
SISCER Mod 12

Survival Analysis

Lecture 5

Ying Qing Chen, Ph.D.

Department of Medicine
Stanford University

Department of Biostatistics
University of Washington

In Lecture 4

- What we discussed
 - Cox proportional hazards model
 - Model specification
 - Interpretation
 - Estimation by partial likelihood
 - Stratified Cox proportional hazards model
-

Special topic 1: time-varying covariates

- Time-varying (time-dependent) covariates
 - External covariates
 - Pollen level to asthma attack
 - Maternal CD4 counts and plasma viral loads to infant HIV-infections by breast milk feeding
 - Exposure to second-hand smoking to lung cancer
 - Internal covariates
 - Smoking secession because of doctor's advice on health status
 - Blood pressure for death caused by cadiao-vascular diseases
 - Sexual behavior change because of deteriorating HIV progression
-

Extended Cox model

■ Cox model with time-varying covariates

- General Model:

$$\lambda[t | X_1(t), \dots, X_k(t)] = \lambda_0(t) \exp[\beta_1 X_1(t) + \dots + \beta_k X_k(t)]$$

- ▶ Assume we have $X(t)$ measured for all times t .

- Interpretation:

- ▶ Model for the instantaneous risk of failure **given** survival to time t and the value of covariates up to and including time t .
- ▶ Current covariate value(s); past covariate value(s) used as predictors.

-
- What drives the change in covariates?
 - In general, time-dependent covariates are not as easy to understand conceptually as time-independent covariates
 - This is where the longitudinal data analysis may need to empirically address the change in time-dependent covariates
 - Are the time-varying covariates risk factors?
 - Or they are biomarkers of disease progression? i.e., they are varying because of disease dynamics?
-

Example: atomic bomb survivors study

- Survival data
 - Time-to-event outcome: leukemia incidence
 - Time zero: 1945
 - Risk factor: in the range of 2.5km or not
- Model specification: extended Cox model

$$\lambda(t | X_E) = \lambda_0(t) \exp[\beta X_E + \gamma X_E \cdot t]$$

$$\triangleright X_E = \begin{cases} 1 = \text{less than 2.5km} \\ 0 = \text{greater than 2.5km} \end{cases}$$



$$\lambda(t | X_E) = \lambda_0(t) \exp[\beta X_E + \gamma X_E \cdot t]$$

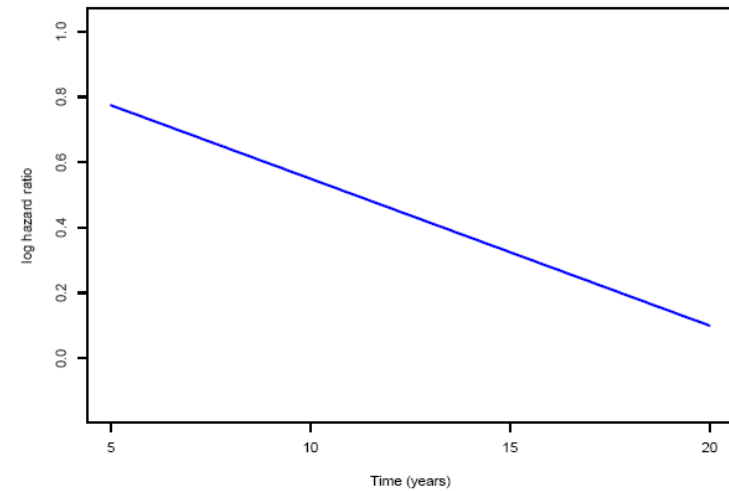
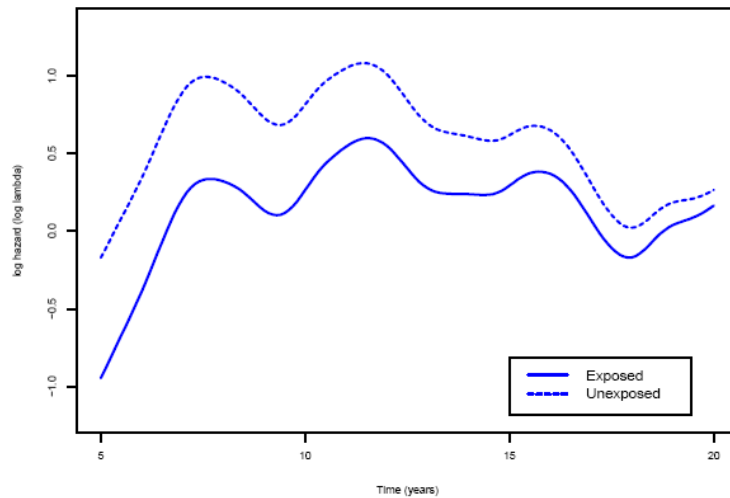
$$\triangleright X_E = \begin{cases} 1 = \text{less than 2.5km} \\ 0 = \text{greater than 2.5km} \end{cases}$$

- This yields the hazard ratio (RR):

$$\frac{\lambda(t | X_E = 1)}{\lambda(t | X_E = 0)} = \exp[\beta + \gamma \cdot t]$$

- Can be used to test:
 - $\triangleright H_0$: RR is constant (PH holds)
 - $\triangleright H_1$: RR is decreasing, or increasing
- Fitting the model allows use of Wald tests, and likelihood ratio tests for individual coefficients or multiple coefficients.

HR depends on time (log HR)



Example: Stanford heart transplant data

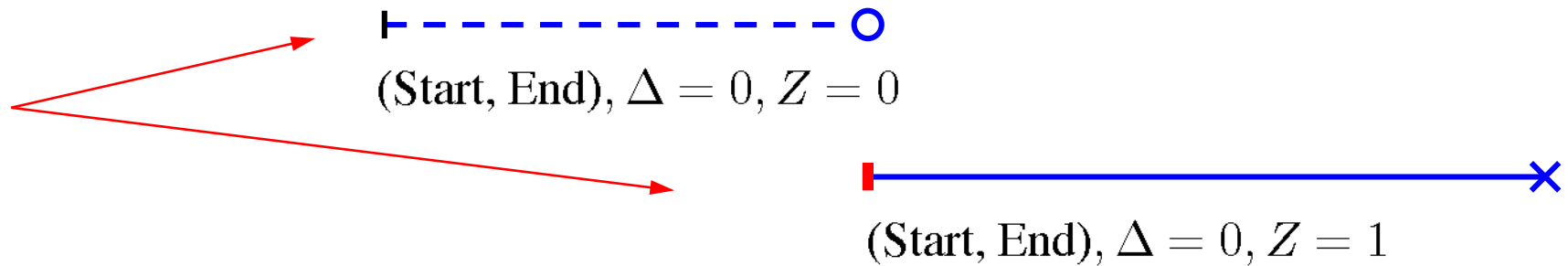
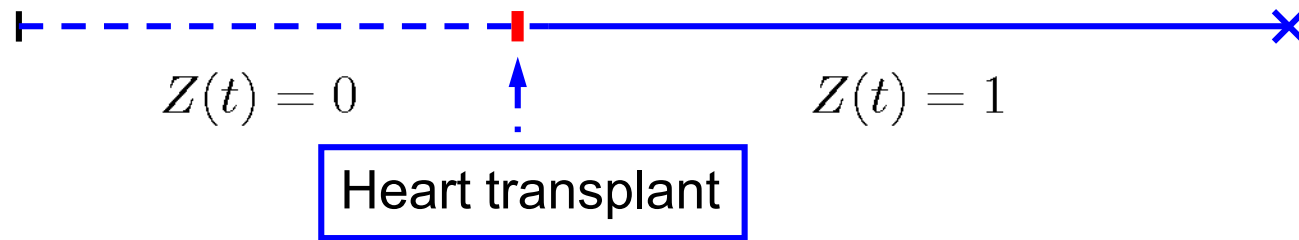
- Subjects recruited into program beginning in 1967.
- Transplant when an HLA matched heart could be found.
 - ▷ Some received transplant.
 - ▷ Some died before a suitable donor heart could be found.
- **Q**: Does a heart transplant improve survival?
 - ▷ event = death from any cause.
 - ▷ time = days since entry into the program.
 - ▷ $X_E(t) = \begin{cases} 1 = \text{transplant before } t \\ 0 = \text{no transplant before } t \end{cases}$
- Model:

$$\lambda[t | X_E(t)] = \lambda_0(t) \exp[\beta \cdot X_E(t)]$$

-
- **Data:** 103 records for patients entered and followed until April 1974.
 - See Crowley and Hu (1977) for details.
 - **Key Variables:**
 - ▷ Year / Month / Day of acceptance to program.
 - ▷ Year / Month / Day of transplant (if done).
 - ▷ Year / Month / Day of end of follow-up.
 - ▷ Year / Month / Day of birth.
 - ▷ Mismatch score.
 - We will need to create two record for those subjects that change from unexposed to exposed (i.e. have a transplant)
-

Data split

- Construct the so-called “covariate process data”



STATA codes

```
***
*** create analysis variables
***

gen transplant = (txyear != 0)

replace byear = byear + 1900
replace accyear = accyear + 1900
replace txyear = txyear + 1900
replace lastyear = lastyear + 1900

gen bdays = mdy( bmonth, bday, byear )
gen accdays = mdy( accmonth, accday, accyear )
gen txdays = mdy( txmonth, txday, txyear )
gen fudays = mdy( lastmonth, lastday, lastyear )

gen age48 = int( (accdays - bdays )/365 ) - 48
gen age48trans = transplant * int( (txdays - bdays )/365 ) - 48

gen survtime = fudays - accdays + 1
gen waittime = transplant * ( txdays - accdays + 1 )
```

```
***
*** analysis without time-dependent exposure
***
```

```
stset survtime, failure(status)
```

```
stcox transplant, nohr
```

```
stcox transplant age48, nohr
```

```
. stcox transplant, nohr
```

```
Cox regression -- Breslow method for ties
```

```
No. of subjects =          103          Number of obs   =          103
No. of failures =           75
Time at risk    =          31954
Log likelihood  = -285.46262          LR chi2(1)       =          25.73
                                          Prob > chi2     =          0.0000
```

```
-----+-----
      _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----+-----
transplant | -1.3183   .244019    -5.40   0.000    -1.7966   -.84007
-----+-----
```

```
***
*** generate two records / subject if transplanted
***
expand 2 if transplant
```

