Expansion of HIV Testing & Implications for STD Management

National Network of STD/HIV Prevention Training Centers
in Collaboration with the HIV Medicine Association
46th Annual Meeting of IDSA
Washington, DC
Friday, October 24, 2008

Agenda

- Introductory Remarks
  - Jeanne Marrazzo, University of Washington
- Keynote Presentation: New Diagnostic Tools & Approaches
  - Bernard Branson, Centers for Disease Control and Prevention
- STD Co-Infection in Acute HIV: Indications & Methodologies for Targeted Screening
  - Peter Leone, University of North Carolina
- Integration of STD/HIV Screening: Novel Approaches & Strategies for HIV Case Detection
  - Cornelis Rietmeijer, Denver Public Health Department

STD Management Updates

- Herpes Simplex Virus
  - Connie Celum, University of Washington
- Syphilis Update
  - Gail Bolan, California Department of Public Health

Expansion of HIV Testing and Implications for STD Management

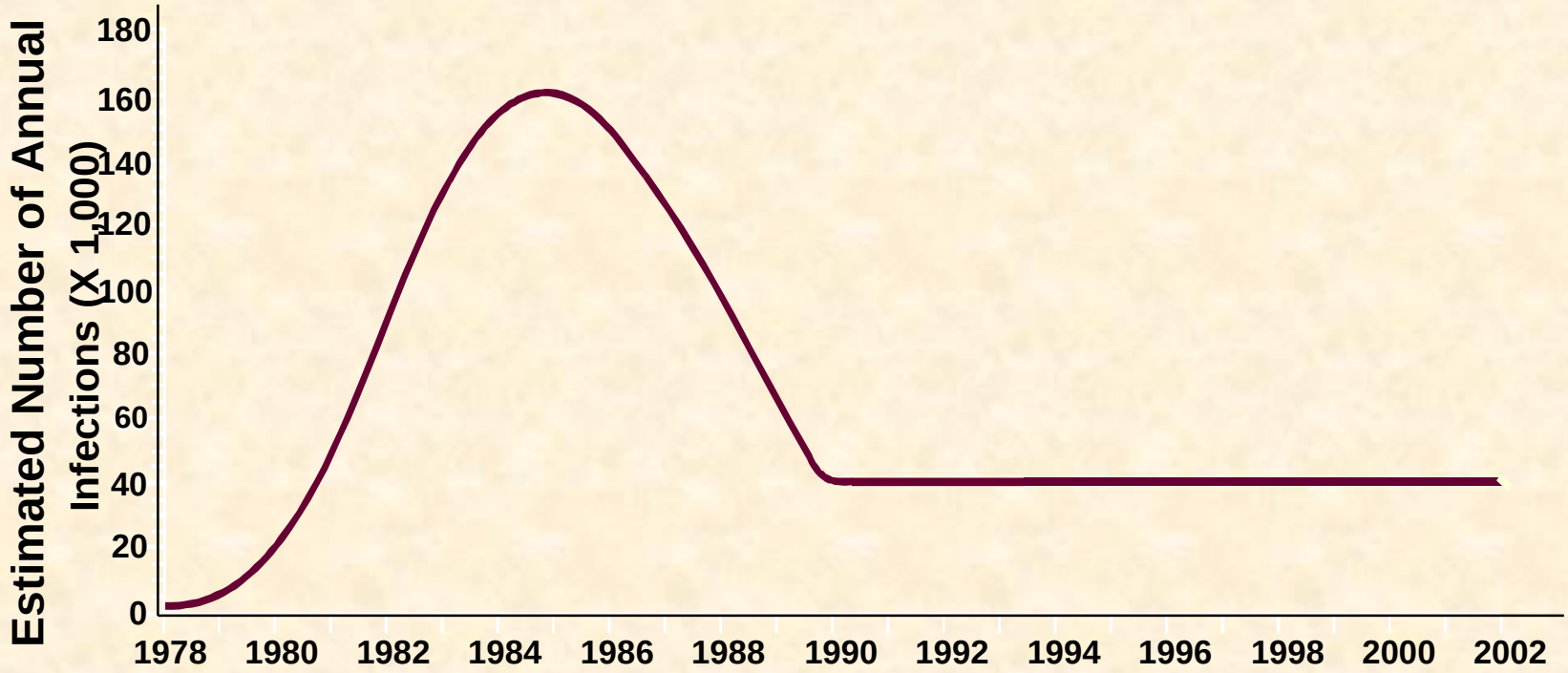
National Network of STD/HIV Prevention Training Centers

in collaboration with

the HIV Medicine Association

Jeanne Marrazzo, MD, MPH
University of Washington Center for AIDS & STD
Seattle STD/HIV Prevention Training Center

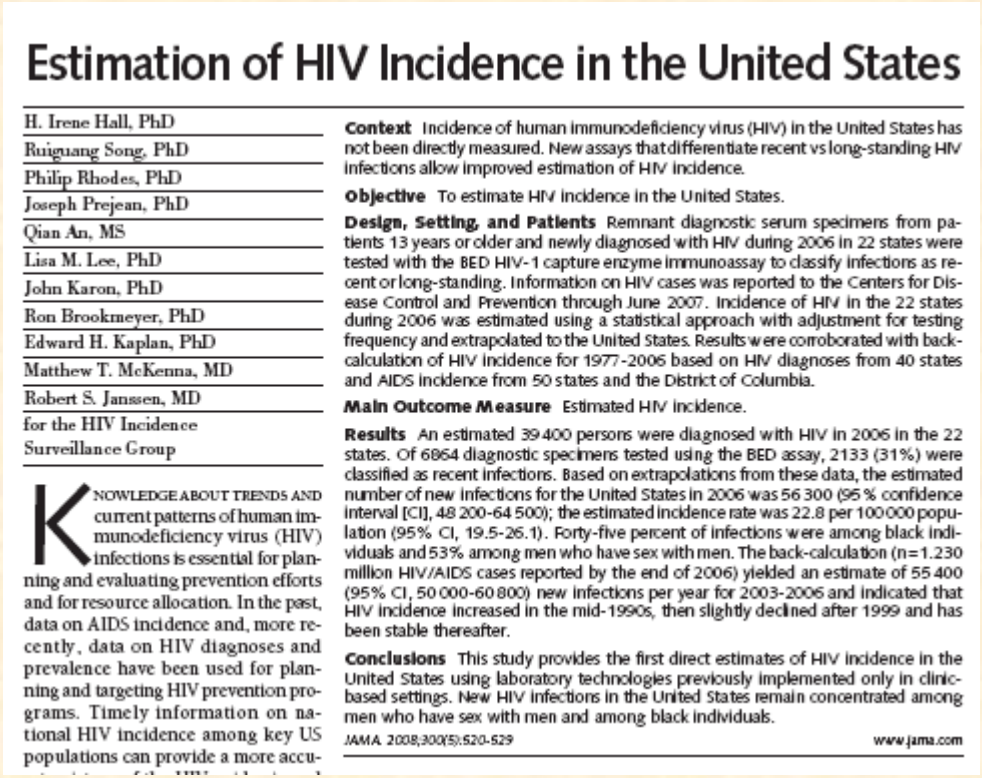
Estimated Number of New HIV Infections Annually



Ask Screen Intervene

Revised Estimates in U.S.

- **56,300 new infections, 2006 (40% increase)**
  - **73% men**
  - **53% MSM**
  - **45% NH Blacks**
  - **17% Hispanics**



Estimation of HIV Incidence in the United States

H. Irene Hall, PhD
Ruiguang Song, PhD
Philip Rhodes, PhD
Joseph Prejean, PhD
Qian An, MS
Lisa M. Lee, PhD
John Karon, PhD
Ron Brookmeyer, PhD
Edward H. Kaplan, PhD
Matthew T. McKenna, MD
Robert S. Janssen, MD
for the HIV Incidence Surveillance Group

Context Incidence of human immunodeficiency virus (HIV) in the United States has not been directly measured. New assays that differentiate recent vs long-standing HIV infections allow improved estimation of HIV incidence.

Objective To estimate HIV incidence in the United States.

Design, Setting, and Patients Remnant diagnostic serum specimens from patients 13 years or older and newly diagnosed with HIV during 2006 in 22 states were tested with the BED HIV-1 capture enzyme immunoassay to classify infections as recent or long-standing. Information on HIV cases was reported to the Centers for Disease Control and Prevention through June 2007. Incidence of HIV in the 22 states during 2006 was estimated using a statistical approach with adjustment for testing frequency and extrapolated to the United States. Results were corroborated with back-calculation of HIV incidence for 1977-2006 based on HIV diagnoses from 40 states and AIDS incidence from 50 states and the District of Columbia.

Main Outcome Measure Estimated HIV incidence.

Results An estimated 39 400 persons were diagnosed with HIV in 2006 in the 22 states. Of 6864 diagnostic specimens tested using the BED assay, 2133 (31%) were classified as recent infections. Based on extrapolations from these data, the estimated number of new infections for the United States in 2006 was 56 300 (95% confidence interval [CI], 48 200-64 500); the estimated incidence rate was 22.8 per 100 000 population (95% CI, 19.5-26.1). Forty-five percent of infections were among black individuals and 53% among men who have sex with men. The back-calculation (n=1.230 million HIV/AIDS cases reported by the end of 2006) yielded an estimate of 55 400 (95% CI, 50 000-60 800) new infections per year for 2003-2006 and indicated that HIV incidence increased in the mid-1990s, then slightly declined after 1999 and has been stable thereafter.

Conclusions This study provides the first direct estimates of HIV incidence in the United States using laboratory technologies previously implemented only in clinic-based settings. New HIV infections in the United States remain concentrated among men who have sex with men and among black individuals.

JAMA. 2008;300(5):520-529 www.jama.com

KNOWLEDGE ABOUT TRENDS AND current patterns of human immunodeficiency virus (HIV) infections is essential for planning and evaluating prevention efforts and for resource allocation. In the past, data on AIDS incidence and, more recently, data on HIV diagnoses and prevalence have been used for planning and targeting HIV prevention programs. Timely information on national HIV incidence among key US populations can provide a more accu-

JAMA, July 2008

HIV Prevention:
More *Challenges Since October 2008*

- **Closure of the STEP and Phambili studies**
  - **T-cell vaccine (Merck's MRKAd5 HIV-1 gag/pol/nef trivalent vaccine)**

“Yet the pandemic still rages, with 2.7 million new infections in 2007. Indeed, for every infected person who began receiving antiretroviral therapy in 2007, 2.5 people were newly infected.”

Johnson MI, Fauci AS. *NEJM* 2008:359;888-91

HIV Prevention:
More *Challenges Since October 2008*

- **Lack of protective effect for**
  - **Cervical diaphragm (Padian *Lancet* 2007)**
  - **The vaginal microbicide cellulose sulfate (van Damme *NEJM* 2008)**
  - **Acyclovir suppression in HIV- heterosexual women in Tanzania (Watson-Jones *NEJM* 2008)**

San Francisco Chronicle

Anticipated 'slam dunk' AIDS treatment fails

Sabin Russell, Chronicle Medical Writer
Tuesday, February 5, 2008

(02-05) 04:00 PST Boston -- A once-promising experiment to see whether treating genital herpes with a common drug could dramatically reduce susceptibility to HIV infection has found no protection whatsoever - a shocking setback for researchers hoping to find a pill that would slow the spread of the AIDS epidemic.

Results of the long-awaited study, which included gay men in San Francisco, Seattle, New York and Peru, as well as women in Africa, were released in Boston Monday at the 15th annual Conference on Retroviruses and Opportunistic Infections, the premier annual scientific meeting of AIDS researchers.

Nearly 20 years of various studies on herpes had shown that herpes infection nearly tripled the risk of contracting HIV. The assumption was simple: Use acyclovir, a proven anti-herpes drug, to knock down that infection, and the odds of avoiding HIV would dramatically improve - by at least 50 percent, on par with the prevention benefit now attributed to male circumcision.

Suppressing Genital Herpes to Prevent HIV Acquisition, CROI Boston 2008 and Lancet 2008

Failure of Another Vaginal Microbicide Candidate

Kaiser Daily HIV/AIDS Report

Science & Medicine | Experimental Microbicide Carraguard Does Not Provide Protection Against HIV, Study Finds
[Feb 20, 2008]

The experimental microbicide Carraguard is safe but does not provide women with protection against HIV, according to results from clinical trials conducted in three locations in South Africa, the *Seattle Post-Intelligencer* reports (Paulson, *Seattle Post-Intelligencer*, 2/18). Microbicides include a range of products -- such as gels, films and sponges -- that could help prevent the sexual transmission of HIV and other infections (*Kaiser Daily HIV/AIDS Report*, 2/6).

Population Council,
Microbicides, New Delhi 2008

EDITORIAL | Annals of Internal Medicine

The Deadliest Catch: Fishing for HIV in New Waters

Pilcher CD, Hare CB

Ann Intern Med 2008;149:204-5

Today's Session: Expansion of HIV Testing

- **New Diagnostic Tools & Approaches**
  - **Bernard Branson, MD**
- **STD Co-Infection in Acute HIV: Indications & Methodologies for Targeted Screening**
  - **Peter Leone, MD**
- **Integration of STD/HIV Screening: Novel Approaches & Strategies for HIV Case Detection**
  - **Kees Rietmeijer, MD, PhD**

Continued Challenges in STD Management

- Resurgence of classic & new STD in HIV+
- Clear synergy between STD and HIV transmission & acquisition
- STD diagnostic tools remain problematic
- Effective STD diagnosis management in HIV+ compromised by
  - Lack of antibiotic choices
  - Limited capacity for partner management, complicated by internet partner selection
  - Methamphetamine

Today's Session
STD/HIV Management Updates

- **Herpes Simplex Virus**
  - **Connie Celum, MD**
- **Syphilis**
  - **Gail Bolan, MD**
- **Panel Discussion**
  - **Faculty**

New Tools and Approaches for HIV Diagnosis

Bernard M. Branson, M.D.

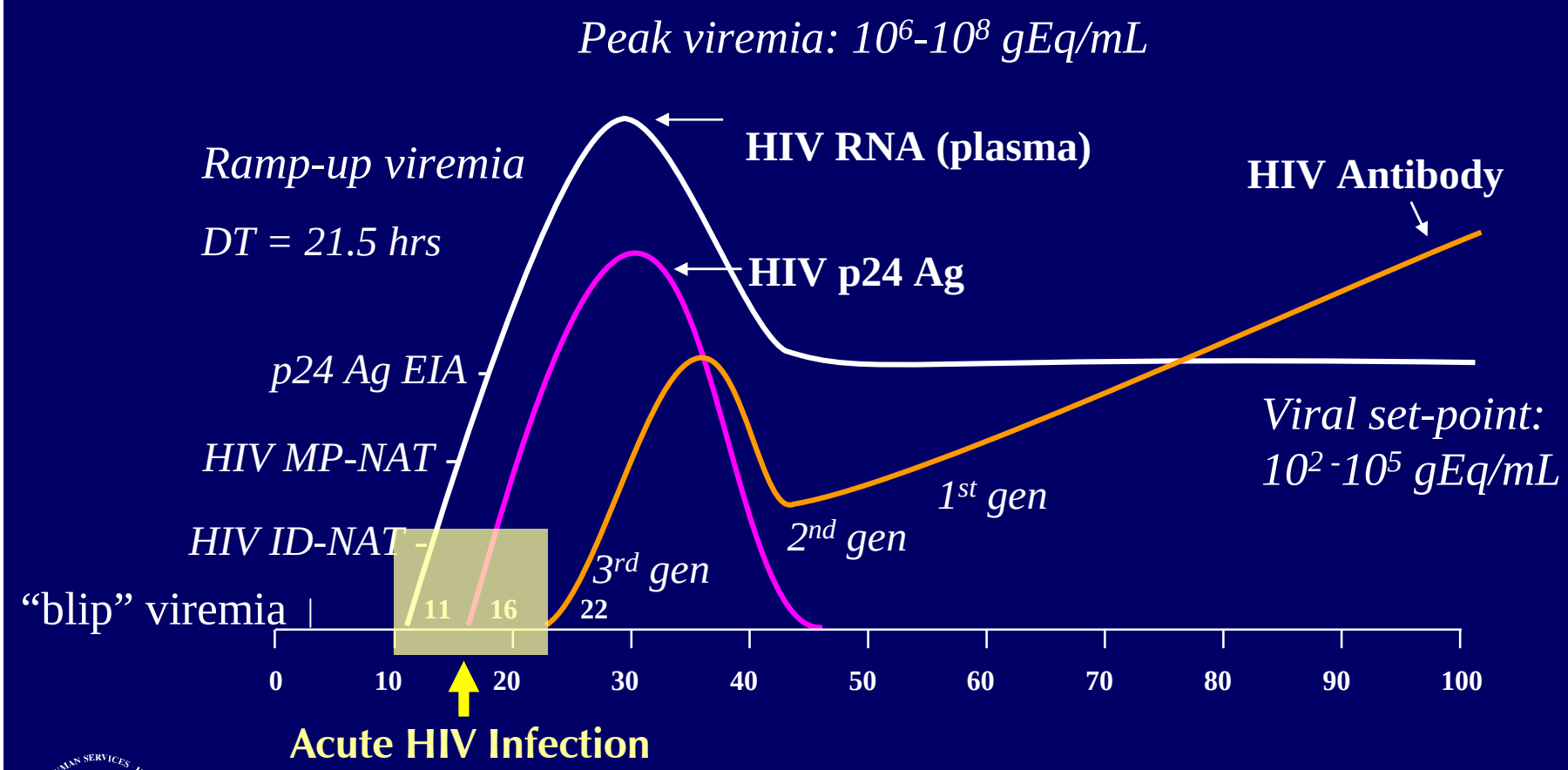
Associate Director for Laboratory Diagnostics
Divisions of HIV/AIDS Prevention
National Center for HIVAIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

