Presentation Outline

• Why measure HIV incidence?
• HIV incidence assays - how did we get where we are today?
• New insights & developments
• The way forward
At this stage of the epidemic...
Why Determine HIV Incidence?

• Characterize the epidemic in a population
  – Monitor changes over time
  – Identify important sub-populations for interventions

• Assess impact of programs

• Identify populations for HIV intervention trials
  – Endpoint of intervention trials

• Identify individuals for interventions
  – Prioritization
  – Interrupt transmission
Standard Methods for Incidence Determination are Unsatisfactory

- Indirect methods; repeat cross-sectional measurements; modeling
- Prospective follow-up is expensive and unrepresentative
- Enrollment in cohorts leads to behavior change
- Back calculation methods not timely or reliable
Employs data from two recent household-based HIV prevalence surveys:

Dominican Republic, Mali, Niger, Tanzania, Zambia
HIV Incidence Using Early Diagnostic Tests


Days

Detection limit

Seroconversion

Response

Infection

RNA Ab-
P24+
Ab -
P24

Detection limit

Development of Assays for Serologic Testing Algorithms for Recent HIV Seroconversion (STARHS) or Recent Infection Testing Algorithms (RITA)
New Testing Strategy to Detect Early HIV-1 Infection for Use in Incidence Estimates and for Clinical and Prevention Purposes

Robert S. Janssen, MD; Glen A. Satten, PhD; Susan L. Stramer, PhD; Bhupat D. Rawal, PhD; Thomas R. O'Brien, MD, MPH; Barbara J. Weiblen, MS; Frederick M. Hecht, MD; Noreen Jack, MBBS, MPH; Farley R. Cleghorn, MD, MPH; James O. Kahn, MD; Margaret A. Chesney, PhD; Michael P. Busch, MD, PhD

Abbott EIA 3A11 assay: sensitive/less-sensitive ("detuned")
Recent Infection Testing Algorithm (RITA)

- RNA
- p24
- Ab

Seroconversion

RITA duration

Antibody cutoff:
- Quantity (LS-EIA)
- Proportion (BED)
- Avidity
- Isotype
- Specificity of Ag

Detection limit
RITA and Misclassification

Misclassified Long-standing

Misclassified Recent

Cutoff

Mean 170 days

Days

SOD

0 0.5 1 1.5 2 2.5 3 3.5

0 200 400 600 800 1000 1200
HIV Incidence and RITA: Cross-Sectional Surveys

Incidence = \frac{F1 \times N_{(recent)}}{N_{(neg)} + F1 \times N_{(recent)}} \times 100

F1 = \frac{365}{\text{RITA duration}}
HIV Incidence and RITA: Cross-Sectional Surveys

Survey size = 1000

HIV-seropositive = 100 (10%)

Recent on incidence assay = 10

RITA duration = 170 days

\[
\text{Incidence} = \frac{2.15 \times 10}{900 + 21.5} \times 100 = 2.33\% \text{ per year}
\]
RITA and Misclassification

Days

SOD

Misclassified Long-standing

Misclassified Recent

Cutoff

Mean

170 days

Presented at the 4th INTEREST Workshop
25-28 July 2010, Maputo Mozambique
Quantitative Detection of Increasing HIV Type 1 Antibodies after Seroconversion: A Simple Assay for Detecting Recent HIV Infection and Estimating Incidence

Bharat S. Parekh, M. Susan Kennedy, Trudy Dobbs, Chou-Pong Pau, Robert Byers, Timothy Green, Dale J. Hu, Suphak Vanichseni, Nancy L. Young, Kachit Choopanya, Timothy D. Mastro, and J. Steven McDougal

-BED competitive capture EIA
-Indirectly measures HIV-IgG as a proportion of total IgG
HIV Type 1 Incidence Estimates by Detection of Recent Infection from a Cross-Sectional Sampling of Injection Drug Users in Bangkok: Use of the IgG Capture BED Enzyme Immunoassay

DALE J. HU,1 SUPHAK VANICHSENI,2 PHILIP A. MOCK,3 NANCY L. YOUNG,3 TRUDY DOBBS,1 ROBERT H. BYERS, JR.,1 KACHIT CHOOPANYA,2 FRITS VAN GRIENSVEN,3 DWIP KITAYAPORN,3,4 J. STEVEN MCDOUGHAL,1 JORDAN W. TAPPERO,3 TIMOTHY D. MASTRO,1,3 and BHARAT S. PAREKH1

Trends of HIV-1 Seroincidence Among HIV-1 Sentinel Surveillance Groups in Cambodia, 1999–2002