With time-varying covariates

```
sort id
by id: gen posttran = ( _n == 2 )
by id: gen t1 = survtime if _n == _N
by id: replace t1 = waittime if _n == 1 & transplant
by id: replace status = 0 if _n == 1 & transplant
```

Split record
according to
covariate process

```
*** Note: subject id=38 died the same day as the transplant, so we need
***         to force death time to be after transplant time.
```

```
replace t1 = 5.1 if id == 38 & posttran == 1
```

```
stset t1 status, id(id)
```

```
*** Note: STATA assumes that the entry time of the second record is the
***         censoring time of the first record if a subject has two records.
***         Alternative would be to use entry time option.
```

```
stcox posttran, nohr
```

```
stcox posttran age48, nohr
```

Not age-adjusted

```
. stcox posttran, nohr
      failure _d: status
      analysis time _t: t1
      id: id

No. of subjects =          103      Number of obs   =          172
No. of failures =           75
Time at risk    =        31954.1

LR chi2(1)      =          0.17
Prob > chi2     =          0.6778

-----+-----
      _t |   Coef.   Std. Err.   z   P>|z|   [95% Conf. Interval]
-----+-----
posttran |   .12449   .30091    0.41  0.679   -.46529   .71428
-----+-----
```

Age-adjusted

```
. stcox posttran age48, nohr

No. of subjects =          103      Number of obs   =          172
No. of failures =           75
Time at risk    =        31954.1

LR chi2(2)      =          5.31
Prob > chi2     =          0.0702

-----+-----
      _t |   Coef.   Std. Err.   z   P>|z|   [95% Conf. Interval]
-----+-----
posttran |  -.00615   .31158   -0.02  0.984   -.61685   .60454
age48    |   .03108   .01444    2.15  0.031    .00276   .05939
-----+-----
```

Summary

- We can allow non-PH hazard models to be estimated using interactions with baseline (or time-dependent) covariates and time, or specific functions of time.
 - We can allow analysis of survival that incorporates time-dependent covariates.
 - The information for risk set needs to contain the current value for each time-dependent covariate.
 - ▷ We can “split” an individual’s follow-up into components over which we assume the time-dependent covariate is constant.
 - STATA has the command `stsplit` that helps generate the necessary data structure. However, it may be easier to create the “split” record using an alternative data base programming language (SAS, S+).
-

References

Annu. Rev. Public Health. 1999. 20:145-57
Copyright © 1999 by Annual Reviews. All rights reserved

TIME-DEPENDENT COVARIATES IN THE COX PROPORTIONAL-HAZARDS REGRESSION MODEL

Lloyd D. Fisher and D. Y. Lin

Department of Biostatistics, University of Washington, Seattle, Washington
98195-7232; e-mail: lfisher@biostat.washington.edu; danyu@biostat.washington.edu

KEY WORDS: survival analysis, longitudinal analysis, censored data, model checking

ABSTRACT

The Cox proportional-hazards regression model has achieved widespread use in the analysis of time-to-event data with censoring and covariates. The covariates may change their values over time. This article discusses the use of such time-dependent covariates, which offer additional opportunities but must be used with caution. The interrelationships between the outcome and variable over time can lead to bias unless the relationships are well understood. The form of a time-dependent covariate is much more complex than in Cox models with fixed (non-time-dependent) covariates. It involves constructing a function of time. Further, the model does not have some of the properties of the fixed-covariate model; it cannot usually be used to predict the survival (time-to-event) curve over time. The estimated probability of an event over time is not related to the hazard function in the usual fashion. An appendix summarizes the mathematics of time-dependent covariates.

Special topic 2: assessment of model adequacy

- Most critical assumption for the Cox model
 - Proportionality between hazard functions
 - Needs to be carefully examined
 - Example: Brain cancer trial
 - Randomized trial of 222 patients with brain tumors
 - BCNU (Carmustine) medicated polymers
 - Control polymers
 - Chen & Wang (2000, *Journal of the American Statistical Association*)
-

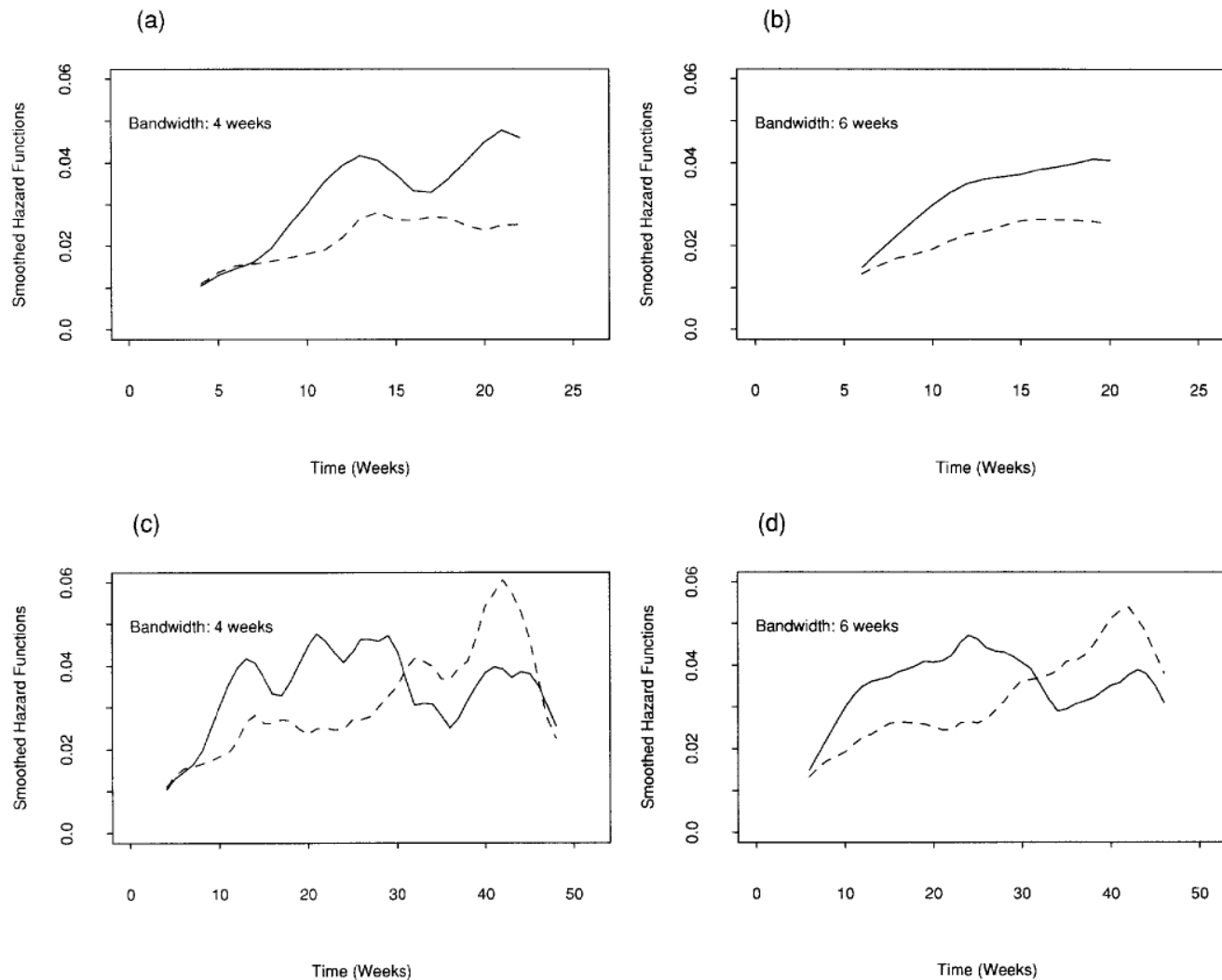


Figure 1. Smoothed Hazard Functions for the Two Groups (—, placebo; - - -, BCNU) in the BCNU Trial. (a) 4-week smoothing bandwidth for the first 26 weeks; (b) 6-week smoothing bandwidth for the first 26 weeks; (c) 4-week smoothing bandwidth for the first 52 weeks; (d) 6-week smoothing bandwidth for the first 52 weeks.

Graphical assessment

- **Graphical approaches**
 - ▷ $-\log\{-\log[S(t | X)]\}$ plots
 - ▷ Observed and fitted $S(t | X)$
 - ▷ Residual plots

log-log plot

- Recall: Under a PH assumption

$$S(t | X) = [S_0(t)]^{\exp(\beta X)}$$

$$\log[S(t | X)] = \exp(\beta X) \cdot \log[S_0(t)]$$

$$\log\{-\log[S(t | X)]\} = \beta X + \log\{-\log[S_0(t)]\}$$

- This implies that the separation between -log-log plots should be constant over time:

$$\beta = \log\{-\log[S(t | X = 1)]\} - \log\{-\log[S(t | X = 0)]\}$$

- Idea:

- ▶ Plot $\log\{-\log[\widehat{S}(t | X)]\}$ versus time and look for “parallel” curves.

