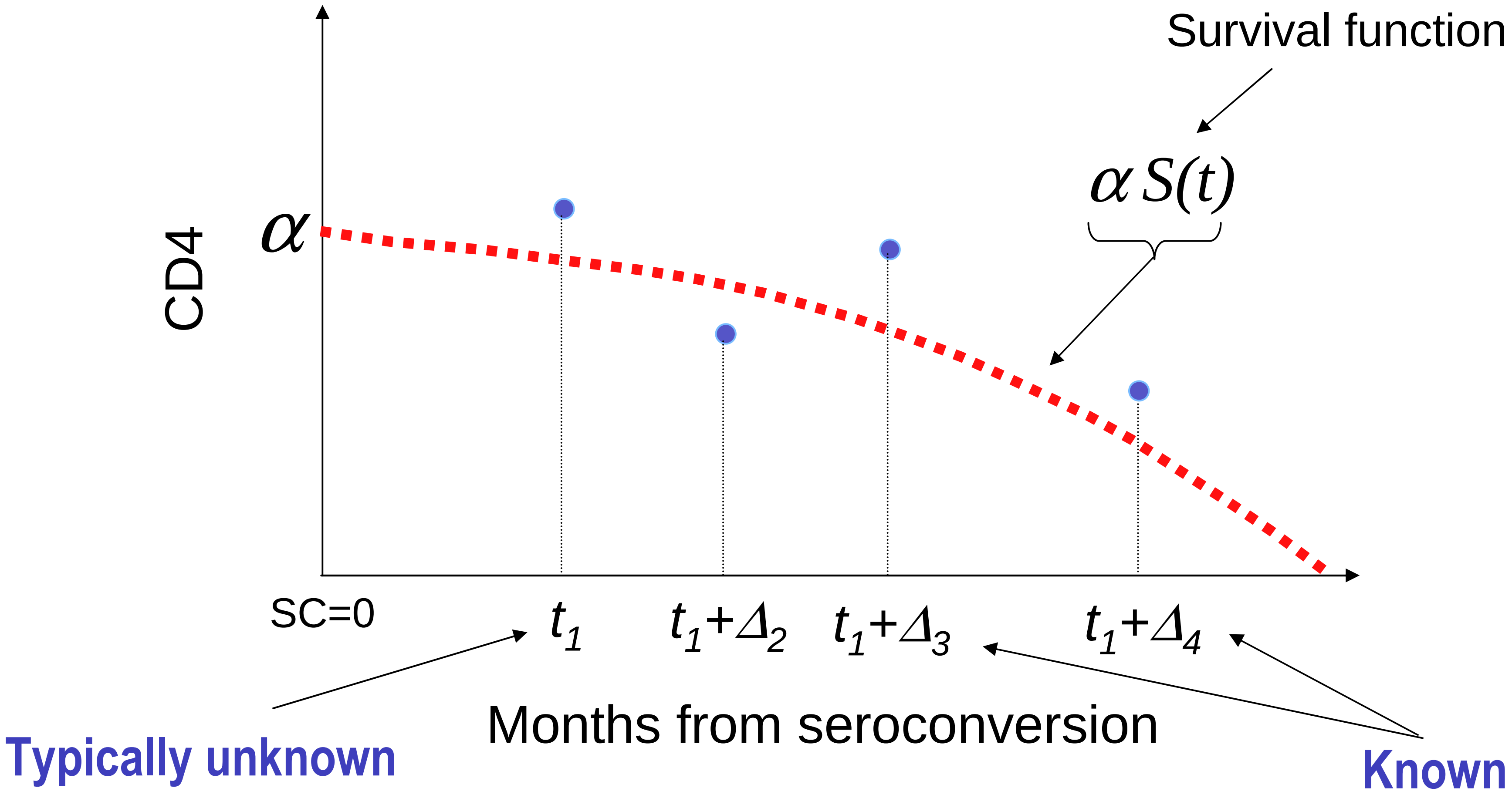
Rauch et al (2008) CID ***46****, 1921-5.*

Natural CD4% progression – from first CD4

For a single individual:



