Recent advances in development and application of assays/algotithms for detection of recent HIV infections and estimation of incidence

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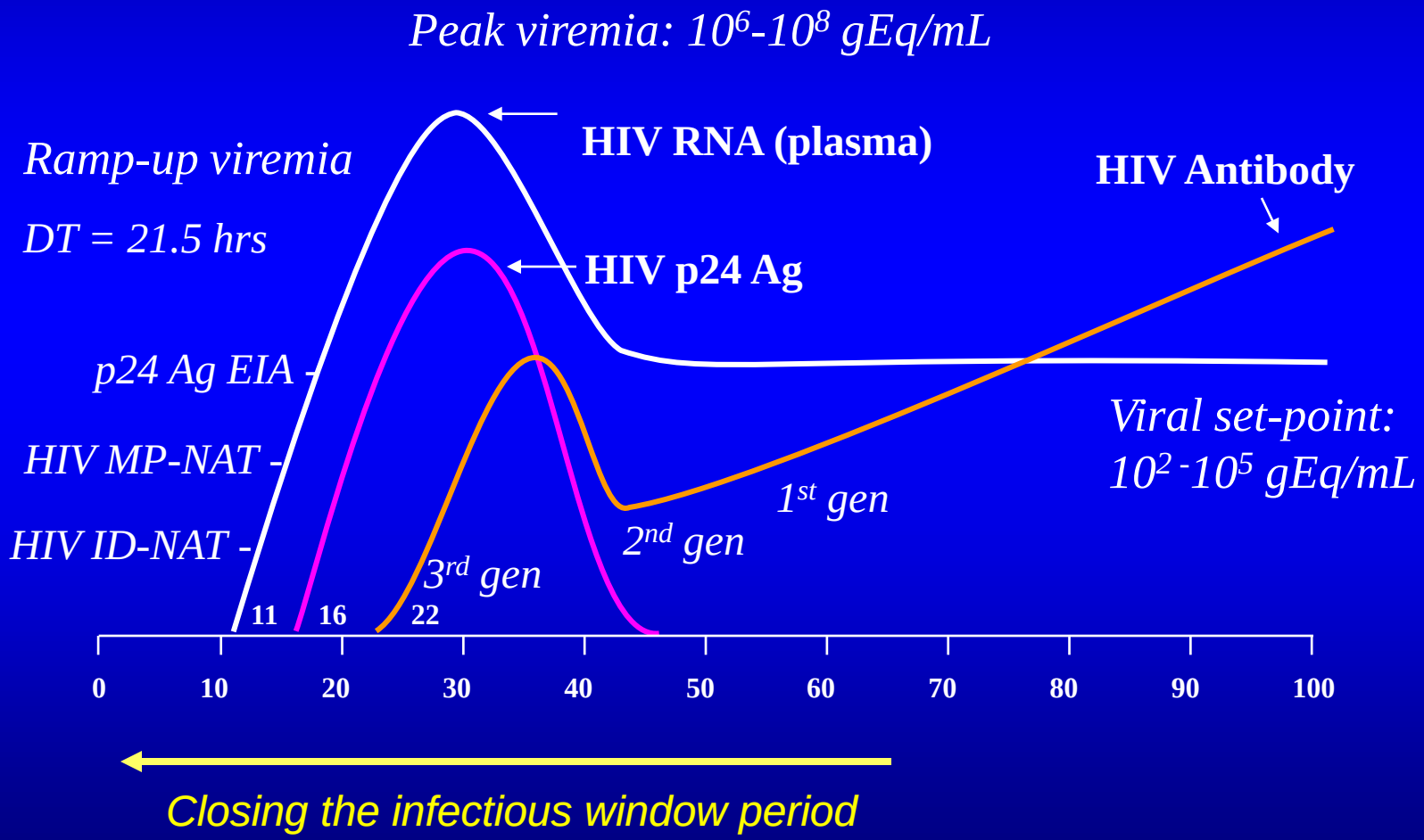
CDC/APHL HIV Diagnostics Conference, 2010

Why its important to detect pre-SC window-phase HIV infections?

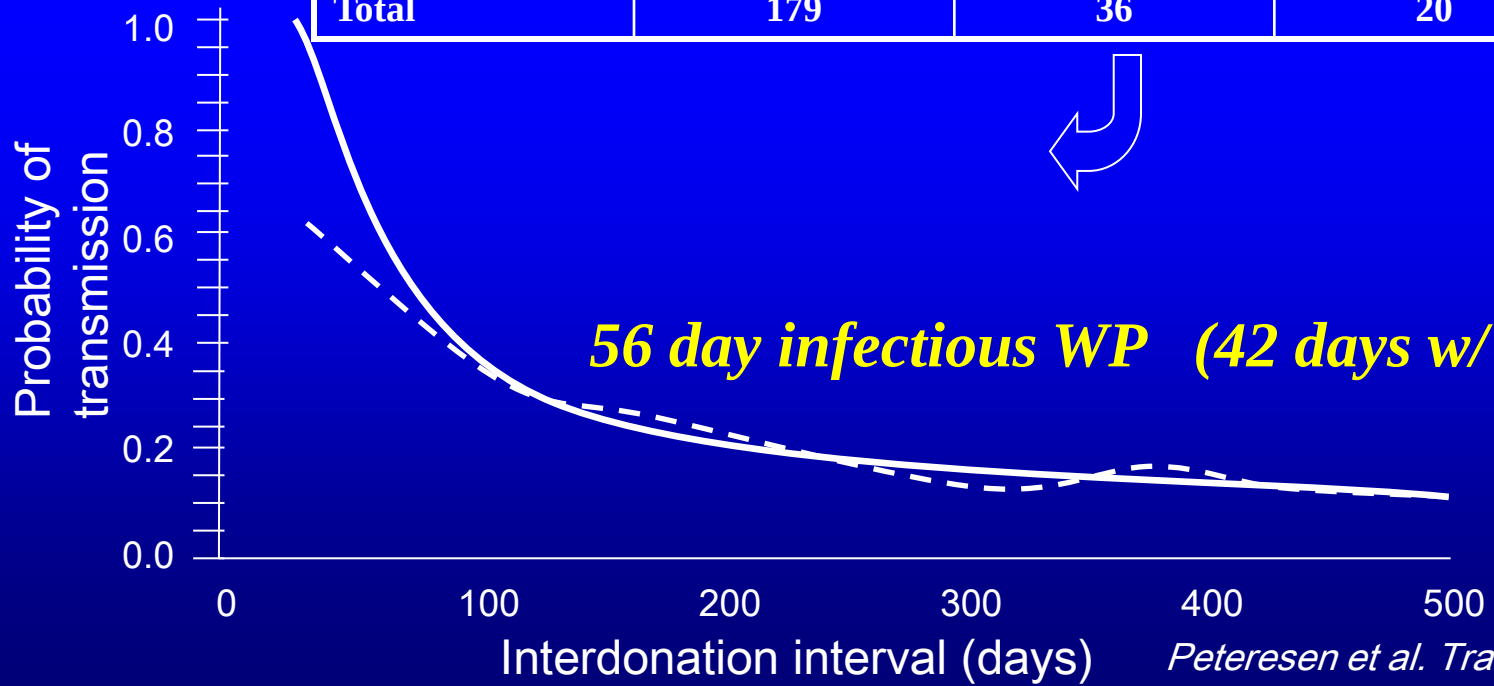
- Prevent viral transmission by blood transfusions and organ and tissue transplants
- Identify early infections in public health screening and diagnostic settings
  - acute-viremic phase of infection is highly infectious
  - more effective response to treatment if initiated during acute compared to chronic stages?
  - prevent secondary transmission by contact tracing and counseling to modify risk behaviors
- Identify subjects in primary infection for pathogenesis, treatment and vaccine research