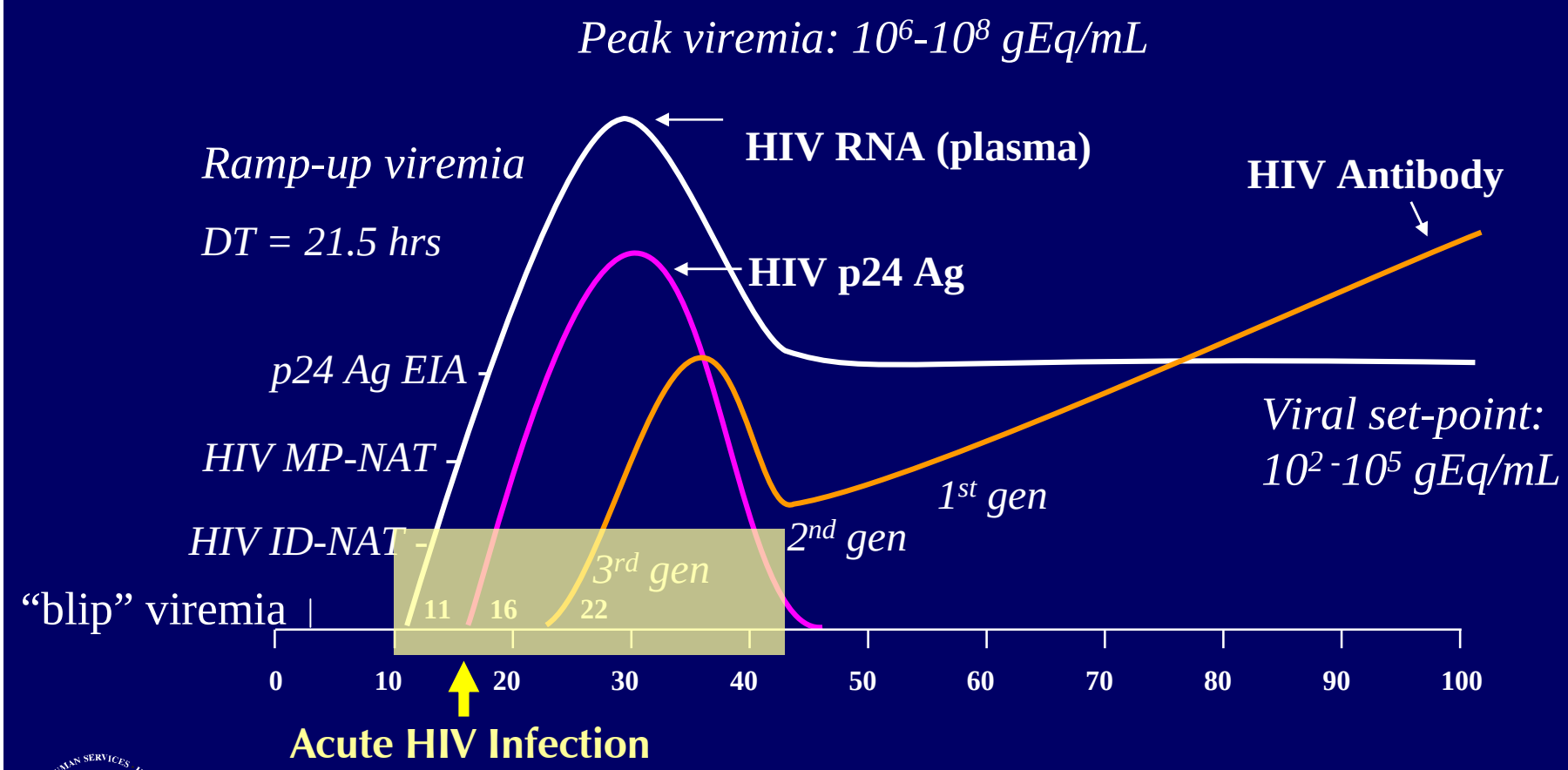
2006 CDC Revised Recommendations for HIV Testing

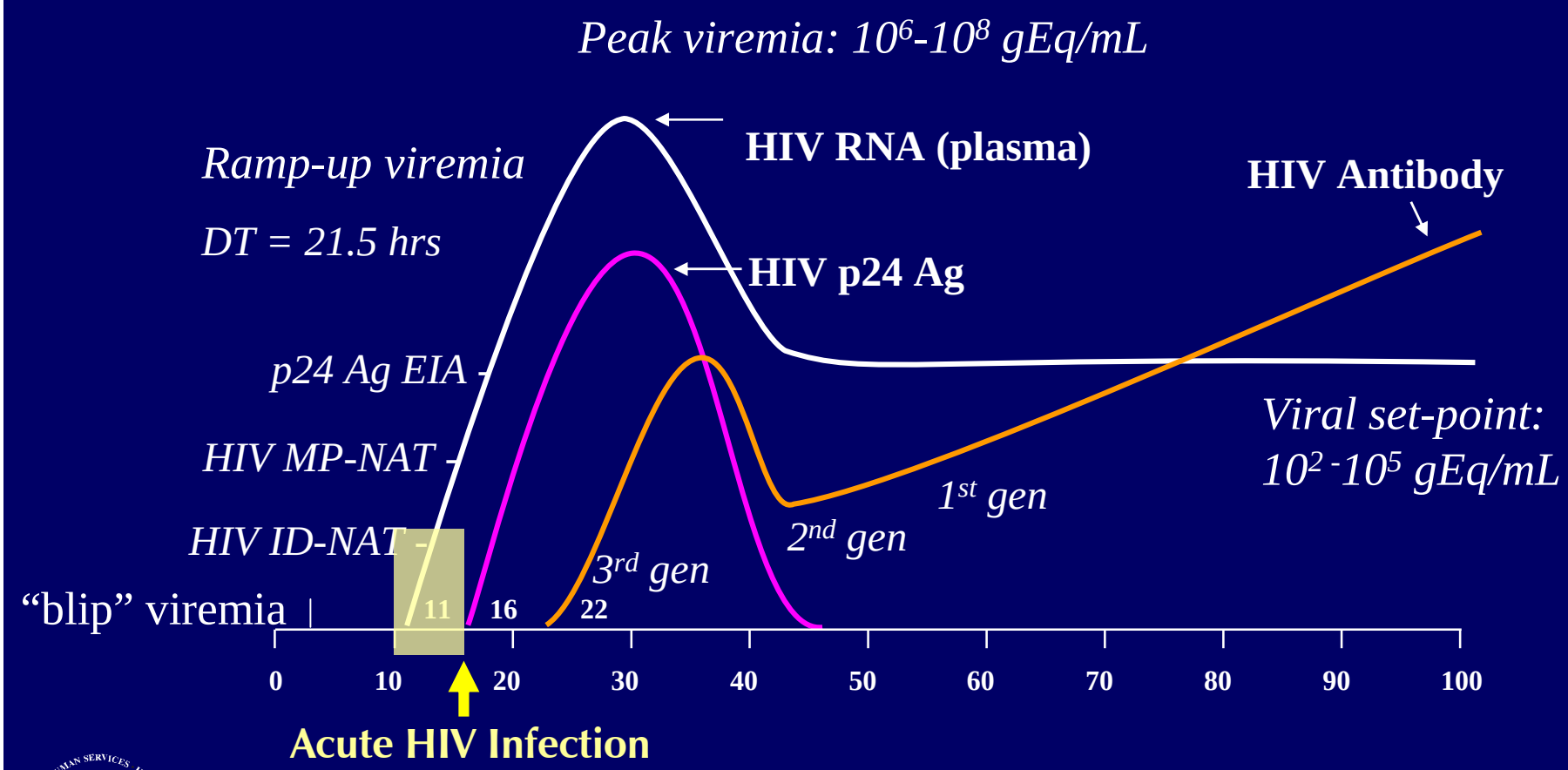
- Routine, voluntary HIV screening for all persons 13-64 in health care settings, regardless of risk
- When acute retroviral infection is a possibility, use an RNA test in conjunction with an HIV antibody test.
- Health-care providers should encourage patients and their prospective sex partners to be tested for HIV before initiating a new sexual relationship.

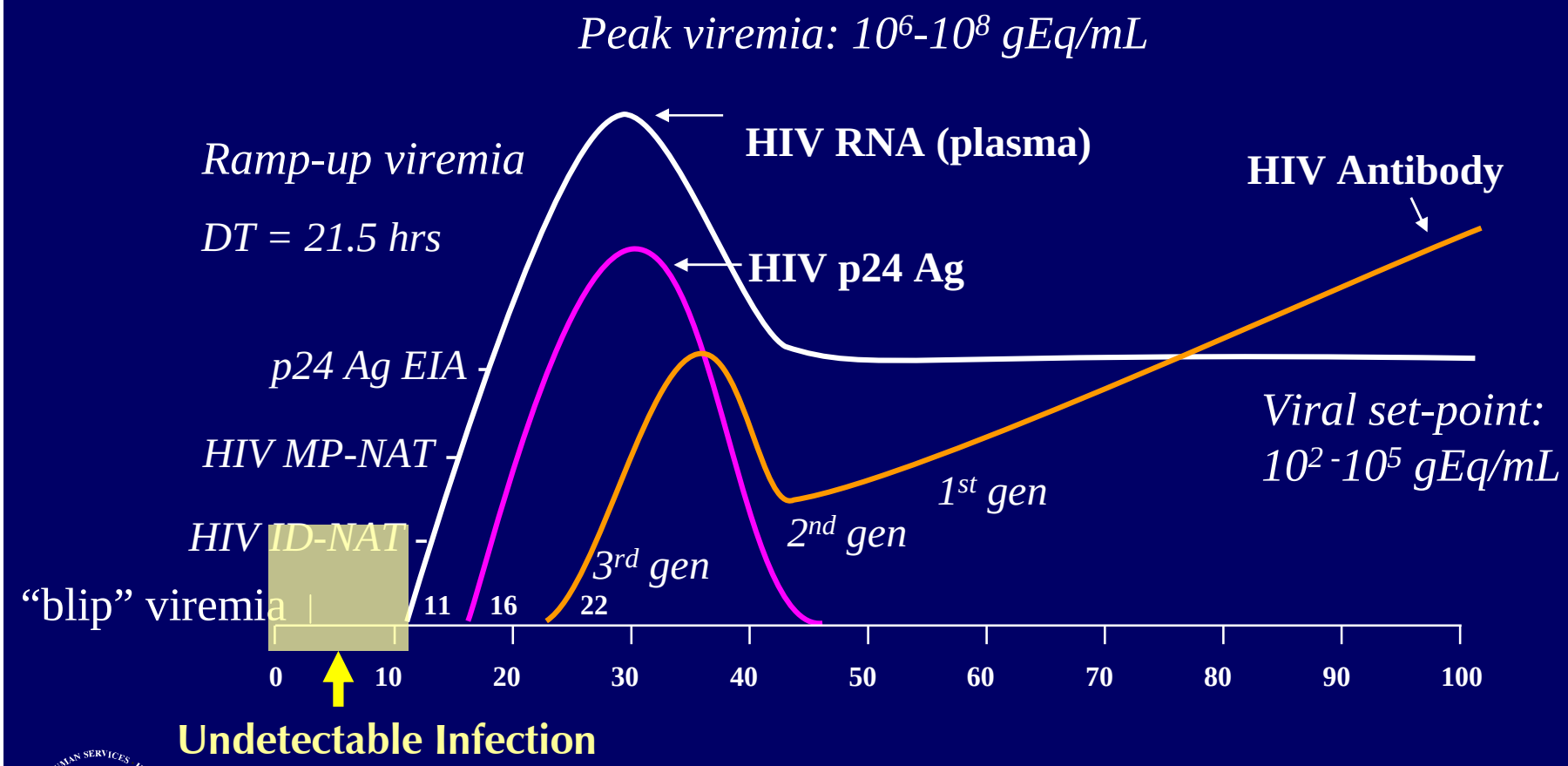
CDC

HIV Viremia and Antibody Response




Peak viremia: 10^6-10^8 gEq/mL
Ramp-up viremia
DT = 21.5 hrs
HIV RNA (plasma)
HIV Antibody
HIV p24 Ag
p24 Ag EIA
HIV MP-NAT
HIV ID-NAT
"blip" viremia
1st gen
2nd gen
3rd gen
Viral set-point:
10^2 - 10^5 gEq/mL
11
16
22
0
10
20
30
40
50
60
70
80
90
100
Acute HIV Infection


Peak viremia: 10^6-10^8 gEq/mL
Ramp-up viremia
DT = 21.5 hrs
HIV RNA (plasma)
HIV Antibody
HIV p24 Ag
p24 Ag EIA
HIV MP-NAT
HIV ID-NAT
"blip" viremia
Viral set-point:
10^2 - 10^5 gEq/mL
1st gen
2nd gen
3rd gen
11
16
22
0
10
20
30
40
50
60
70
80
90
100
Acute HIV Infection


Peak viremia: 10^6-10^8 gEq/mL
Ramp-up viremia
DT = 21.5 hrs
HIV RNA (plasma)
HIV Antibody
HIV p24 Ag
p24 Ag EIA
HIV MP-NAT
HIV ID-NAT
"blip" viremia
Viral set-point:
10^2 - 10^5 gEq/mL
1st gen
2nd gen
3rd gen
11
16
22
0
10
20
30
40
50
60
70
80
90
100
Undetectable Infection

July 21, 1989 / Vol 38 / No. S-7

MMWR
MORBIDITY AND MORTALITY
WEEKLY REPORT

Printed and distributed by the Massachusetts Medical Society,
publishers of *The New England Journal of Medicine*

Recommendations
and
Reports

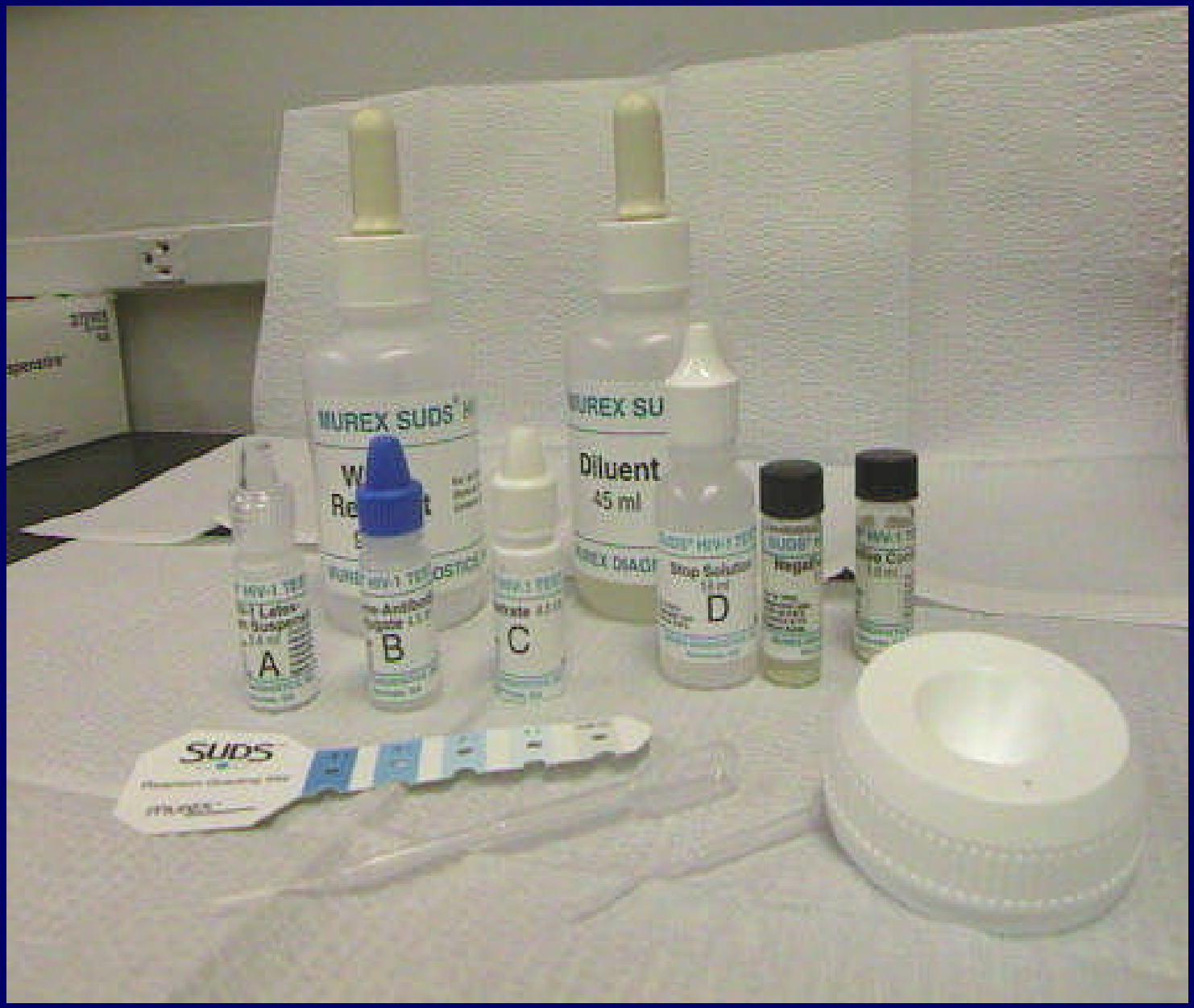
Interpretation and Use of the Western Blot Assay for Serodiagnosis of Human Immunodeficiency Virus Type 1 Infections

Diagnostic Algorithm: 1989

- The Public Health Service recommends that no positive test results be given to clients/patients until a **screening test has been repeatedly reactive** (i.e., greater than or equal to two tests) on the same specimen **and a supplemental, more specific test** such as the Western blot has been used to validate those results

1989 Almanac

- Berlin Wall dismantled
- Tiananmen Square
- Exxon Valdez
- U.S. invades Panama



SUDS: Single Use Diagnostic System for HIV-1

Blue color with reactive HIV test

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

March 27, 1998 / Vol. 47 / No. 11

MMWR™

MORBIDITY AND MORTALITY WEEKLY REPORT

Update: HIV Counseling and Testing Using Rapid Tests — United States, 1995

Approximately 25 million persons each year in the United States are tested for antibody to human immunodeficiency virus (HIV). Publicly funded counseling and testing (CT) programs conduct approximately 2.5 million of these tests each year. CT can have important prevention benefits (*1*); however, in 1995, 25% of persons testing HIV-positive and 33% of persons testing HIV-negative at publicly funded clinics did not return for their test results (*2*). Rapid tests to detect HIV antibody can be performed in an average of 10 minutes (*3*), enabling health-care providers to supply definitive

Recommendation …and a Promise

- Health-care providers should **provide preliminary positive test results** before confirmatory results are available in situations where tested persons benefit.