Vonthanak Saphonn, MD, PhD,*† Bharat S. Parekh, PhD,‡ Trudy Dobbs,‡
Chivun Mean, MD, PhD,* Leng Hor Bun, MD,* Sun Penh Ly, MD, MS,*
Sopheab Heng, MD, MPH,* and Roger Detels, MD, MS†

Temporal Trends in HIV Type 1 Incidence among Inner-City Childbearing Women in Atlanta: Use of the IgG-Capture BED-Enzyme Immunoassay

STEVEN NESHEIM,1 BHARAT PAREKH,2 KEVIN SULLIVAN,1,3 MARC BULTERYS,4 TRUDY DOBBS,2 MICHAEL LINDSAY,5 MIGUEL CASHAT-CRUZ,3 BOB BYERS,4 and FRANCIS LEE1

- Reviewed data from multiple studies from Africa, Asia and lab validation studies
- “…suggests that the current BED-based method overestimates incidence.”
- “…incidence of a third to a half of prevalence.”
- “appears 2-3 times higher than…other methods…”
- “recommends that at present the BED-assay not be used for routine surveillance applications.”
Comparison of HIV Type 1 Incidence Observed during Longitudinal Follow-Up with Incidence Estimated by Cross-Sectional Analysis Using the BED Capture Enzyme Immunoassay

J. STEVEN McDougall,1 BHARAT S. PAREKH,1 MICHAEL L. PETERSON,2 BERNARD M. BRANSON,1 TRUDY DOBBS,1 MARTA ACKERS,1 and MARC GURWITH2

Proposed adjustments for false-recent misclassification.
Improved HIV-1 incidence estimates using the BED capture enzyme immunoassay

John W. Hargrove\textsuperscript{a,f}, Jean H. Humphrey\textsuperscript{a,c}, Kuda Mutasa\textsuperscript{a}, Bharat S. Parekh\textsuperscript{d}, J. Steve McDougal\textsuperscript{d}, Robert Ntozini\textsuperscript{a}, Henry Chidawanyika\textsuperscript{a}, Lawrence H. Moulton\textsuperscript{c}, Brian Ward\textsuperscript{e}, Kusum Nathoo\textsuperscript{b}, Peter J. Iliff\textsuperscript{a} and Ekkehard Kopp\textsuperscript{f}

Proposed determination and use of a factor epsilon (ε) to correct for misclassification of long-standing infections as recent.
National HIV incidence measures – new insights into the South African epidemic

Use of the BED assay on dried blood spot specimens from a national household HIV survey to estimate HIV incidence.

Adjusted incidence estimates reflected the underlying transmission dynamics in South Africa.

Presented at the 4th INTEREST Workshop
25-28 July 2010, Maputo Mozambique
High HIV incidence in a community with high HIV prevalence in rural South Africa: findings from a prospective population-based study

Till Bärnighausen\textsuperscript{a,b}, Frank Tanser\textsuperscript{a}, Zanomsa Gqwede\textsuperscript{a}, Clifford Mbizana\textsuperscript{a}, Kobus Herbst\textsuperscript{a} and Marie-Louise Newell\textsuperscript{a,c}

- Determined a local BED false recent rate = 1.7%
- Founds similar HIV incidence \(\sim 3/100\) PY for BED with this FRR, compared to longitudinal HIV incidence
Presented at the 4th INTEREST Workshop
25-28 July 2010, Maputo Mozambique

BED False Recent Rates, by Setting

Vietnam - South: 1%
South Africa - KZN: 1.7%
Vietnam - North: 5%
Zimbabwe - post partum women: 5.2%
Rwanda - high risk women: 6.4%
China IDU: 6.6%
El Salvador BSS: 11%
South Africa - Tygerberg: 11%
Kenya AIS: 15%
Uganda Rakai: 15.3%

Percent (%)

Andrea Kim, CDC, 2010
Representative household survey:
18,525 with blood specimens
HIV prevalence = 6.4%
HIV incidence = 2.6% (BED unadjusted)
HIV incidence = 1.8% (BED adjusted)
“Small perturbations to the tail of the window period distribution can have large effects on the accuracy of current incidence estimates.”
Accuracy of serological assays for detection of recent infection with HIV and estimation of population incidence: a systematic review

Rebecca Guy, Judy Gold, Jesus M Garcia Calleja, Andrea A Kim, Bharat Parekh, Michael Busch, Thomas Rehle, John Hargrove, Robert S Remis, John M Kaldor, for the WHO Working Group on HIV Incidence Assays*
Challenges to Using Antibody Maturation to Identify Recent Infection

• Variable immune response among individuals
  – Antibody response related to viral level