HIV acute and early infection



HIV-1 transmission by transfusion of blood from SC donors according to the interdonation interval

Interdonation interval (days)	Total	HIV-1 transmission	
		Number	Percentage
45 - 90	17	13	76
91 - 180	29	8	28
181 - 360	48	9	19
361 - 540	39	5	13
541 - 720	14	0	0
> 720	32	1	3
Total	179	36	20



56 day infectious WP (42 days w/ EIA 2.0)

Peteresen et al. Transf. 1994 34 : 283-9

HIV Stage Progression based on 51 Seroconverting Plasma Donors

Fiebig stage classification for sub-stages of HIV-1 primary infection, and the average and cumulative duration of each phase.

Stage	Duration of each phase (days)	Cumulative duration (days)
Eclipse	10 (7,21)	10 (7,21)
I (vRNA+)	7 (5,10)	17 (13,28)
II (p24Ag+)	5 (4,8)	22 (18,34)
III (ELISA+)	3 (2,5)	25 (22,37)
IV (Western Blot ±)	6 (4,8)	31 (27,43)
V (Western Blot +, p31−)	70 (40,122)	101 (71,154)
VI (Western Blot +, p31+)	Open-ended	

Fiebig et al. AIDS, 17:1871-9, 2003
Lee et al. J Theor Biol, 2009

The Incidence Rate / Window Period (WP) Model Allows Prediction of Test Yields for Direct HIV Assays (p24 Ag, HIV RNA) vs. EIA Antibody Test

Test Yield (per unit) =

Incidence Rate (person-years)
x Decrease in WP (fraction of year)

Projected WP Closure and Yield of p24 Ag, MP and ID NAT Assays Relative to a Sensitive HIV-1/2 EIA Antibody Test in the Detection of WP HIV Infection

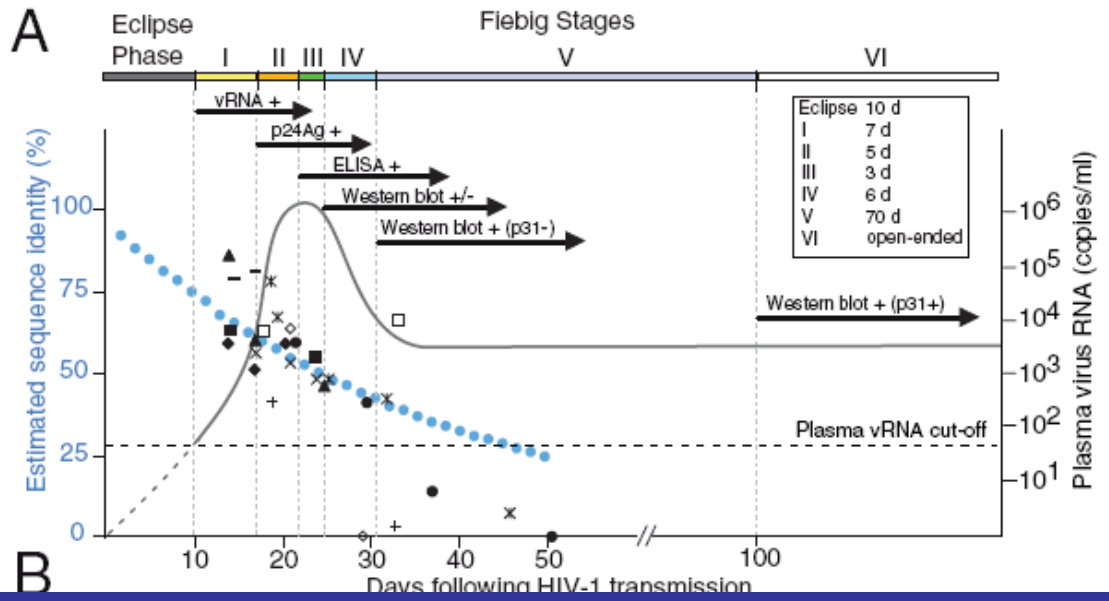
Assay	Sensitivity [gEq / mL]	WP Closure [days]	Yield, WP HIV Infections per 1,000 Persons Tested in Various Screening Settings [Representative Incidence Rate / Person-Years]		
			Blood Donors [2 / 100,000 = 0.002%]	STD Clinic [1 / 1,000 = 0.1%]	High Risk Clinic [1 / 10 = 10%]
p24 Ag	10,000	6	0.00033	0.016	1.6
MP NAT	1,000	9	0.00049	0.025	2.5
ID NAT	50	13	0.00071	0.036	3.6

Fiebig et al. AIDS, 17:1871-9, 2003

PNAS

Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection

Brandon F. Keele[a], Elena E. Giorgi[b,c], Jesus F. Salazar-Gonzalez[a], Julie M. Decker[a], Kimmy T. Pham[a], Maria G. Salazar[a], Chuanxi Sun[a], Truman Grayson[a], Shuyi Wang[a], Hui Li[a], Xiping Wei[a], Chunlai Jiang[d], Jennifer L. Kirchherr[d], Feng Gao[d], Jeffery A. Anderson[e], Li-Hua Ping[f], Ronald Swanstrom[f], Georgia D. Tomaras[g], William A. Blattner[h], Paul A. Goepfert[a], J. Michael Kilby[a], Michael S. Saag[a], Eric L. Delwart[i], Michael P. Busch[i], Myron S. Cohen[e], David C. Montefiori[g], Barton F. Haynes[d], Brian Gaschen[b], Gayathri S. Athreya[b], Ha Y. Lee[j], Natasha Wood[k], Cathal Seoighe[k], Alan S. Perelson[b], Tanmoy Bhattacharya[b,l], Bette T. Korber[b,l], Beatrice H. Hahn[a,m], and George M. Shaw[a,m,n]



