

BIOSTAT/STAT 587 A

Estimation of subtype-specific
infectiousness of HIV

Lecture 18

March 5, 2009

References

- Hudgens, M.G., Longini, I.M., Halloran, *et al.*: Estimating the HIV transmission probability in injecting drug users in Thailand. *Applied Statistics* **50**, 1-14 (2001)
- Hudgens, M.G., Satten, G.A. and Longini, I.M.: Nonparametric maximum likelihood estimation for competing risks survival data subject to interval censoring and truncation. *Biometrics* **57**, 74-80 (2001).
- Hudgens, M.G., Longini, I.M., *et al.*: Subtype-specific transmission probabilities for Human Immunodeficiency virus type 1 among injecting drug users in Bangkok, Thailand. *American Journal of Epidemiology* **155**, 159-168 (2002).
- Yang, Y., Gilbert, P., Longini, I.M. and Halloran, M.E.: Estimating vaccine efficacy per infectious contact: A Bayesian framework with adjustment for measurement error. *Annals of Applied Statistics* **2**, 1409-1431 (2008).

env
Surface Glycoprotein SU
gp120

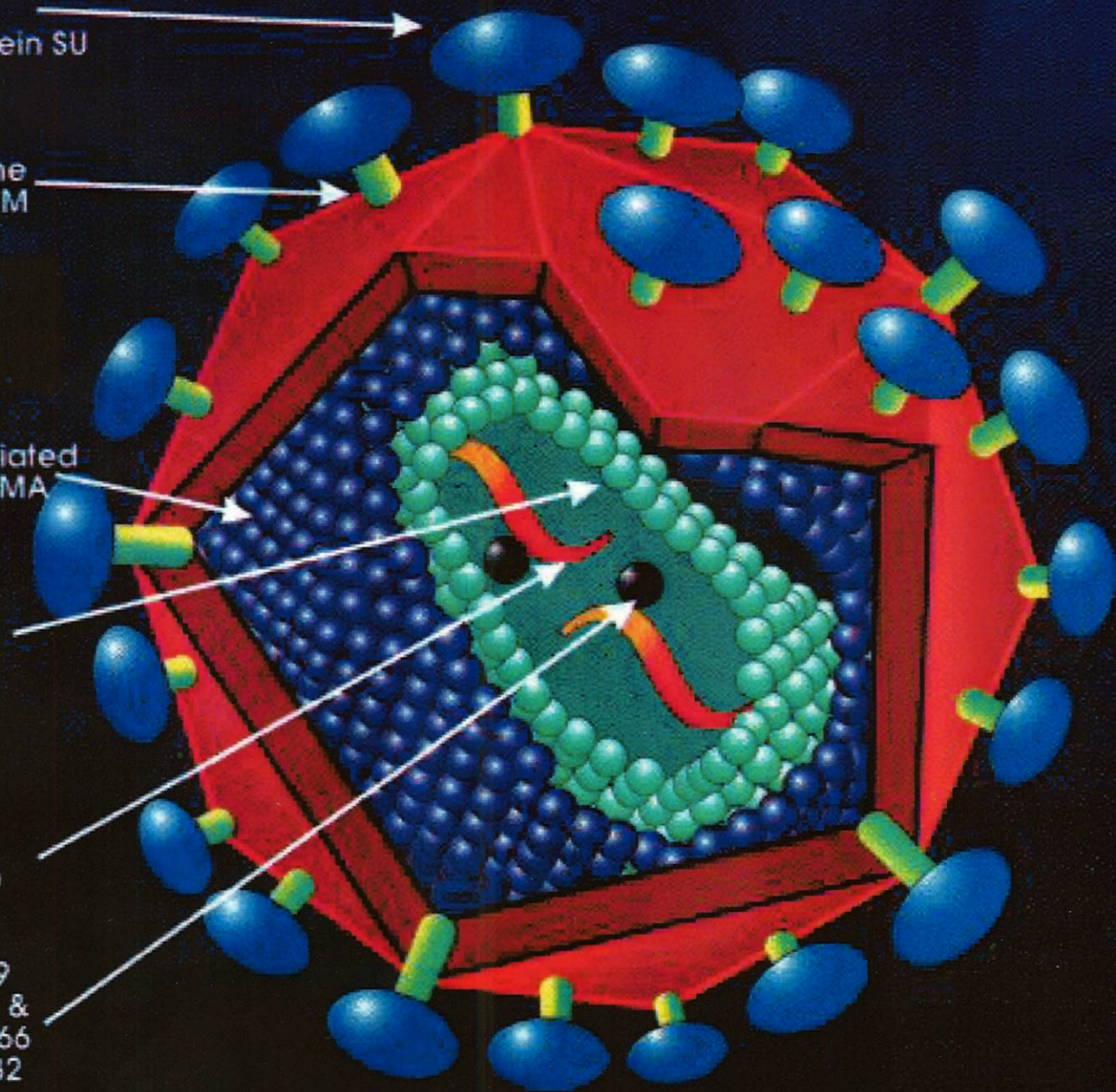
env
Transmembrane
Glycoprotein TM
gp41

gag
Membrane Associated
(Matrix) Protein MA
p17

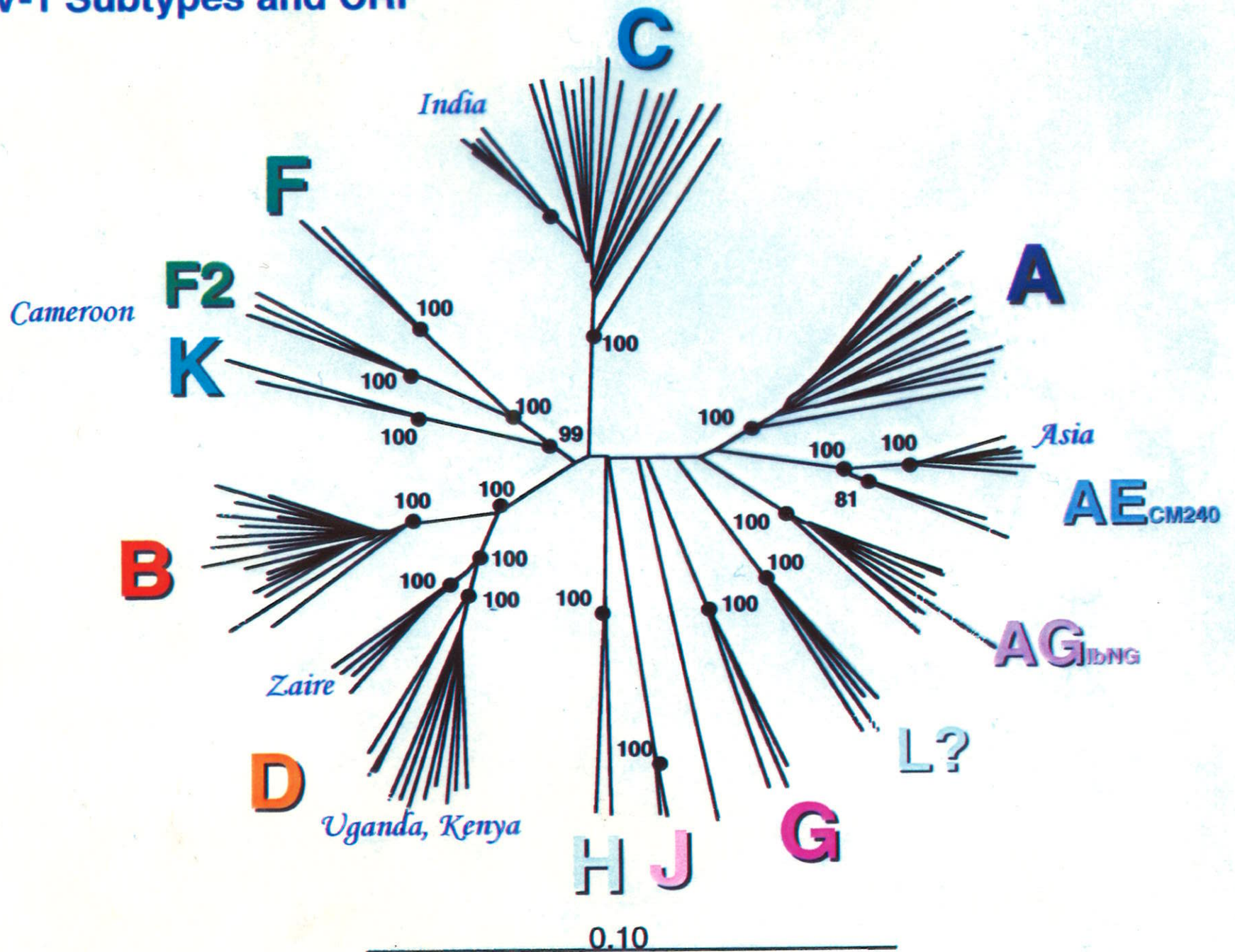
gag
Capsid CA
(Core Shell)
p24

RNA
(2 molecules)

pol
Protease PR p9
Polymersase RT &
RNase H RNH p66
Integrase IN p32



HIV-1 Subtypes and CRF



GOALS

- Evaluate the important risk factors for the transmission of subtypes B and E
- Estimate the subtype B and E specific transmission probabilities
- Evaluate the factors governing the transmission differences of subtypes B and E
 - Transmission probabilities
 - Dynamics of infection
- Estimate HIV vaccine efficacy
 - Phase III GP120 Vaccine Trial in Thailand
3/99 - 8/2003

10U's

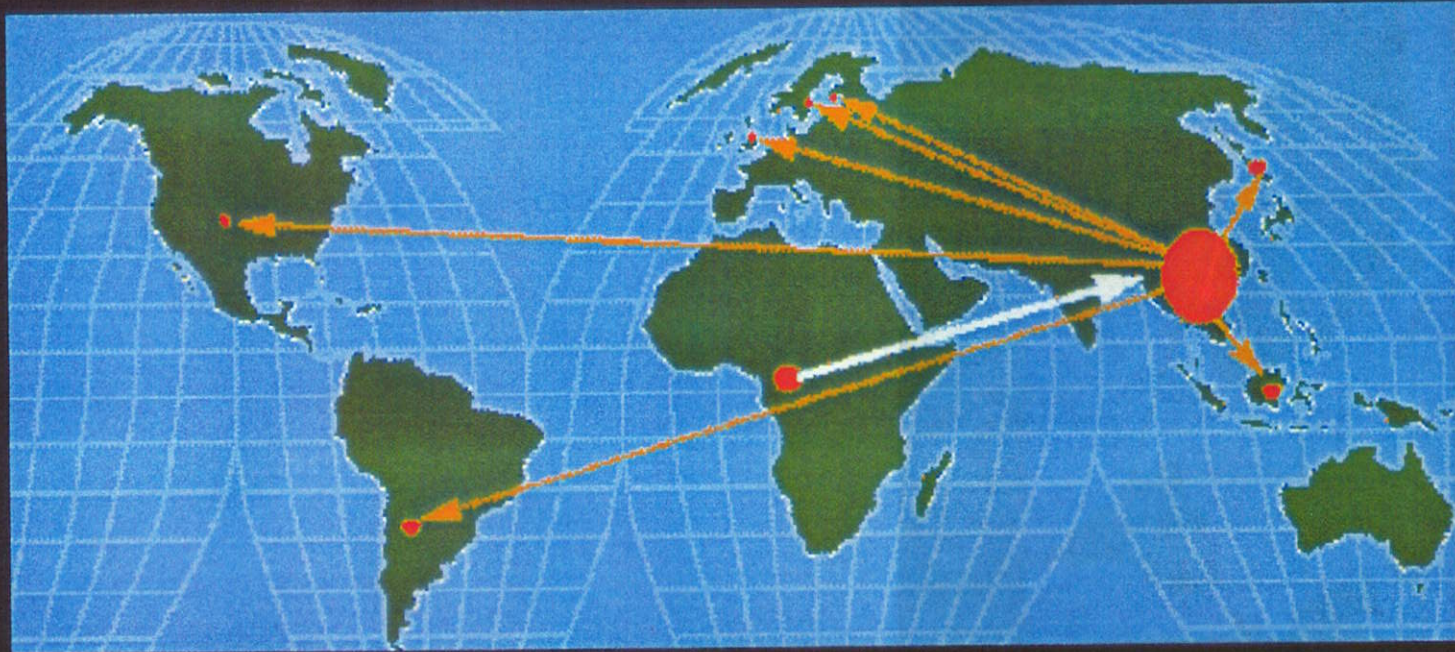
THAILAND

1993
20%



1998
80%

Subtype E recombinant HIV