For a single individual:



cf. seroconverters

Model:

$$y_i = \alpha S(t_1 + \Delta_i) + \varepsilon_i$$

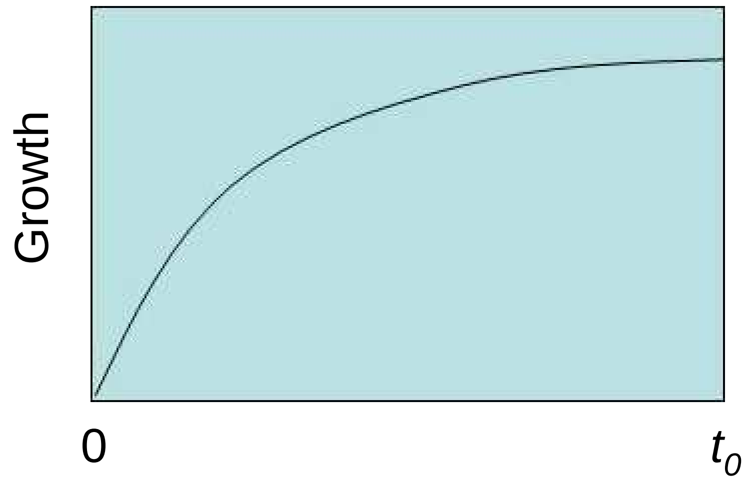
Individual specific
(random effects)

Covariates

eg. “reverse” von Bertalanffy

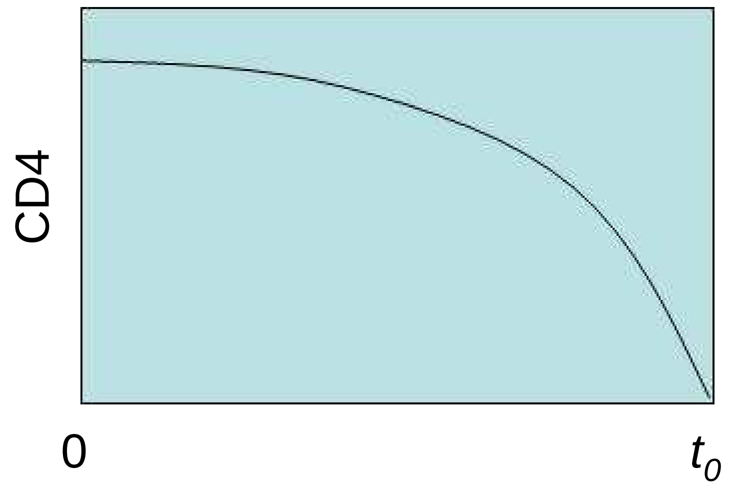
$$y_i = \alpha^* (1 - \exp(-k[t_0 - t_i])) + \varepsilon_i$$