102 acutely infected plasma donor panels

3476 complete *env* sequences from single genome amplifications

Inferred consensus sequence at estimated time of virus transmission

78 donors infected by single virion; 24 by 2-5 virions

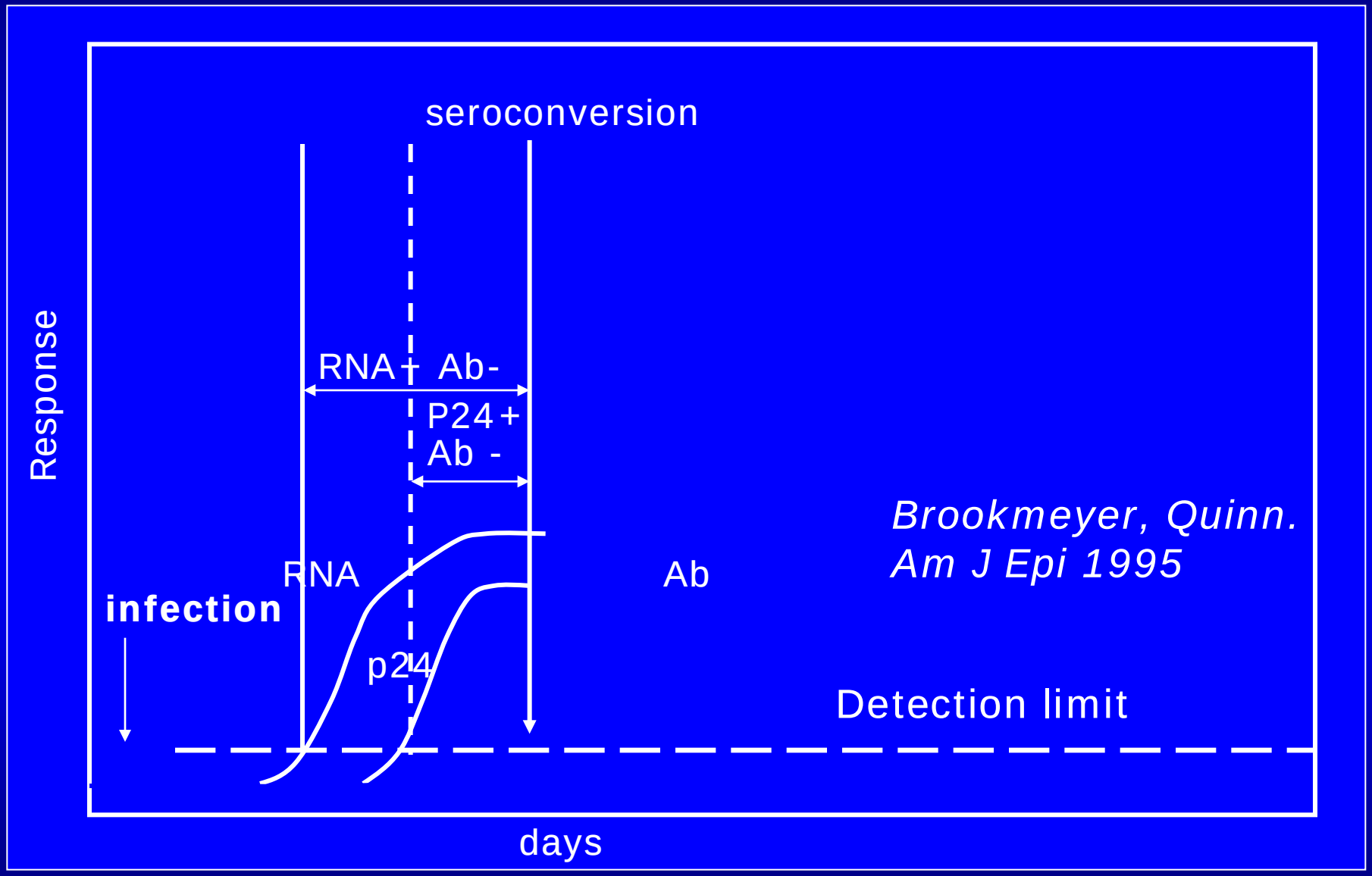
Why Determine HIV Incidence?

- 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

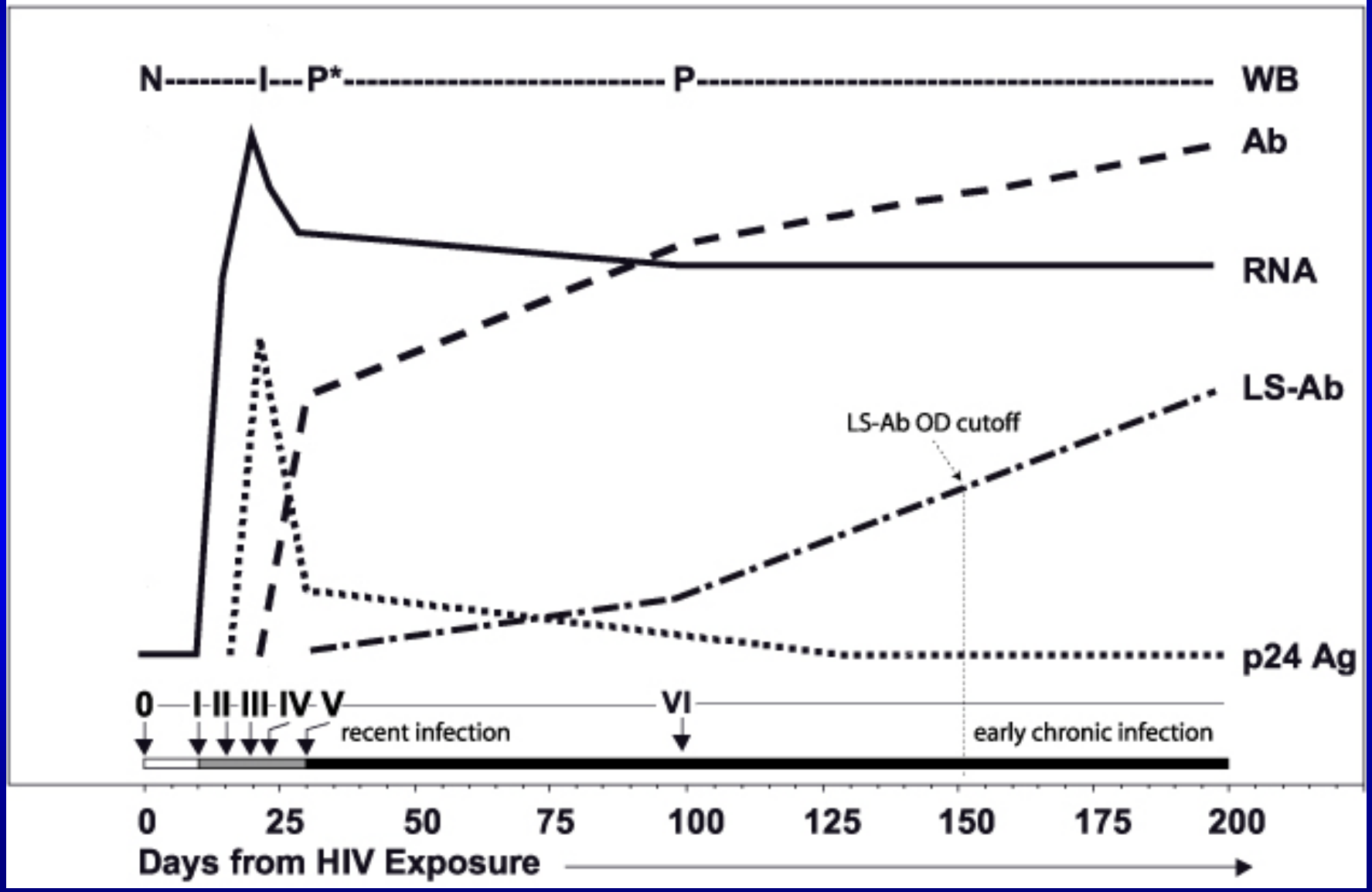
- Indirect methods; repeat cross-sectional measurements; modeling
- Prospective follow-up is expensive and unrepresentative
- Enrollment in cohorts leads to behavior change
- Back calculation methods not timely or reliable