- Comments:

- ▶ $-\log\{-\log[\widehat{S}(t | X)]\}$ or $\log\{-\log[\widehat{S}(t | X)]\}$
 - ▶ Plot against time, or $\log(\text{time})$.
 - ▶ Use Kaplan-Meier for $\widehat{S}(t | X)$ (either unadjusted or adjusted).
 - ▶ Crossing (in the middle) is an indication of trouble.
 - ▶ Interpret plots recognizing that there is *variation* since these are *estimates* of the survival functions.
-

-
- Issues:
 - ▷ How parallel is parallel?
 - * subjective decision.
 - * conservative strategy: assume PH is OK.
 - ▷ Categorization of continuous predictors.
 - ▷ Adjusted versus unadjusted $\hat{S}(t | X)$.
-

STATA codes

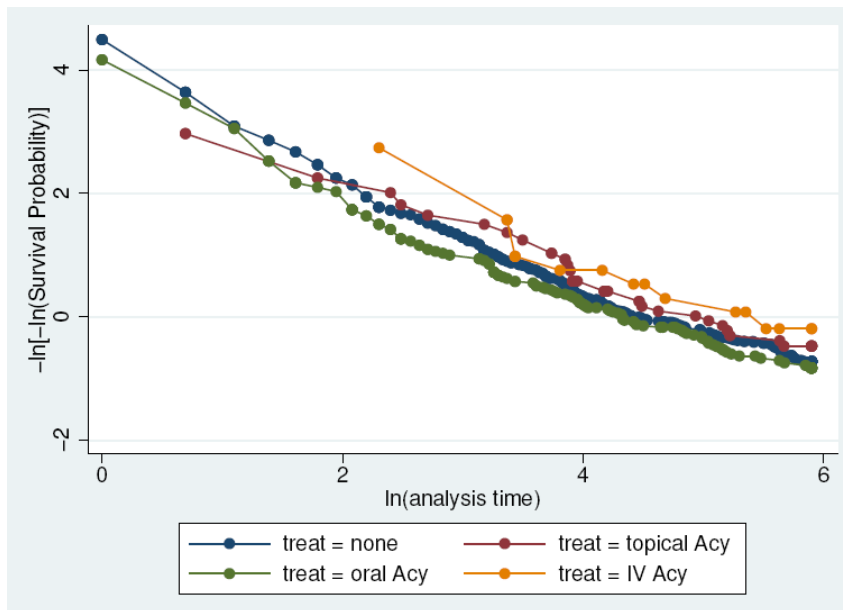
```
*****  
*** log -log plots ***  
*****
```

```
stphplot, by(group)  
stphplot, by(treat)
```

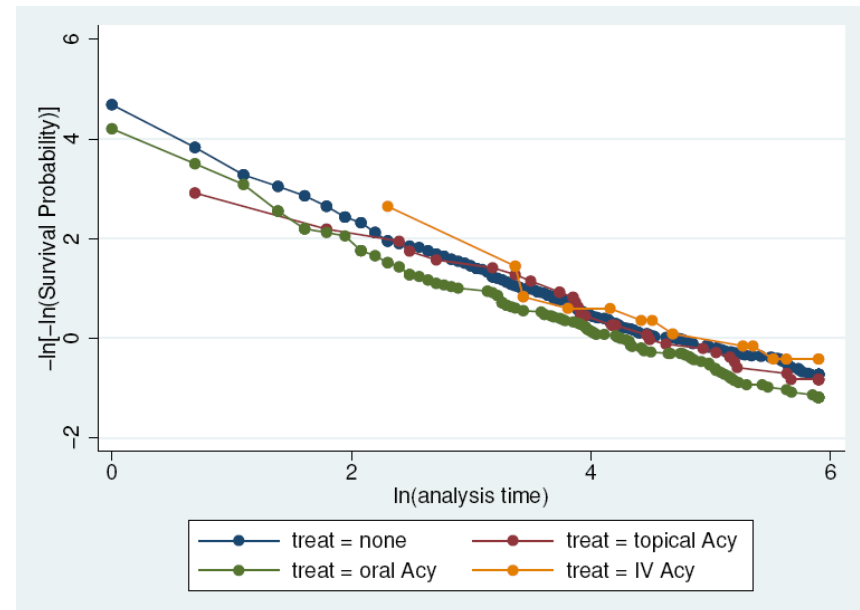
```
xi: stphplot, strata(group) adjust(age female durprime i.treat)  
xi: stphplot, strata(treat) adjust(age female durprime i.group)
```



Unadjusted

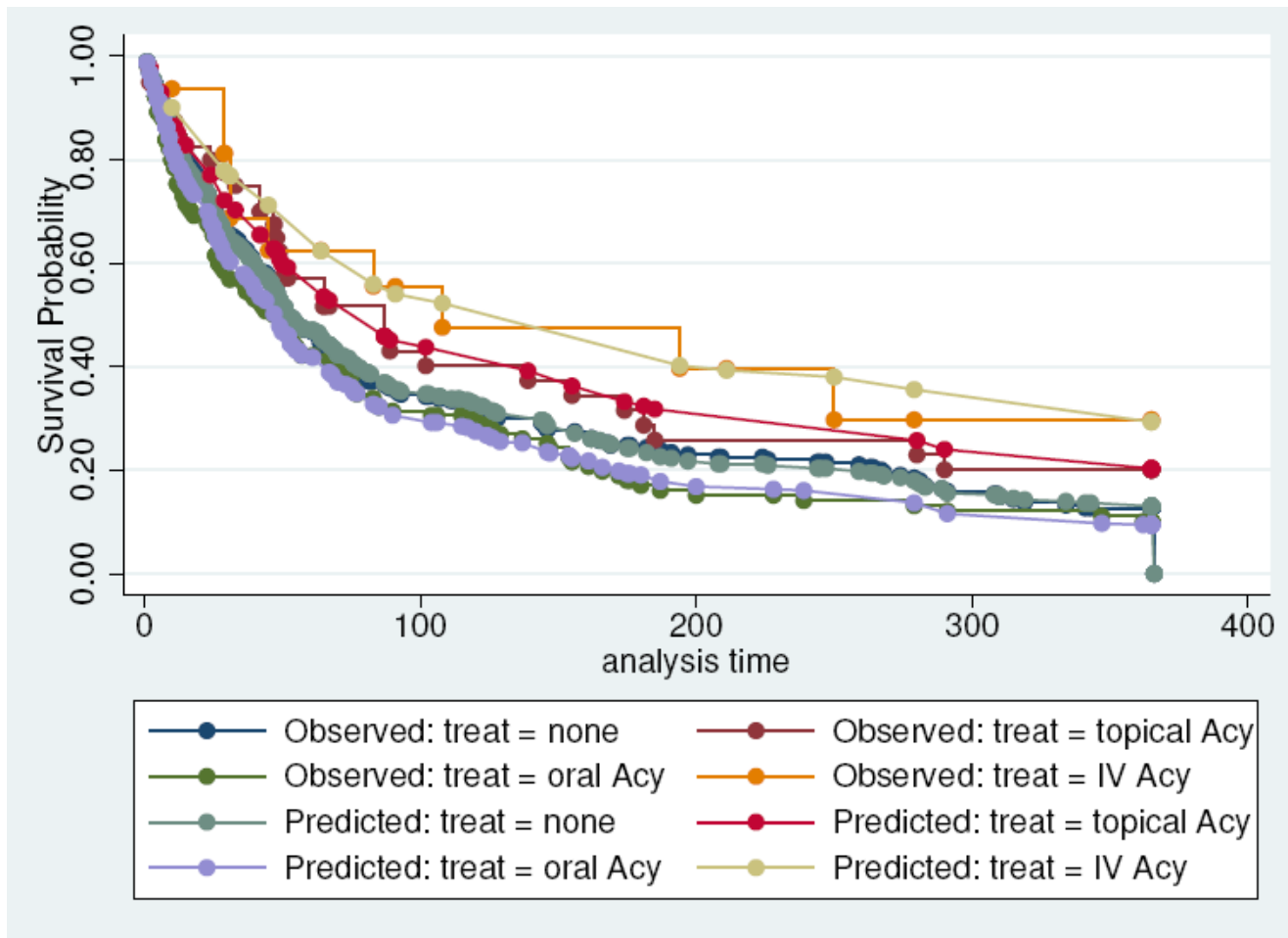


Adjusted



Comparing observed and expected survival curves

- Idea:
 - ▷ Compare Kaplan-Meier estimates to fitted survival curves obtained from Cox regression.
 - Issues:
 - ▷ If we adjust for other predictors in the Cox regression then we may impact the fitted survival. This can make comparison to KM estimates difficult (unless we can adjust those as well).
 - ▷ How close is close?
 - * Subjective decision
 - ▷ Continuous covariates.
-



Confirmatory goodness-of-fit test

- ★ Several packages (STATA - yes!) now include hypothesis tests for proportionality of hazards.
- Such tests are obtained from a fitted Cox regression and test the proportional hazards assumption:

$$H_0 : \beta_j(t) = \beta_j$$

$$H_1 : \beta_j(t) \text{ has a trend in time}$$

- Here $\exp(\beta_j(t))$ represents the hazard ratio comparing $X_j = 1$ to $X_j = 0$ at time t , controlling for other predictors:

$$\begin{aligned} \frac{\lambda(t \mid X_1 = 1, X_2 = x_2)}{\lambda(t \mid X_1 = 0, X_2 = x_2)} &= \frac{\lambda_0(t) \exp(\beta_1(t) \cdot (1) + \beta_2 x_2)}{\lambda_0(t) \exp(\beta_1(t) \cdot (0) + \beta_2 x_2)} \\ &= \exp(\beta_1(t)) \\ &? \exp(\beta_1) \end{aligned}$$

- These tests use a certain residual (Schoenfeld residual) that can also be used to check the PH assumption.

```
*****  
*** testing for PH assumption      ***  
*****  
  
xi: stcox i.treat i.group age female durprime, ///  
      nohr schoenfeld(resid0*) scaledsch(resid1*)  
  
stphtest, log detail
```

Test of proportional hazards assumption

Time: Log(t)

	rho	chi2	df	Prob>chi2
_Itreat_1	0.00813	0.03	1	0.8721
_Itreat_2	-0.03002	0.36	1	0.5460
_Itreat_3	0.03066	0.35	1	0.5548
_Igroup_2	-0.08578	2.69	1	0.1010
_Igroup_3	-0.09582	3.32	1	0.0684
age	-0.03376	0.37	1	0.5449
female	-0.09334	3.33	1	0.0681
durprime	-0.09343	3.62	1	0.0571
global test		11.57	8	0.1716

More techniques: analysis of residuals

- For Cox regression there are several types of residuals!
 - ▷ Cox-Snell: overall model fit
 - ▷ Martingale: functional form for X 's
 - ▷ **Schoenfeld**: checking the PH assumption
 - ▷ Score, Deviance: leverage, outliers
- **Schoenfeld**:
 - ▷ Let $X_{(i)} = (X_{1i}, X_{2i}, \dots)$ be the covariate associated with the observed failure time, $t_{(i)}$. Let \mathcal{R}_i represent the subjects that are at-risk for this failure time.