CENTRAL AFRICAN REPUBLIC

SUBTYPE E \longrightarrow B

Early 1990's

Hetero.

IDU

80% B

100% E

20% E



Late 1990's

IDU

20% B

80% E

TRANSMISSION

Infection hazard rate:

Incidence = contact rate \times trans. prob. \times prev. infect.

$$\lambda(t|c(t)) = c(t) p \pi(t) \rightarrow \frac{I(t)}{h}$$

- epidemic dynamics are expressed through $\pi(t)$

Basic Reproductive Number:

$$R_0 = \int c p D$$

if $R_0 \leq 1$, then transmission is cut off

$$\lambda(t_{ij}|c_{ij}) = c_{ij} p \pi$$

$$\Delta(t_{ij}|c_{ij}) = c_{ij} p \pi t_{ij}$$

$$P_r(S_{ij} = 0 | c_{ij}) = e^{-\Delta(t_{ij}|c_{ij})}$$

MULTITYPE-SPECIFIC TRANSMISSION

Suppose we have J subtypes or categories
based on genetic distance

$$\lambda_j(t | c(t)) = c(t)p_j\pi_j(t), \quad j = 1, \dots, J$$

$$\lambda(t | c(t)) = \sum_{j=1}^J \lambda_j(t | c(t))$$

$$S(t) = e^{-\Lambda(t)} = \prod_{j=1}^J e^{-\Lambda_j(t)}$$

e.g., B, E, not typed, $J = 3$.

e.g., ordered genetic distances from V3 loop

SUBTYPE-SPECIFIC TRANSMISSION
(continued)

$$\Lambda_B(t) = p_B \int_0^t c(\tau) \pi_B(\tau) d\tau$$

$$\Lambda_E(t) = p_E \int_0^t c(\tau) \pi_E(\tau) d\tau$$

$$\Lambda(t) = \Lambda_B(t) + \Lambda_E(t)$$

$$S(t) = e^{-\Lambda(t)} = e^{-\Lambda_B(t)} e^{-\Lambda_E(t)}$$

MARGINAL PROBABILITY OF FAILURE

Cumulative incidence functions

$$I_B(t|c(t)) = \int \lambda_B(\tau|c(\tau)) S(\tau) d\tau$$

$$I_E(t|c(t)) = \int \lambda_E(\tau|c(\tau)) S(\tau) d\tau$$

Spline regression

- Hazard at time t for failure type j modeled by spline

$$\lambda_j(t|\boldsymbol{\alpha}) = \sum_{k=-3}^K B_k(t) \exp(\alpha_{jk}),$$

where $B_k(t)$ are basis functions (Rosenberg, 1995)

- Overall survival function

$$S(t|\boldsymbol{\alpha}) = \exp \left\{ - \int_0^t \sum_j \lambda_j(\tau|\boldsymbol{\alpha}) d\tau \right\}$$