HIV Incidence Using Early Diagnostic Tests



Fiebig et al.: Dynamics of HIV Viremia

Figure 2



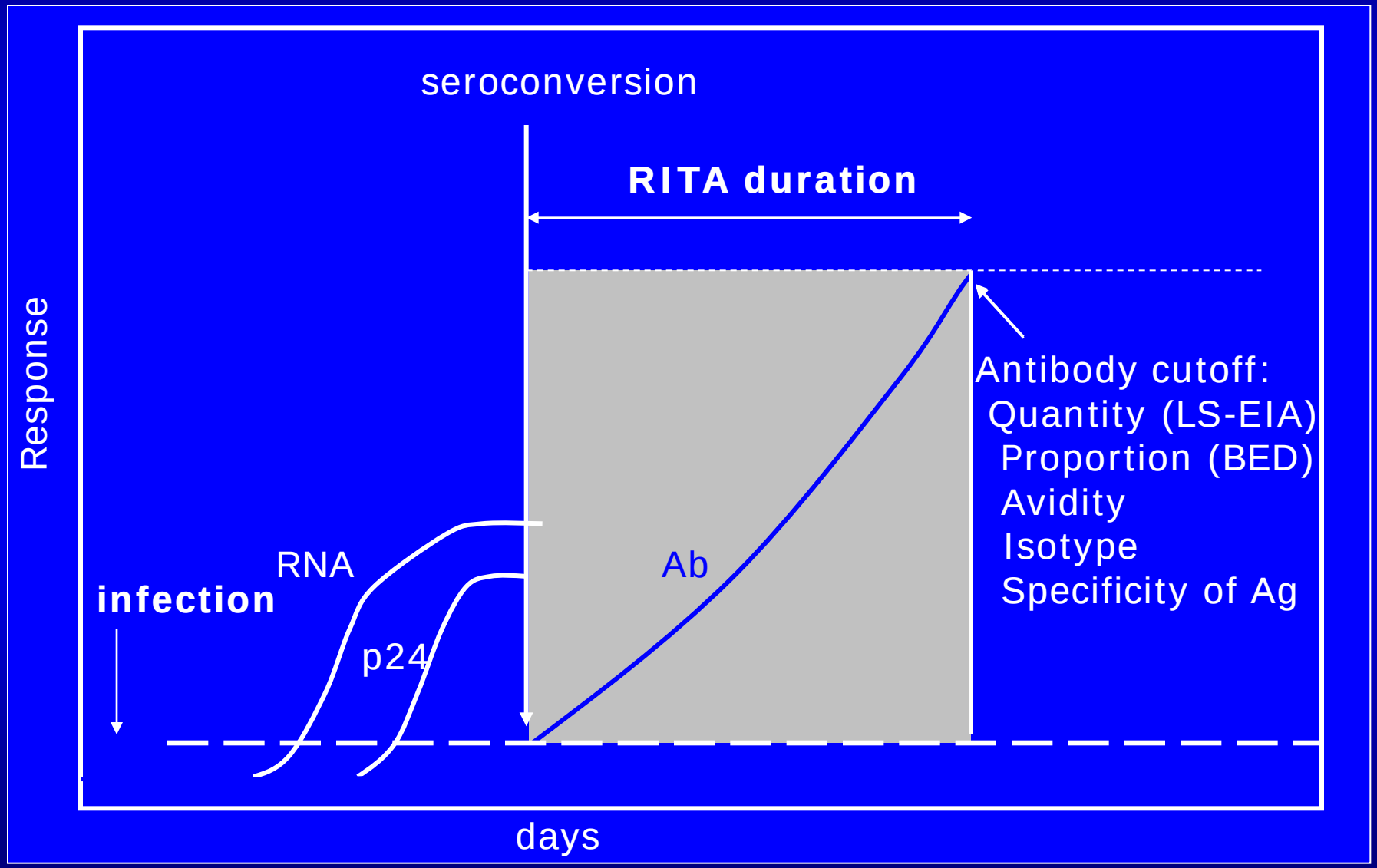
JAMA®
The Journal of the American Medical Association

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)



Cross-Sectional Incidence Formula

$$\text{Annualized Incidence} = \frac{(\#\text{ who test recent}) \times (365/\text{window period})}{\#\text{ at risk}} \times 100$$

$$I = \frac{(365/w)\, N_{recent}}{N_{seronegative} + \tfrac{1}{2}(365/w)\, N_{recent}} \times 100$$

HIV Incidence and RITA: Cross-Sectional Surveys

Survey size = 1000

HIV-seropositive = 100 (10%)

