Proportional Hazards Models With Continuous Marks

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Stat/Biost 572

April 23, 2013

Scientific Motivation

- Randomized vaccine efficacy trials against HIV
- Five major trials (beyond Phase II-A) since 1998
- Major difficulty: Differential vaccine efficacy (VE)
- Genetic diversity of HIV between and within infected individuals
- Vaccines less effective against differing infecting forms

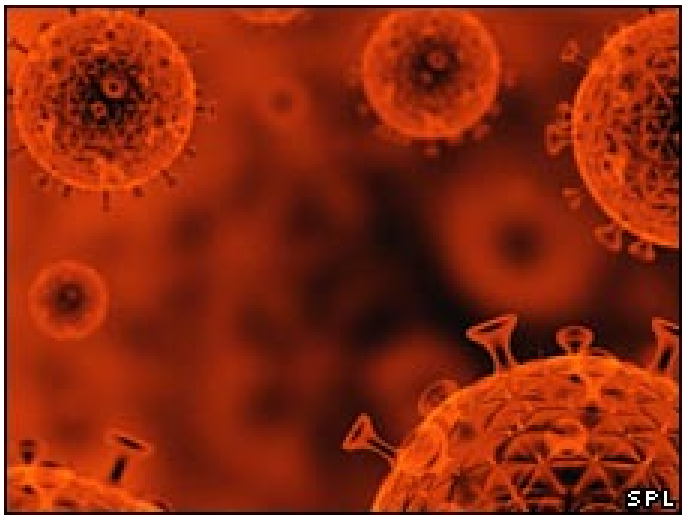


Image: Science Photo Library

Differential vaccine efficacy: a **huge** problem

- The problem: Evaluating the possibility of broad protection

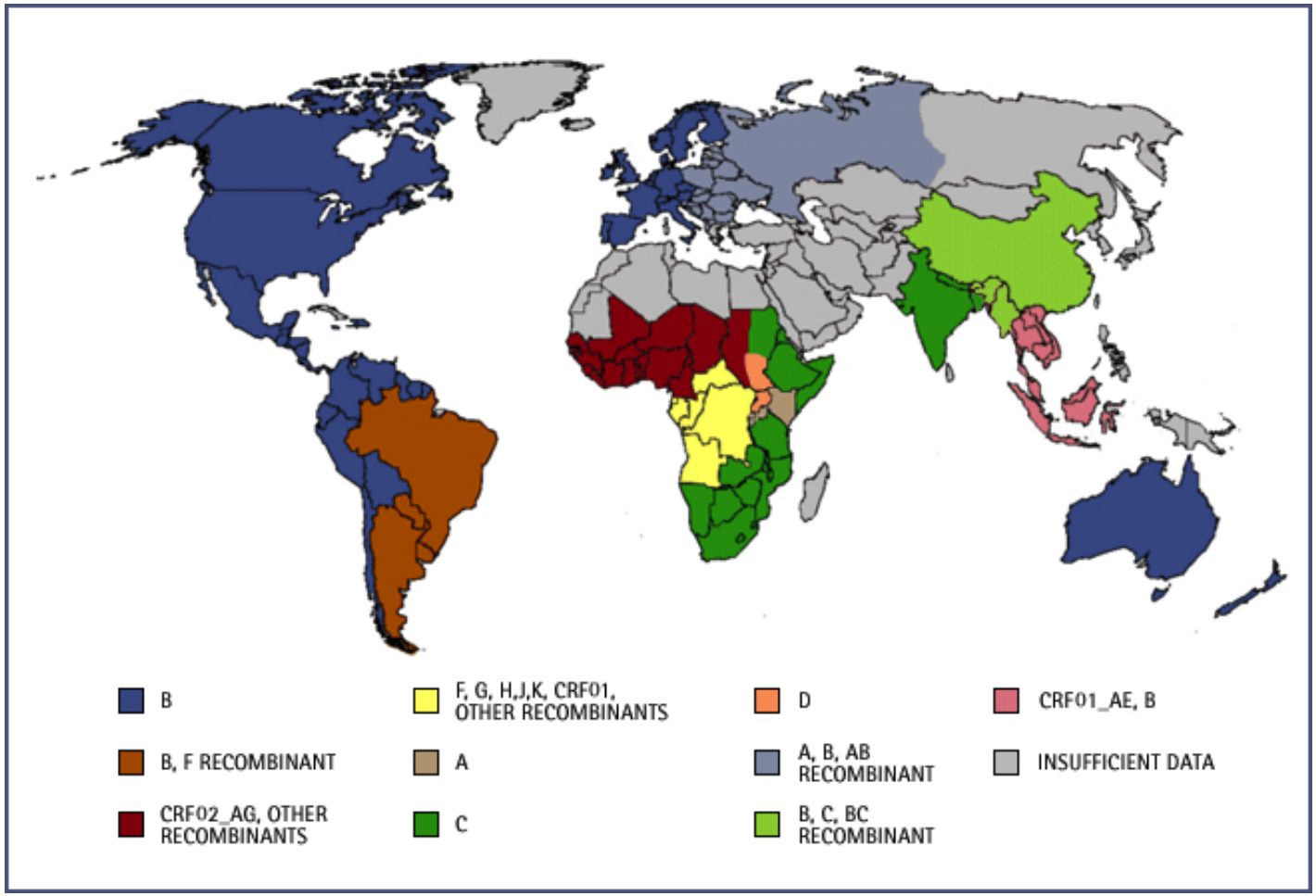
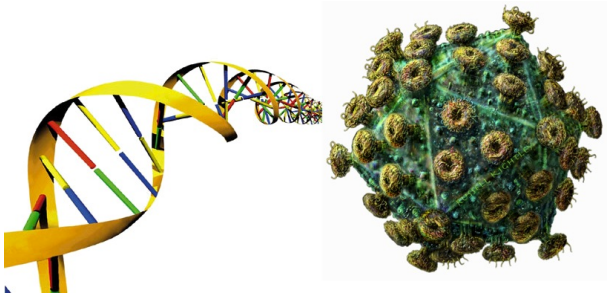


