CHINA
Mortality trends

HIV/AIDS mortality increase

0-14
15-49
>=50
合 计

2007 2008 2009 2010 2011 2012
WORLDWIDE: UNAIDS

HIV PREVALENCE - 6 million

HIV INCIDENCE 42%
• INTERPRETATION OF TRENDS
• MEASUREMENT ISSUES
• SOME FUTURE DIRECTIONS
VOCABULARY: 3 INDICATORS

• HIV PREVALENCE

• HIV INCIDENCE

• HIV/AIDS MORTALITY RATE
  -deaths among persons with HIV/AIDS
  -(usually) regardless of cause of death
INTERPRETATION of TRENDS
MORTALITY
(assume complete reporting of deaths)

BAD NEWS OR GOOD NEWS?
INCIDENCE VS. MORTALITY

New HIV infections

Deaths

Calendar Year

BAD NEWS OR GOOD NEWS?
INTERPRETING TRENDS

HIV mortality ↑ as current HIV incidence ↓ because...

... persons infected years ago are dying

... mortality trends do NOT reflect recent incidence trends
HIV INCIDENCE VS. MORTALITY

- Sharp rise in incidence

Diagram showing new HIV infections and deaths over calendar years from 1978 to 1990.
FURTHERMORE

...mortality can still ↑
even though ART (TX) is preventing some deaths
VOCABULARY

• HIV MORTALITY RATE

\[
\frac{\text{total HIV deaths during year in population}}{\text{Population size}}
\]

• CASE FATALITY RATE

\[
\frac{\text{deaths during year from among HIV cases}}{\text{alive HIV cases}}
\]
CHINA
Mortality trends

HIV/AIDS mortality increase

1/100,000

0-14
15-49
>=50
合计

2007 2008 2009 2010 2011 2012
ART coverage improved and case-fatality declined

Case fatality rate (%)

ART coverage (%)

2005 2006 2007 2008 2009 2010 2011 2012 2013

Case fatality (%) ART coverage (%)
CASE FATALITY VS. MORTALITY RATES:
(complete reporting of deaths)

CAN TRENDS MOVE IN OPPOSITE DIRECTIONS?

YES!

- Case fatality ↓ because of better survival (tx, access)
- Mortality rates ↑ because of high incidence in the past even though there have been recent improvements in survival of cases
CASE FATALITY VS. MORTALITY RATES: complete reporting of deaths

NOTE

\[ P(\text{HIV DEATH}) = P(\text{HIV CASE*}) \times P(\text{HIV DEATH |HIV CASE*}) \]

Mortality rate = Prevalence rate \times Case fatality rate

↓ or ↑ \quad \uparrow \quad ↓

*Case here refers to advanced HIV disease to control for changing case mix
Further Complication in China: Measurement only deaths with prior HIV test counted

Test for HIV

Follow-up for death

Death Possibly missed

No Prior HIV test

Hospital admission (AIDS)

death-missed

HIV test

death-missed

Death possibly missed
If counting of deaths requires prior HIV tests,

...then increases in testing can cause increases in the reported mortality rate

... even though the true mortality rate is constant or even decreasing.
HIV PREVALENCE TRENDS

NEW INFECTIONS → PREVALENCE → DEATHS
• Prevalence may ↓ or ↑ depending on whether HIV deaths > or < than new infections

• Prevalence can be constant even though incidence and deaths are rising

• Prevalence may ↑ (↓) because survival ↑ (↓)

• Prevalence may ↑ (↓) because incidence ↑ (↓)
<table>
<thead>
<tr>
<th>Incidence</th>
<th>mortality</th>
<th>prevalence</th>
<th>possible explanation</th>
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<tbody>
<tr>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>waning epidemic</td>
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<tr>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>very recent incidence increase</td>
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<tr>
<td>↑</td>
<td>↑</td>
<td>=</td>
<td>new infections= deaths</td>
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<tr>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>good news; tx and prevention improvements</td>
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</table>
Incidence peaked.
Trends in incidence, prevalence and mortality rates can be difficult to interpret. They may go in opposite directions. All indicators need to be considered. Challenges in measuring indicators make interpretation even more difficult.
MEASUREMENT ISSUES
“INDIA SLASHES ESTIMATE OF HIV INFECTED PEOPLE”

Science, 2007

WORLD HIV PREVALENCE DOWN 6 MILLION

UNAIDS, 2008
# NATL SURVEYS OF HIV PREVALENCE

**household, probability-based**

## Demographic & Health Surveys

<table>
<thead>
<tr>
<th>Central/West Africa</th>
<th>East Africa</th>
<th>Southern Africa</th>
<th>Asia</th>
<th>Caribbean</th>
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<tbody>
<tr>
<td>Benin</td>
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<tr>
<td>Senegal</td>
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</table>
HIV PREV RATIO = NATL SURVEYS / ANC

Gouws (2008)
SAMPLING

• REPRESENTATIVENESS
• KEY POPULATIONS
• MARGINALIZED POPULATIONS
• MSM, SW, PWID
HIV INCIDENCE
HIV INCIDENCE: APPROACHES

- Changes in HIV Prevalence
- Cohort Study
- Cross-sectional Biomarker Approach
CHANGES IN PREVALENCE

2 serial cross-sectional HIV prevalence surveys

\[ \Delta \text{prevalence} = \text{new infections} - \text{deaths} + \text{net migration} \]

ISSUES

Sensitive to assumptions about deaths
Prohibitively large sample sizes
Survey 1
\( \hat{p}_1 \)

Survey 2
\( \hat{p}_2 \)

\[ \hat{I} = \frac{\left( \hat{p}_2 - \hat{p}_1 R \right)}{\hat{q}_1 \delta} \]