Recent on incidence assay = 10

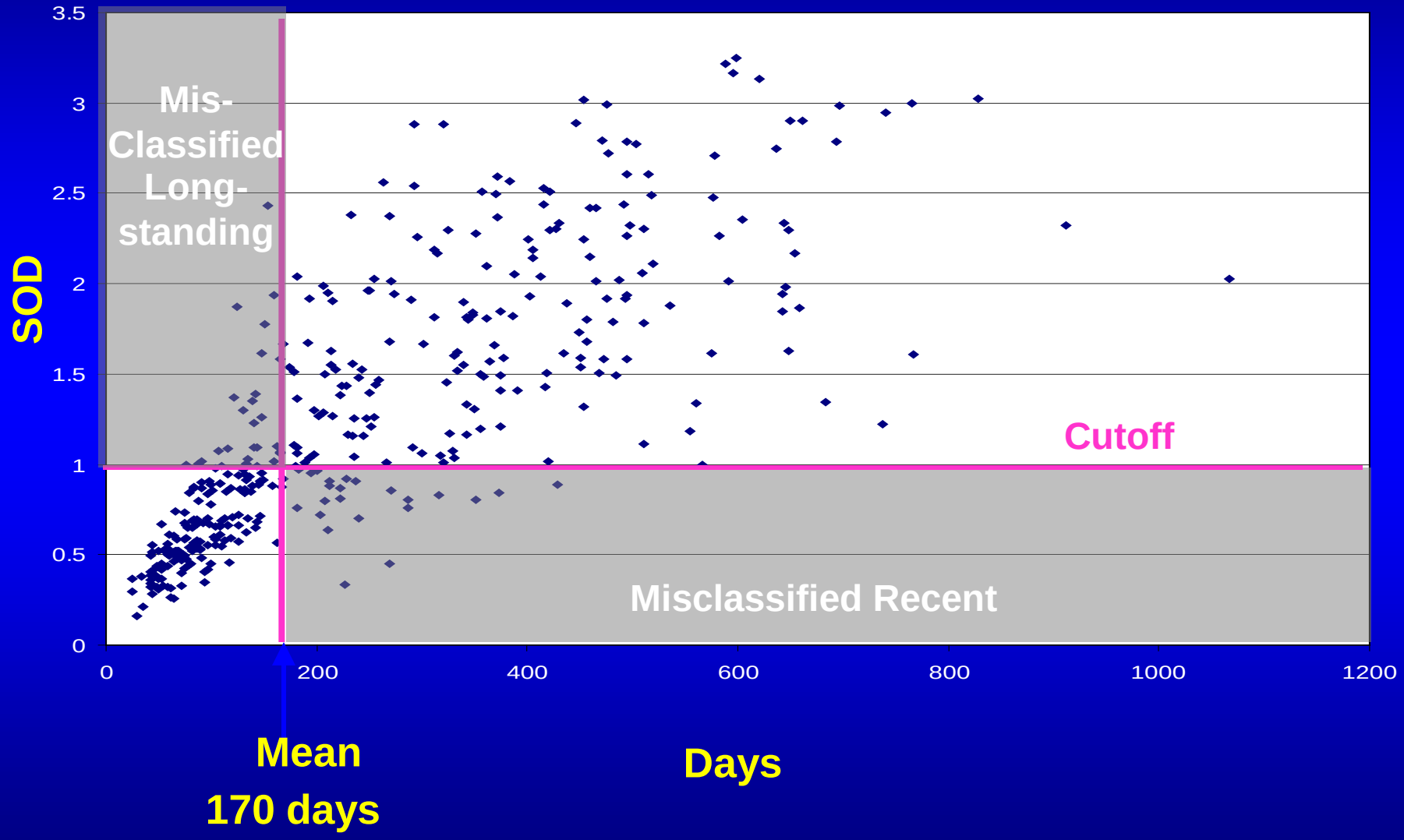
RITA duration = 170 days

$$\text{Incidence} = \frac{2.15 \times 10}{900 + 21.5} \times 100 = 2.33\% \text{ per year}$$

The Ideal Assay for Recent Infection

- Describes a distinct “detection window” of relatively uniform duration
- Is universally positive in recent infection and negative later in infection (or vice versa)
- Is unaffected by:
  - virus subtype
  - mode of transmission
  - therapy
  - OI and AIDS
  - Age, sex, race
- Has a relatively long window, all else being equal

RITA and Misclassification



AIDS Research and Human Retroviruses
The Official Journal of the International Retrovirology Association

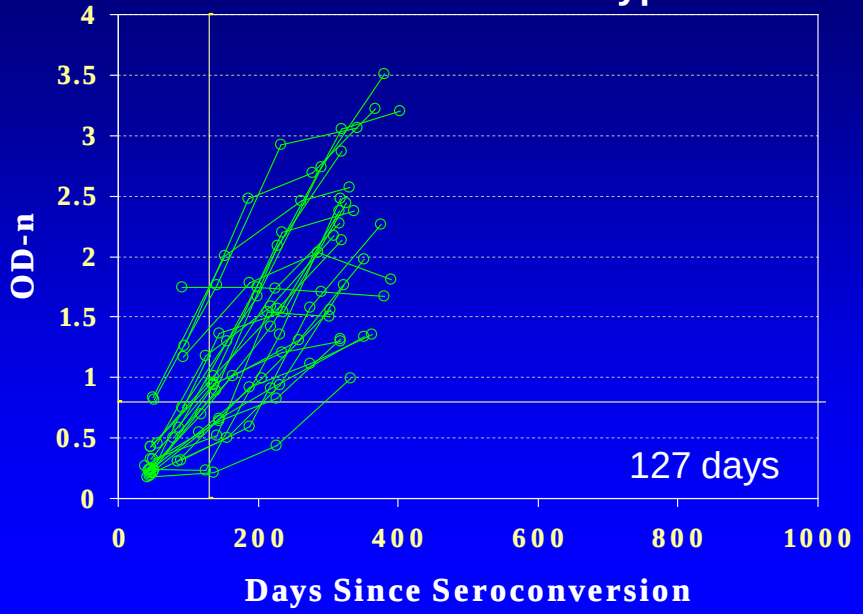
AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 18, Number 4, 2002, pp. 295–307

Quantitative Detection of Increasing HIV Type 1 Antibodies after Seroconversion: A Simple Assay for Detecting Recent HIV Infection and Estimating Incidence

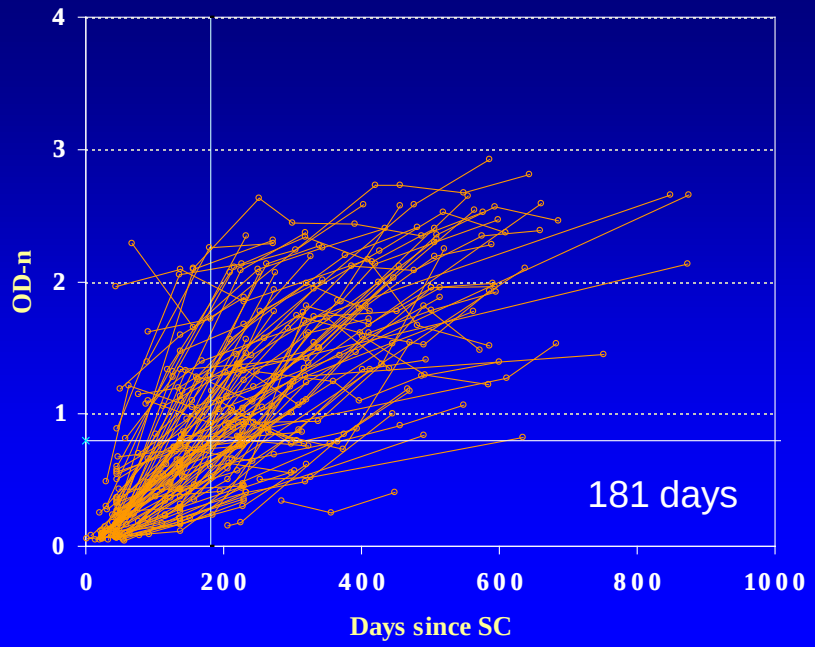
BHARAT S. PAREKH,[1] M. SUSAN KENNEDY,[1] TRUDY DOBBS,[1] CHOU-PONG PAU,[1] ROBERT BYERS,[1] TIMOTHY GREEN,[1] DALE J. HU,[1] SUPHAK VANICHSENI,[2] NANCY L. YOUNG,[3] KACHIT CHOOPANYA,[2] TIMOTHY D. MASTRO,[1,3] and J. STEVEN McDOUGAL[1]

- BED competitive capture EIA
- Indirectly measures HIV-IgG as a proportion of total IgG