- Cumulative incidence function

$$F_j(t|\boldsymbol{\alpha}) = \int_0^t \lambda_j(\tau|\boldsymbol{\alpha}) S(\tau|\boldsymbol{\alpha}) d\tau$$

- Covariates - proportional hazards model

$$\lambda_j(t|\boldsymbol{\alpha}, \mathbf{x}(t)) = \lambda_j(t|\boldsymbol{\alpha}) \exp(\beta^j \mathbf{x}(t))$$

SUBTYPE-SPECIFIC TRANSMISSION (Under Competing Risk Assumption)

$$\pi(t) = \pi_B(t) + \pi_E(t)$$

- $\pi_E(t)/\pi(t)$ governed by dynamics

Infection hazard rates:

$$\lambda_B(t|\mathbf{c}(t)) = c(t) p_B \pi_B(t) \exp(\beta_B \mathbf{x}(t))$$

$$\lambda_E(t|\mathbf{c}(t)) = c(t) p_E \pi_E(t) \exp(\beta_E \mathbf{x}(t))$$

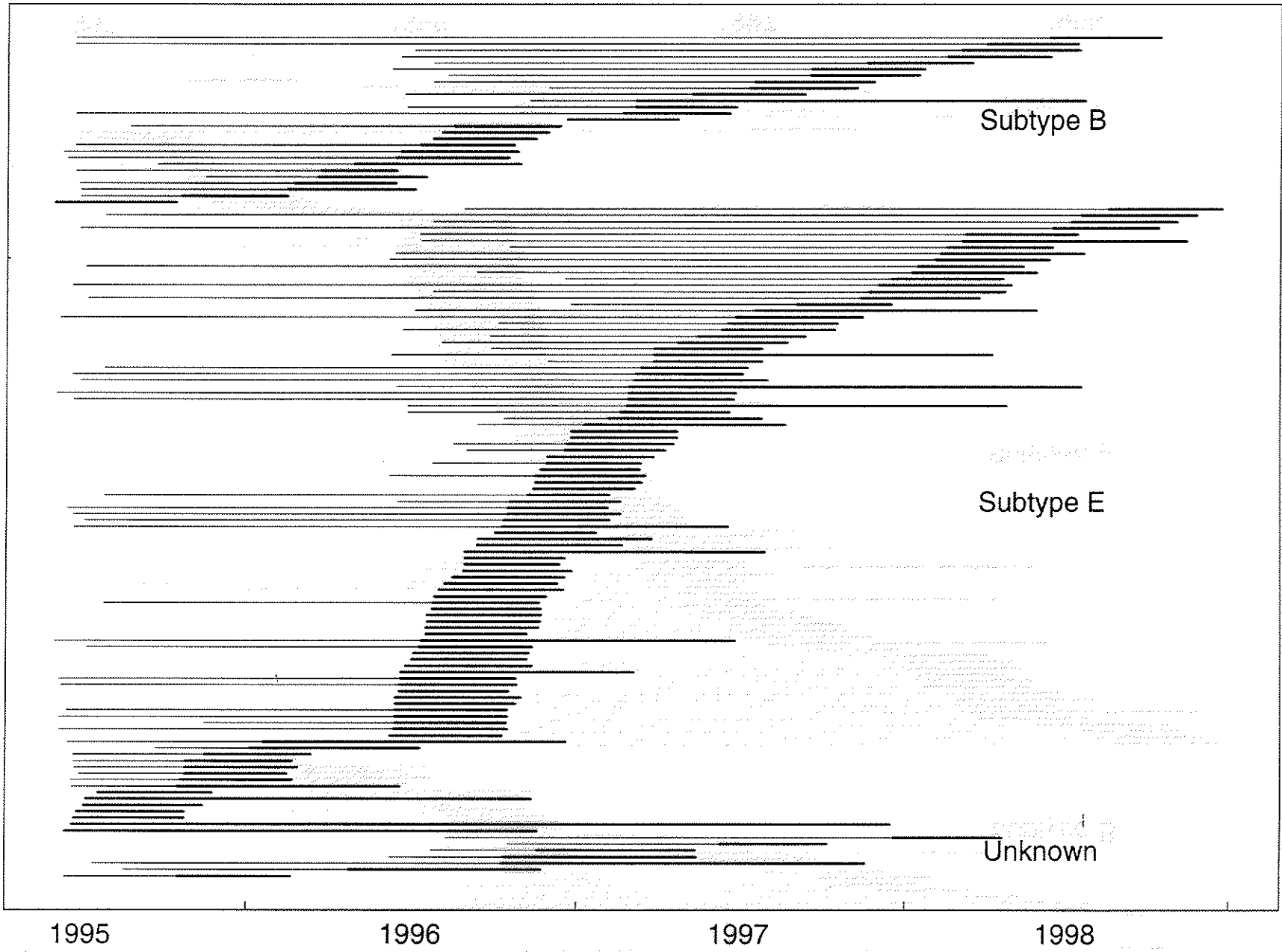
$$\lambda(t|\mathbf{c}(t)) = \lambda_B(t|\mathbf{c}(t)) + \lambda_E(t|\mathbf{c}(t))$$

MODELS

1. NON PARAMETRIC : NPMLE
2. SEMI PARAMETRIC : SPLINES
3. PARAMETRIC : TRANSMISSION
MODEL

BMA COHORT DATA

- Cohort of 1209 IDU's enrolled between 1995 - 1996 in two groups
- Follow-up ~ 4 months
- Aver. 26 months
 - first wave (499) aver. 32 months
 - second wave (710) aver. 22 months
- 133 observed seroconversions (interval-censored, truncated)
- Key covariates include needle sharing and injecting frequencies, gender, incarceration status
- Subtypes: B (27), E (99), not typed (7), among those typed, 79% E