- When additional rapid tests become available for use in the United States, the **PHS will re-evaluate algorithms using specific combinations** of two or more rapid tests for screening and confirming HIV infection.

Process for Developing New HIV Testing Algorithms

- APHL/CDC HIV Steering Committee
  - Priority to develop new algorithms with directives from APHL Board of Directors, CDC
- Algorithm Workgroups
  - Point of care (POC)
  - Laboratory
- Data gathering –retrospective and prospective

Organizations, Agencies and Groups Represented on Workgroups

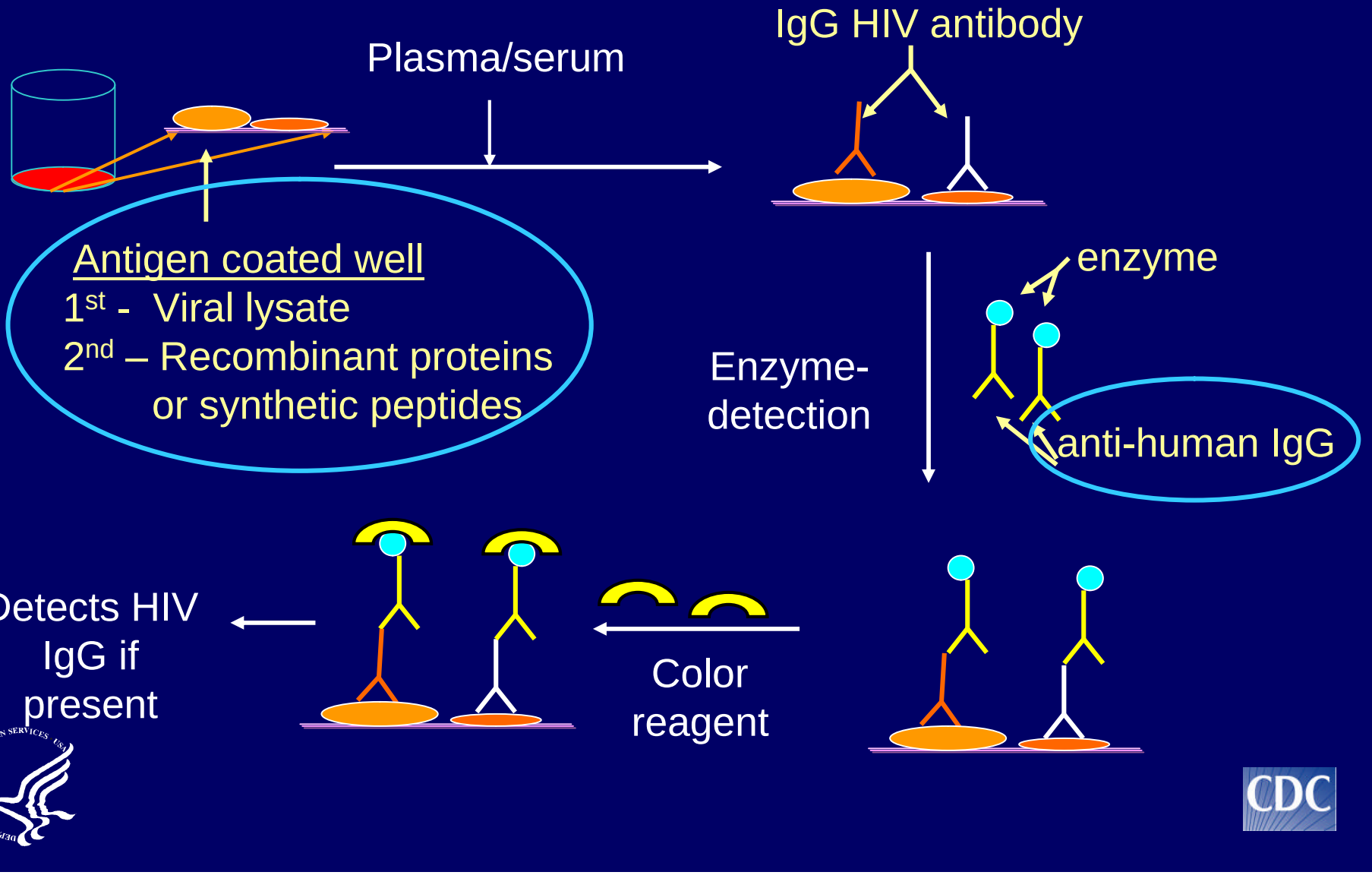
- APHL
- ACLA
- ASM
- Blood Banks
- CAP
- CDC
- Commercial Labs
- DoD
- FDA
- HIV Program Staff

Strategies and presentations online at
Hivtestingconference.org

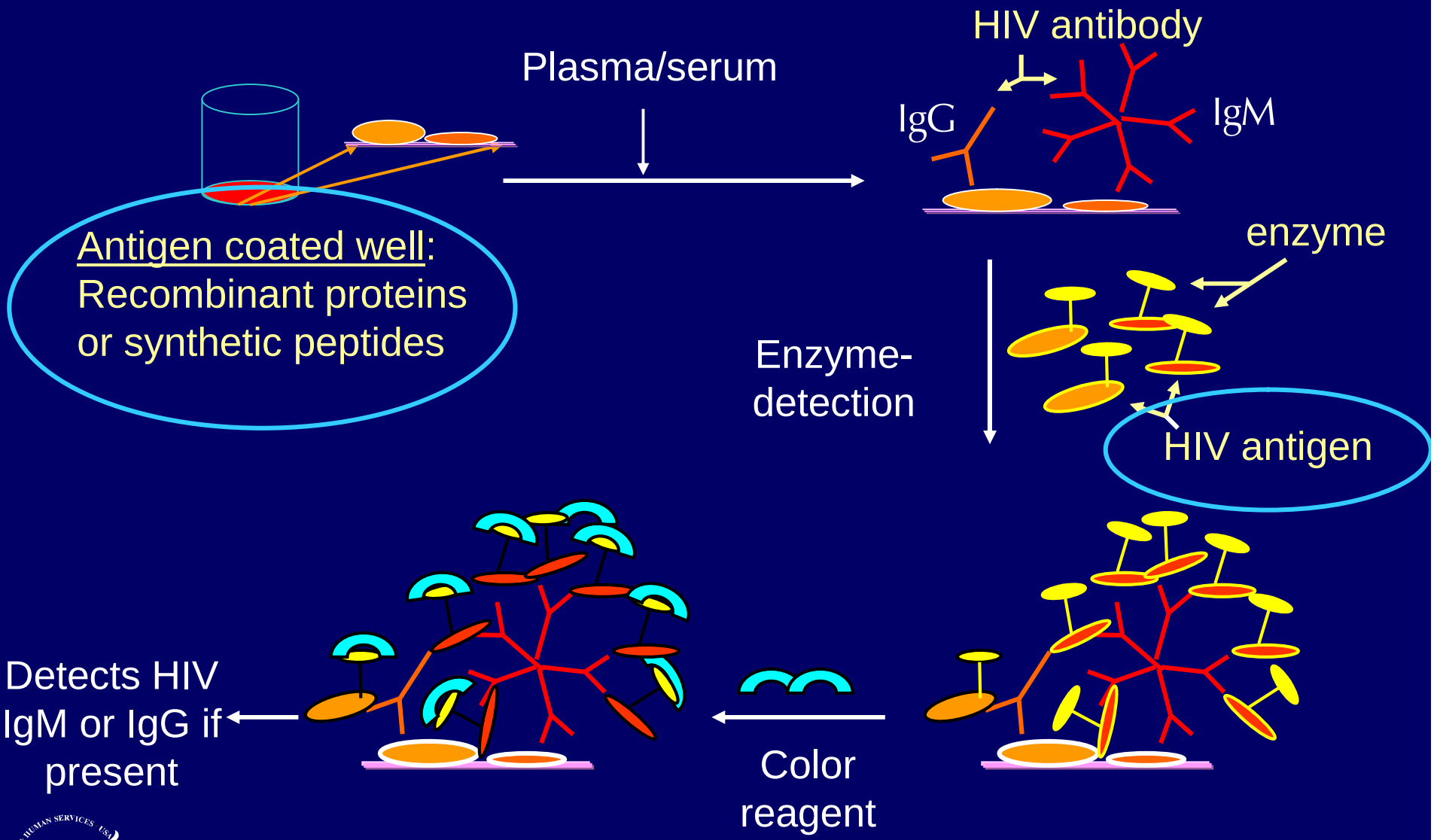
First, a little lesson on serology testing formats

- Feel free to take a nap if you understand:
  - 1st, 2nd, 3rd and 4th generation EIA

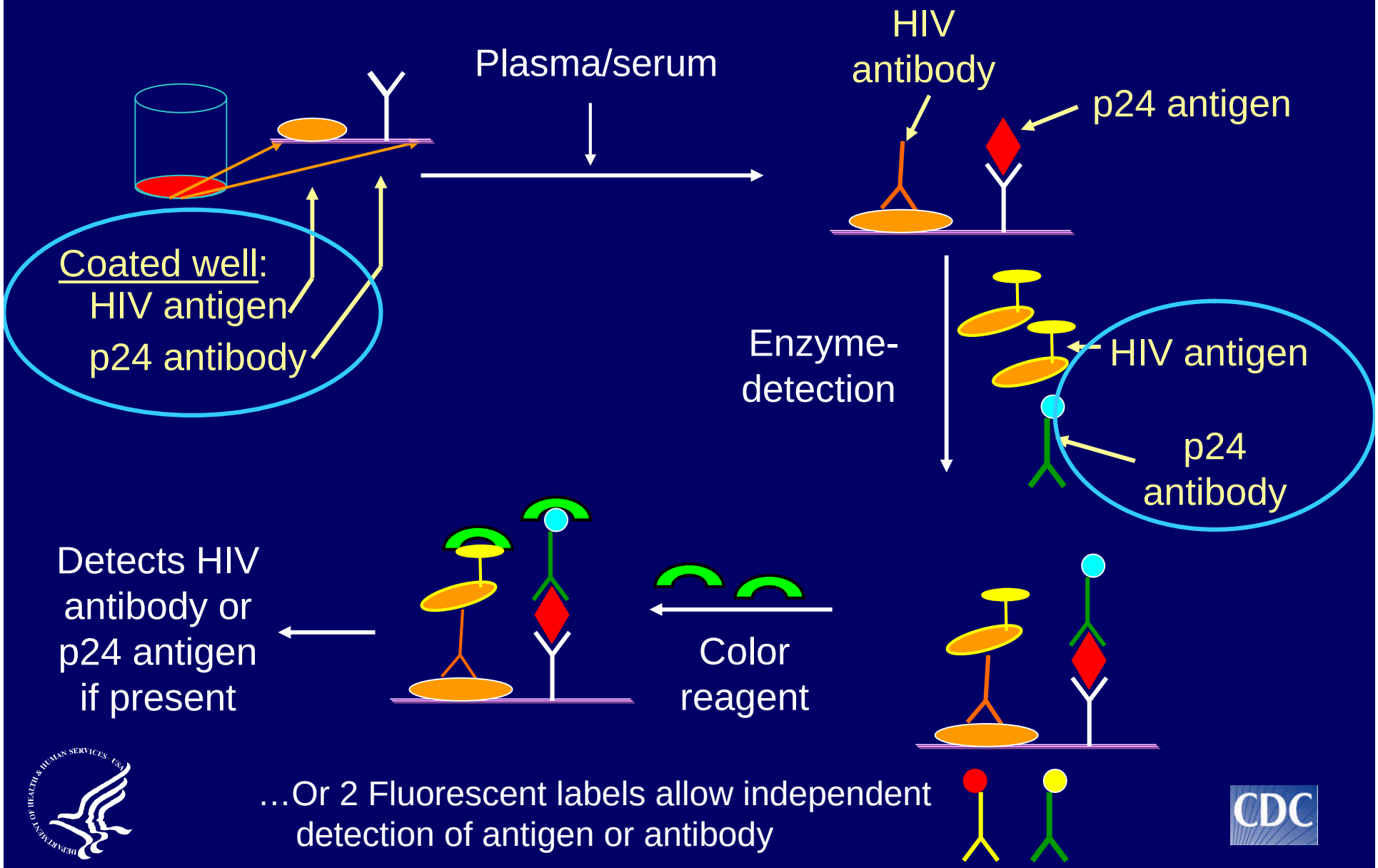
1st and 2nd Generation EIA



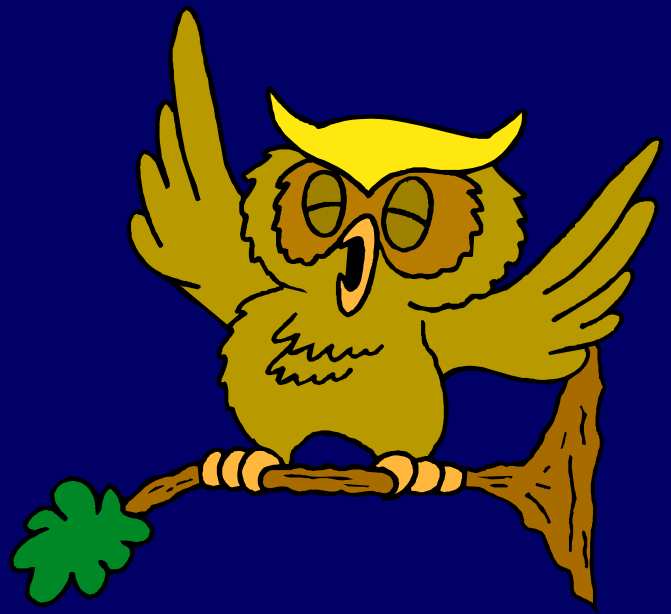
3rd Generation "Sandwich" EIA



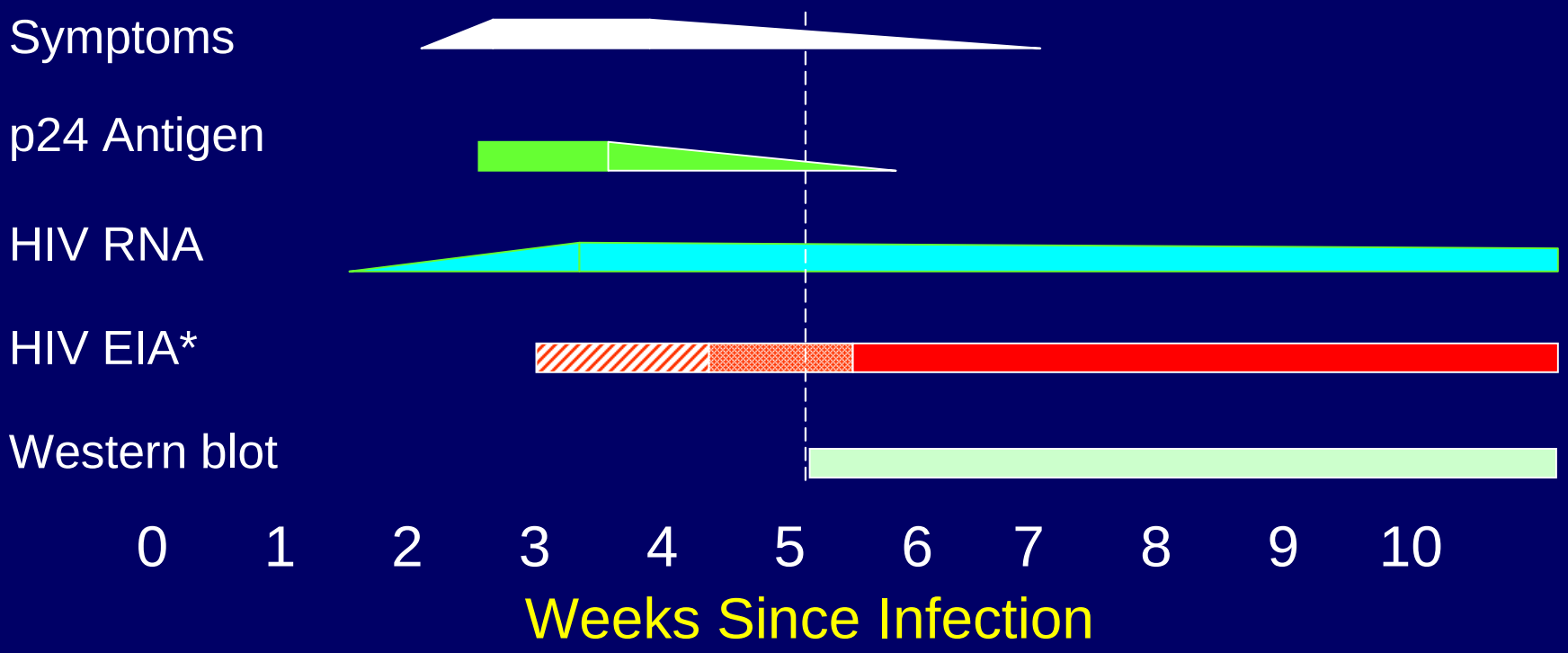
4th Generation Combo EIA



Time to wake up!