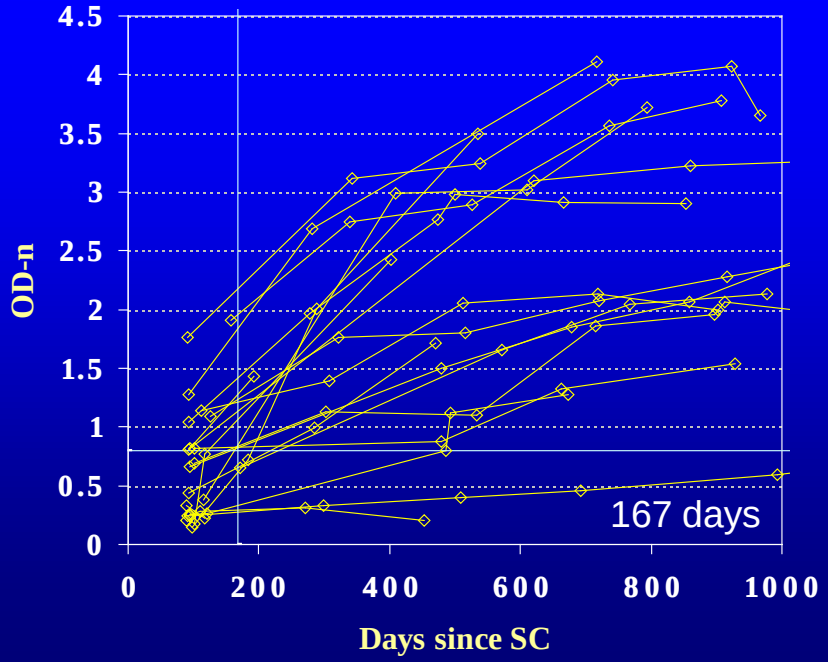
Amsterdam Cohort/ subtype B



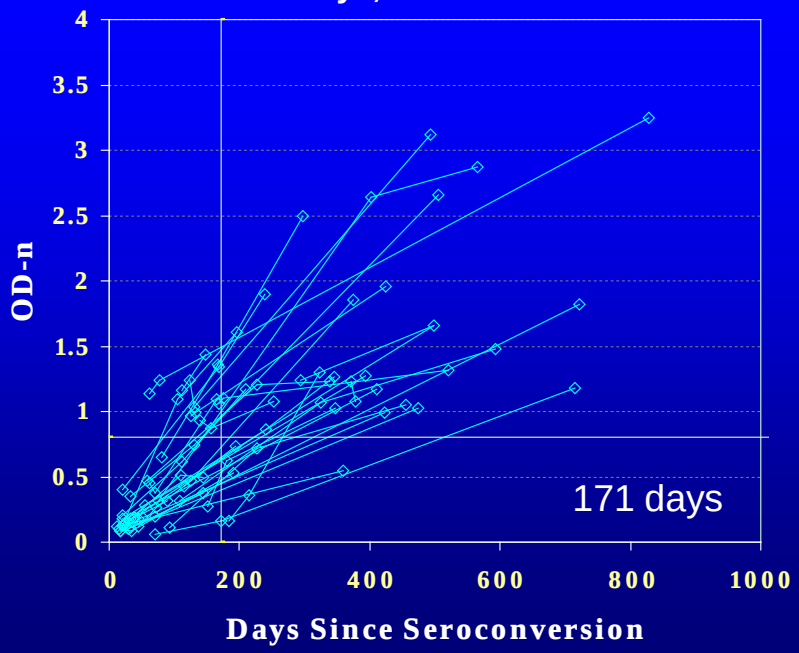
Zimbabwe Seroconverters/C



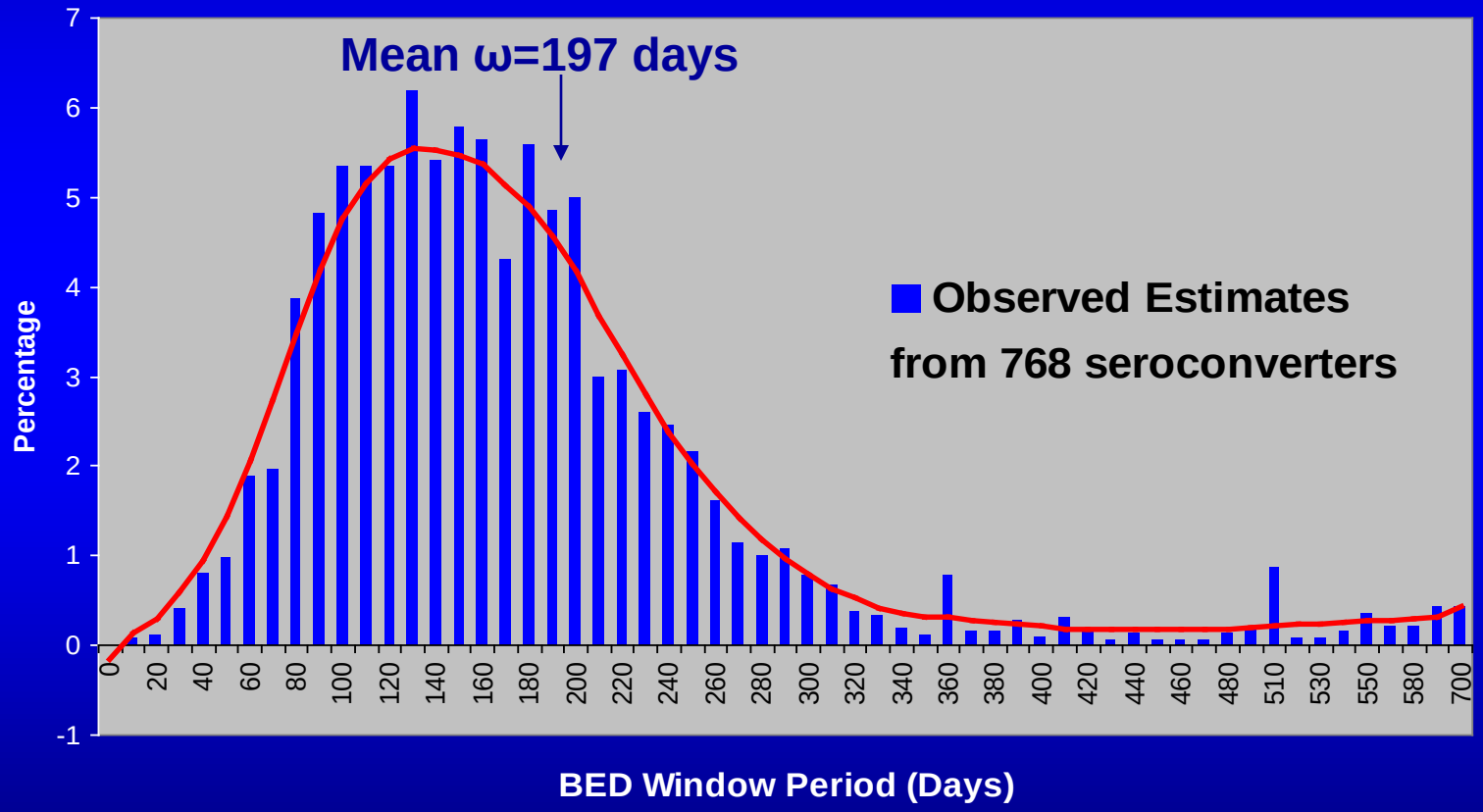
ENARP Serovonverters/C



Kenya, A and D



Distribution of Window Periods for BED



5.9% > 2x mean ω to reach cutoff

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 (long-term specificity)
  - Elite controllers (low viral levels)
    - Accumulate in population
  - ART use (low viral levels)
  - Advanced HIV disease (AIDS)

AIDS
Official Journal of the International AIDS Society

Improved HIV-1 incidence estimates using the BED capture enzyme immunoassay

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

Proposed determination and use of a factor epsilon (ε) to correct for misclassification of long-standing infections as recent.