▷ Define:

$$r_{ji} = X_{ji} - [\text{weighted average of the } X_j \text{'s for } \mathcal{R}_i]$$

$$r_{ji} = \text{“observed”} - [\text{“expected” under PH model}]$$

$$= X_{ji} - \sum_{k \in \mathcal{R}_i} \left(\frac{w_k}{W_i} \right) \cdot X_{jk}$$

$$w_k = \exp(\beta_1 X_{1k} + \beta_2 X_{2k} + \dots)$$

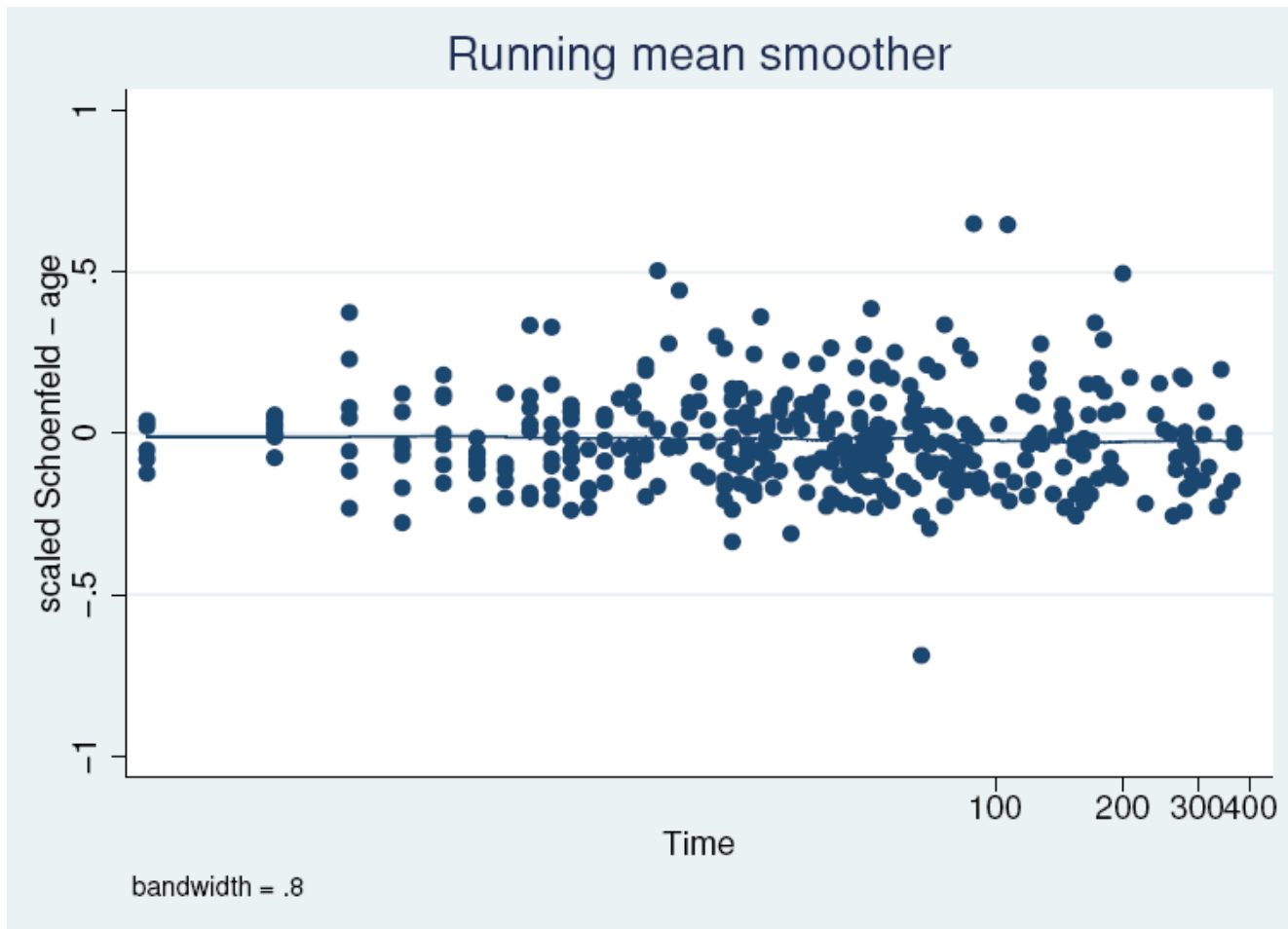
$$W_i = \sum_{k \in \mathcal{R}_i} w_k$$

- ▷ There is a residual for each predictor variable.
- ▷ The residuals are only for the *observed* failure times.

-
- Use: Plot residual versus time.
 - Interpretation:
 - ▷ ◦ If a smooth through the residuals is **constant** over time, then the agreement between the observed covariate (for the person who failed) and the prediction assuming a PH model is good.
⇒ PH assumption looks fine.
-

- Interpretation:

- ▶ ○ If an **increasing** trend is observed, then the observed failures are occurring more often than expected among subjects with **high** values at later follow-up times.
⇒ Hazard ratio is **increasing** over time. PH violated.
 - ▶ ○ If a **decreasing** trend is observed, then the observed failures are occurring more often than expected among subjects with **low** values at the later follow-up times.
⇒ Hazard ratio is **decreasing** over time. PH violated.
-



Summary

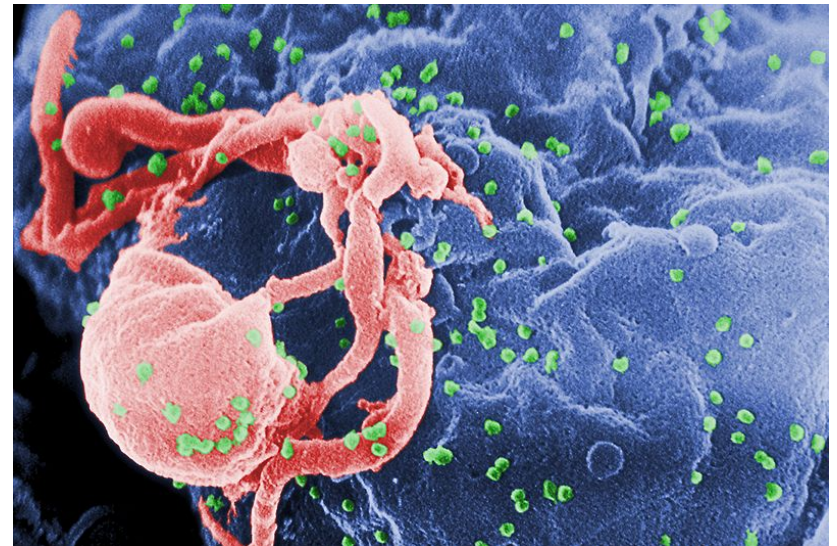
- log -log Plots.
 - Comparing Kaplan-Meier Curves to Fitted Survival under the model.
 - PH Testing based on Schoenfeld Residuals.
 - Scaled Schoenfeld residuals can display the hazard ratio as a function of time – hints at form of $\beta(t)$.
 - **Next:** using Cox regression to estimate time-varying hazard ratios by including a covariate-by-time interaction.
-

A Real Clinical Trial Example: The HPTN 052 Study

- Background
- Design Considerations
- Statistical Methods Development Example
- Additional Issues

Background

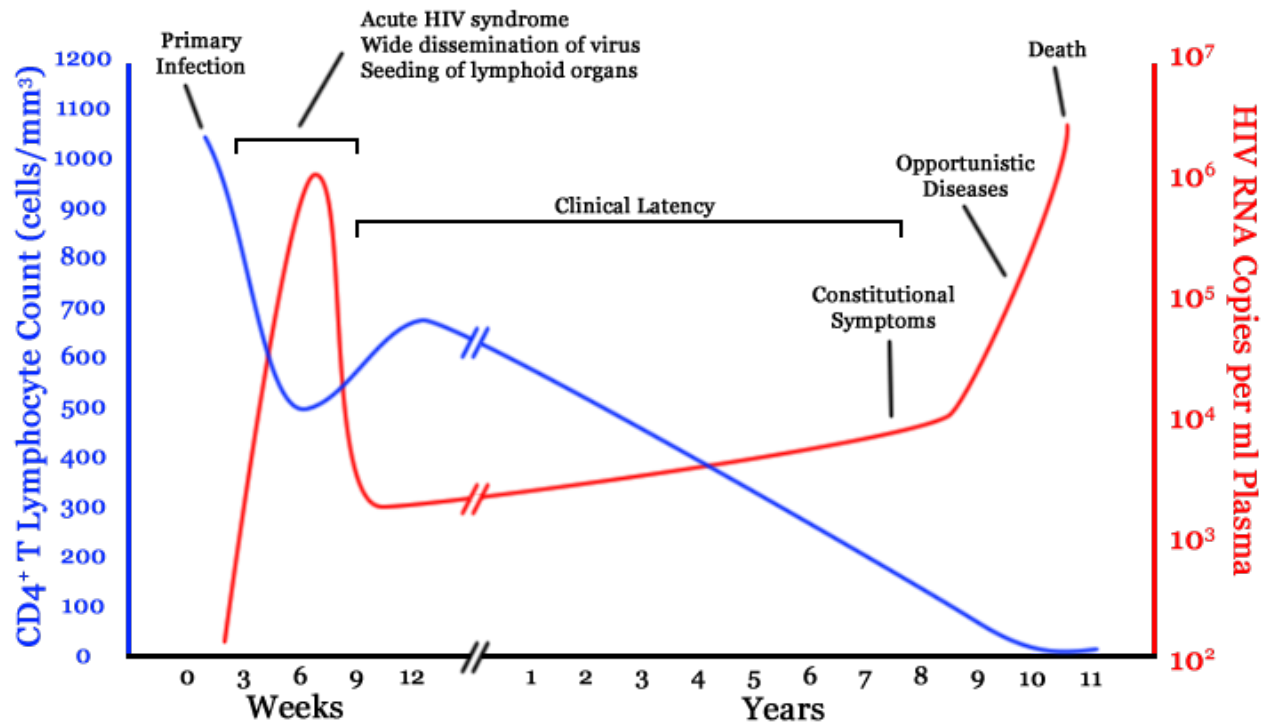
- About HIV
 - A lentivirus belonging to the retrovirus family
 - Presents as free viral particles or virus within infected immune cells
 - Acquired by transfer of blood, semen, vaginal fluid, pre-ejaculate or breast milk
 - Major routes: unprotected sex, contaminated needles, breastfeeding and vertical transmission at birth