Detection of HIV by Diagnostic Tests



**3rd generation, IgM-sensitive EIA*

**2nd generation EIA*

**viral lysate EIA*

After Fiebig et al, AIDS 2003; 17(13):1871-9

EIAs Used by Public Health Labs - 2004

	FDA approval date	*% used by PHL labs, 2004*
Vironostika HIV-1 Microelisa	*1987*	*63%*
Abbott HIVAB HIV-1/2	1992	20%
Genetic Systems rLAV	1998	20%
Gen Sys HIV-1/HIV-2	2000	18%
Gen Sys HIV-1/2 Plus O	2003	10%
Siemens 1/O/2 eHIV	2006	
Ortho Vitros Anti-HIV 1+2	2008	

viral lysate EIA *2nd generation EIA* *3rd generation, IgM-sensitive EIA*

EIAs Used by Public Health Labs - 2004

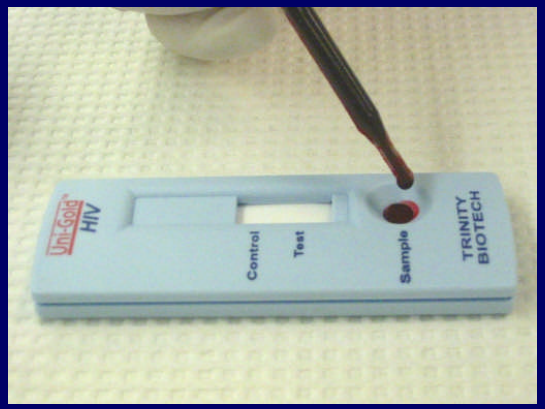
	FDA approval date	*% used by PHL labs, 2004*
Vironostika HIV-1 Microelisa	*1987*	*63%*
Abbott HIVAB HIV-1/2	1992	20%
Genetic Systems rLAV	1998	20%
Gen Sys HIV-1/HIV-2	2000	18%
Gen Sys HIV-1/2 Plus O	2003	10%
Siemens 1/O/2 eHIV	2006	
Ortho Vitros Anti-HIV 1+2	2008	

viral lysate EIA *2nd generation EIA* *3rd generation, IgM-sensitive EIA*

EIAs Used by Public Health Labs - 2004

	FDA approval date	*% used by PHL labs, 2004*
Vironostika HIV-1 Microelisa	*1987*	*63%*
Abbott HIVAB HIV-1/2	1992	20%
Genetic Systems rLAV	1998	20%
Gen Sys HIV-1/HIV-2	2000	18%
Gen Sys HIV-1/2 Plus O	2003	10%
Siemens 1/O/2 eHIV	2006	
Ortho Vitros Anti-HIV 1+2	2008	

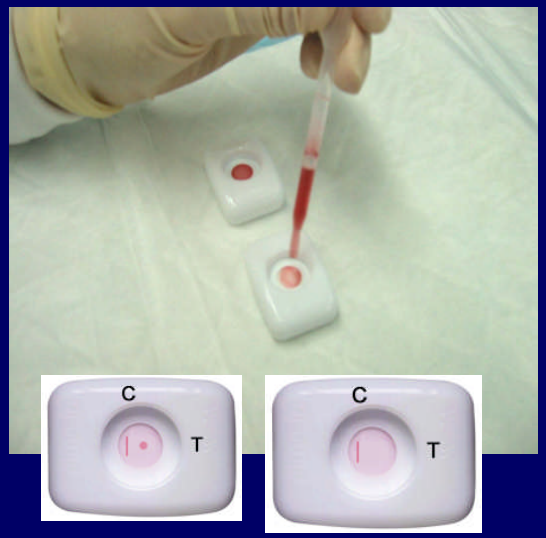
viral lysate EIA *2nd generation EIA* *3rd generation, IgM-sensitive EIA*



Uni-Gold Recombigen

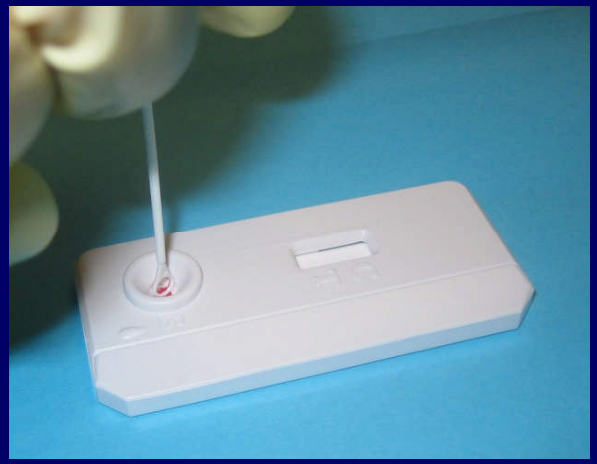
Multispot HIV-1/HIV-2

Clearview Complete HIV 1/2

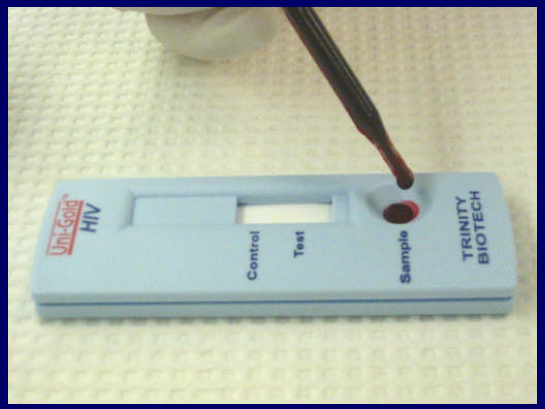


Reveal G3

OraQuick Advance



Clearview HIV 1/2 Stat Pak



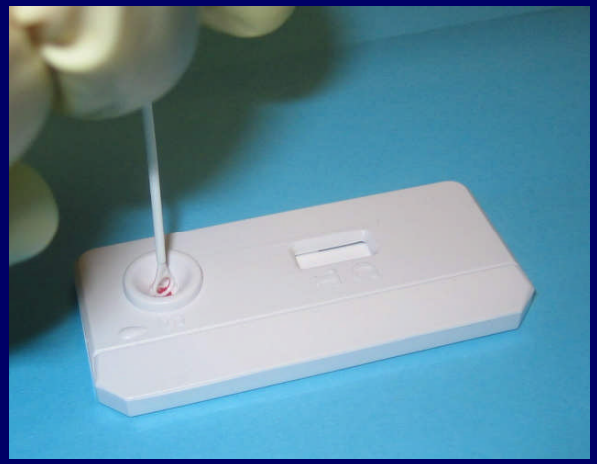
Uni-Gold Recombigen

Multispot HIV-1/HIV-2

Clearview Complete HIV 1/2

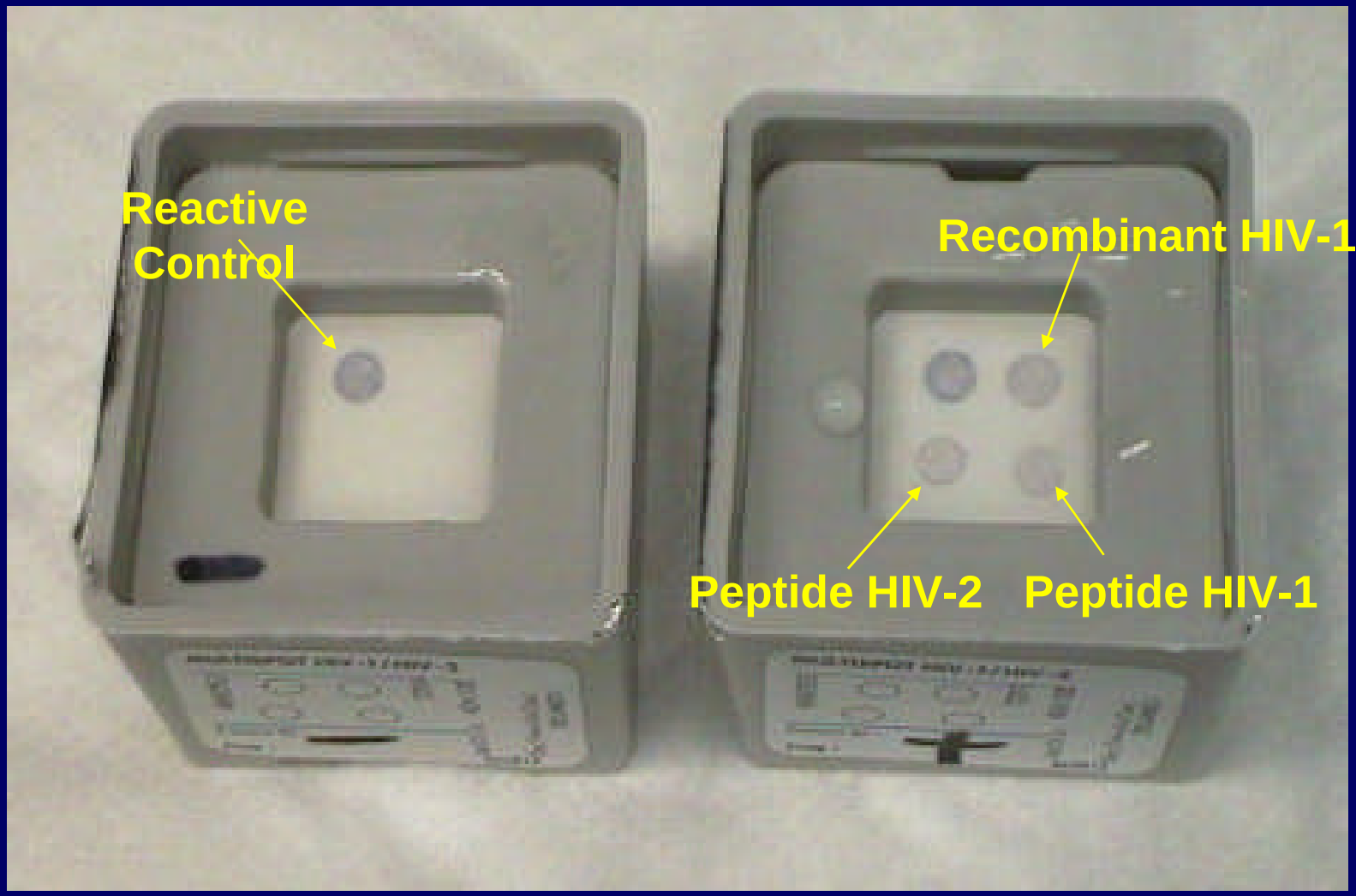
Reveal G3

OraQuick Advance



Clearview HIV 1/2 Stat Pak

Multispot: Differentiates HIV-1 from HIV-2



FDA-Approved Rapid HIV Tests

	Sensitivity *(95% C.I.)*	Specificity *(95% C.I.)*
Oral fluid		
OraQuick Advance	99.3 *(98.4 - 99.7)*	99.8 *(99.6-99.9)*
Whole blood		
Un-Gold Recombigen	100 *(99.5 – 100)*	99.7 *(99.0 – 100)*
Clearview Stat-Pak	99.7 *(98.9 – 100)*	99.9 *(98.6 – 100)*
Clearview Complete	99.7 *(98.9 – 100)*	99.9 *(98.6 – 100)*
Serum/plasma		
Reveal G3	99.8 *(99.2 – 100)*	99.9 *(98.6 – 100)*
Multispot	100 *(99.9 – 100)*	99.9 *(99.8 – 100)*

CDC

Senitivity: Influenza Rapid Tests

A: 92.5%

B: 95%

A: 77%

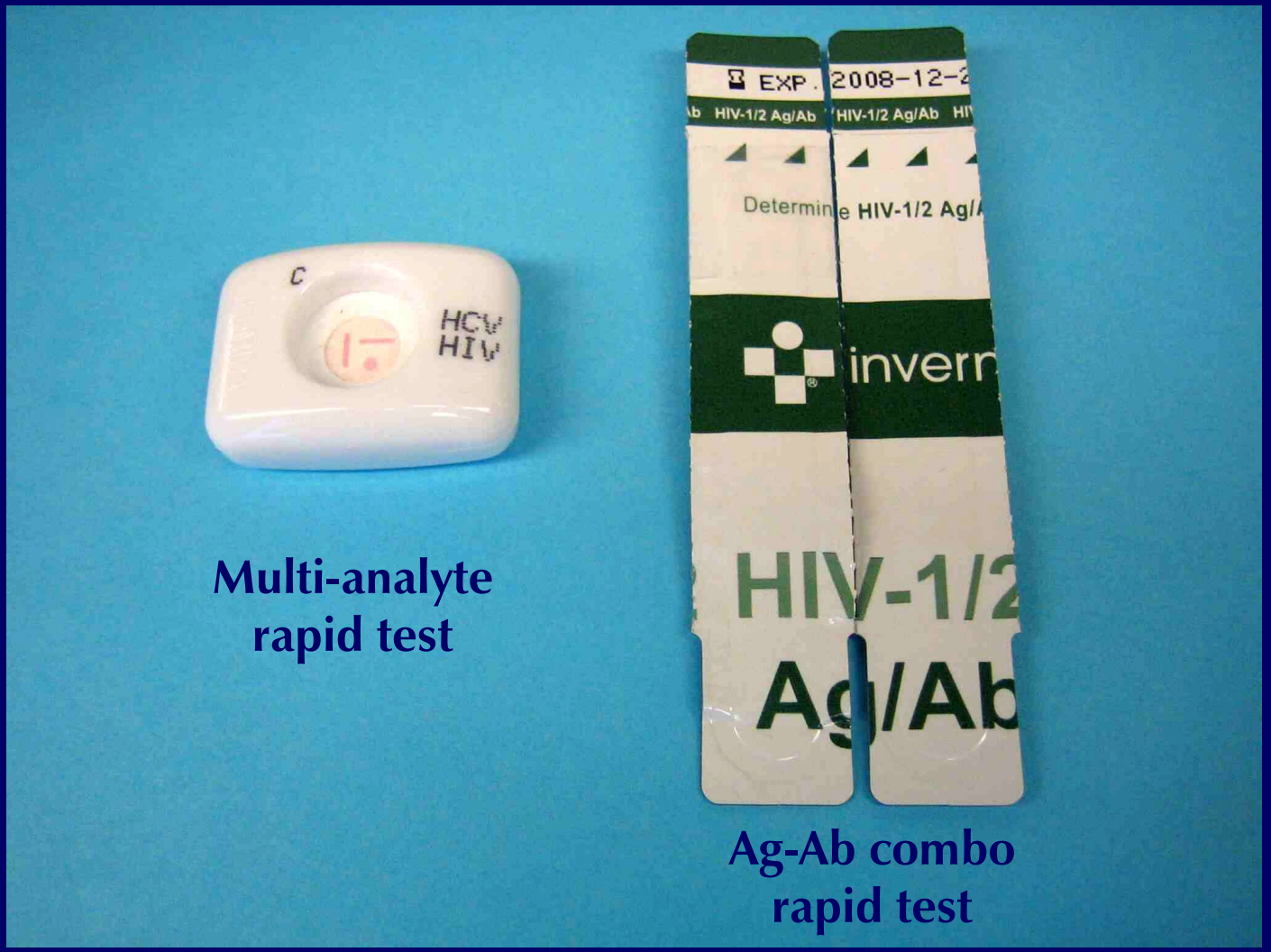
B: 82%

A: 81%

B: 65%

2008 State of the Art

On the Horizon…



Multi-analyte rapid test

Ag-Ab combo rapid test

Abbott Architect 4th generation EIA

3rd *vs.* 4th generation HIV serology

	2005	2006	2007	*Total*
Newly identified HIV cases	**289 (22,532)**	**230 (11,275)**	**250 (9,376)**	***769 (43,183)***
Total AHI cases	**53 (18.3%)**	**43* (18.6%)**	**30* (12%)**	***126 (16.3%)***
3rd generation EIA	**35 (66%)**	**28 (67%)**	**17 (56.5%)**	***80 (63.2%)***
4th generation EIA	**49 (92%)**	**42 (97.7%)**	**27 (90%)**	***118 (93.2%)***

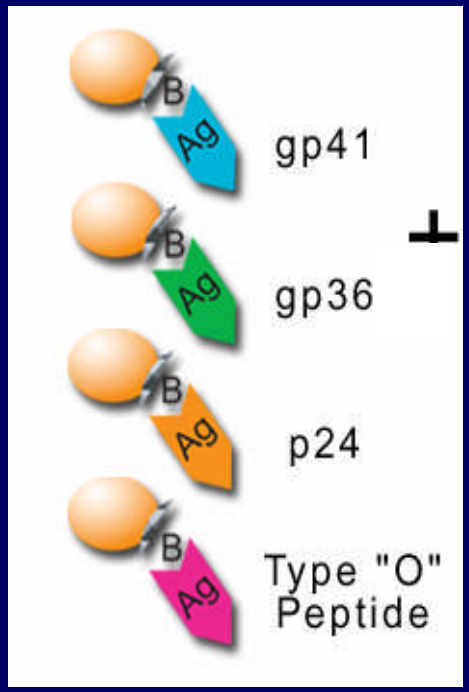
- Cunningham P, unpublished data, Australia

Diagnostic Assays Recently Approved by the FDA

The ADVIA® Centaur™ Random Access HIV 1/O/2 Enhanced (EHIV)

Siemens HIV 1/O/2 Enhanced (EHIV)

- 50 µl specimen
- 3rd generation "sandwich" format
- Random access chemiluminescent immunoassay
- FDA-approved July 2006