• Variability by HIV-1 subtypes

• False-recent status
  – Elite controllers (low viral levels)
    • Accumulate in population
  – ART use (low viral levels)
  – Advanced HIV disease (AIDS)
Assay Calibration and Validation

• Requires large numbers of well-characterized seroconversion panels
  – Various populations and sub-populations
    • Geographic, transmission modes, etc.
  – Various HIV-1 subtypes
  – Early and long-standing infections
  – Co-infections (TB, malaria)

• Such specimens aren’t readily available in sufficient volume in a central location
HIV Incidence Assays

- “Detuned” assays
  - Abbott 3A11 - unavailable
  - bioMérieux Vironostika HIV-1 – unavailable
- BED-Capture EIA, (Calypte)
- Avidity assays
  - Run on Abbott AxSYM
  - Run on Ortho Vitros analyzer
- IDE-V3 assay
- IgG3 anti-HIV
- Inno-LIA HIV adaptation

Murphy G, Parry JV. Eurosurveillance. 2008
Development of Two Avidity-Based Assays to Detect Recent HIV Type 1 Seroconversion Using a Multisubtype gp41 Recombinant Protein

Xierong Wei, Xin Liu, Trudy Dobbs, Debra Kuehl, John N. Nkengasong, Dale J. Hu, and Bharat S. Parekh

A two-well avidity index assay
A one-well limiting antigen avidity assay
New Insights and Developments
Perspectives on HIV Incidence
Assays and Uses
Development of Assays to Estimate HIV Incidence
Key Issues
Chapel Hill Meeting, May 2009

• Need to clarify terminology
• Review of market assessment
• Explore new biomarkers (virus evolution)
• Establish optimal specifications and requirements
• Identify critical path to advance assays
  – Industry perspectives
• Define the infrastructure and specimens required for assay validation
Innovations in Incidence Estimation Methods

• A new paradigm for incidence estimation from cross-sectional data. T.A. McWalter and A. Welte, SACEMA
  – IAS-2009: MOPDB-105

• URL for Assay Based Incidence Estimation spreadsheet:
  http://www0.sun.ac.za/sacema/collaboration/ABIE/
Contours of Sample Size Required for Coefficient of Variation of 15% as a Function of Incidence and FPR

Presented at the 4th INTEREST Workshop
25-28 July 2010, Maputo Mozambique
“False” Incident BED vs. Avidity
Individuals Infected >365 Days and on ARV
Canadian Cohort

N=73

46.50%
8.25%

BED
Avidity

Less “false” recent infections with Avidity
Chronically Infected Virally Suppressed Subjects on ARVs (VL < 400 cps/ml)

JHU Moore Clinic

N = 134

Rakai

N = 22

ARV therapy has less effect on avidity.
Algorithm for Incidence Testing: Rakai 2002

Presented at the 4th INTEREST Workshop
25-28 July 2010, Maputo Mozambique

- HIV EIA & WB: 8488
- HIV Negative Sample: 7383
  - BED Assay: 1105
    - Avidity Assay: 319
      - No AIDS: 166
  - Chronically infected: 315
  - Chronically infected: 160
    - PCR +: 160
      - Chronically infected: 133

Key:
- negative
- positive
Issues to Address and the Way Forward
Summary

• Current HIV incidence assays are imperfect tools
  – False-recent misclassification is a problem
  – Guidance on use is evolving
• Market forces are not driving assay development
• Multi-test algorithms have promise
• We know how to evaluate assays, but the required specimens are not readily available
• Mathematical issues are being resolved
What Needs to be Done

• WHO Technical WG on HIV Incidence Assays
  – www.who.int/diagnostics_laboratory/links/hiv_incidence_assay

• Guidance on assay use

• Solidify consensus on mathematical issues

• Define the assay development pathway

• Define and assemble specimens for assays calibration and validation

• Engage industry on assay development

Presented at the 4th INTEREST Workshop
25-28 July 2010, Maputo Mozambique
Let’s make sure the glass is filled
Acknowledgements

- Oliver Laeyendecker
- Sue Eshleman
- Bharat Parekh
- Bernie Branson
- Andrea Kim
- Connie Sexton
- Mary Lynn Baniecki
- Karine Dube
- Megan Averill
- Renee Ridzon
- Bill Rodriguez
- Christine Rousseau
- Mike Busch
- Chris Pilcher
- John Kaldor
- Txema Garcia-Calleja
- Gaby Vercauteren
- Thomas Rehle
- Alex Welte
- Tom McWalter
- Tim Hallett
- Mike Cohen
- Joanne Micallef
- Gary Murphy