ESTIMATION

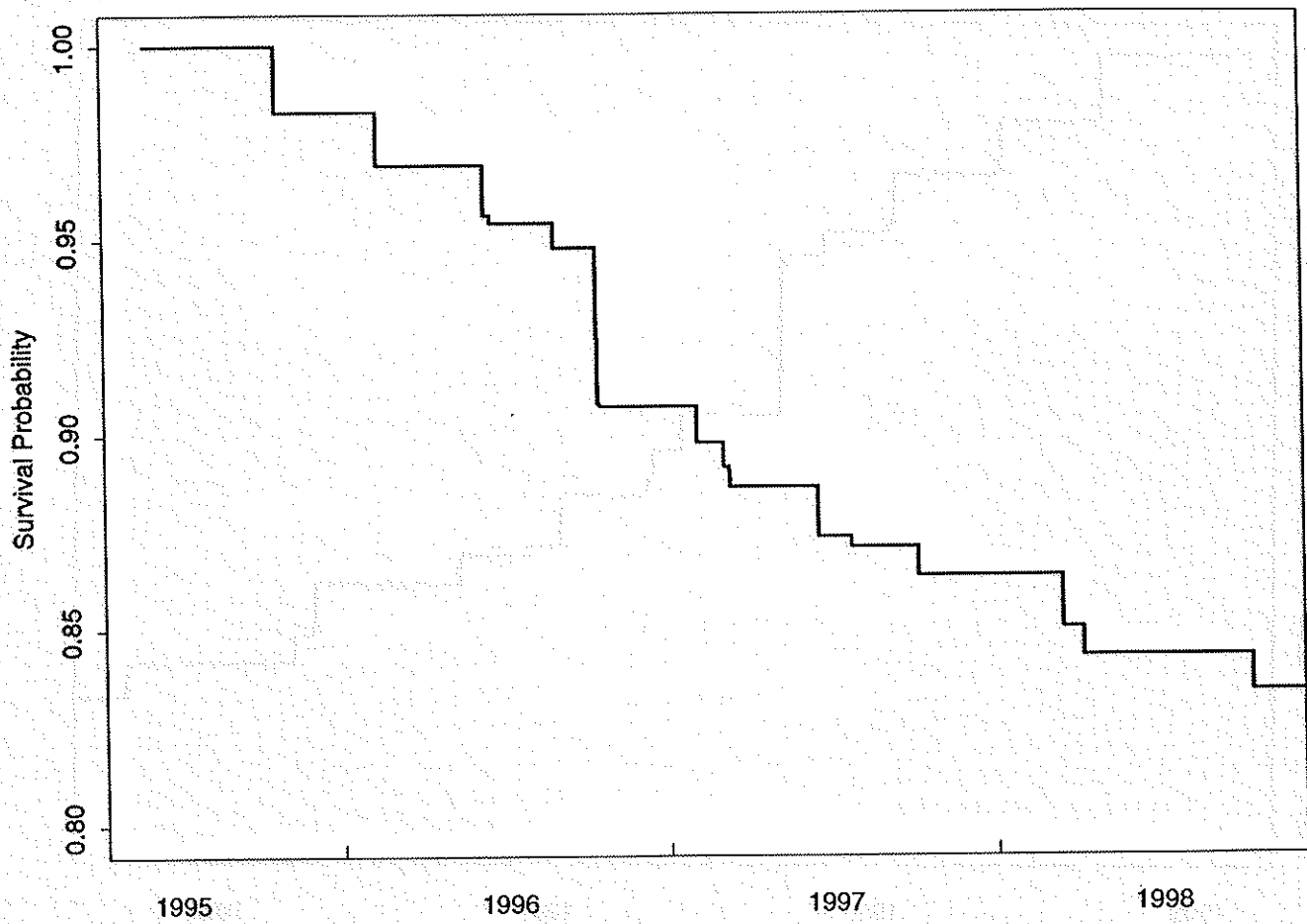
- $I_B(t)$ and $I_E(t)$
- $\lambda_B(t|c(t))$ and $\lambda_E(t|c(t))$
- p_B and p_E
- Covariates
 - Jail
 - Jail, no IDU
 - Jail, IDU
 - Gender
 - Age

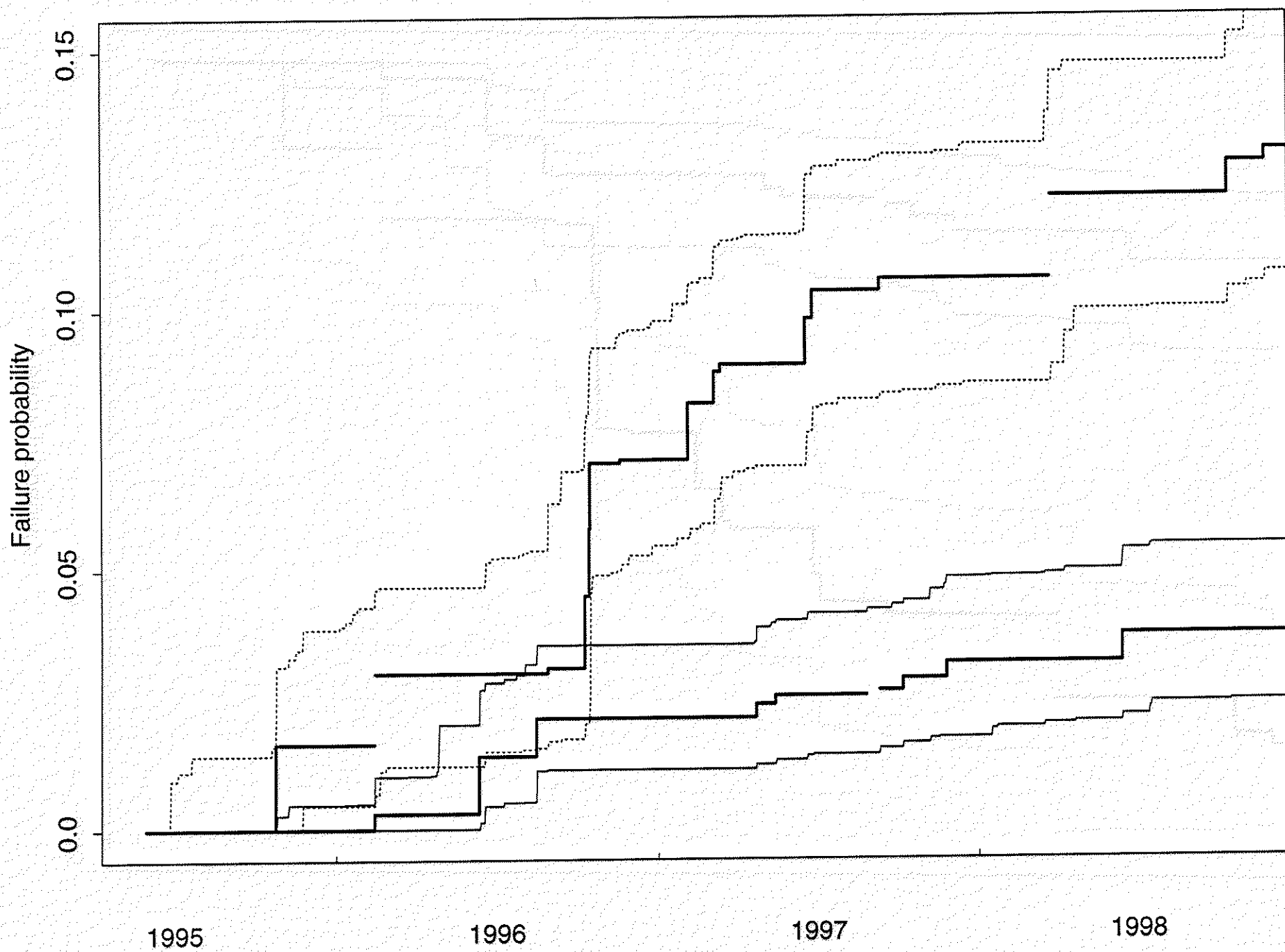
Enrollment Statistics

Covariate	No	Yes	Missing
Needle injecting history	0	1091(97%)	29(3%)
Jail history	367(33%)	752(67%)	1(<1%)
Inject in jail	392(52%)	354(47%)	6(<1%)
Casual sex history	1035(92%)	66(6%)	19(2%)
Needle sharing history	716(64%)	402(35%)	2(<1%)

BMA cohort survival NPMLE

(ignoring failure type)