On-board Refrigeration of 30 Different Assays

STAT sample requests without pausing

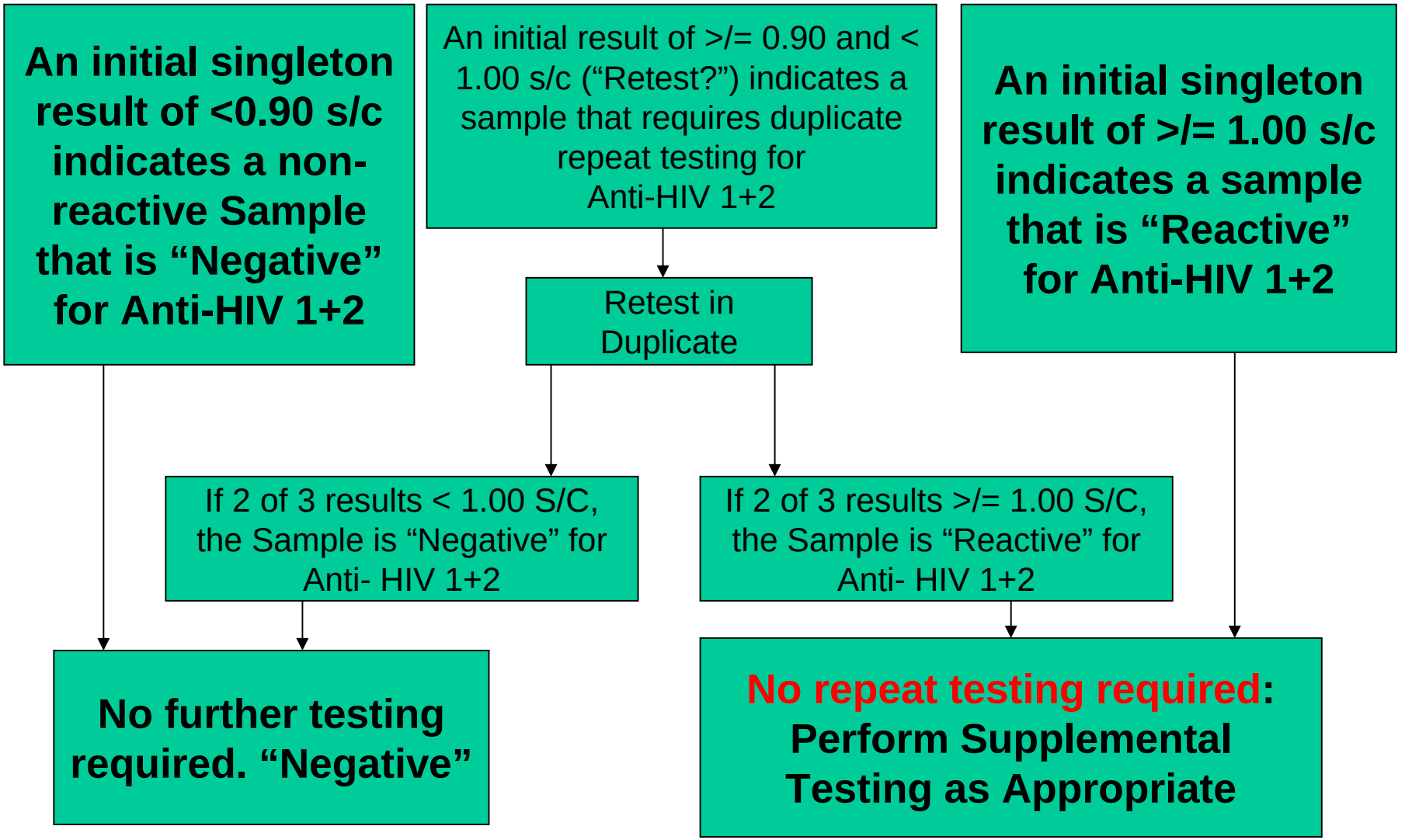
Results in ~60 minutes

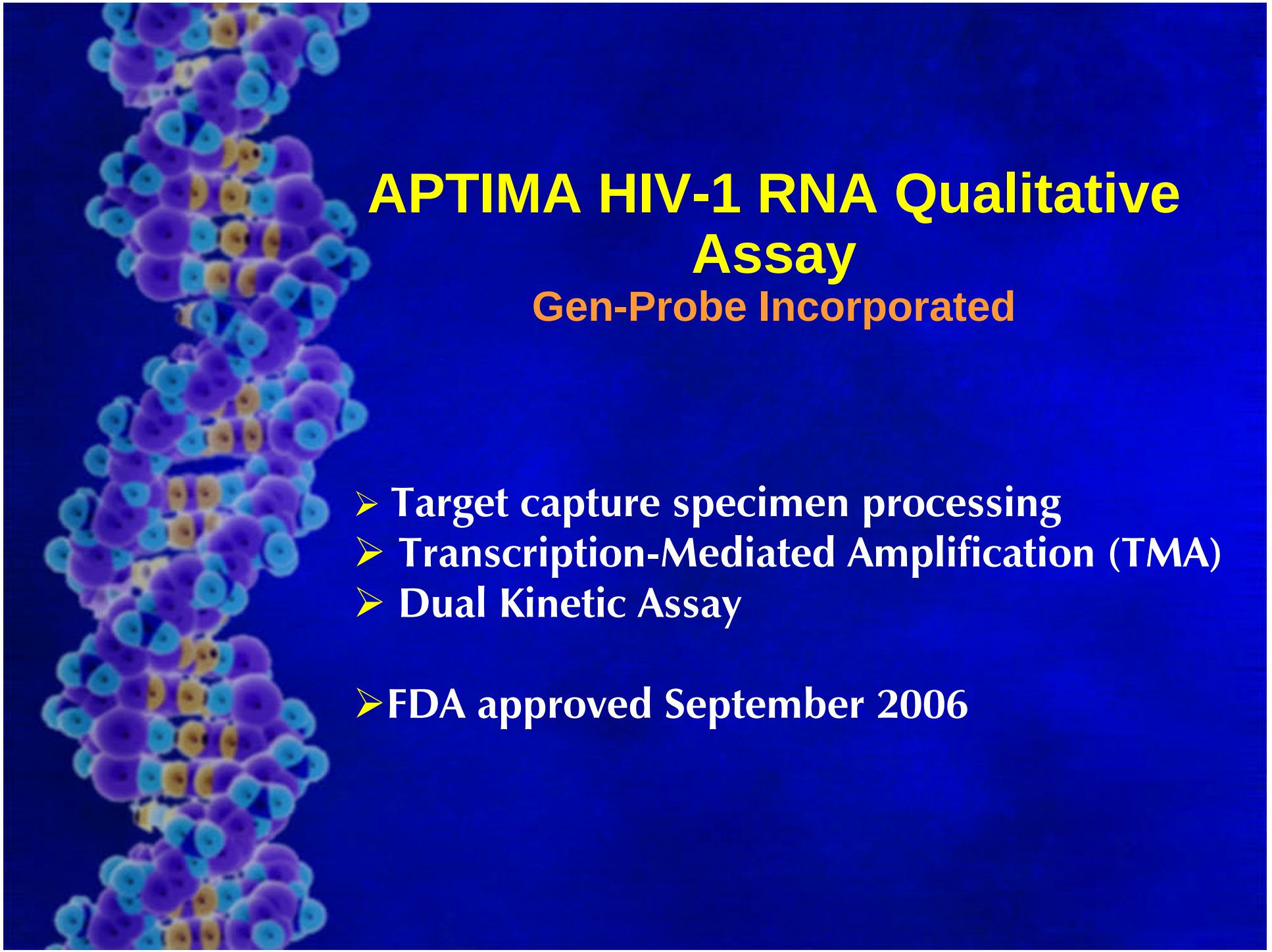
Ortho VITROS ECi/ECiQ

Ortho VITROS Anti-HIV 1+2

- 80 μl specimen, random access
- 3rd generation chemiluminescent immunoassay
  - **HIV 1 Env 13 -** gp 120 and gp 41 region
  - **HIV-1 Env 10** - gp41 region which extends beyond the C-terminus of Env 13
  - **HIV-1 p24** - full length core protein of HIV-1
  - **HIV-2 Env AL** - region from gp 36 of HIV-2
- FDA approved March 2008

Result Algorithm




APTIMA HIV-1 RNA Qualitative Assay
Gen-Probe Incorporated
Target capture specimen processing
Transcription-Mediated Amplification (TMA)
Dual Kinetic Assay
FDA approved September 2006

Qualitative RNA Assay: Intended Use

- Aid to HIV-1 diagnosis
- Diagnosis of acute HIV-1 infection in antibody-negative persons
- Confirmation of HIV-1 infection in antibody-positive persons when it is reactive

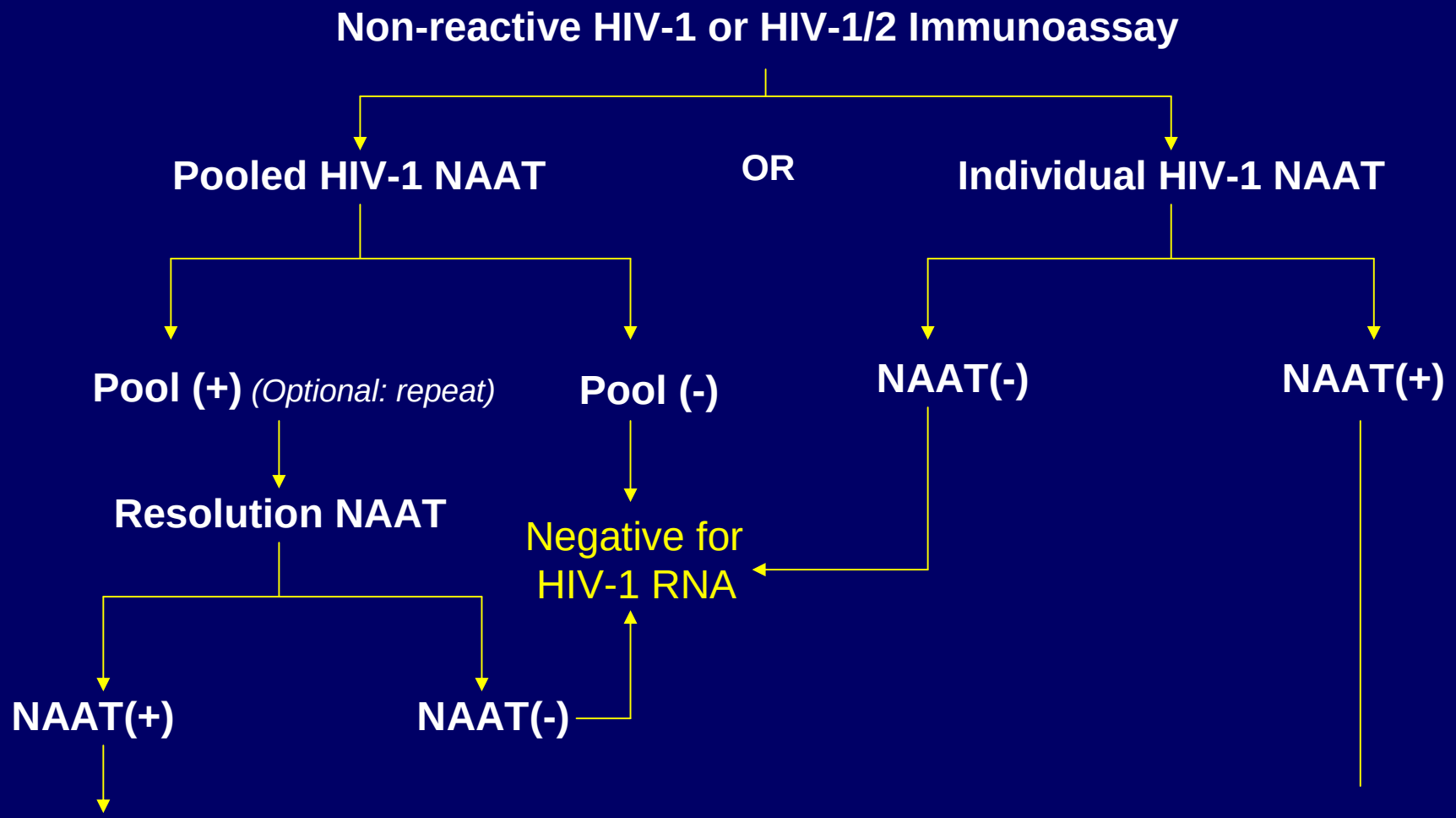
Clinical Syndrome of Acute HIV

- 40-90% develop symptoms of Acute HIV
- 50%-90% with symptoms seek medical care
- Of those diagnosed with Acute HIV, 50% of patients seen at least 3 times before diagnosis