Scanning electron micrograph of HIV-1 (in green) budding from cultured lymphocyte. Multiple round bumps on cell surface represent sites of assembly and budding of virions.

Background

■ Natural history of untreated HIV/AIDS



Background

- HIV Prevention
 - No effective vaccine is available in prevention of HIV infection
 - Moderate efficacy about 30% risk reduction
 - Hopefuls include
 - Novel vaccine candidates
 - Microbicide gels
 - Pre-Exposure Prophylaxis (PrEP) with ART
 - Avoidance of exposure used to be the only reliable way to escape infection
- Prevention to target HIV-infected?
 - Would ART benefit prevention of HIV transmission
 - Treatment-as-Prevention (TasP)
 - When to start?

HPTN 052: Immediate vs Delayed

■ Immediate therapy

□ Potential benefits

- Lower risk of early transmission
- More sustained virologic response
- Lower risk of permanent CD4 drop

□ Potential risks

- More toxicities
- Lower adherence
- Reduce option for ART when risk of disease is high
- Increase in risky sexual behavior
- High cost / less convenient

■ Delayed therapy

□ Potential benefits

- Less toxicities
- Higher adherence
- ART available when risk of disease is high
- Lower drug resistance
- Lower cost / more convenient

□ Potential risks

- Higher risk of early transmission
- Higher risk of irreversible CD4 drop
- Less sustained virologic response

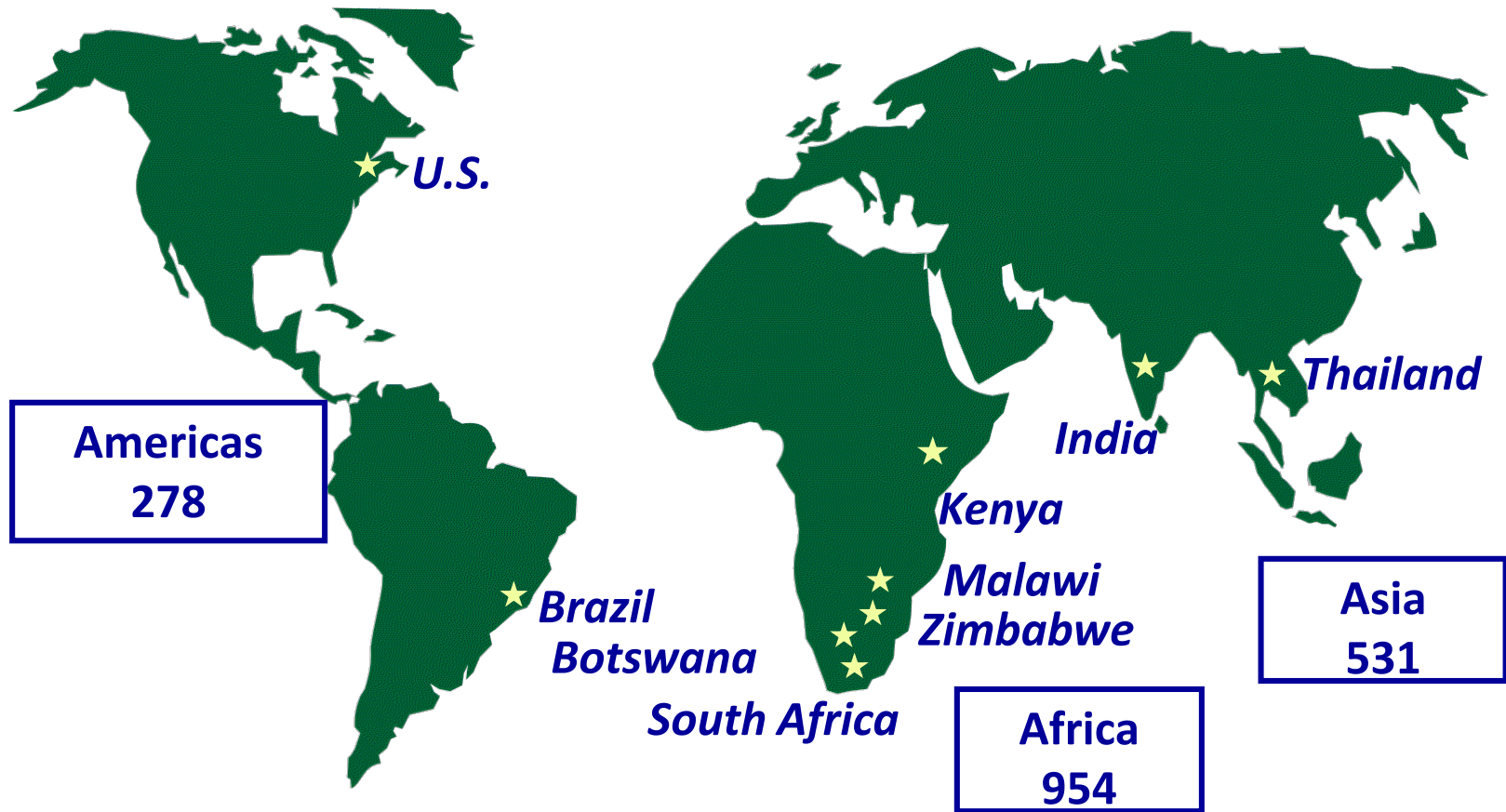
HPTN 052 Study

- Goal
 - Compare long-term effectiveness of two ART strategies in HIV transmission among sero-discordant couples
- Study population
 - HIV discordant couples with index partners of CD4+ counts between 350-550
- Two treatment strategies
 - Immediate therapy: ART initiation upon enrollment
 - Delayed therapy: ART initiation when CD4 counts falls between 200-250 or developing AIDS-defining illness

Trial design

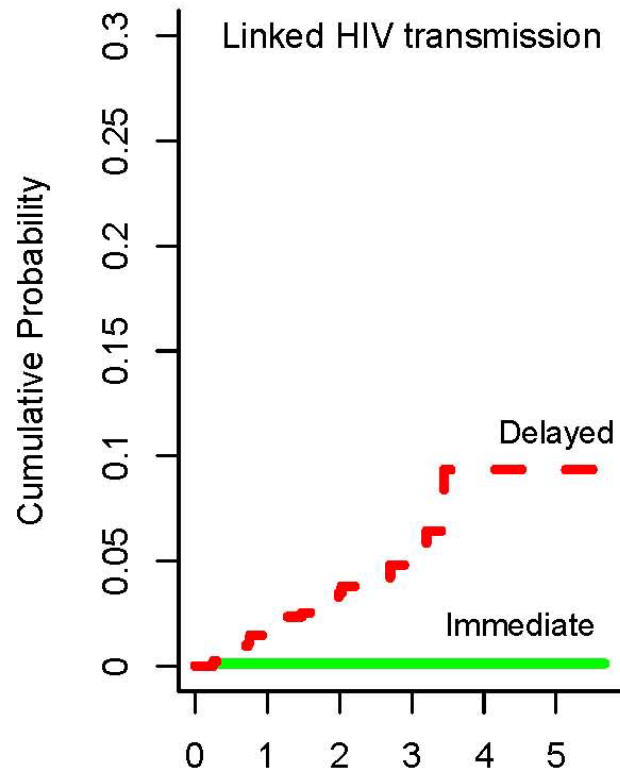
- Multi-site, two-arm, control-randomized (1:1) trial
 - 3 continents/8 countries/12 clinical sites
- 1.5 years accrual with 5 years of follow-up
 - 5 years of follow-up per participant
 - Up to 6.5 years of study duration
- Primary endpoint
 - Incident HIV infections occurring in the partners of randomized HIV-infected index cases
 - Only acquisition from the index partner will be included in the primary analysis
 - Each endpoint will need to be confirmed such that the viral envelope sequence in the index case matches that of the partner.