$h(t)$

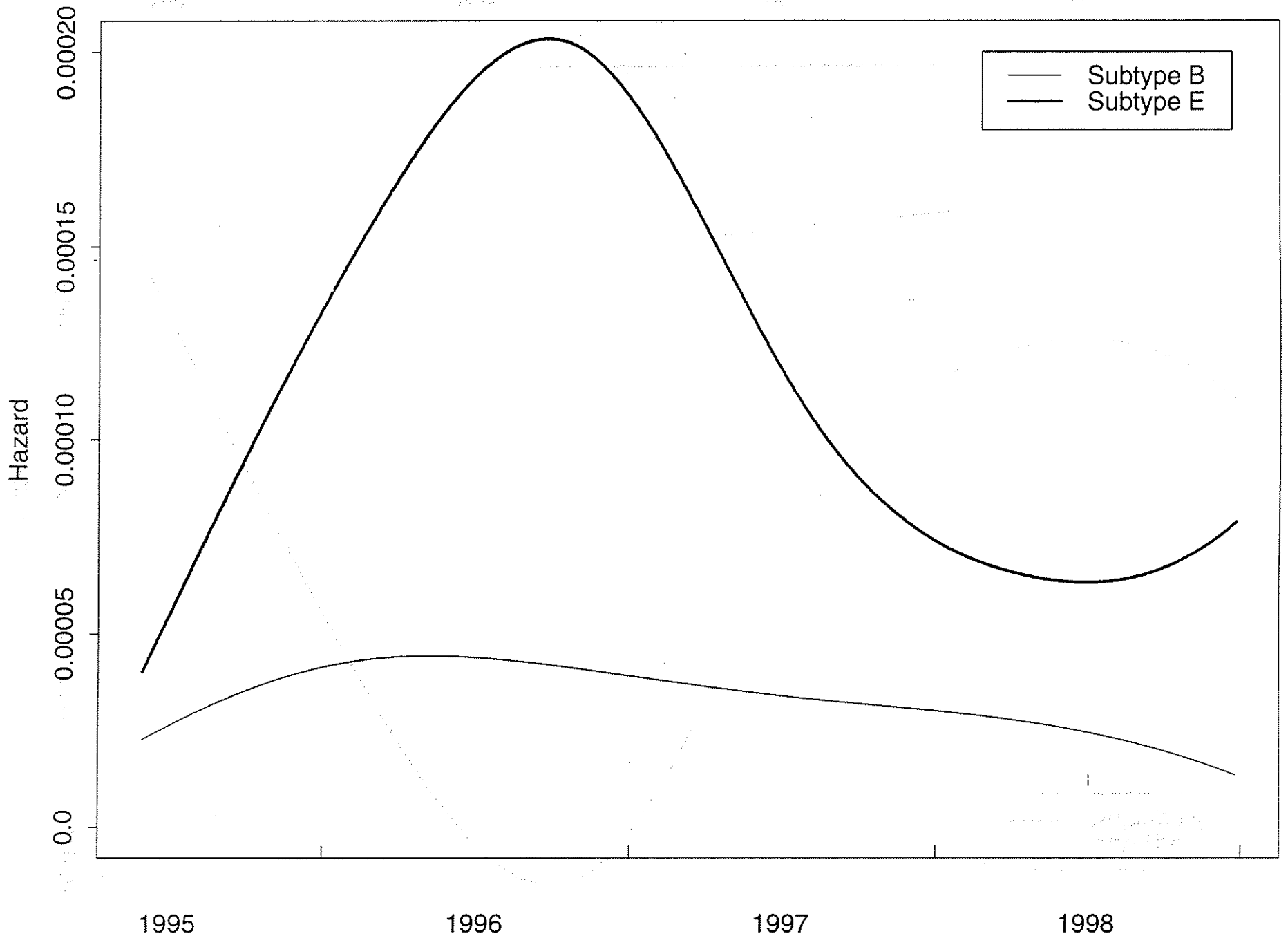


TABLE 3. Covariate effect estimates for the B-spline and transmission probability models from injecting drug users enrolled in the Bangkok Metropolitan Administration cohort study from 1995 to 1998.

Covariate	Parameter	B-spline regression model			Transmission probability model		
		Estimate	95 % CI*	<i>p</i> -value	Estimate	95 % CI	<i>p</i> -value
Female gender	$\exp\{\beta_{Gender}^E\}$	1.60	0.89, 2.87	0.10	1.68	0.87, 2.98	0.12
Jail	$\exp\{\beta_{Jail}\}$	1.62	1.05, 2.46	0.04	1.66	1.01, 2.63	0.04
Inject in jail	$\exp\{\beta_{Jail+Inject}\}$	3.79	2.31, 5.91	< 0.0001	4.47	2.63, 7.19	<0.0001
Age	$\exp\{\beta_{Age}^E\}$	0.99	0.96, 1.02	0.35	0.98	0.96, 1.02	0.23

* CI, confidence interval

$\lambda(t)$

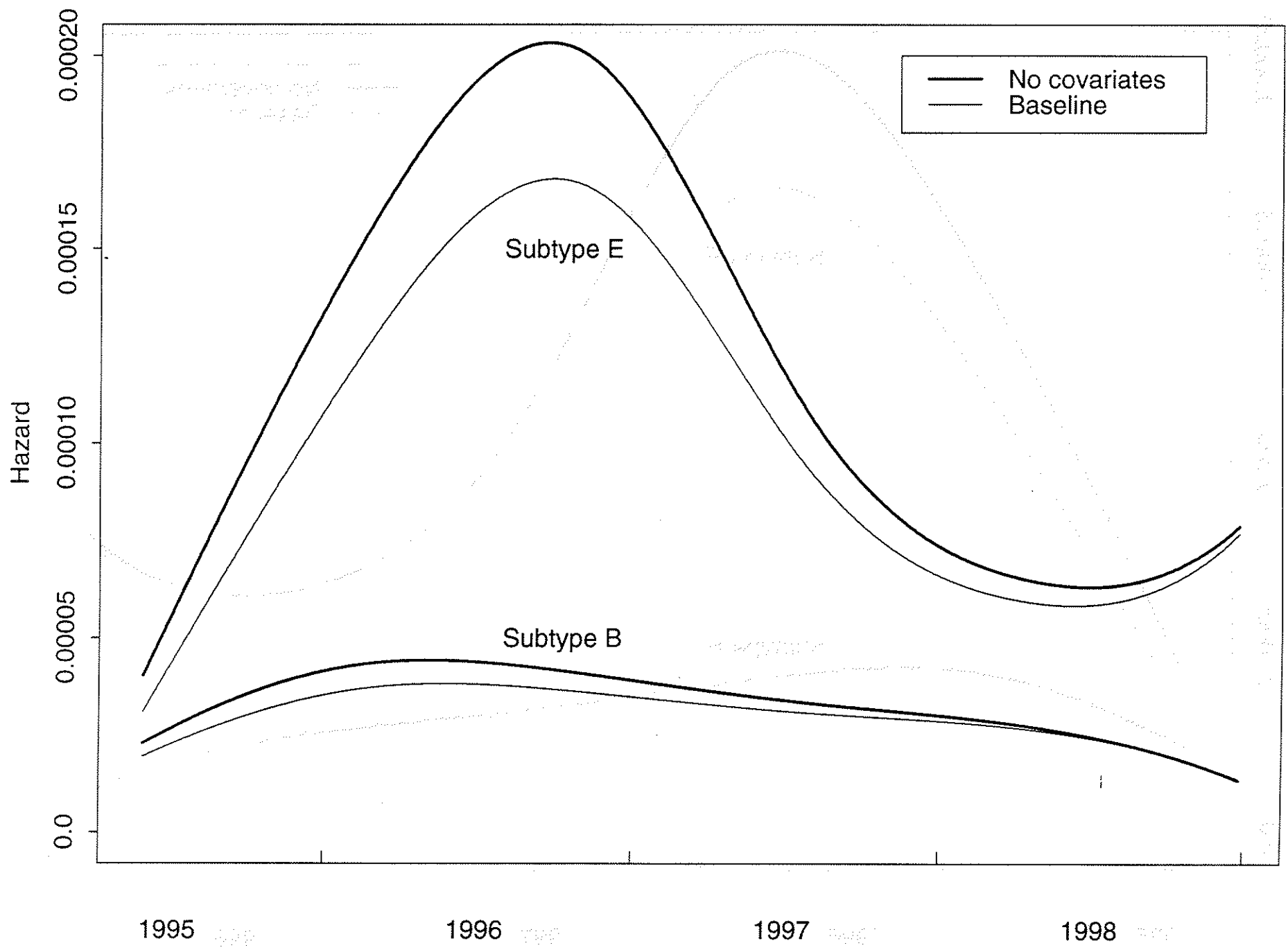


TABLE 2. Observed proportion of Bangkok injecting drug users with subtype E from the 1995-1996 screening phase of the Bangkok Metropolitan Administration cohort study and additional screening in 1999 and 2000.