Image: International Aids Vaccine Initiative Report: August 2003 [Francine McCutchan, Henry M. Jackson Foundation]

Characterizing genetic diversity

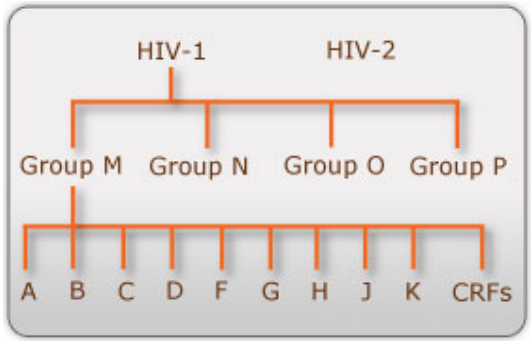
Sequence HIV from infected:



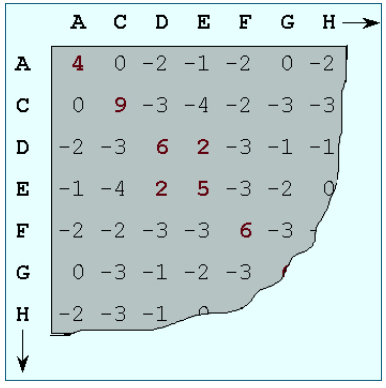
Mismatches at sequence loci:

```
PIVQNLQGQM VHQAISPRTL NAWVKVVEEK
.......... ..R......T ..........
.......... ..R......T ..........
.......... T.A....... ..........
.......... ..R....... ..........
.V........ T.A..G.... ....G.....
```

Use discrete categories:



Substitution matrix (weights):



	A	C	D	E	F	G	H
A	4	0	-2	-1	-2	0	-2
C	0	9	-3	-4	-2	-3	-3
D	-2	-3	6	2	-3	-1	-1
E	-1	-4	2	5	-3	-2	0
F	-2	-2	-3	-3	6	-3	
G	0	-3	-1	-2	-3		
H	-2	-3	-1	0			

- Methodology for continuous measures is the focus of this study

Statistical methods

- Goal: Evaluate VE in presence of competing risks, defined by a *mark* (covariate observed only in cases of failure).
- Mark-specific VE in time-to-event data:

$$VE(t, v) = 1 - \frac{\lambda(t, v|X = 1)}{\lambda(t, v|X = 0)}$$

$$\lambda(t, v|X = x) = \lim_{\Delta t \to 0} \frac{\Pr(T \in [t, t + \Delta t), V = v|X = x, T > t)}{\Delta t}$$

  - T: failure time
  - V: mark variable
  - X: Vaccine (1) or placebo(0). Could be a vector, including other covariates of interest.