HIV Incidence Assays

- "Detuned" assays
  - Abbott 3A11 - unavailable
  - bioMérieux Vironostika HIV-1 – Avioq
  - Ortho Vitros ECi
- BED-Capture EIA (Calypte; Trinity)
- Avidity assays
  - Run on Abbott AxSYM
  - Bio-Rad
  - Run on Ortho Vitros analyzer
- IDE-V3 assay
- IgG3 anti-HIV
- Inno-LIA HIV adaptation

CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Aug. 2005, p. 918–921 Vol. 12, No. 8
1071-412X/05/$08.00+0 doi:10.1128/CDLI.12.8.918–921.2005

Modification of Rapid Human Immunodeficiency Virus (HIV) Antibody Assay Protocols for Detecting Recent HIV Seroconversion

Stephen D. Soroka, Timothy C. Granade, Debra Candal, and Bharat S. Parekh*

Division of HIV/AIDS Prevention, National Center for HIV/AIDS, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia 30333

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DOI: 10.1089/aid.2009.0133

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

Eurosurveillance
Free of charge for authors, free of charge for readers.
September 2008

Review articles

Assays for the detection of recent infections with human immunodeficiency virus type 1

G Murphy (gary.murphy@hpa.org.uk)[1], J. V. Parry[1,2]
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2. Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom

Review articles

Principles and uses of HIV incidence estimation from recent infection testing - a review

S Le Vu (s.levu@invs.sante.fr)[1], J Pillonel[1], Caroline Semaille[1], P Bernillon[1], Y Le Strat[1], L Meyer[2], J C Desenclos[1]
1. Department of Infectious Diseases, HIV/AIDS-STI-HCV Unit, Institut de veille sanitaire (French Institute for Public Health Surveillance, InVS), Saint-Maurice, France
2. Department of Epidemiology, Institut national de la santé et de la recherche médicale/Institut national d'études démographiques (National Institute of Health and Medical Research/National Institute for Demographic Studies, INSERM/INED/Paris XI U569), Le Kremlin-Bicêtre, France

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

Assay Calibration and Validation

- Establish “RITA Interval” and “False Recent Rate”
- Requires large numbers of well-characterized seroconversion panels and FRR 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

WHO HIV Technical Working Group on HIV Incidence

Review

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 García 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*

We systematically reviewed the accuracy of serological tests for recent infections with HIV that have become widely used for measuring population patterns incidence of HIV. Across 13 different assays, sensitivity to detect recent infections ranged from 42–100% (median 89%). Specificity for detecting established infections was between 49·5% and 100% (median 86·8%) and was higher for infections of durations longer than 1 year (median 98%, range 31·5–100·0). For four different assays, comparisons were made between assay-derived population incidence estimates and a reference incidence estimate. The median percentage difference between the assay-derived incidence and reference incidence was 26·0%. Serological assays have reasonable sensitivity for the detection of recent infection with HIV, but are vulnerable to misclassifying established infections as recent—potentially leading to biases in incidence estimates. This conclusion is highly qualified by the apparent absence of a standardised approach to assay evaluation. There is an urgent need for an internationally agreed framework for evaluating and comparing these tests.

Lancet Infect Dis 2009; 9: 74

*Other members listed at the end of the paper

Centre for Population Healt Burnet Institute, Melbourn VIC, Australia (R Guy PhD, J Gold BBiomedSci); Nationa Centre in HIV Epidemiolog and Clinical Research, University of New South W Sydney, NSW, Australia (R C Prof J M Kaldor PhD); HIV/AI

Assays to Estimate HIV Incidence and Detect Acute HIV Infection

Global Landscape & Market Assessments

fhi Family Health International

BILL & MELINDA GATES *foundation*

Guidance Document

When and how to use assays for recent infection to estimate HIV incidence at a population level

Prepared on behalf of the World Health Organization Technical Working Group on HIV Incidence Assays

With support of a grant from the Bill & Melinda Gates Foundation

Steps involved in applying RITA to estimate HIV incidence

Step 1: Identify study population

- The study population for which incidence will be calculated should be clearly defined.
- The sampling frame that provides the subset for incidence testing should also be well defined.
- Refer to Chapter 4 for guidance on this step.

Step 2: Identify HIV positive individuals

- Identify HIV positive individuals by testing the study population or the sampled subgroup for anti-HIV antibody or HIV RNA or DNA.
- Choice of tests and testing strategy should be based on local guidelines and consistent with WHO guidelines for HIV testing.

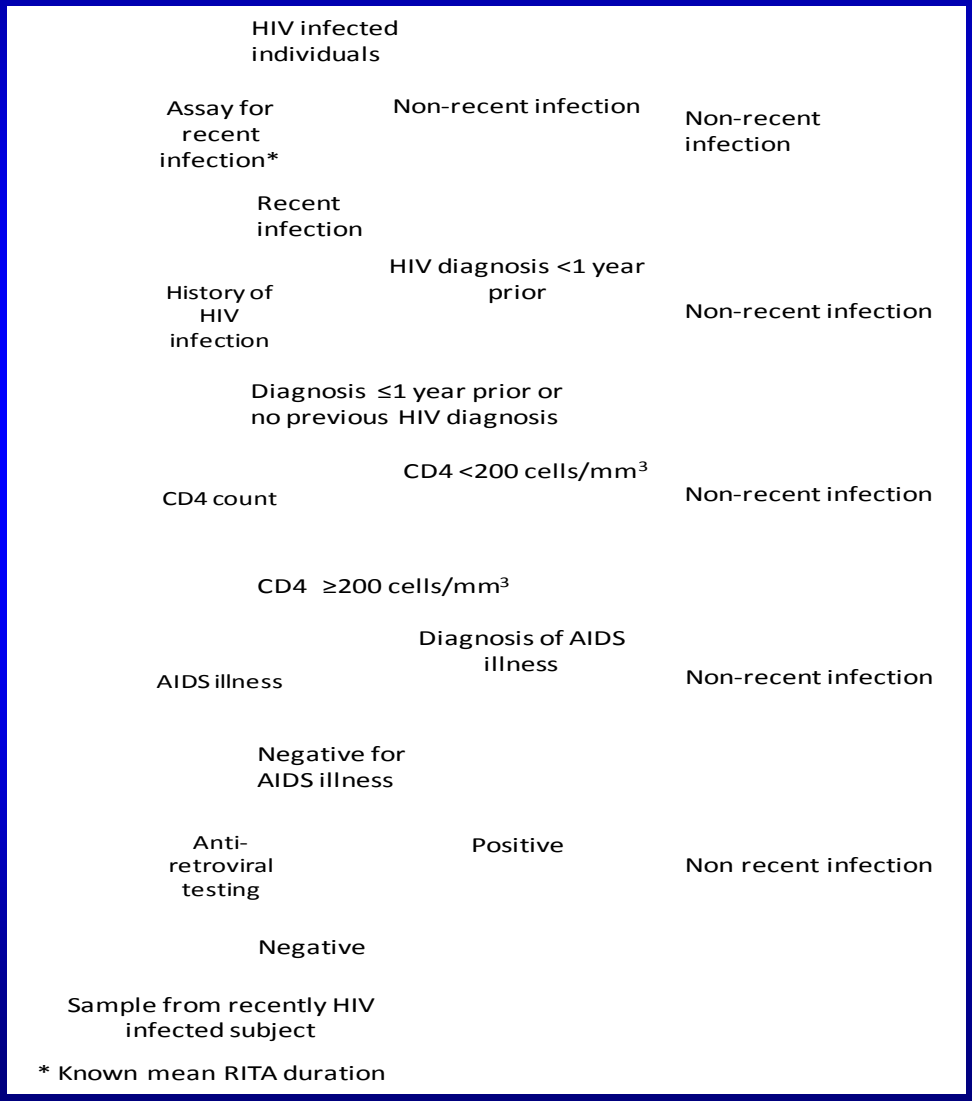
Step 3: Apply the Recent Infection Testing Algorithm (RITA)