- Kahn et al, NEJM 1998
- Weintrob et al, Arch Int Med 2003

Pooled RNA Screening for Early HIV Infection

Strategy 4. Acute HIV Infection Testing

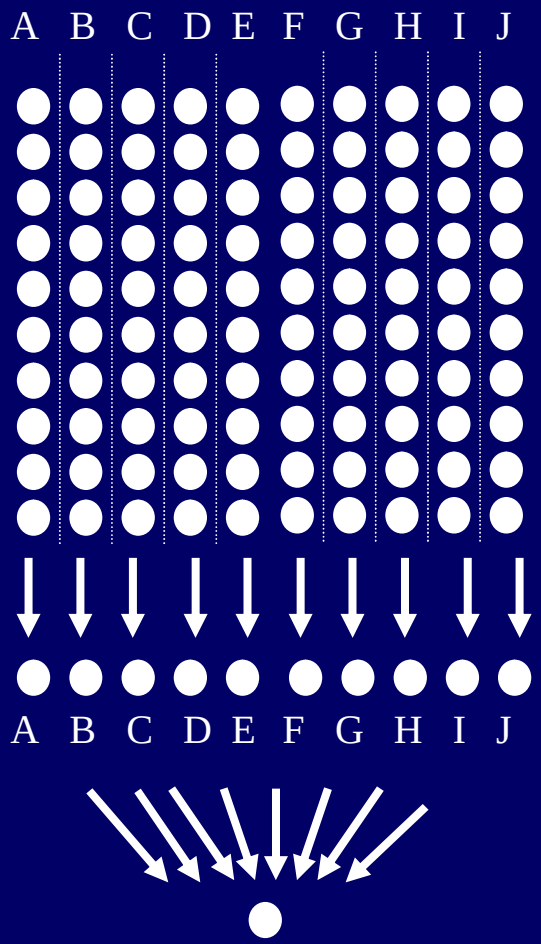


Pooled NAAT Screening for Early HIV Infection

100
Individual
specimens
(HIV antibody negative)

10 Pools of 10

1 Screening
Pool

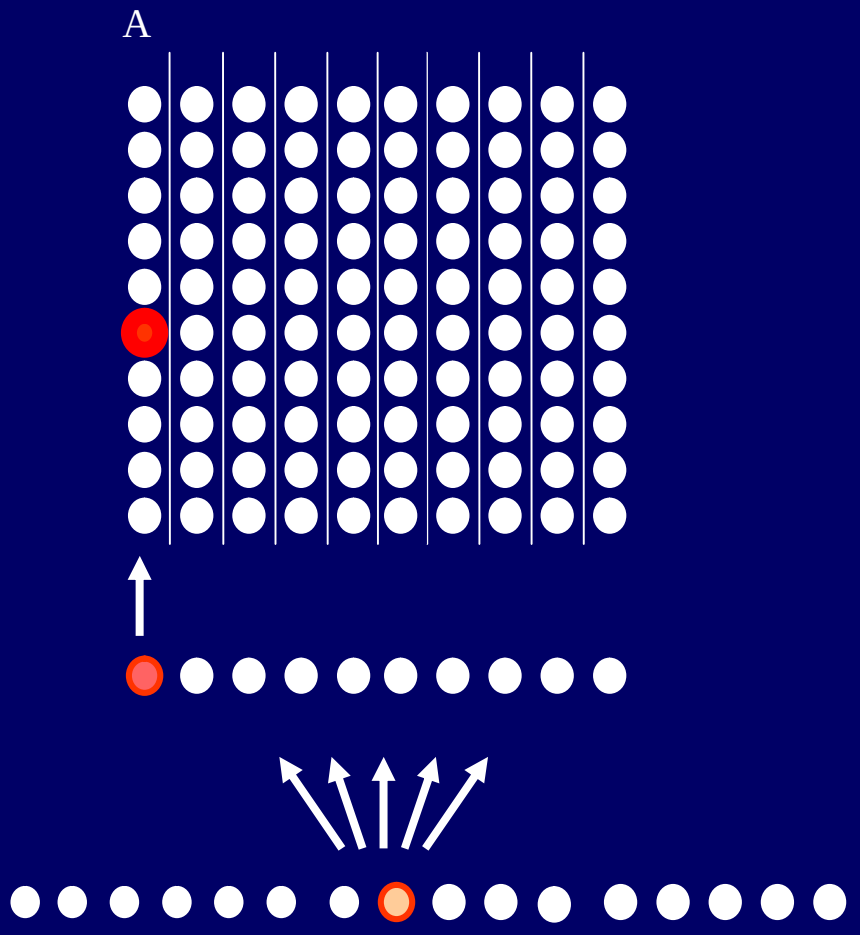


Resolution Testing

Individual NAAT testing on 10 specimens

10 pools of 10 tested with NAAT

Screening Pools of 100 specimens tested with NAAT

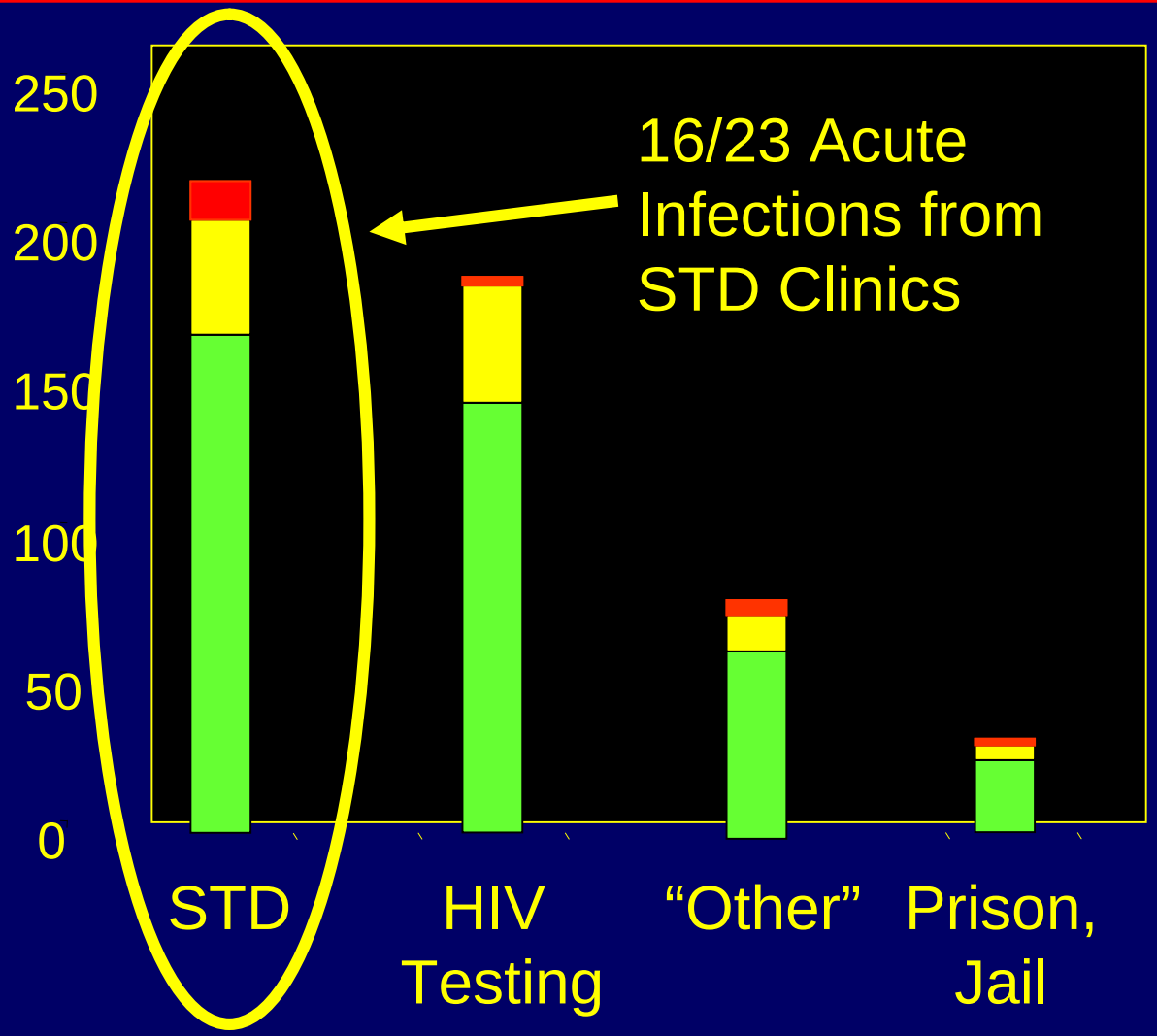


Yield from Pooled RNA Screening

Site	Number tested	HIV Ab+	RNA+/ Ab-
N.C. - 2003	109,250	583 (0.5%)*	23 (0.02%)

*Screened with Vironostika EIA

Infection by testing site: NC



Acute

Recent

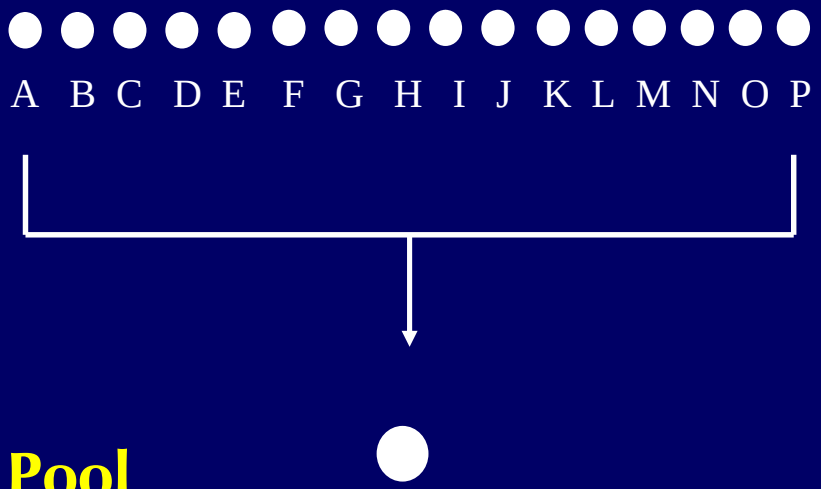
Unknown Duration

Not shown:
Prenatal/OB
FP Drug Treatment
General Medical TB
Field visits

CDC AHI Study: Pooling Procedure

1-Stage Pooling

16 Specimens



1 Master Pool

Yield from Pooled RNA Screening

Site	Number tested	HIV Ab+	RNA+/ Ab-
N.C. - 2003	109,250	583 (0.5%)*	23 (0.02%)
Florida - 2007	45,288	561 (1.2%)†	11 (0.02%)
L.A. - 2007	30,289	354 (1.2%)*	28 (0.09%)

*Screened with Vironostika EIA
†Screened wit Bio-Rad 1-2 Plus O

Antibody-negative specimens (EIA, or rapid test)

Could be in Window Period (infected but no detectable antibody response yet)

250 ul of each of 10 specimens combined into one tube

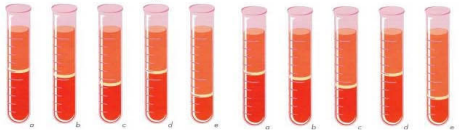
test pooled specimen by branched DNA (bDNA) or RT-PCR

RNA Detected } ***positive pool***

RNA Not Detected

negative pool

return to + pool constituents test each by RT-PCR or bDNA



Yield from Targeted RNA Testing

Site	Number tested	HIV Ab+	RNA+/ Ab-
SFCC - 2004	3,789	125 (3.2%)	11 (0.3%)
L.A. - 2004	2,523	22 (0.9%)	1 (0.05%)
Atlanta - 2004	2,202	66 (2.9%)	4 (0.2%)
Seattle - 2005	3,525	81 (2.3%)	7 (0.2%)
SFCC-RT 2007	1,092	82 (7.5%)	11 (1.1%)

CDC

Yield from Targeted RNA Testing

Site	Number tested	HIV Ab+	RNA+/ Ab-
SFCC - 2004	3,789	125 (3.2%)	11 (0.3%)
L.A. - 2004	2,523	22 (0.9%)	1 (0.05%)
Atlanta - 2004	2,202	66 (2.9%)	4 (0.2%)
Seattle - 2005	3,525	81 (2.3%)	7 (0.2%)
SFCC-RT 2007	1,092	82 (7.5%)	11 (1.1%)
L.A. - 2007	30,289	354 (1.2%)*	28 (0.09%)

*Screened with Vironostika EIA

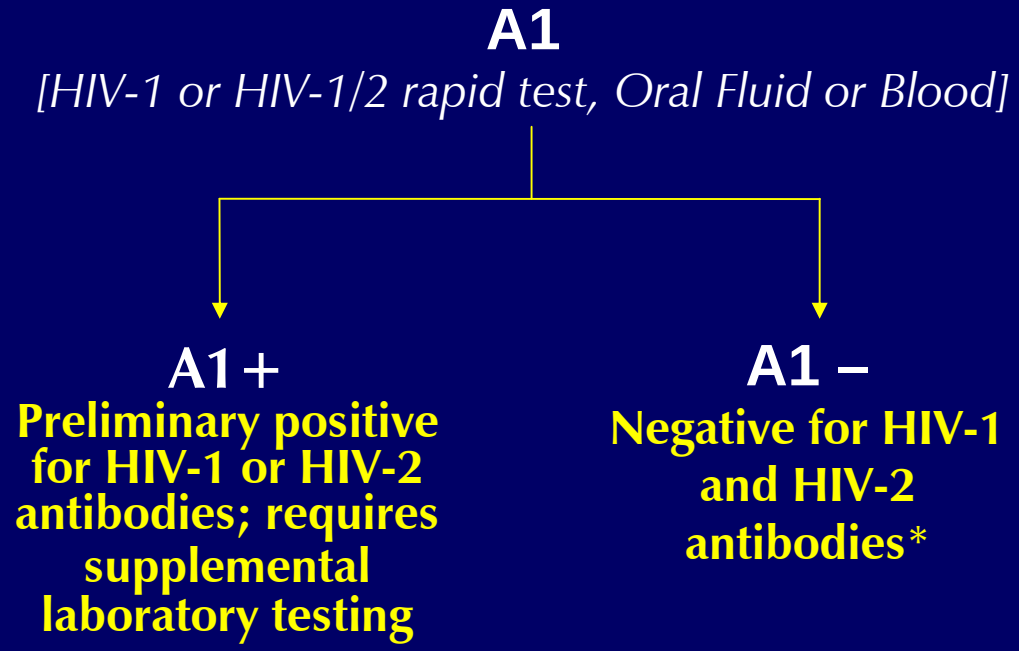
Yield from Targeted RNA Testing

Site	Number tested	HIV Ab+	RNA+/ Ab-
SFCC - 2004	3,789	125 (3.2%)	11 (0.3%)
L.A. - 2004	2,523	22 (0.9%)	1 (0.05%)
Atlanta - 2004	2,202	66 (2.9%)	4 (0.2%)
Seattle - 2005	3,525	81 (2.3%)	7 (0.2%)
SFCC-RT 2007	1,092	82 (7.5%)	11 (1.1%)
L.A. - 2007	30,289	354 (1.2%)*	28 (0.09%)
L.A. - 2007	30,289	366 (1.2%)†	16 (0.05%)

*Screened with Vironostika EIA

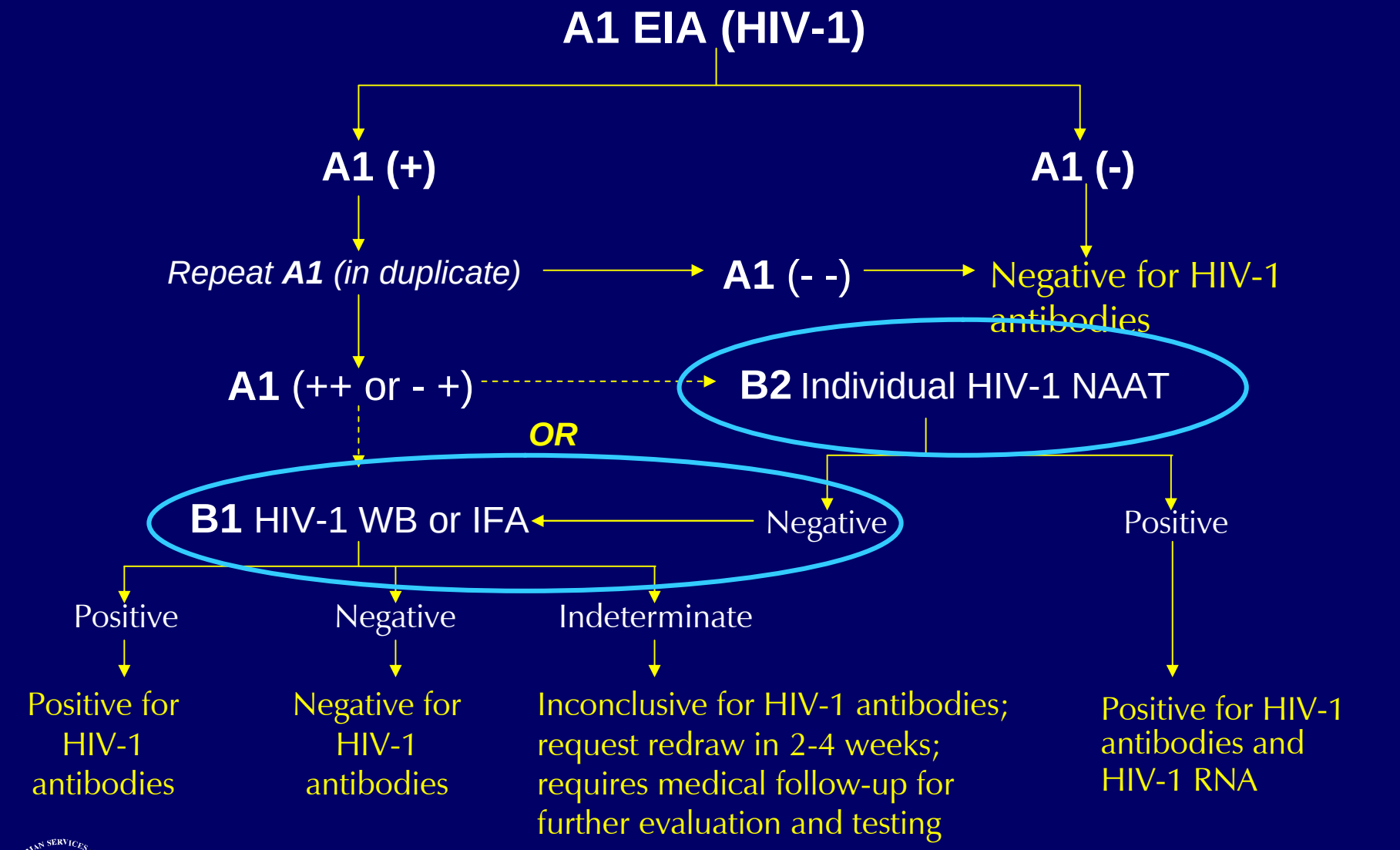
†Screened with Bio-Rad 1-2 Plus O

POC Strategy 1: Single Rapid Test for HIV Screening

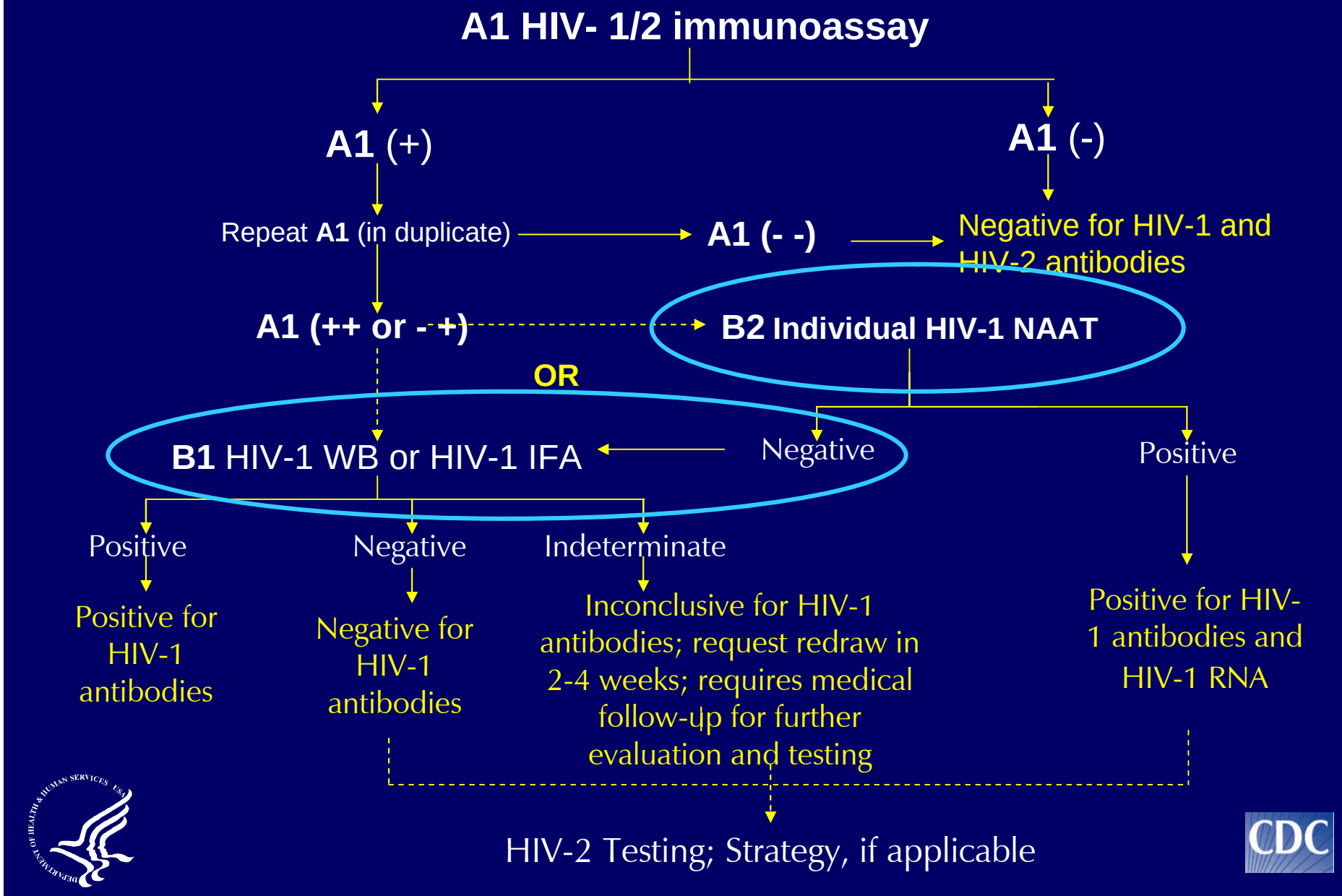


***If using an HIV-1 only rapid test, Negative for HIV-1 antibodies only**

Lab Strategy 1: HIV-1 EIA/WB/IFA/NAAT



Lab Strategy 2: HIV-1/2 EIA/WB/IFA/NAAT



CDC Alternative Algorithm Study

- Infected and uninfected U.S. blood donors: 997
  - *621 HIV+, 513 HIV-, 41 Indeterminate*
- International: 178 total, 128 non-B subtypes
  - Blood donors: 64
  - CDC Cameroon study: 114
- Seroconversion panels:
  - *183 specimens from 15 pts*
- HIV-2 specimens: 32