Enrollment

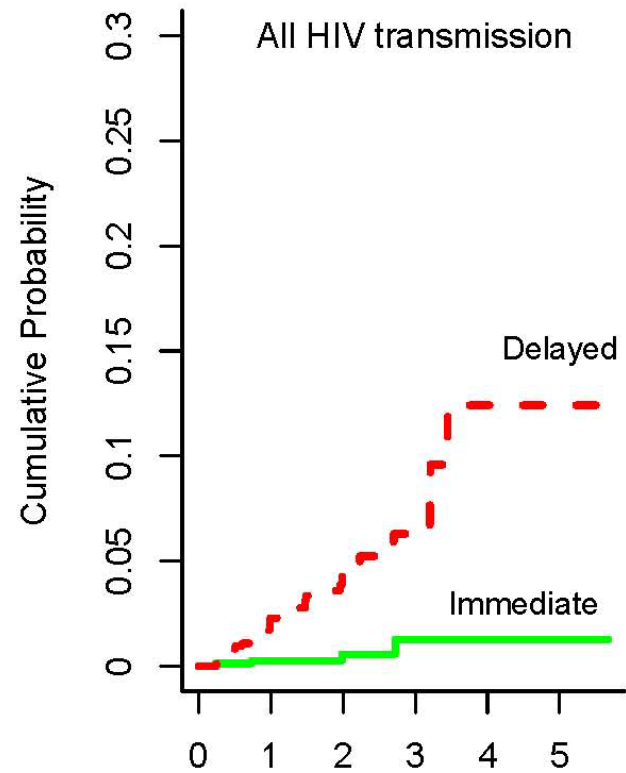


Trial Results Released in 2011

	Im	De	HR	Efficacy	95% CI
Linked Transmission	1	27	0.037	96.3%	72-99%
All transmission	4	35	0.114	88.6%	68-96%
Clinical events	40	65	0.594	40.6%	12-60%
Composite events	23	79	0.265	73.5%	56-83%



No. at Risk	Years since Randomization					
	0	1	2	3	4	5
Immediate	893	658	298	79	31	24
Delayed	882	655	297	80	26	22



No. at Risk	Years since Randomization					
	0	1	2	3	4	5
Immediate	893	658	298	79	31	24
Delayed	882	655	297	80	26	22

Primary Results Paper in 2011



The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 11, 2011

VOL. 365 NO. 6

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D.,
Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D.,
Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D.,
Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D.,
Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D.,
Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch.,
Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaud, Ph.D.,
Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D.,
David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

News Media

CBS News.com CBS Evening News The Early Show 48 Hours Mystery 60 Minutes Sunday Morning Face the Nation Up to the Minute

CBSNEWS Log in | Register

Shop Motorola ATRIX 4G from AT&T

WATCH NOW TINY HELMET CAMS CAPTURED BIN LADEN RAID MINUTE-BY-MINUTE

Home > Video > CBS Evening News Videos

HIV Transmission Study



PLAY CBS NEWS VIDEO

0:45 / 2:39

SHARE

Add a Comment Share this Video: [f Recommend](#) [Tweet 0](#) [Submit](#)

Major breakthrough in HIV prevention

A study claims treating HIV patients early on can dramatically lower the chances they'll transmit the virus to their sexual partners. Dr. Jon LaPook reports.

RECOMMENDED

-  **Major breakthrough in HIV prevention**
2:39 | May 12, 2011
-  **Helmet cams captured bin Laden raid**
2:49 | May 12, 2011

USAA Retirement Guide

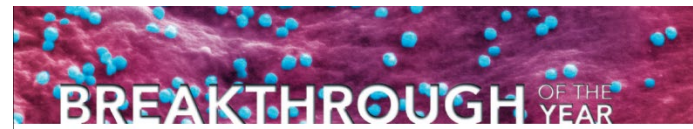
Free comprehensive guide to USAA Retirement Solutions.

Download Now

usaa.com/retirement



Background: The HPTN 052 Study Science's Breakthrough of the Year 2011



HIV Treatment as Prevention

On 1 December, George Washington University in Washington, D.C., hosted "The Beginning of the End of AIDS," a splashy World AIDS Day event that featured three U.S. presidents, business magnates, and rock stars. The catalyst that brought them together was something Anthony Fauci, the top U.S. government HIV/AIDS scientist, told the crowd even 1 year ago would have seemed "wishful thinking": a clinical trial dubbed HPTN 052 and its "astounding" result.

HIV/AIDS researchers have long debated whether antiretroviral drugs (ARVs) used to treat HIV-infected people might have a double benefit and cut transmission rates. To some it was obvious: ARVs reduce HIV levels, so individuals should be less infectious. Skeptics contended that this was unproven. Indeed, a consensus statement issued by the Swiss Federal Commission for HIV/AIDS in 2008 that said effective ARV

to which the viral load in blood predicts the risk of HIV transmission," they cautioned.

Then in May of this year, the 052 clinical trial conducted by the HIV Prevention Trials Network, reported that ARVs reduced the risk of heterosexual transmission by 96%. "Now we have absolute, confirmed data," said Fauci at an AIDS conference this summer in Rome where researchers first presented the HPTN 052 data in detail. Fauci, who heads the U.S. National Institute of Allergy and Infectious Diseases—the main funder of the 573 million trial—said the challenge now was to apply the results. "We just need to take that data and run with it," he said. "The idea of the tension between treatment and prevention, we should just forget about it and just put it behind us, because treatment is prevention." Because of HPTN 052's profound implications for the future response to the AIDS epidemic, *Science* has chosen it as its Breakthrough of the Year.

Myron Cohen, an HIV/AIDS researcher at the University of North Carolina, Chapel Hill, who heads the ongoing HPTN 052 trial, said the finding's impact surprised him. "People were interested in the idea of treatment as prevention, but it created a hurricane-force wind behind the strategy," Cohen says. "The result was so unambiguous."

As Cohen and colleagues explained in the 11 August *New England Journal of Medicine*, HPTN 052 enrolled 1763 "discordant" couples in which one person at the study's start had a known HIV infection. The infected partner could not be taking ARVs and had to have between 350 and 550 CD4 cells per milliliter, which indicates that the person had some immune damage but had yet to develop AIDS (defined as fewer than 200 CD4s). Five countries in sub-Saharan Africa participated, as did Brazil, India, Thailand, and the United States. The study randomly assigned half the infected people to start ARVs immediately, while the other half delayed treatment until CD4 counts dropped below 250.

The researchers planned to compare the groups until 2015. But on 28 April, an independent monitoring board that periodically reviewed the data stunned Cohen and his collaborators when it recommended that the results of the trial be made public as soon as possible. Of the 28 people who become infected with HIV that genetically matched the viruses in their long-term partners, only one was in the early treatment group—which also experienced 41% fewer serious health problems associated with HIV.

Infected people in the delayed arm of the study were offered ARVs immediately. The HPTN 052 results and other recent successes have raised hopes that combining such interventions can now end AIDS epidemics in entire countries, if not the world. ARVs are not a vaccine; people must take them for decades, which is difficult to do and costly. But many call HPTN 052 a "game changer" because of its near 100% efficacy. "It has had an impact on our vision for the future," says Françoise Barré-Sinoussi, a virologist at the Pasteur Institute in Paris who shared the Nobel Prize for helping to discover HIV. Researchers must continue—and even intensify—efforts to develop an effective AIDS vaccine and cure, Barré-Sinoussi stresses, but she notes that countries can apply treatment as prevention today.

Julio Montaner, a prominent advocate of the strategy at the University of British Columbia, Vancouver, in Canada says HPTN 052 has persuaded leaders such as U.S. President Barack Obama—whose administration recently announced a policy goal of creating "an AIDS-free generation"—to take action. "Clinicians and policymakers are always asking for the ultimate evidence," Montaner says. "HPTN 052 was the unequivocal piece of the puzzle to close any doubts."

Given resource constraints and logistical hurdles, treatment as prevention isn't going to sweep the world anytime soon. But HPTN 052 has made imaginations race about the what-ifs like never before, spotlighting the scientifically probable rather than the possible. And now a growing number of HIV/AIDS experts are insisting that the irresponsible and appalling thing to do is nothing.

—JOE COHEN

Online

For an expanded version of this section, with podcast, video, links, and more, see www.sciencemag.org and sciencecareers.org.



Double duty. This year a study proved that anti-HIV drugs both treat and prevent HIV infections.

treatment could virtually stop heterosexual transmission was denounced as "appalling," "inconclusive and irresponsible," "dangerous," and "misleading." The Joint United Nations Programme on HIV/AIDS and the World Health Organization also responded with alarm, urging people to continue using condoms and stressing that semen or vaginal secretions might harbor the virus even when blood tests showed no trace of it. "More research is needed to determine the degree

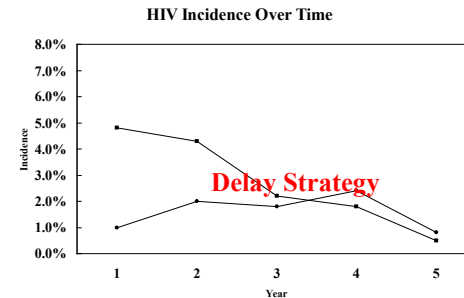
Downloaded from www.sciencemag.org on December 22, 2011

Final Trial Results in 2015

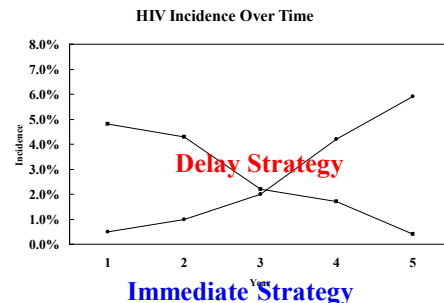
	As of 05/11/2011			After 05/11/2011			Overall		
	PY	# HIV (Rate)	# Linked (Rate)	PY	# HIV (Rate)	# Linked (Rate)	PY	# HIV (Rate)	# Linked (Rate)
Total	3482	46 (1.32)	37 (1.06)	5012	32 (0.64)	9 (0.18)	8494	78 (0.92)	46 (0.54)
Early arm	1751	4 (0.23)	1 (0.06)	2563	15 (0.59)	2 (0.08)	4314	19 (0.44)	3 (0.07)
Delayed arm	1731	42 (2.43)	36 (2.08)	2449	17 (0.69)	7 (0.29)	4180	59 (1.41)	43 (1.03)
Rate ratio		0.09	0.03		0.86	0.28		0.31	0.07
Risk reduction		91%	97%		14%	72%		69%	93%