Screening Period	Number E	Total	Proportion E	95 % CI*
5/1995-11/1995	68	194	0.35	0.28, 0.42
5/1996-12/1996	344	603	0.57	0.53, 0.61
3/1999-12/1999	419	569	0.74	0.70, 0.77
1/2000- 8/2000	745	963	0.77	0.75, 0.80

* CI, confidence interval

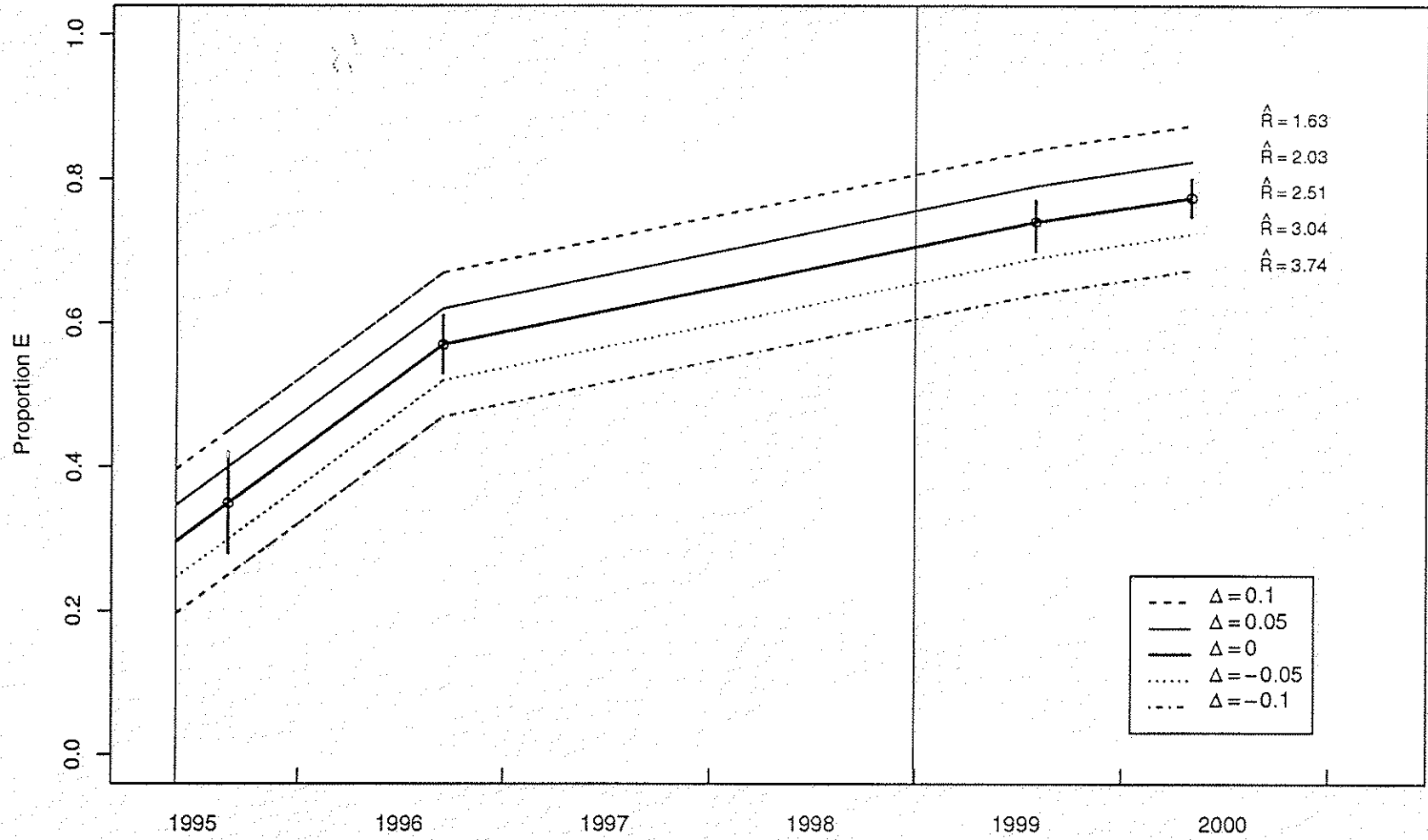
TABLE 4. Transmission probability estimates for different subtype distributions from injecting drug users in the Bangkok Metropolitan Administration cohort study from 1995 to 1998.

Model	Δ^{\S}	$p_B^* \cdot 10^2$		$p_E^{\dagger} \cdot 10^2$		R^{\ddagger}	
		Estimate	95 % CI \P	Estimate	95 % CI	Estimate	95 % CI
Unadjusted $\#$							
	0.00	0.45	0.29, 0.65	1.12	0.87, 1.41	2.51	1.65, 3.94
	0.10	0.59	0.38, 0.85	0.96	0.74, 1.20	1.63	1.07, 2.58
	0.05	0.50	0.33, 0.73	1.03	0.80, 1.29	2.03	1.33, 3.21
	-0.05	0.40	0.26, 0.58	1.22	0.95, 1.54	3.04	2.01, 4.84
	-0.10	0.36	0.23, 0.52	1.35	1.05, 1.70	3.74	2.44, 5.93
Adjusted $**$							
	0.00	0.63	0.41, 0.92	1.57	1.21, 1.98	2.48	1.63, 3.88
	0.10	0.82	0.54, 1.21	1.34	1.03, 1.69	1.64	1.05, 2.54
	0.05	0.72	0.47, 1.04	1.44	1.11, 1.83	2.00	1.31, 3.16
	-0.05	0.57	0.37, 0.82	1.71	1.33, 2.16	3.02	1.97, 4.77
	-0.10	0.51	0.33, 0.75	1.89	1.46, 2.40	3.70	2.42, 5.81

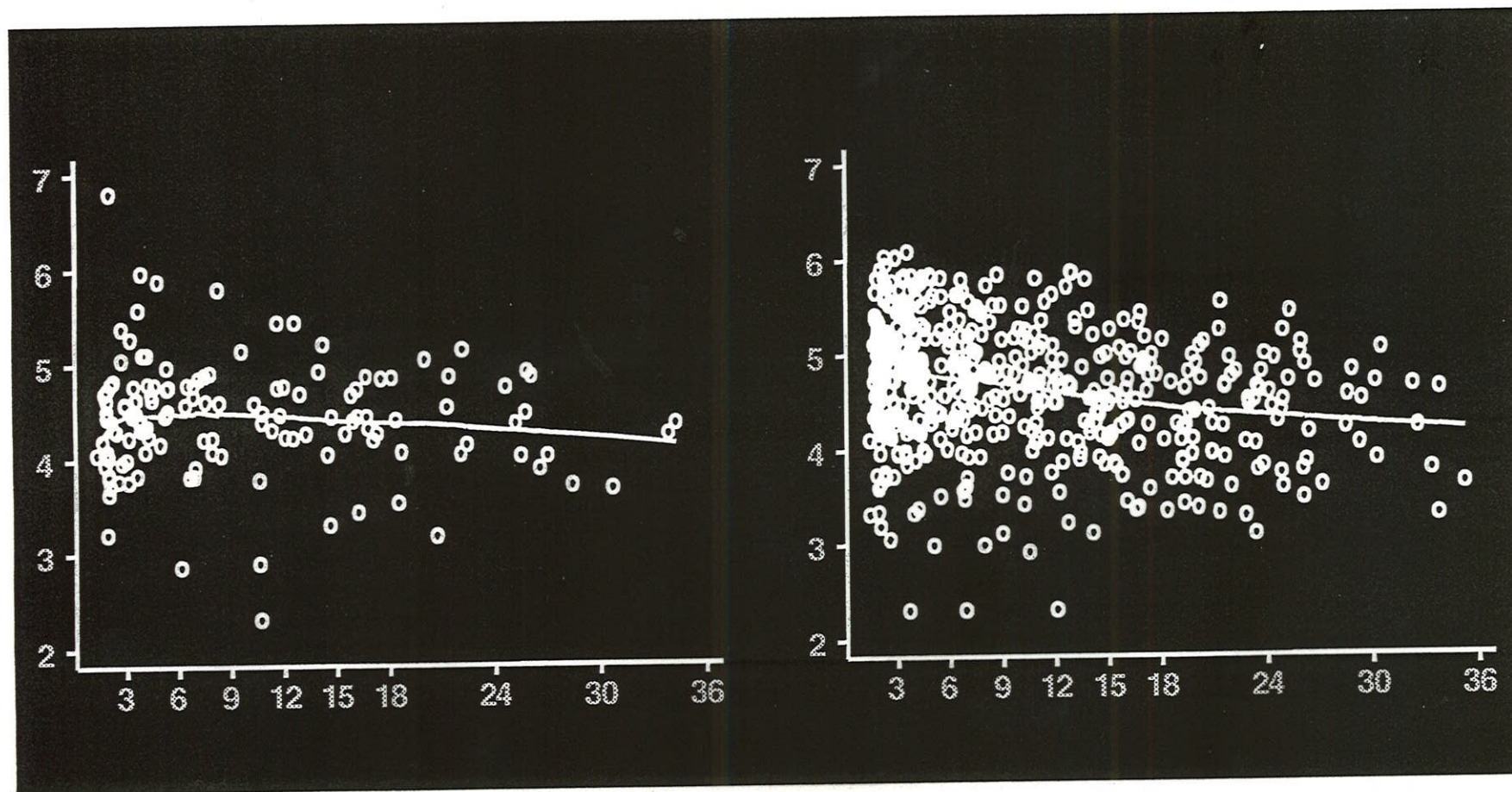
* p_B , subtype B transmission probability
 \dagger p_E , subtype E transmission probability
 \ddagger R , relative transmission probability p_E/p_B
 \S Δ , sensitivity analysis vertical shift in proportion E
 \P CI, confidence interval
 $\#$ Log contact rate coefficient γ fixed at one
 $**$ γ estimated