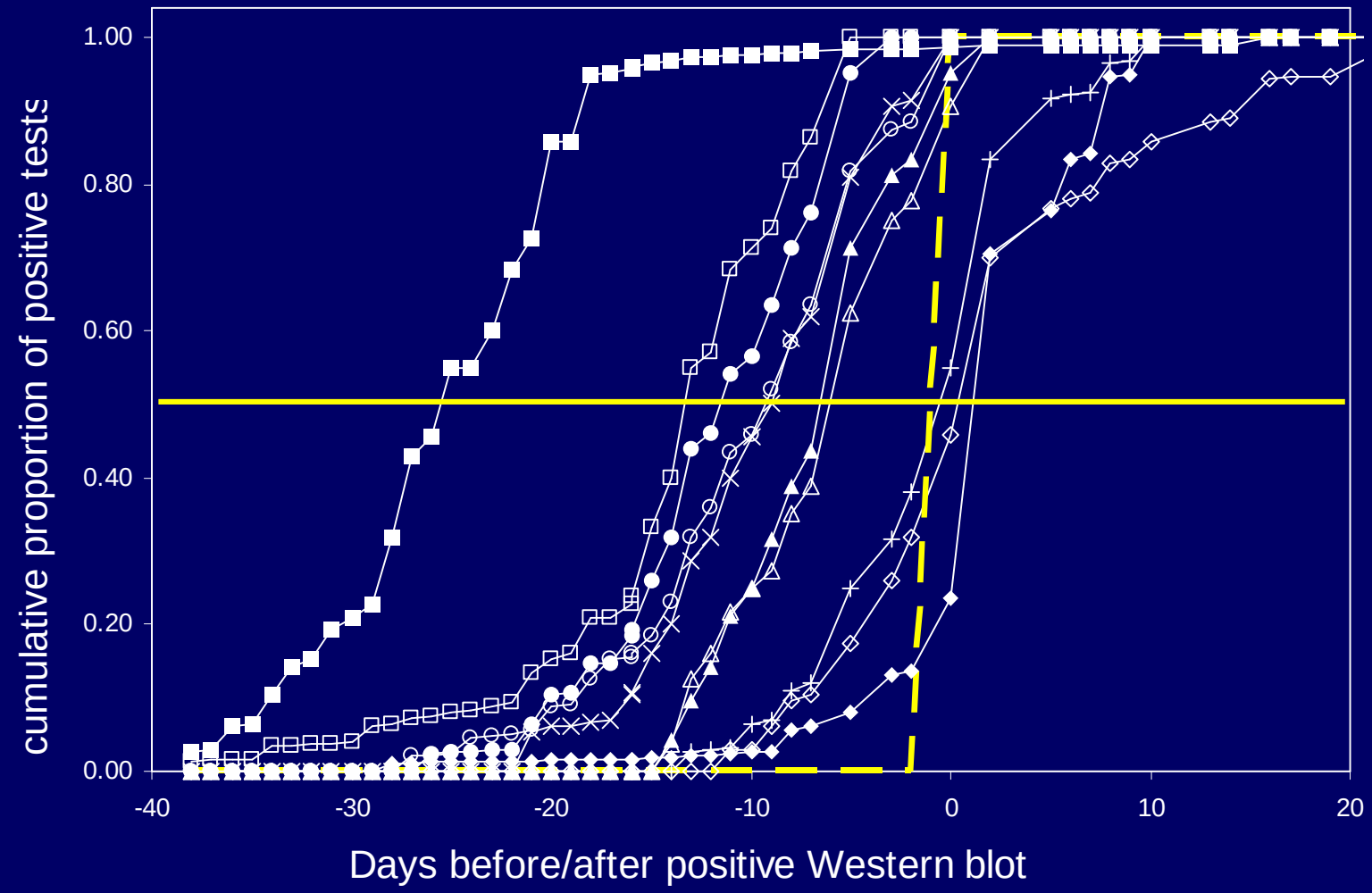
- Owen et al, J. Clin. Microbiol .May 2008

CDC Alternative Algorithm Study

Test *621 HIV+, 513 HIV-*	Sensitivity	Specificity
Genetic Systems HIV-1/2+O	99.8	99.4
Abbott rDNA	99.4	97.7
Vironostika HIV-1 + O	99.7	99.0
Genetic Systems HIV-1/2 peptide	98.7	99.8
Genetic Systems rLAV	97.4	100.0
Vironostika HIV-1 microelisa	99.0	98.4
Oraquick Advance	98.6	99.8
Reveal G2	99.0	99.8
Uni-Gold Recombigen	98.4	99.4
Procleix *[Aptima]*	97.4	99.6
CDC RNA	95.8	99.4
Ampliscreen	92.6	96.9

- Owen et al, J. Clin. Microbiol. May 2008

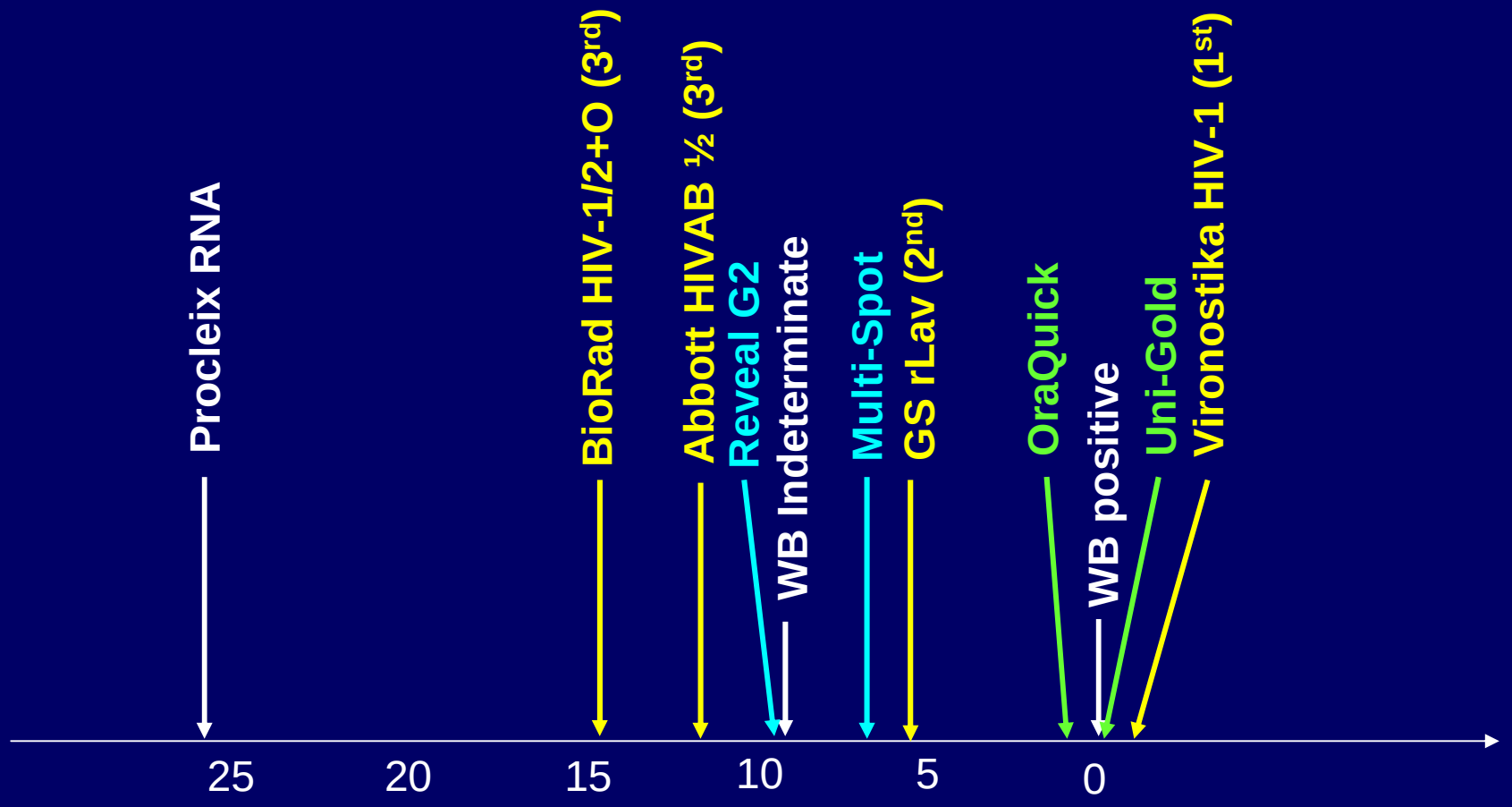
Current Assays with 15 Seroconverter Panels



183 specimens from 15 seroconverters

- Owen et al, J. Clin. Microbiol. May 2008

Current Assays with 15 Seroconverter Panels



185 specimens from 15 seroconverters

Owen et al, J. Clin. Microbiol. May 2008

/ironostika		Viral Load	HIV-1/2/O	UG	MS	OQ	SP
EIA Result	WB	copies/ml	EIA Result	RT	RT	RT	RT
NR	I	5,770	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	I	12,183	R	R	NR	NR	NR
NR	N	77	NR	NR	NR	NR	NR
NR	I	6,373	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	12,852	NR	NR	NR	NR	NR
NR	I	14,062	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	R	R
NR	N	3,921	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	**R**	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	1,177	NR	NR	NR	NR	NR
NR	N	>500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	43,173	NR	NR	NR	NR	NR
NR	I	30,734	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	102,288	NR	NR	NR	NR	NR
NR	N	327,333	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	389,850	NR	NR	NR	NR	NR
NR	I	413,186	NR	**R**	R1	NR	NR
NR	I	446,770	NR	NR	NR	NR	NR
NR	N	358,030	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	427,490	NR	NR	NR	NR	NR
NR	N	210,204	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR

- 42 RNA+ specimens, screening test negative:
  - Vironostika 22
  - Oraquick 17
  - Bio-Rad 3

Louie et al, J Clin Microbiol 2008

CDC

/ironostika EIA Result	WB	Viral Load copies/ml	HIV-1/2/O EIA Result	UG RT	MS RT	OQ RT	SP RT
NR	I	5,770	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	I	12,183	R	R	NR	NR	NR
NR	N	77	NR	NR	NR	NR	NR
NR	I	6,373	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	12,852	NR	NR	NR	NR	NR
NR	I	14,062	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	R	R
NR	N	3,921	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	**R**	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	1,177	NR	NR	NR	NR	NR
NR	N	>500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	43,173	NR	NR	NR	NR	NR
NR	I	30,734	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	102,288	NR	NR	NR	NR	NR
NR	N	327,333	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	389,850	NR	NR	NR	NR	NR
NR	I	413,186	NR	**R**	R1	NR	NR
NR	I	446,770	NR	NR	NR	NR	NR
NR	N	358,030	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	427,490	NR	NR	NR	NR	NR
NR	N	210,204	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR

- 42 RNA+ specimens, screening test negative:
  - Vironostika 22
  - Oraquick 17
  - Bio-Rad 3
- Number detected by:
  - Western blot 0
  - Bio-Rad Plus O 22

Louie et al, J Clin Microbiol 2008

CDC

Vironostika		Viral Load	HIV-1/2/O	UG	MS	OQ	SP
EIA Result	WB	copies/ml	EIA Result	RT	RT	RT	RT
NR	I	5,770	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	I	12,183	R	R	NR	NR	NR
NR	N	77	NR	NR	NR	NR	NR
NR	I	6,373	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	12,852	NR	NR	NR	NR	NR
NR	I	14,062	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	R	R
NR	N	3,921	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	**R**	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	1,177	NR	NR	NR	NR	NR
NR	N	>500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	43,173	NR	NR	NR	NR	NR
NR	I	30,734	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	102,288	NR	NR	NR	NR	NR
NR	N	327,333	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	389,850	NR	NR	NR	NR	NR
NR	I	413,186	NR	**R**	R1	NR	NR
NR	I	446,770	NR	NR	NR	NR	NR
NR	N	358,030	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	427,490	NR	NR	NR	NR	NR
NR	N	210,204	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR

- 42 RNA+ specimens, screening test negative:
  - Vironostika 22
  - Oraquick 17
  - Bio-Rad 3
- Number detected by:
  - Western blot 0
  - Bio-Rad Plus O 22
  - Unigold 11

Louie et al, J Clin Microbiol 2008

CDC

EIA Result	WB	copies/ml	EIA Result	RT	RT	RT	RT
NR	I	5,770	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	I	12,183	R	R	NR	NR	NR
NR	N	77	NR	NR	NR	NR	NR
NR	I	6,373	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	12,852	NR	NR	NR	NR	NR
NR	I	14,062	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	R	R
NR	N	3,921	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	**R**	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	1,177	NR	NR	NR	NR	NR
NR	N	>500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	43,173	NR	NR	NR	NR	NR
NR	I	30,734	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	102,288	NR	NR	NR	NR	NR
NR	N	327,333	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	389,850	NR	NR	NR	NR	NR
NR	I	413,186	NR	**R**	R1	NR	NR
NR	I	446,770	NR	NR	NR	NR	NR
NR	N	358,030	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	427,490	NR	NR	NR	NR	NR
NR	N	210,204	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	R1	NR/NR	NR

- 42 RNA+ specimens, screening test negative:
  - Vironostika 22
  - Oraquick 17
  - Bio-Rad 3
- Number detected by:
  - Western blot 0
  - Bio-Rad Plus O 22
  - Unigold 11
  - Multispot 7

Louie et al, J Clin Microbiol 2008

CDC

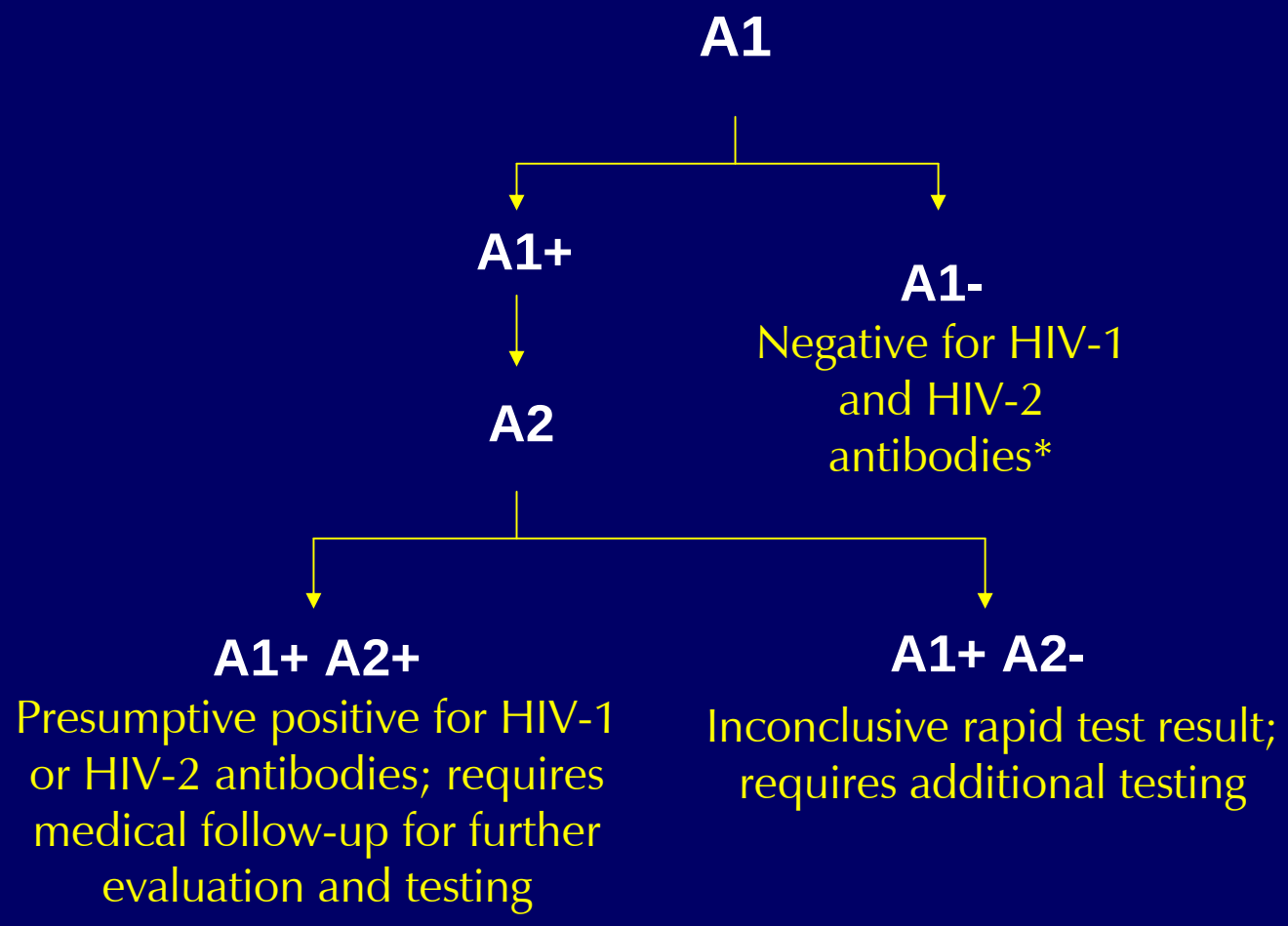
Vironostika EIA Result	WB	Viral Load copies/ml	HIV-1/2/O EIA Result	UG RT	MS RT	OQ RT	SP RT
NR	I	5,770	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	I	12,183	R	R	NR	NR	NR
NR	N	77	NR	NR	NR	NR	NR
NR	I	6,373	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	12,852	NR	NR	NR	NR	NR
NR	I	14,062	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	R	R
NR	N	3,921	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	**R**	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	1,177	NR	NR	NR	NR	NR
NR	N	>500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	43,173	NR	NR	NR	NR	NR
NR	I	30,734	NR	NR	NR	NR	NR
NR	N	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	R	**R**	R1	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	102,288	NR	NR	NR	NR	NR
NR	N	327,333	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	I	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	389,850	NR	NR	NR	NR	NR
NR	I	413,186	NR	**R**	R1	NR	NR
NR	I	446,770	NR	NR	NR	NR	NR
NR	N	358,030	NR	NR	NR	NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR
NR	N	427,490	NR	NR	NR	NR	NR
NR	N	210,204	R	**R**	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR	NR
NR	N	≥500,000	NR	NR	NR	NR/NR	NR
NR	N	≥500,000	R	NR	NR	NR	NR

