MEASURING HIV INCIDENCE:
APPROACHES & CHALLENGES
VOCABULARY

HIV PREVALENCE
HIV INCIDENCE
U.S. Centers for Disease Control
2008

HIV PREVALENCE = 1.1 MILLION

HIV INCIDENCE= 56,000
HIV PREVALENCE
AIDS DX DATE = HIV INFECTION DATE + INCUBATION

\[ E(y_i) = \int_0^{t_i} I(s) F(t_i - s) - F(t_{i-1} - s) \, ds \]

\[ E(y) = \beta Z \]

\[ \text{var}(y) = \sigma^2 E(y) \]
BACK-CALCULATION: ICEBERG EFFECT

Symptomatic cases

Cases still incubating
BACK-CALCULATION: ICEBERG EFFECT

AIDS CASES

Tested & found HIV+ (Not yet AIDS)

UNSEEN HIV INFECTIONS (INCUBATING)
DECONVOLUTION
U.S. HIV PREVALENCE=1.1 million (JAMA, 2008)

- STATISTICAL DECONVOLUTION
- UNCERTAINTIES
  - INCUBATION PERIOD
  - COMPLETENESS OF CASE REPORTING
  - PARAMETRIC MODEL FOR $\alpha(s), I(s)$
  - RECENT INFECTIONS
CURRENT HIV INCIDENCE

MEASURES THE LEADING EDGE OF THE EPIDEMIC

• COHORT STUDY

• CROSS-SECTIONAL BIOMARKER APPROACH
CURRENT HIV INCIDENCE

COHORT STUDY

\[ \text{Incidence} = \frac{\text{incident infections}}{\text{person time}} \]

ISSUES

Assembling cohort is difficult
Counseling may reduce HIV risk
Incidence is changing over time
Selection bias: who returns for follow-up?
CURRENT HIV INCIDENCE

BIOMARKER APPROACH

• CROSS-SECTIONAL SAMPLE

• COLLECT BIOMARKERS OF RECENT INFECTION AT BASELINE

• SNAPSHOOT APPROACH
BIOMARKER APPROACH
BIOMARKER APPROACH

ASSAY 1

INFECTED

WINDOW PERIOD

ASSAY 2

\[ S(t) \] window period survival distrib.
\[ \mu = \text{mean window period} \]
\[ P(\text{Window}) = \int_{0}^{\infty} g(t) S(t) \, dt \]

\[ \approx g \int S(t) \]

\[ = g \mu \]

\( \mu = \text{mean window period} \)

\( g = \text{pdf of window entry times} \)
BIOMARKER APPROACH

PROPORTION IN THE WINDOW = INCIDENCE × \( \mu \)

\[ \hat{I} = \frac{x}{N \mu} \]

X= # in window : assay 1 +, assay 2 -
N= # assay 2 –

• CROSS-SECTIONAL SAMPLE

• NO FOLLOW-UP!

• SNAPSHOT ESTIMATOR
ANTIBODY BIOMARKERS

ASSAY 1 (HIV antibody assay)

ASSAY 2
less sensitive HIV antibody assay

time since infection
BIOMARKERS FOR RECENT INFECTION

DETUNED ASSAY* \( \mu = 129 \text{ days} \)
BED ASSAY* \( \mu = 156 \text{ days} \)

*Need to assay only those HIV antibody +
56,300 ANNUAL NEW HIV INFECTIONS IN U.S.  
JAMA 2008

- BASED ON CROSS-SECTIONAL BIOMARKER APPROACH (BED ASSAY)
- ESTIMATE PROBABILITY PERSON GETS HIV TEST
- 19 EXTRAPOLATED TO 50 STATES
U.S.
EUROPE
INDIA
THAILAND
CARIBBEAN
AFRICA
CONTROVERSY

CDC

“The BED biomarker assay is the preferred approach for calculating HIV incidence in the U.S.”

UNAIDS

“Does not recommend the BED assay for determining incidence”
BIOMARKER ESTIMATE = 2 X HIGHER THAN COHORT
Hargrove (2008)

• Follow-up bias?

• “False recents”
  McWalter and Welte (2009)
  Wang and Lagakos (2009)
INCIDENCE NOT CONSTANT?

\[ \hat{I} \rightarrow \bar{I} \approx \int_0^\infty I(t) f_B(t) \, dt \]

\[ f_B(t) = \frac{S(t)}{\mu} = \text{backward recurrence density} \]

\[ \psi = \int t f_B(t) = \int t \frac{S(t)}{\mu} \, dt \]

\[ \bar{I} \approx I(\psi) + \frac{I''(\psi)V}{2} \]

KAPLAN AND BROOKMEYER, OPERATIONS RESEARCH
SHADOW $\psi = \text{mean of backward recurrence}$

$$\bar{I} \approx I(\psi)$$

$$\psi = \int t f_B(t) = \int t \frac{S(t)}{\mu} dt = \mu(1 + CV^2)$$
SHADOW DEPENDS ON MEAN AND CV OF WINDOW