Design Considerations: Sample Size

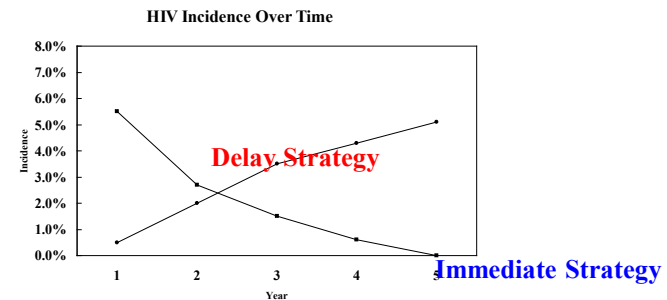
- What did we expect?
 - Immediate and delayed therapies might work differentially on HIV progression over time



Immediate Strategy



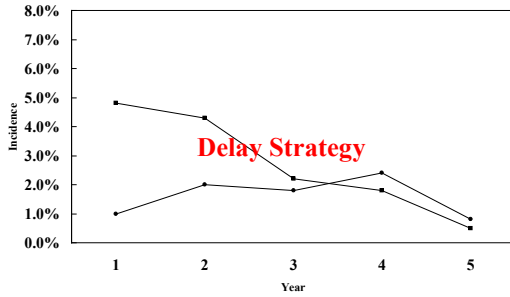
Immediate Strategy



Immediate Strategy

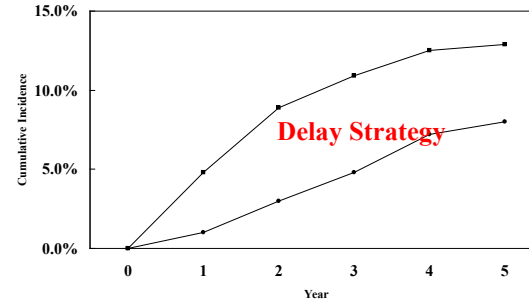
Possible Consequences (I)

HIV Incidence Over Time



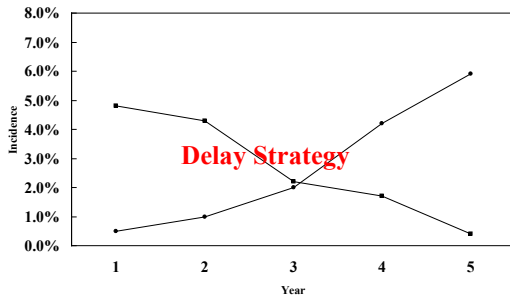
Immediate Strategy

Cumulative HIV Incidence



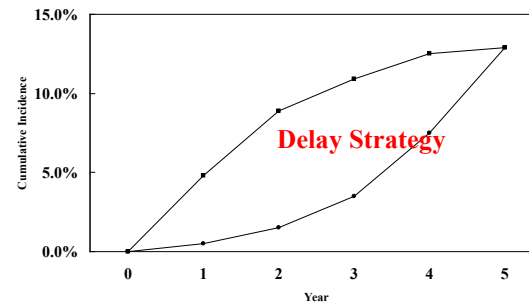
Immediate Strategy

HIV Incidence Over Time



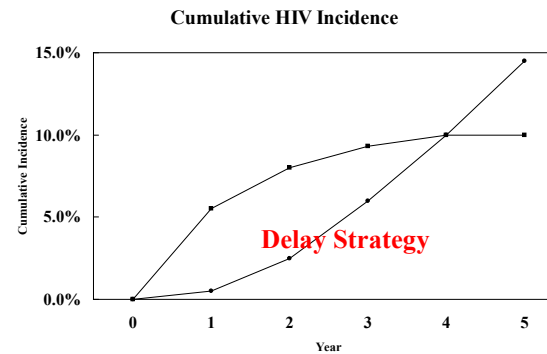
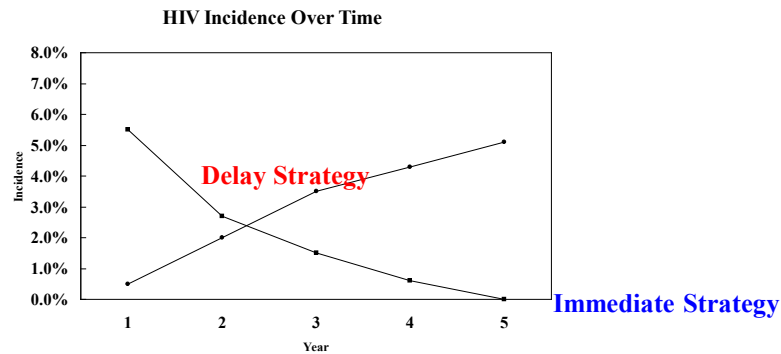
Immediate Strategy

Cumulative HIV Incidence



Immediate Strategy

Possible Consequences (II)



Immediate Strategy

- From a statistical modeling perspective
 - Time-varying incidence rates of a cohort: hazard functions
 - Early difference is not predictive of later difference
 - If using the popular Cox proportional hazards model
 - non-proportional hazards
 - cross-over in hazard functions

Statistical Issues

- How would we accommodate a less systematic expectation (e.g., non-additive or non-multiplicative difference)?
 - What type of endpoints shall we use?
 - Time-to-event?
 - What statistical procedure shall we use?
 - Kaplan-Meier/Log-Rank/Cox Model?

Sample Size for HPTN 052

■ Step 1

- Expected differences in cumulative HIV rates at the end of the trial are computed under the assumption that participants in the delayed arm do not initiate ART at any point in time during follow-up. We will calculate the expected differences and the average effectiveness

■ Step 2

- Taking into account the delay time to initiation of ART in the delayed arm, we will re-calculate the average effectiveness (and power) computed in Step 1.

■ Assumption 1

- Annual HIV incidence rates (rates of acquisition) among the partners of index cases who received HIV primary care plus placebo only (e.g., no initiation of ART at any point in time):

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Cumulative 1-year HIV incidence rates	5%	5%	3%	3%	1%	1%	1%

- 5-year cumulative incidence rate: 15.9%

■ Assumption 2

- Expected effectiveness for Arm 1 (immediate initiation of ART) compared to HIV primary care plus placebo only over time under two scenarios of decreasing effectiveness over time

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
(1) High effectiveness early with rapid decrease to 20%	80%	60%	40%	20%	20%	20%	20%
(2) Medium effectiveness early with decrease to 10%	50%	40%	30%	20%	10%	10%	10%

- HIV incidence rates: 7.8% (high effectiveness), 10.4% (medium effectiveness)

■ Assumption 3

- Assume 5 years fixed follow-up with 5% annual loss to follow-up

Effectiveness	Number of Required Study Couples	
	80% Power	90% Power
50%	640	860
45%	820	1100
40%	1070	1440
35%	1450	1940
25%	3020	4050

- A total sample size of 1750 provides 90% power to detect an effectiveness of 37% as in the rather extreme case of scenario (2).

■ Assumption 4

- Assuming uniform distribution of CD4 cell counts in the study population ($350 \leq \text{CD4} \leq 550$), a rate of CD4 cell loss of 60 cells per year, and 10% annual incidence of AIDS-defining illnesses. The following table represents the expected proportion of participants on Arm 2 who will initiate ART over five years of follow-up

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Percentage of participants in Arm 2 initiating ART	10%	27%	56%	80%	100%	100%	100%

- Median ART-initiation time in delayed arm is 2.8 years

■ Assumption 5

- A risk reduction from 25% to 50% is anticipated for the partners of those initiating ART during follow-up. This assumption combined with assumptions 1 and 3 will yield an expected five-year HIV cumulative rate for the participants of the delayed arm.
- 5-year cumulative incidence rates:
 - 14.4% (25% effectiveness)
 - 13.8% (35% effectiveness)
 - 12.9% (50% effectiveness)

Power

Scenario	Expected Cumulative HIV Rate at the End of Trial for Arm 1	Percentage of Rate Reduction for Index Cases in Arm 2 Initiating ART	Expected Cumulative HIV Rates at the End of Trial for Arm 2	Power	Effectiveness
(1) High effectiveness early with rapid decrease to 20%	8.3%	25%	14.9%	98%	46%
		35%	14.2%	95%	43%
		50%	13.2%	87%	39%
(2) Medium effectiveness early with decrease to 10%	11.1%	25%	14.9%	61%	27%
		35%	14.2%	46%	24%
		50%	13.2%	25%	17%

Summary of Power Analysis

- With sample size 1750
 - Scenario 1
 - 90% power to detect a 5.1% absolute difference (12.9% versus 7.8%) in 5-year cumulative HIV incidence rates
 - This power is achieved under a reduction of risk of acquisition for partners of those who initiate ART in the delayed arm during follow-up as high as 50%.
 - Scenario 2
 - 66% power to detect a 3.5% absolute difference (14.4% versus 10.9%) in the 5-year cumulative HIV incidence rates
 - If the decrease in risk of acquisition for partners of those on arm 2 who initiate ART is more than 25%, the trial will be greatly underpowered under this scenario. In this case, the absolute difference in the 5-year cumulative HIV rate will be less than 3.2%, which might not be of clinical importance.