(L) γ ← ADJUST

Figure 2:



HIV-1 Plasma RNA Levels after Seroconversion by HIV-1 Subtype, IDUs, Bangkok



B

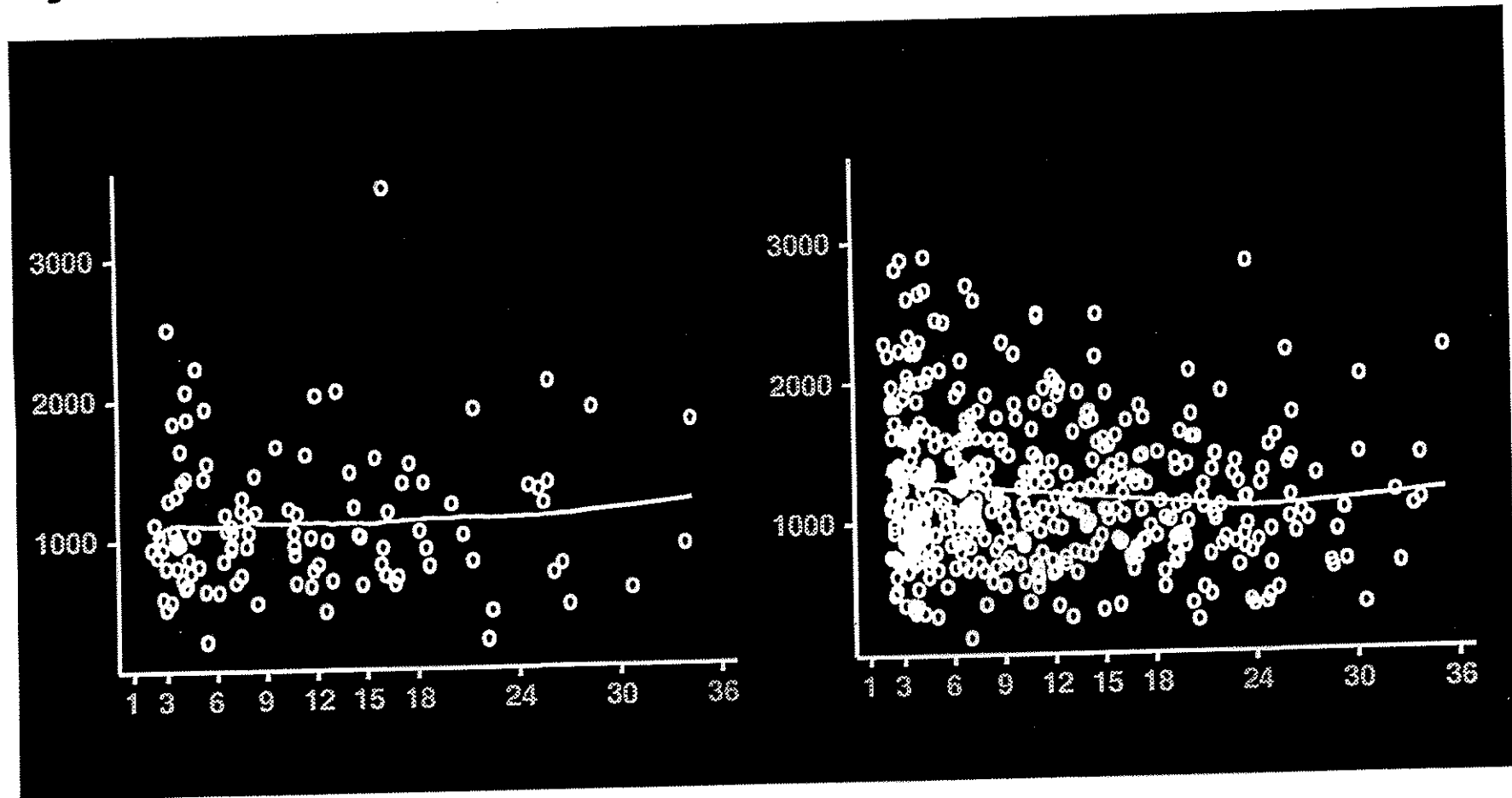
E

HIV-1 Plasma RNA Levels* after Seroconversion by HIV-1 Subtype, IDUs, Bangkok

Time of determination	HIV-1 Subtype		p
	B'	E	
< 3 months	18,000	54,000	0.006
At 6 months	34,000	63,000	0.05
At 12 months	29,000	47,000	0.2
At 18 months	25,000	26,000	0.6

* median copies/mL

CD8 Cell Counts after Seroconversion by HIV-1 Subtype, IDUs, Bangkok



CD4 / CD8 Cell Counts after Seroconversion by HIV-1 Subtype, IDUs, Bangkok

	HIV-1 Subtype		p
	B' n=22	E n=86	
CD4 count, mean (cells/mL)			
< 3 months	564	583	0.8
at 6 months	531	505	0.5
at 12 months	495	481	0.8
at 24 months	409	407	1.0
CD8 count, mean (cells/mL)			
< 3 months	920	1335	0.01
at 6 months	1178	1255	0.5
at 12 months	1096	1210	0.6
at 24 months	1127	1097	0.9

DIRECT BIOLOGICAL EVIDENCE

- Higher early viral load

(Hu, *et al.*, *AIDS*, 2001; Qinn, *et al.*, *NEJM*, 200)

- Subtype E found to have the most potent long terminal repeat (LTR) among the major subtypes.

LTR encodes the transcriptional promoter.