von Bertalanffy

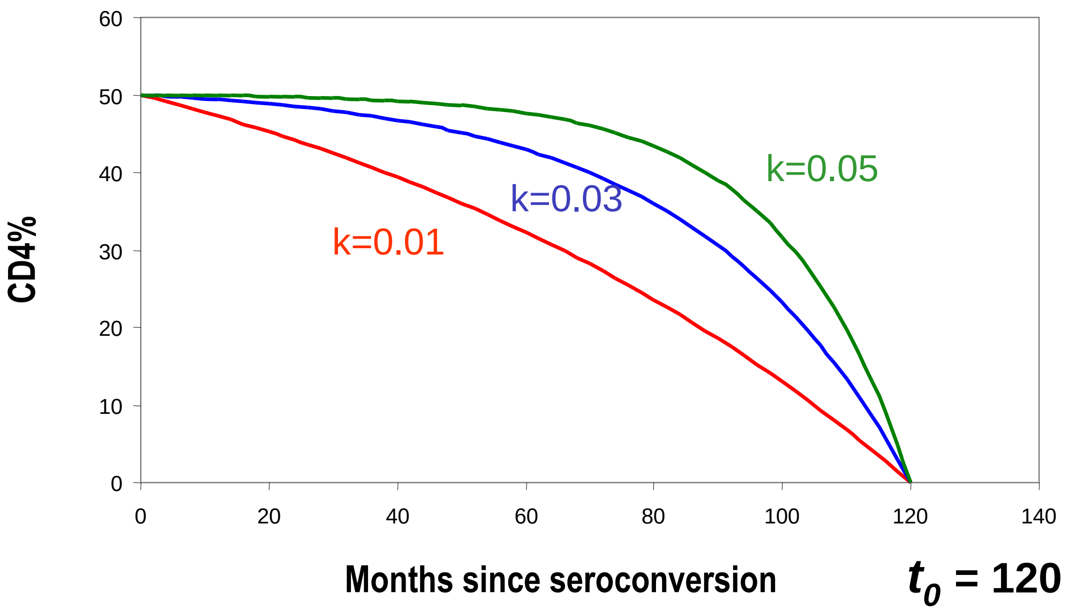


Rate of growth proportional to remaining growth

“reverse” von Bertalanffy



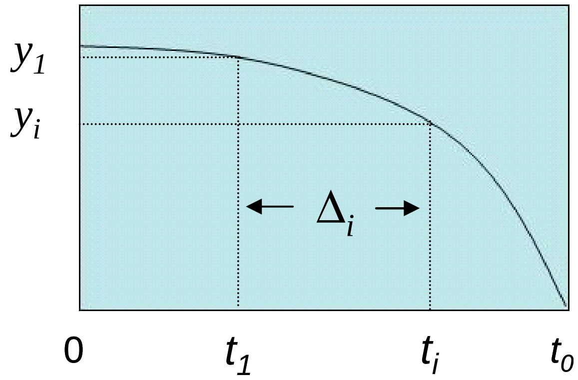
Rate of decline proportional to current “loss”



Estimating equation:

$$\eta_i = (y_1 - y_i) - (\alpha^* - y_i)(1 - \exp(-k\Delta_i))$$

$$E(\eta_i) = 0$$ if k is ~ non-random.



Solve $X^T \eta = 0$

➔ consistent estimates

Inferential properties from general estimating equation theory – **requires only 2 measures/person**

James, *Biometrics* 1991

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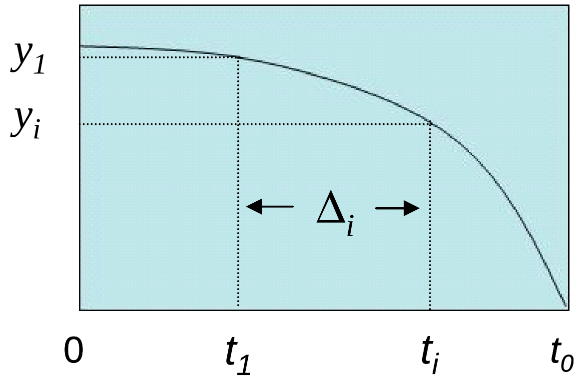
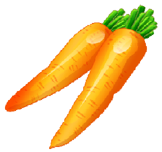


Solve  $^T \eta = 0$

➔ consistent estimates

Inferential properties from general estimating equation theory – **requires only 2 measures/person**

James, *Biometrics* 1991

eg. $x = 1$ *if carry Bw4, 0 if not*

$$\alpha^* = \exp(\alpha_1 + \alpha_2 x) \qquad \alpha_1 (k_1 ?)$$

$$k = \exp(k_1 + k_2 x)$$

individual specific

Solve

$$\sum \eta_i = 0 \qquad \sum \Delta_i \eta_i = 0$$

$$\sum x_i \eta_i = 0 \qquad \sum x_i \Delta_i \eta_i = 0$$

Optimality?

Non-linear mixed model:

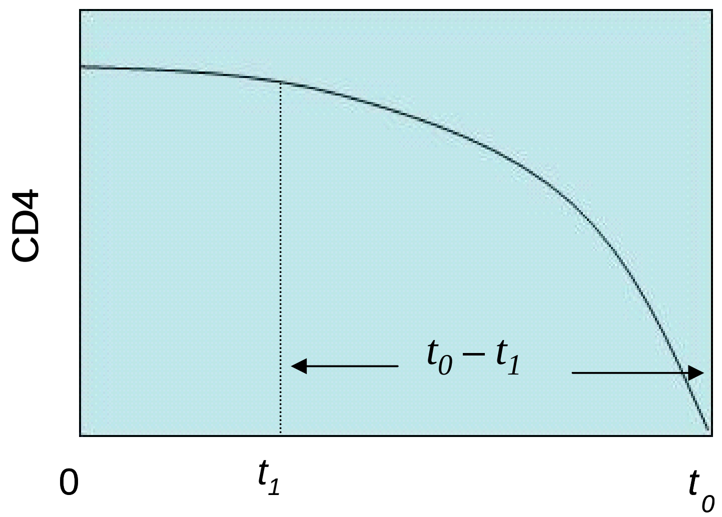
$$y_i = \alpha^* (1 - \exp(-k[\underbrace{t_0 - t_1}_{\text{random effect}} - \Delta_i])) + \varepsilon_i$$

random effect

Assume log-linear effects as before

↓

S+ / R / SAS ….



cf. Palmer *et al*, *Biometrics* 1991
Taffe & May, *Stats. Med.* 2008

Incorporating known seroconverter dates:

Unknown seroconversion date:

$$y_i = \alpha^* (1 - \exp(-k[\underbrace{t_0 - t_1}_{\text{RE}} - \underbrace{\Delta_i}_{\text{fixed}}])) + \varepsilon_i$$

Known seroconversion date:

$$y_i = \alpha^* (1 - \exp(-k[\underbrace{t_0}_{\text{RE}} - \underbrace{t_1 - \Delta_i}_{\text{fixed}}])) + \varepsilon_i$$

Combine using indicators - possibly different parameters in each case

Example:

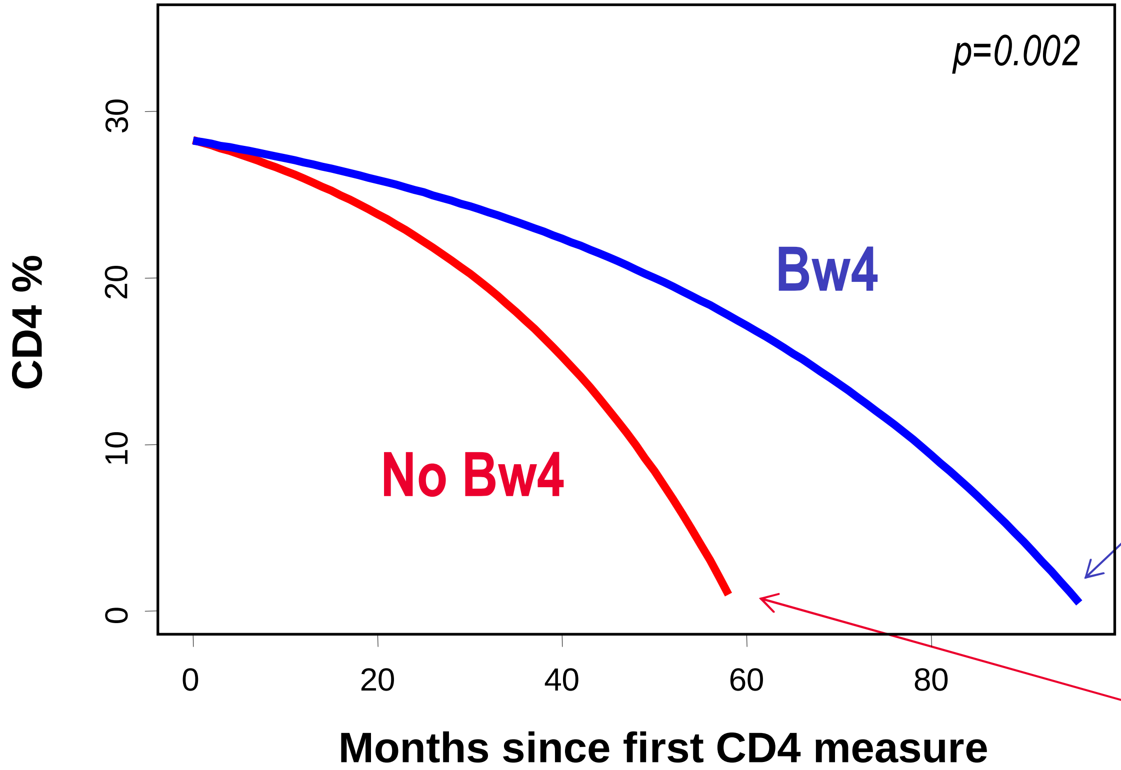
115 Caucasian males from WAHIV with at least 4 pre-ART CD4% measures over at least 12 months, no seroconversion date and went onto treatment.