\( R = \) relative survival

(no migration)

Brookmeyer and Konikoff, 2011
SAMPLE SIZES WITH CV=0.20 OF HIV INCIDENCE RATE, $R=0.80$

Brookmeyer and Konikoff, 2011
SENSITIVITY TO MORTALITY ASSUMPTIONS

Brookmeyer and Konikoff, 2011
UNAIDS
Median survival changed from 9 to 11 years, incidence changed from 4.1 to 2.5 million
COHORT STUDY

\[ \text{HIV INCIDENCE RATE} = \frac{\text{incident infections}}{\text{person time}} \]

ISSUES

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

- CHANGES IN HIV PREVALENCE
- COHORT STUDY
- CROSS-SECTIONAL BIOMARKER APPROACH
BIOMARKER APPROACH

• A SINGLE CROSS-SECTIONAL SAMPLE

• COLLECT BIOMARKERS OF RECENT INFECTION

• SNAPSHOT APPROACH
BIOMARKERS

HIV Antibodies

TIME SINCE INFECTION

HIV ANTIBODY ASSAY
BED ASSAY

window
BIOMARKER APPROACH

CROSS-SECTIONAL SAMPLE

PREVALENCE = INCIDENCE \times \mu

\hat{I} = \frac{X}{N\mu}

X = \# \text{ in window}
N = \# \text{ HIV neg.}
\mu = \text{mean duration infected person is } + \text{ on blue and } -- \text{ on yellow}
\text{mean “window period”}

NO FOLLOW-UP!
NEED \mu
WHERE DOES $\mu$ COME FROM?

EXTERNAL DATA SET:

KNOWN DURATION OF INFECTION (INTERVAL CENSORED) POSSIBLY SERIAL SAMPLES

$\mu$ = mean duration infected person is classified as “recent”
+ ON BLUE AND -- ON YELLOW
mean “window period”

EXAMPLE: HIV + and BED ASSAY -

$\hat{\mu} = 187$ DAYS reference: Hargrove et al. (2008)
REPOSITORY OF SAMPLES
(U.S. CLADE B)

HIVNET 001
MACS
ALIVE
JHU CLINIC

NIH / NIAID R01
Susan Eshleman  JHU
Oliver Laeyendecker NIAID/JHU
R Brookmeyer UCLA
BIOMARKERS OF RECENT INFECTION

BED-CEIA
Biorad Avidity Assay
LAG Avidity Assay
Viral Load
CD4
COST/LOGISTICS

**COST**

- viral load $$$$$$$$$$$
- CD4 count $$$$$$
- Avidity $$
- BED $ 

**LOGISTICS**

CD4 on whole blood; performed in real time
$\hat{\mu} = 101 \text{ days} \quad 95\% \text{ CI } (79,119)$

$\hat{\psi} = 194 \text{ days} \quad 95\% \text{ CI } (109,289)$

$\hat{\mu} = 159 \text{ days} \quad 95\% \text{ CI } (134,186)$

$\hat{\psi} = 184 \text{ days} \quad 95\% \text{ CI } (148,225)$
If BED used by itself as a marker of recent infection, it can overestimate incidence.
## COSTS

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Relative Cost*</th>
</tr>
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<tbody>
<tr>
<td>4 BIOMARKERS</td>
<td>0.44</td>
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<tr>
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<td>0.13</td>
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* Relative to testing all samples with all 4 biomarkers
### COSTS

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<tr>
<td>2 BIOMARKERS (LAG &amp; Avidity)</td>
<td>0.11</td>
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* Relative to testing all samples with all 4 biomarkers
## COSTS

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<th>Relative Cost*</th>
<th>Adjusted rel. cost**</th>
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<td>4 BIOMARKERS</td>
<td>0.44</td>
<td>1.0</td>
</tr>
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<td>0.13</td>
<td>0.47</td>
</tr>
<tr>
<td>2 BIOMARKERS (LAG &amp; Avidity)</td>
<td>0.11</td>
<td>0.33</td>
</tr>
</tbody>
</table>

* Relative to testing *all* samples with all 4 biomarkers
** Relative to the 4 biomarker algorithm adjusting for sample sizes to account for differences in $\mu$
HIV PREVENTION TRIALS NETWORK

• HIV VACCINE PREPAREDNESS STUDY (HIVNET 001)
  U.S. MSM, IDU, high risk women (late 1990’s)
  Celum, Buchbinder, Donnell et al (2001)

• WOMEN’S SEROINCIDENCE STUDY (HPTN 064)
  U.S. high risk women (2009-2012)
  Eshleman, Hughes, Laeyendecker et al 2013

• BROTHERS STUDY (HPTN 061)
  U.S. Black MSM (2009-2012)
  Laeyendecker, Wang, Hughes et al 2013
CURRENT & FUTURE DIRECTIONS

- RATE RATIO

\[
\frac{\hat{I}_2}{\hat{I}_1} = \frac{\frac{X_2}{N_2 \mu}}{\frac{X_1}{N_1 \mu}} = \frac{X_2 N_1}{X_1 N_2}
\]
CURRENT & FUTURE DIRECTIONS

• RATE RATIO

\[
\frac{\hat{I}_2}{\hat{I}_1} = \frac{\frac{X_2}{N_2 \mu}}{\frac{X_1}{N_1 \mu}} = \frac{X_2 N_1}{X_1 N_2}
\]

• Statistical Methods
  (Bayes/continuous; with J. Konikoff, R. Weiss)

• Other subtypes? Countries?

• Representativeness?

• Implementation science
SUMMARY

• Indicator trends can be difficult to interpret.

• Multiple indicators to understand and track trends

• Measurement issues

• New biomarker methods for serial cross-sectional studies promising direction for assessing trends