(Jeeninga, *et al.*, *J Virology*, 2000)

CONCLUSIONS

- Higher incidence for subtype E could be due to
 - epidemic dynamics
 - sharing network
 - higher infectiousness

- Ave. needle sharing transmission probabilities:

Subtype B: 0.004~~5~~²⁹ 95% CI [0.004~~4~~²⁹, 0.009~~9~~⁶⁵]

Subtype E: 0.01~~0~~⁰⁹, 95% CI [0.01~~2~~⁰⁹, 0.02~~0~~⁴]

$$RR = p_E/p_B = 2.5, \text{ 95\% CI [1.6, 3.9]}$$

- We need better estimates of $\pi_E(t)/\pi(t)$ or a sexual partner study to better estimate transmission probabilities

CONCLUSIONS (continued)

- Important covariates
 - Risk increases by 1.7 in jail
 - Risk increases by 4.5 in jail and injecting
 - Risk of subtype E for women 1.7 times that for men
 - Risk of subtype E may decrease somewhat with age

VACCINE EFFICACY

Estimating VE_S :

$$\text{Unvac: } \lambda(t|c(t), \mathbf{x}(t)) = c(t) p \pi(t) \exp(\boldsymbol{\beta} \mathbf{x}(t))$$

$$\text{Vac: } \lambda(t|c(t), \mathbf{x}(t)) = (1 - VE_S) c(t) p \pi(t) \exp(\boldsymbol{\beta} \mathbf{x}(t))$$

Estimating VE_I from steady sexual partners of infected index cases ($\pi(t) = 1$):

$$\text{Unvac: } \lambda(t|c(t), \mathbf{x}(t)) = c(t) p' \exp(\boldsymbol{\beta} \mathbf{x}(t))$$

$$\text{Vac: } \lambda(t|c(t), \mathbf{x}(t)) = (1 - VE_I) c(t) p' \exp(\boldsymbol{\beta} \mathbf{x}(t))$$

Subtype-Specific Expected Numbers of Events for Partner Study

Group	Infected IDU's		Exposed partners		Secondary infections	
	B	E	B	E	B	E
Vaccine trial						
Placebo	27	106	18	72	8	48
Vaccine	21	82	14	56	4	26
Cohort study	10	40	8	34	5	25

VACCINE EFFICACY

Estimating VE_S from IDU's:

$$\text{Unvac: } \lambda(t|c(t),\mathbf{x}(t)) = c(t) p \pi(t) \exp(\beta \mathbf{x}(t))$$

$$\text{Vac: } \lambda(t|c(t),\mathbf{x}(t)) = (1 - VE_S) c(t) p \pi(t) \exp(\beta \mathbf{x}(t))$$

$$\text{Test } H_0: VE_S = 0. \quad \text{Power} \approx 1 \quad (VE_S = 0.4)$$

$$95\% \text{ CI on } VE_S [0.22 - 0.56]$$

Subtype-specific (assume 80% E):

$$\text{Test } H_0: VE_{SE} = 0. \quad \text{Power} \approx 1.00 \quad (VE_{SE} = 0.4)$$

$$95\% \text{ CI on } VE_{SE} [0.20 - 0.58]$$

$$\text{Test } H_0: VE_{SB} = 0. \quad \text{Power} = 0.57 \quad (VE_{SB} = 0.4)$$

$$95\% \text{ CI on } VE_{SB} [0.00 - 0.70]$$

VACCINE EFFICACY (continued)

Estimating VE_I from steady sexual partners of IDU's ($\pi(t) = 1$):

$$\text{Unvac: } \lambda(t|c(t), \mathbf{x}(t)) = c(t) p' \exp(\beta \mathbf{x}(t))$$

$$\text{Vac: } \lambda(t|c(t), \mathbf{x}(t)) = (1 - VE_I) c(t) p' \exp(\beta \mathbf{x}(t))$$

$$\text{Test } H_0: VE_I = 0. \quad \text{Power} = 1 \quad (VE_I = 0.6)$$

$$95\% \text{ CI on } VE_I [0.37 - 0.74]$$

Subtype-specific (assume 80% E):

$$\text{Test } H_0: VE_{IE} = 0. \quad \text{Power} = 0.98 \quad (VE_{IE} = 0.6)$$

$$95\% \text{ CI on } VE_{IE} [0.27 - 0.83]$$

$$\text{Test } H_0: VE_{IB} = 0. \quad \text{Power} = 0.83 \quad (VE_{IB} = 0.6)$$

$$95\% \text{ CI on } VE_{IB} [0.11 - 1.00]$$

SUBTYPE-SPECIFIC INFECTIOUSNESS

Combining partner augmentation from the vaccine trial and cohort (assume 80% E)

Test $H_0: p_B = p_E$, $H_a: 2p_B = p_E$

Power = 0.58

95% CI on RR [1.0 - 6.8]

Table 1: Two randomized multi-center trials conducted for evaluating the efficacy of AIDSVAX, a recombinant glycoprotein 120 HIV-1 vaccine.

	VAX004	VAX003
Time of trial	1998-2002	1999-2003
Location	North America and The Netherlands	Bangkok, Thailand
Type of transmission	Sexual acts	Sharing needles for drug injection
Population size	5403	2527
Male	5095 (94%)	2361 (93%)
Female	308 (6%)	166 (7%)
Randomization ratio (vaccine:placebo)	2:1	1:1
Infected/Randomized		
Placebo	127/1805	105/1260
Vaccine	241/3598	106/1267
HIV-1 subtypes		
B	100%	33 (78%)
E	0	164 (16%)
Unknown	0	14 (6%)

Table 4: VAX004: Summary of the posterior distributions of the transmission probability and the vaccine efficacy per infectious sexual contact for the overall study population and by baseline risk level, compared to the standard analysis

Risk level	p		VE (Bayesian)		VE (Cox ^a)	
	Total ^b	95% C.S.	Median	95% C.S.	Estimate	95% C.I.
Overall	0.0056	0.0044, 0.0071	0.069	-0.15, 0.26	0.06	-0.17, 0.24
Low	0.0020	0.0010, 0.0036	-0.23	-1.48, 0.35	-0.48	-1.93, 0.26
Middle	0.0054	0.0041, 0.0071	0.02	-0.28, 0.25	0.03	-0.25, 0.25
High	0.020	0.013, 0.030	0.56	0.22, 0.75	0.43	0.04, 0.66

^a Results based on Cox proportional hazards model in Gurwith et al. (2005).

Table 6: VAX003: Summary of the posterior distributions of the transmission probability and the vaccine efficacy per infectious needle-sharing act for the overall study population and by baseline risk level and HIV subtype, compared to the standard analysis

Risk Level	Subtype	p		VE (Bayesian)		VE (Cox ^a)	
		Median	95% C.S.	Median	95% C.S.	Estimate	95% C.I.
Overall		0.026	0.021, 0.031	-0.08	-0.43, 0.20	0.001	-0.31, 0.24
	E	0.028	0.022, 0.034	-0.12	-0.52, 0.17	-0.014	-0.38, 0.25
	B	0.019	0.012, 0.029	0.18	-0.57, 0.60		
	E/B	1.45	0.91, 2.39				
Low		0.033	0.024, 0.045	0.06	-0.49, 0.41		
	E	0.034	0.022, 0.048	0.04	-0.66, 0.42		
	B	0.032	0.015, 0.058	0.18	-1.33, 0.67		
	E/B	1.06	0.51, 2.54				
High		0.023	0.017, 0.029	-0.10	-0.60, 0.23		
	E	0.025	0.019, 0.032	-0.21	-0.77, 0.19		
	B	0.015	0.008, 0.026	0.34	-0.63, 0.77		
	E/B	1.68	0.92, 3.31				

^a Results based on Cox proportional hazards model in Pitisuttithum et al. (2006).

Conclusions

- Needle injection is about 4 times as infectious as a sexual contact.
- Depending on relative prevalence, subtype E tends to be more infectious than subtype B, especially in IDUs with a high risk profile at baseline
- GP 120 vaccine probably not effective