- 70 carry Bw4, 45 no Bw4
- average 13.4 measurements per case

Example:

	Value	SE	P
$\log(\alpha^*)$	3.50	0.04	
$\log(t_0-t_1)$	4.08	0.09	
$\log(k)$	-3.42	0.14	
k.Bw4	-0.50	0.15	0.0012
t_0-t_1.Bw4	0.50	0.11	<0.0001

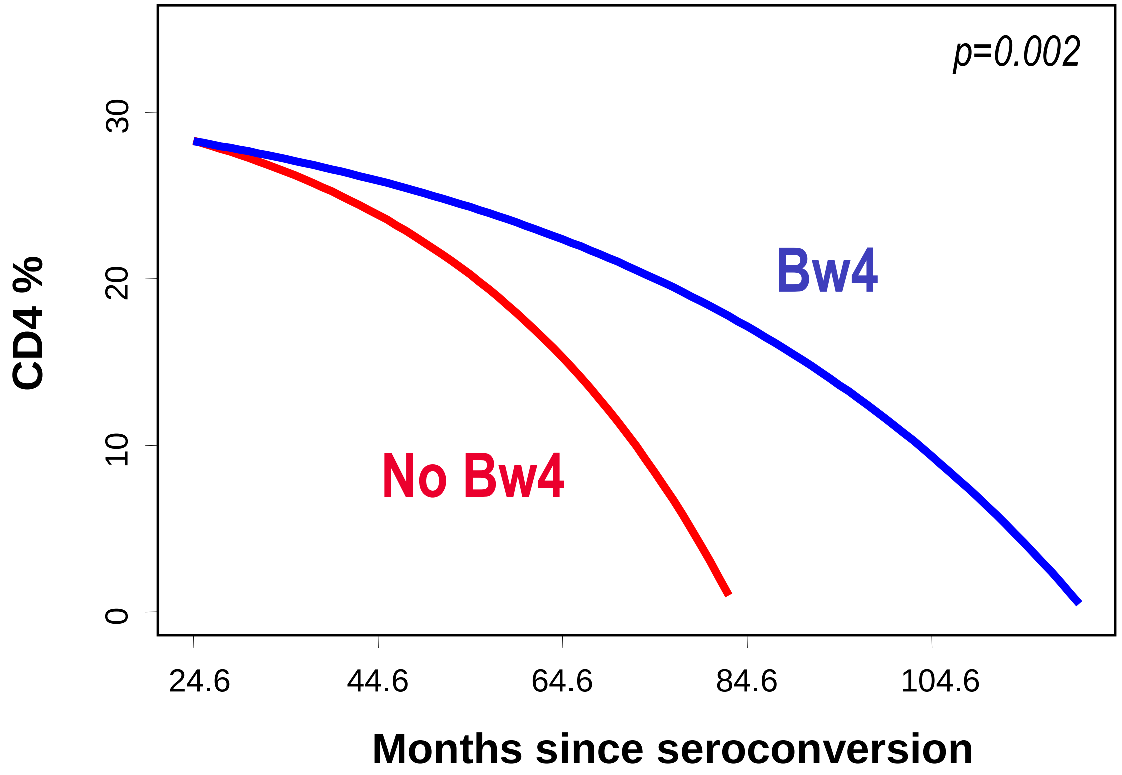
(asymptote p>0.5)



slope –0.66

slope –1.08

IF we believed SC and non-SC have same natural progression:



Median t_1: SC 5.1 mths Non-SC 24.6 mths

Estimating equation *vs* mixed model:

- First and last measurements only for estimating equation
- All measurements for NLME

	Est. Equ.	NLME
$\log(\alpha^*)$	3.40 (0.05)	3.50 (0.04)
log(k)	-2.37 (1.05)	-3.42 (0.14)
k.Bw4	-0.75 (1.37)	-0.50 (0.15)

Thank you