<table>
<thead>
<tr>
<th>Mean window (yrs)</th>
<th>0.50</th>
<th>1.00</th>
<th>2.00</th>
<th>3.00</th>
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<tbody>
<tr>
<td>0.25</td>
<td>0.16</td>
<td>0.25</td>
<td>0.63</td>
<td>1.25</td>
</tr>
<tr>
<td>0.50</td>
<td>0.31</td>
<td>0.50</td>
<td>1.25</td>
<td>2.50</td>
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<tr>
<td>1.00</td>
<td>0.63</td>
<td>1.00</td>
<td>2.50</td>
<td>5.00</td>
</tr>
<tr>
<td>1.50</td>
<td>0.94</td>
<td>1.50</td>
<td>3.75</td>
<td>7.50</td>
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</tbody>
</table>
• BIAS & VARIANCE

• ACCURACY OF ASSAY FOR HIV INCIDENCE:
  MEAN WINDOW ($\mu$)
  SHADOW (CV, $\mu$)

• BIG $\mu$ OR SMALL $\mu$?
  TRADEOFF : BIAS VS VARIANCE
ISSUES WITH BED/DETUNED ASSAY METHOD

• ELITE CONTROLLERS
  • LONG TAILS OF $S(t)$
  • LOW VIRAL LOADS

ISSUE
ELITE CONTROLLERS: MIXTURE MODEL

• FAST PROGRESSORS THROUGH WINDOW = $\gamma$

• SLOW PROGRESSORS THROUGH WINDOW = $1 - \gamma$
  (e.g. elite controllers)

\[ S(t) = \gamma S_1(t) + (1 - \gamma) S_2(t) \]

\[ shadow = \frac{\mu_1^2 (1 + CV_1^2) \gamma + \mu_2^2 (1 + CV_2^2)(1 - \gamma)}{2(\mu_1 \gamma + \mu_2 (1 - \gamma))} \]
MIXTURE MODEL: ELITE CONTROLLERS

\[ S(t) = \gamma S_1(t) \Gamma + (1-\gamma)S_2(t) \]

\[ \mu_1 = 0.5 \text{ yrs} \quad \text{weibull cv}_1 = .36 \]

\[ \mu_2 = 20 \text{ yrs} \quad \text{weibull cv}_2 = .50 \]

<table>
<thead>
<tr>
<th>1 - \gamma</th>
<th>( \mu ) yrs</th>
<th>Shadow yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>.000</td>
<td>0.50</td>
<td>0.28</td>
</tr>
<tr>
<td>.001</td>
<td>0.52</td>
<td>0.75</td>
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<tr>
<td>.005</td>
<td>0.60</td>
<td>2.33</td>
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<td>.010</td>
<td>0.70</td>
<td>3.81</td>
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<tr>
<td>.015</td>
<td>0.79</td>
<td>4.91</td>
</tr>
<tr>
<td>.020</td>
<td>0.89</td>
<td>5.77</td>
</tr>
</tbody>
</table>

WINDOW PERIOD DENSITY MIXTURE MODEL

\[ 1 - \gamma = .001 \quad \psi = 0.75 \text{ yrs} \]
WINDOW PERIOD DENSITY
MIXTURE MODEL

\[ 1 - \gamma = 0.001 \quad \psi = 0.75 \text{ yrs} \]
\[ = 0.010 \quad \psi = 3.81 \text{ yrs} \]
WINDOW PERIOD DENSITY
MIXTURE MODEL

\[ 1 - \gamma = 0.001 \quad \psi = 0.75 \text{ yrs} \]
\[ = 0.010 \quad \psi = 3.81 \text{ yrs} \]
\[ = 0.020 \quad \psi = 5.77 \text{ yrs} \]
• Biomarker incidence higher than cohort estimate in study of new mothers

• A shadow of 2+ years is produced with only 0.5 % elite controllers.

• HIV Incidence:
  Pre-partum vs post partum period
  Counseling/behavior change

Brookmeyer, AIDS(2009); Brookmeyer, JAIDS (2010)
TINY ALMOST IMPERCEPTIBLE DIFFERENCES IN TAIL BEHAVIOR CAN HAVE HUGE EFFECTS!
SOME SUGGESTIONS
TRIM THE TAILS

WEED OUT ELITE CONTROLLERS, AIDS CASES, ON ART

HIV TEST

CD4

Biomarker window?

HIV RNA (viral load)?

Laeyendecker et al, 2009
RNA PCR / ANTIBODY BIOMARKER

- HIV RNA PCR
- ANTIGEN
- HIV ANTIBODY ASSAY
- INSENSITIVE ANTIBODY ASSAY
PERSPECTIVES

• STATISTICAL CONTRIBUTIONS TO MEASURING HIV EPIDEMIC

• INCORPORATE BIOLOGY INTO MODELS

• SMALL CHANGES IN TAILS CAN HAVE BIG EFFECTS!

• ITS NOT ONLY ABOUT A SINGLE NUMBER: TRENDS