- The RITA is applied to specimens of HIV infected individuals. The RITAs which may be utilised are:
  - RITA based on a single assay for recent infection
  - RITA based on a laboratory assay for recent infection combined with other clinical information
- Mean RITA duration must be known and false recent rate (FRR) must be calculated.
- Refer to Chapter 6 for guidance on choice of RITA and the Appendix for the calculation of FRR.

Step 4: Analysis of resulting data

- HIV incidence is calculated using the counts from the RITA, the FRR and mean RITA duration.
- Refer to Chapter 7 for guidance on estimating HIV incidence.

Application of a RITA based on a laboratory assay for recent infection and additional clinical information



Performance in Clade B of BED + Avidity Testing Algorithm

Estimated Window Period using HIVNET & Vaxgen004 (154 subjects , median 4 samples / subject)

Avidity & BED cutoff Values	Mean Recency Period	(95% Conf Limits)
30% , 0.6	117.3	(93.1, 141.4)
40%, 0.8	143.0	(117.8, 168.2)
40%, 1.0	163.6	(138.0, 189.1)
50%, 0.8	147.8	(122.0, 173.5)
80%, 1.0	203.8	(170.0, 237.6)

Misclassification Rate in Known Chronically Infected Individuals (2

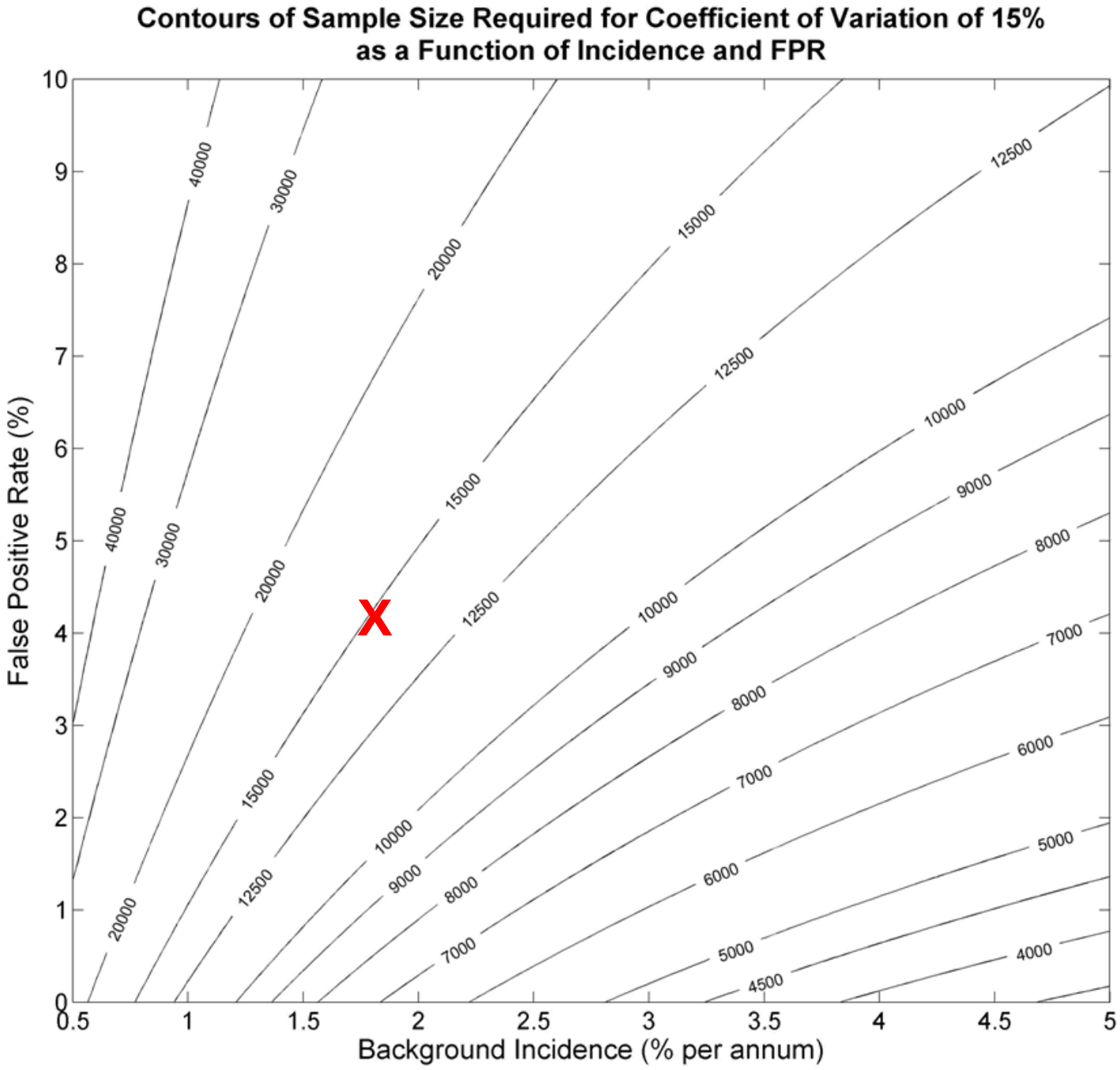
Avidity & BED cutoff Values	MACS N= 341 individuals	ALIVE N= 284 individuals
30% , 0.6	0.58% (2/341)	0.35% (1/284)
40%, 0.8	0.74% (3/341)	0.35% (1/284)
40%, 1.0	0.74% (3/341)	0.35% (1/284)
50%, 0.8	2.35% (8/341)	0.35% (1/284)
80%, 1.0	3.81% (13/341)	3.52% (10/284)

Incidence Comparison at Johns Hopkins Emergency Department 2001 & 2007

Clade B epidemic
Use BED 0.8 & Avidity 40%
Assume 143 day window period
Misclassification rate of 0.7%

	Survey year	
	2001	2007
HIV negative	1366	4154
HIV positive	183	321
Recent positives	8	4
Incidence Estimates	1.26%	0.11%

One sided P value for difference = 0.0008


Contours of Sample Size Required for Coefficient of Variation of 15%
as a Function of Incidence and FPR
False Positive Rate (%)
Background Incidence (% per annum)
0
1
2
3
4
5
6
7
8
9
10
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
40000
30000
20000
15000
12500
10000
9000
8000
7000
6000
5000
4500
4000
X

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- Joanne Micallef
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