Design Considerations: Monitoring Plan

- Goal of a monitoring plan
 - For repeated data analyses
 - Satisfies the ethical need for early termination when initial results are extreme
 - Not terminates a study prematurely when the initial results just appear to be extreme, due to repeated data analyses increasing the chance of false conclusions

Monitoring Plan

- Key issue: what did we monitor?
 - We needed persuasive evidence re Benefit-to-Risk (BTR) accounting for both treatment and prevention issues
 - Monitoring guidelines should be driven by M/M events having the greatest clinical impact by treating a discordant couple as a “therapeutic unit”:
 - Treatment: *Death/WHO Stage 4* events in Index
 - Prevention: *HIV Acquisition* in the Partner
 - Composite monitoring endpoint
 - Earlier occurrence of treatment and prevention endpoints

Sample Size for Monitoring Composite Endpoint

- Time-to-event outcome
 - Control: $\lambda_0(t)$
 - Treatment: $\lambda_1(t) = \lambda_0(t)e^\beta$
 - Hypothesis testing: $H_0: \beta = \beta_0, H_1: \beta = \beta_1$
- In a 1:1 randomization
 - $\alpha = 0.025$, power 0.975
 - $H_0 : \beta = \log 0.8$ vs $H_1 : \beta = \log 0.52$

$$L = \frac{(Z_{1-\alpha} + Z_{1-\beta})^2}{\frac{1}{4}(\beta_1 - \beta_0)^2} = 340$$

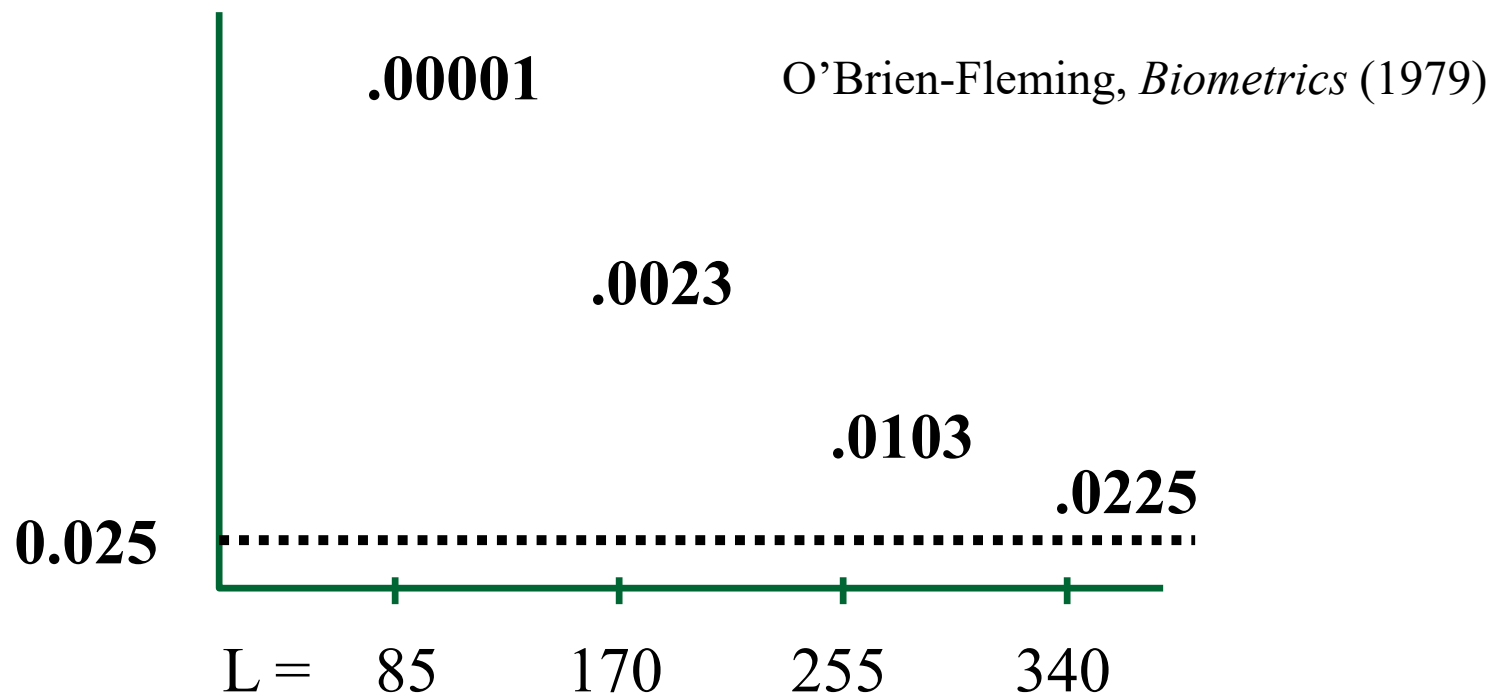
- This trial has power 90% w.r.t.

$$H_0 : \beta = \log 0.8 \text{ vs } H_1 : \beta = \log 0.56$$

O'Brien-Fleming Boundaries

■ Analyses

- 3 interim analyses and 1 final analysis
- Preserve 1-sided false-positive rate of 0.025



- Recommended boundaries for favorable benefits

IF (of Total expected events)	To reject null hypothesis	Expected # of events	I- # events	D- # events	Excess Events	p-value
25%	0.3352	85	21	64	43	0.00001
50%	0.5178	170	58	112	54	0.0023
75%	0.5986	255	95	160	65	0.0103
100%	0.6436	340	133	207	74	0.0225

- Recommended boundaries for unfavorable lack-of-benefits

IF	To reject the alternative	Expected Events	I-events	D-events	Excess Events	p-value
25%	1.9093	85	56	29	27	0.00001
50%	1.2359	170	94	76	18	0.0023
75%	1.0691	255	132	123	9	0.0103
100%	0.9943	340	170	170	0	0.0225

Performance standards on quality of trial conduct

Performance Standard	Targeted Level of Performance	Minimally Acceptable Level of Performance for this Criterion
Rate of Trial Enrollment	1668 couples for 18 months; 60/month for first 6 months; 110/months for next 12 months	75% of target rates
Average HIV Infection Rate per annum (cumulated in 6.5-year follow-up)	1.65% (10.74%)	1.12% (7.31%)
Adherence Rate	95%	90%
Retention Rate per annum	98% of participants	96% of participants
Decreased Viral Load once on ART	Non-detectable viral load	0.5 log 10 in immediate in first 3 years
Median Delay Time	2.8 years	1 year

Methods development example: semiparametric regression model based on survival probabilities

- Proportional odds model

$$\log \frac{S(t | Z)}{1 - S(t | Z)} = \alpha(t) + \beta^T Z,$$

- Available methods

- Murphy, et al. (1997, *JASA*)
- Yang & Prentice (1999, *JASA*)

- Time-varying covariates

- Transformation model with frailty
 - Kosorok, et al. (2002, *Ann Stat*)
 - Zeng & Lin (2006, *Biometrika*)

An extended proportional odds model

- Proportional odds model with time-varying covariates

$$\log \frac{P\{S(t) = 1\}}{1 - P\{S(t) = 1\}} = \alpha(t) + \beta Z(t), S(t) = P\{D(t) = 1\}$$

- Estimation by Differential Equations

$$\mathcal{F}_t = \sigma\{N_i(u), Y_i(u), \tilde{Z}_i; 0 \leq u \leq t, i = 1, 2, \dots, n\}$$

$$B_i(t; \beta) = \exp\{\beta^T Z_i(t)\}$$

$$E\{dN_i(t) \mid \mathcal{F}_{t-}; \beta_0, R_0\} = \frac{Y_i(t)}{B_i(t; \beta_0) + R_0(t)} \{dR_0(t) - R_0(t)d \log B_i(t; \beta_0)\}$$

$$M_i(t; \beta, R) = N_i(t) - \int_0^t Y_i(u) \{B_i(u; \beta) + R(u)\}^{-1} \{dR(u) - R(u)d \log B_i(u; \beta)\}$$

$$\begin{aligned} \sum_{i=1}^n \{B_i(t; \beta_0) + R_0(t)\} dN_i(t) - \sum_{i=1}^n Y_i(t) \{dR_0(t) - R_0(t)d \log B_i(t; \beta_0)\} \\ = \sum_{i=1}^n \{B_i(t; \beta_0) + R_0(t)\} dM_i(t; \beta_0, R_0). \end{aligned}$$

Estimation equations for baseline function

$$\sum_{i=1}^n [\{B_i(t; \beta) + R(t)\}dN_i(t) - Y_i(t)\{dR(t) - R(t)d \log B_i(t; \beta)\}] = 0$$

$$dR(t) + R(t)d \log P_n(t; \beta) = dQ_n(t; \beta)$$

where

$$P_n(t; \beta) = \exp\left[-\int_0^t \sum_{i=1}^n \{dN_i(u) + Y_i(u)d \log B_i(u; \beta)\} / \sum_{i=1}^n Y_i(u)\right], \text{ and}$$

$$Q_n(t; \beta) = \int_0^t \sum_{i=1}^n B_i(u; \beta)dN_i(u) / \sum_{i=1}^n Y_i(u).$$

$$\hat{R}_n(t; \beta) = P_n(t; \beta)^{-1} \int_0^t P_n(u-; \beta)dQ_n(u; \beta)$$

More Details

- Chen, Y. Q., Masse, B., Wang, L., Ou, S.-S., Li, X., Donnell, D., Marybeth, M., Gamble, T., Ribauldo, H., Cohen, M. S. and Fleming, T. S. (2012) Statistical considerations for a randomized trial to evaluate the effectiveness of antiretroviral therapy plus HIV primary care versus HIV primary care alone to prevent the sexual transmission of HIV-1 serodiscordant couples. *Contemporary Clinical Trials*, 33: 1280-1286.
- Chen, Y. Q., Hu, N., Cheng, S., Phillipa, M. and Zhao, L.-P. (2012) Estimating regression parameters in an extended proportional odds model, *Journal of the American Statistical Association*, 107: 318-330.

Special topics yet to cover

- Competing risks
 - Truncated time-to-event outcomes
 - Interval-censored outcomes
 - Measure of surrogacy
 - Alternative regression models
 - Model predictiveness
 - ROC for time-to-event outcomes
 - Attributable risk functions
 - Multivariate survival times
 - Study designs
 - etc, etc
-

Seattle, Seattle, Seattle...



Thanks to

- Our great TA: Eric Morenz
- And mostly to: Everyone of You!



Q & A