Discrete competing risks

- Prentice *et al.* (1978) proposed model for finite risk categories (v = 1,...,m) under the proportional hazards model:

$$\lambda(t, v|X) = \lambda_0(t, v) \exp(\beta(v)^T X)$$

- Baseline hazard λ_0 factors out in partial likelihood:

$$\mathcal{L}_v(\beta_v) = \prod_{i=1}^{d_v} \frac{e^{\beta_v^T X_{v(i)}(t)}}{\sum_{j=1}^{n} Y_{v(j)}(t_{v(i)}) e^{\beta_v^T X_{v(j)}(t)}}$$

  - $t_{v(1)} < ... < t_{v(d_v)}$: uncensored failure times with cause v
  - $X_{v(i)}(t)$: covariate vector for $v(i)$th individual (possibly t-dependent)
  - $Y_{v(i)}(t)$: indicator of $v(i)$th individual being at risk for v at t.

Continuous competing risks

- The authors extend this model to continuous (bounded) marks (*w.l.o.g.*, assume $v \in (0, 1)$)
- Address a bivariate mark-specific hazard function:

$$\lambda(t, v|X = x) = \lim_{\Delta t, \Delta v \to 0} \frac{\Pr(T \in [t, t + \Delta t), V \in [v, v + \Delta v)|X = x, T > t)}{\Delta t \Delta v}$$

Continuous competing risks

- Localized log partial likelihood contains a kernel function K:

$$\ell_v(\beta_v) = \sum_{i=1}^{n} \int_0^1 \int_0^\tau K_h(u-v) \times \left[\beta^T(v) X_i(t) - \log \left(\sum_{j=1}^{n} Y_j(t) e^{\beta^T(v) X_j(t)} \right) \right] \times N_i(dt, du)$$

  - $K_h(\cdot)$: Kernel function with bandwidth h
  - $t \in (0, \tau)$: Follow-up period
  - $N_i(t, v) = I(X_i \leq t, \delta_i = 1, V_i \leq v)$ is a marked point counting process, with δ_i being a failure indicator
- Kernel function "borrows" from observations with mark near v

Point estimation and asymptotic results

- Estimation of $\beta(v)$ (log hazard ratio).
  - $\hat{\beta}(v)$ solves score equations derived from localized partial likelihood
  - Find solution using Newton-Raphson algorithms
- Authors show asymptotic consistency and normality of $\hat{\beta}(v)$ as well as the cumulative vaccine efficacy, $\widehat{CV}(v) = \int_0^v 1 - \exp(\hat{\beta}(u))du$.
- Also find a tractable estimator $\hat{\rho}^2(v)$ of the asymptotic variance of $\widehat{CV}(v)$

Hypothesis testing

- Test for overall vaccine efficacy:

  H_{10} : $VE(v) = 0$ for all $v \in [a, b]$ *vs.*
  - H_{1a} (general): $VE(v) \neq 0$ for some v
  - H_{1m} (monotone): $VE(v) \geq 0$ (> 0 for some v)
- Test for differences in vaccine effect:

  H_{20} : $VE(v)$ does not depend on $v \in [a, b]$ *vs.*
  - H_{2a} (general): $VE(v)$ depends on $v \in [a, b]$
  - H_{2m} (monotone): $VE(v)$ decreases as v increases over $[a, b]$

Summary

- Problem: Vaccine development hindered by genetic diversity of HIV and differential VE.
  - Previous methods only work with discrete marks of failure
- Solution: Develop MLE and hypothesis testing approaches for failure time data with *continuous* marks of failure.
- What's next?
  - Simulation studies to assess power and size of hypothesis tests
  - Analyze results from VaxGen 004, a Phase III trial $n = 5403$.
  - Compare to discrete competing risk analyses: does power really increase?