- 42 RNA+ specimens, screening test negative:
  - Vironostika 22
  - Oraquick 17
  - Bio-Rad 3
- Number detected by:
  - Western blot 0
  - Bio-Rad Plus O 22
  - Unigold 11
  - Multispot 7
  - Stat-Pak 1
  - OraQuick 1

Louie et al, J Clin Microbiol 2008

POC Strategy 2: Two Rapid Tests in Sequence on Blood

[A1 and A2 must be different rapid tests]



**If using an HIV-1 only rapid test, Negative for HIV-1 antibodies only*

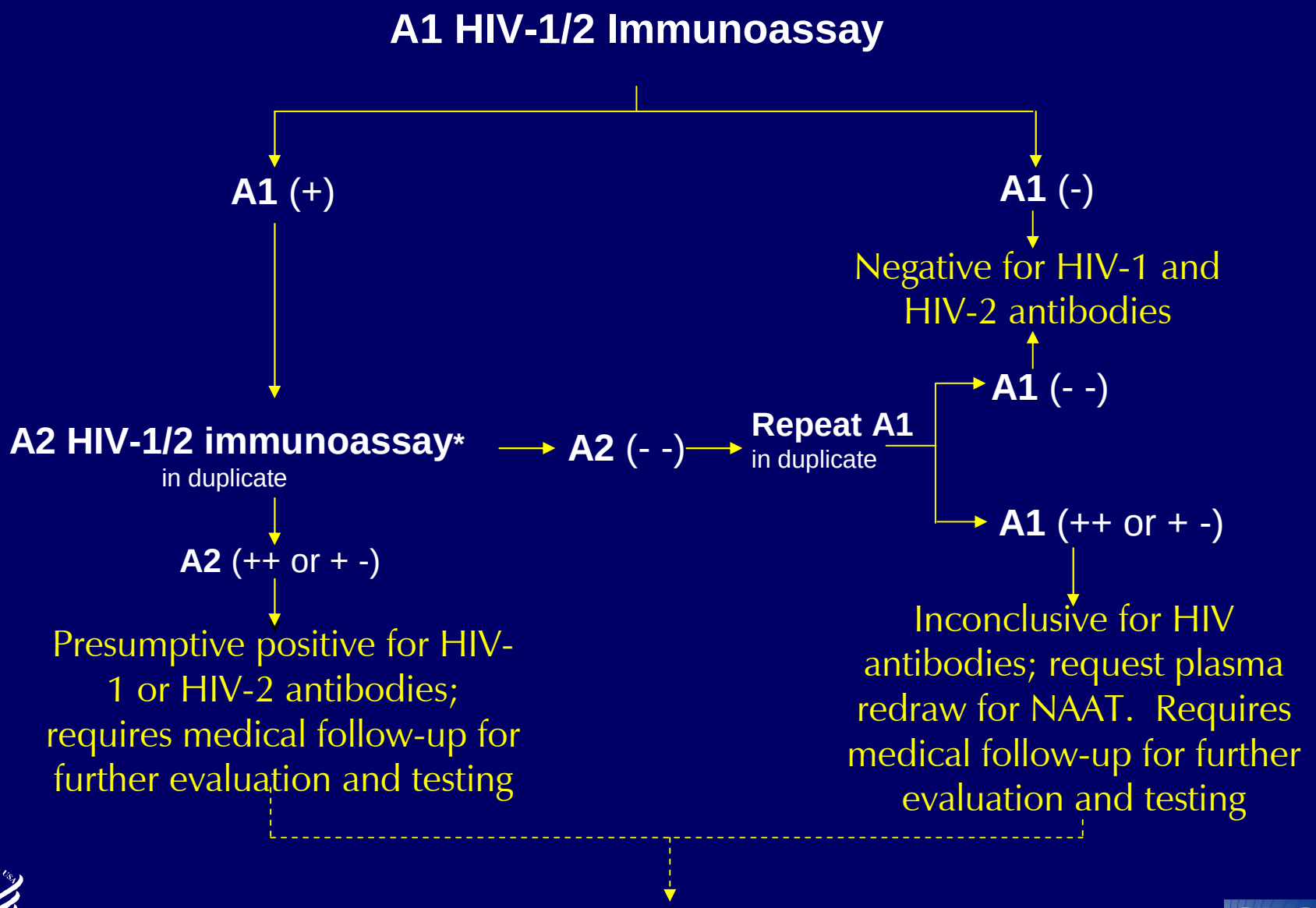
Results – 2 Rapid Tests, Sequential

Prospective, 222 HIV+, 4288 HIV- High-Risk Patients

Tests		Algorithm Results				
1st test	2nd test	Further testing	True Positive	False Negative	True Negative	False Positive
CLIA-Waived						
OQ-b	SP-b	2	221	1	4288	0
OQ-o	UG-b	4	149	4	4287	0
SP-b	OQ-b	1	221	2	4288	0
CLIA- Moderate Complexity						
OQ-b	UG-pl	8	215	1	4288	0
SP-b	MS-PL	2	220	2	4288	0
MS-PL	Re-PL	35	219	1	4256	1

CDC

Lab Strategy 3. HIV-1/2 Dual Immunoassay



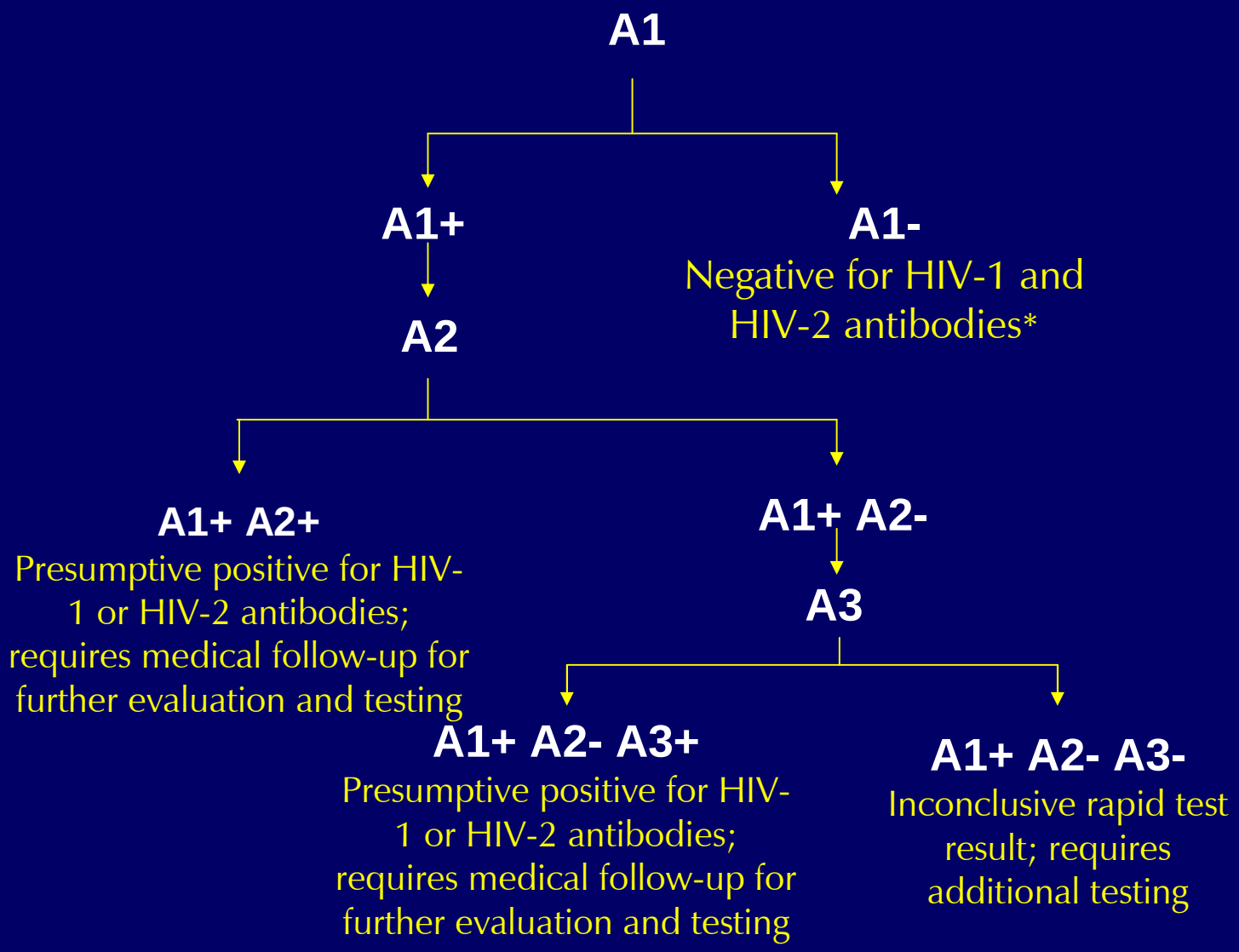
Specificity – Optimized Algorithm (both tests positive)

	GS HIV-1/2+O	Abbott	Vir HIV-1+O	GS HIV-1/2 peptide	GS rLAV	Vir HIV-1	Ora-quick	Reveal	Uni-Gold	Procleix	CDC RNA	Ampli-screen
GS HIV-1/2+O	99.8 / 99.4	99.4	99.7	98.7	97.4	99.0	98.6	99.0	98.4	97.3	95.6	92.4
Abbott	99.6	99.4 / 97.7	99.2	98.6	97.1	98.9	98.4	98.9	98.2	97.3	95.7	92.4
Vir HIV-1+O	100.0	100.0	99.7 / 99.0	98.7	97.4	99.0	98.6	99.0	98.4	97.3	95.7	92.4
GS HIV-1/2 peptide	100.0	100.0	100.0	98.7 / 99.8	97.3	98.4	98.6	98.7	98.0	97.1	95.7	92.4
GS rLAV	100.0	100.0	100.0	100.0	97.4 / 100	97.3	97.1	97.3	96.8	95.7	94.2	91.0
Vir HIV-1	100.0	99.8	99.8	100.0	100.0	99.0 / 98.4	98.2	98.7	98.2	97.1	95.5	92.2
Oraquick	100.0	100.0	100.0	100.0	100.0	100.0	98.6 / 99.8	98.6	97.8	96.9	95.5	92.2
Reveal	100.0	100.0	100.0	100.0	100.0	100.0	100.0	99.0 / 99.8	98.0	97.3	95.7	92.4
Uni-Gold	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	98.4 / 99.4	96.4	94.8	91.2
Procleix	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	97.4 / 99.6	95.7	92.6
CDC RNA	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	95.8 / 99.4	91.43
Ampliscreen	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	92.6 / 96.9

Sensitivity – Optimized Algorithm (either test positive)

	GS HIV-1/2+O	Abbott	Vir HIV-1+O	GS HIV-1/2 peptide	GS rLAV	Vir HIV-1	Oraquick	Reveal	Uni-Gold	Procleix	CDC RNA	Ampli-screen
GS HIV-1/2+O	99.8 / 99.4	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8	100.0	100.0	100.0
Abbott	97.5	99.4 / 97.7	99.8	99.5	99.7	99.5	99.5	99.5	99.5	99.5	99.5	99.5
Vir HIV-1+O	98.4	96.7	99.7 / 99.0	99.7	99.7	99.7	99.7	99.7	99.8	99.8	99.8	99.8
GS HIV-1/2 peptide	99.2	97.5	98.8	98.7 / 99.8	98.9	99.4	98.7	99.0	99.1	99.0	98.9	98.9
GS rLAV	99.4	97.7	99.0	99.8	97.4 / 100	99.2	98.9	99.2	98.9	99.2	99.0	99.0
Vir HIV-1	97.9	96.3	97.7	98.2	98.4	99.0 / 98.4	99.4	99.4	99.3	99.4	99.4	99.4
Oraquick	99.2	97.5	98.8	99.6	99.8	98.2	98.6 / 99.8	99.0	99.1	99.0	98.9	98.9
Reveal	99.2	97.5	98.8	99.6	99.8	98.2	99.6	99.0 / 99.8	99.5	99.2	99.2	99.2
Uni-Gold	99.0	97.3	98.8	99.2	99.4	97.8	99.2	99.2	98.4 / 99.4	99.3	99.1	99.1
Procleix	99.0	97.3	98.6	99.4	99.6	98.1	99.4	99.4	99.0	97.4 / 99.6	97.6	97.4
CDC RNA	98.8	97.1	98.4	99.2	99.4	97.9	99.2	99.2	98.8	99.0	95.8 / 99.4	96.9
Ampliscreen	96.3	94.5	95.9	96.7	96.9	95.3	96.7	96.7	96.3	96.5	96.3	92.6 / 96.9

Strategy 4: Three Screening Tests Performed in Sequence

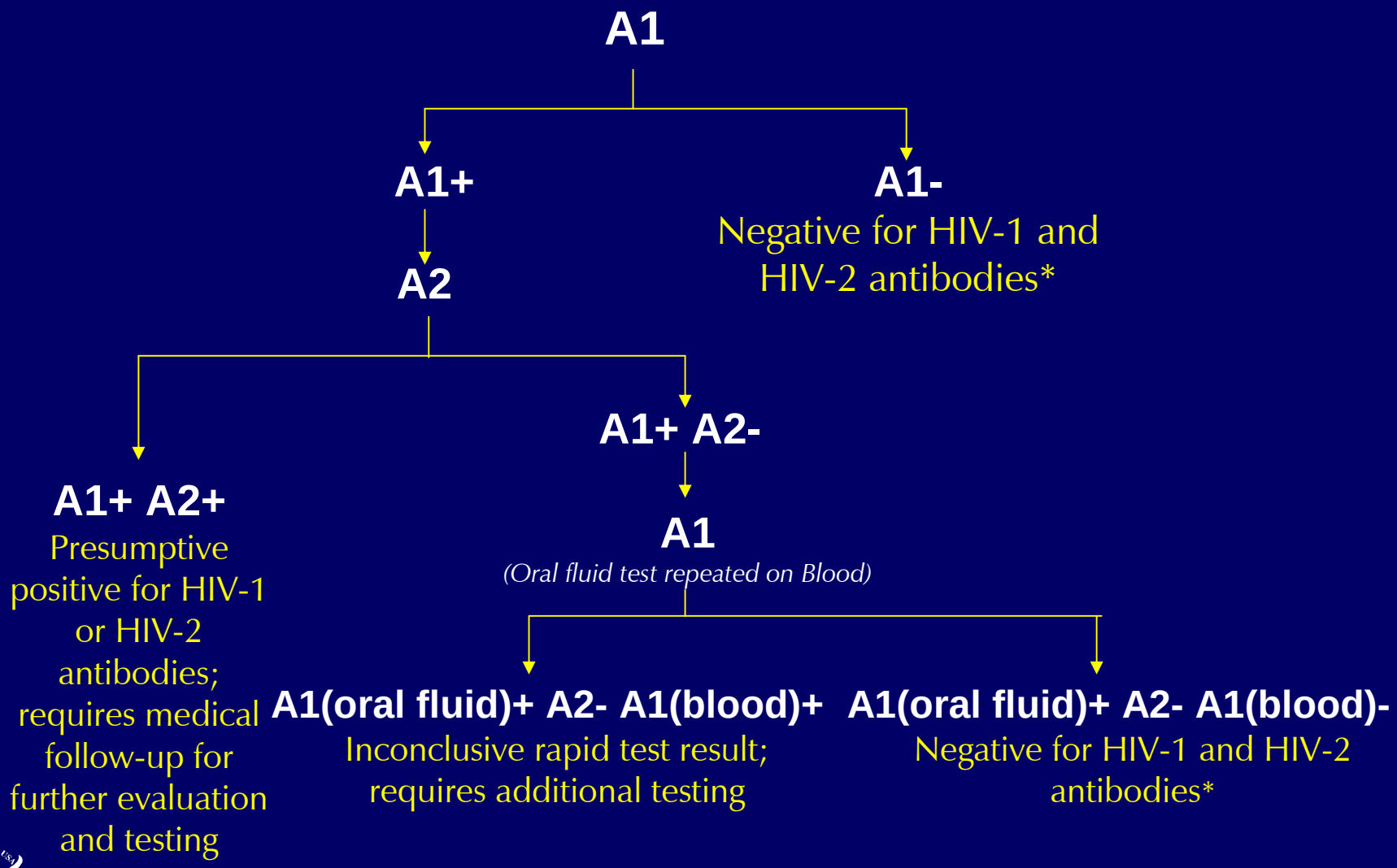


*If using an HIV-1 only rapid test, Negative for **HIV-1 antibodies only***

CDC Alternative Algorithm Study
621 HIV+, 513 HIV-

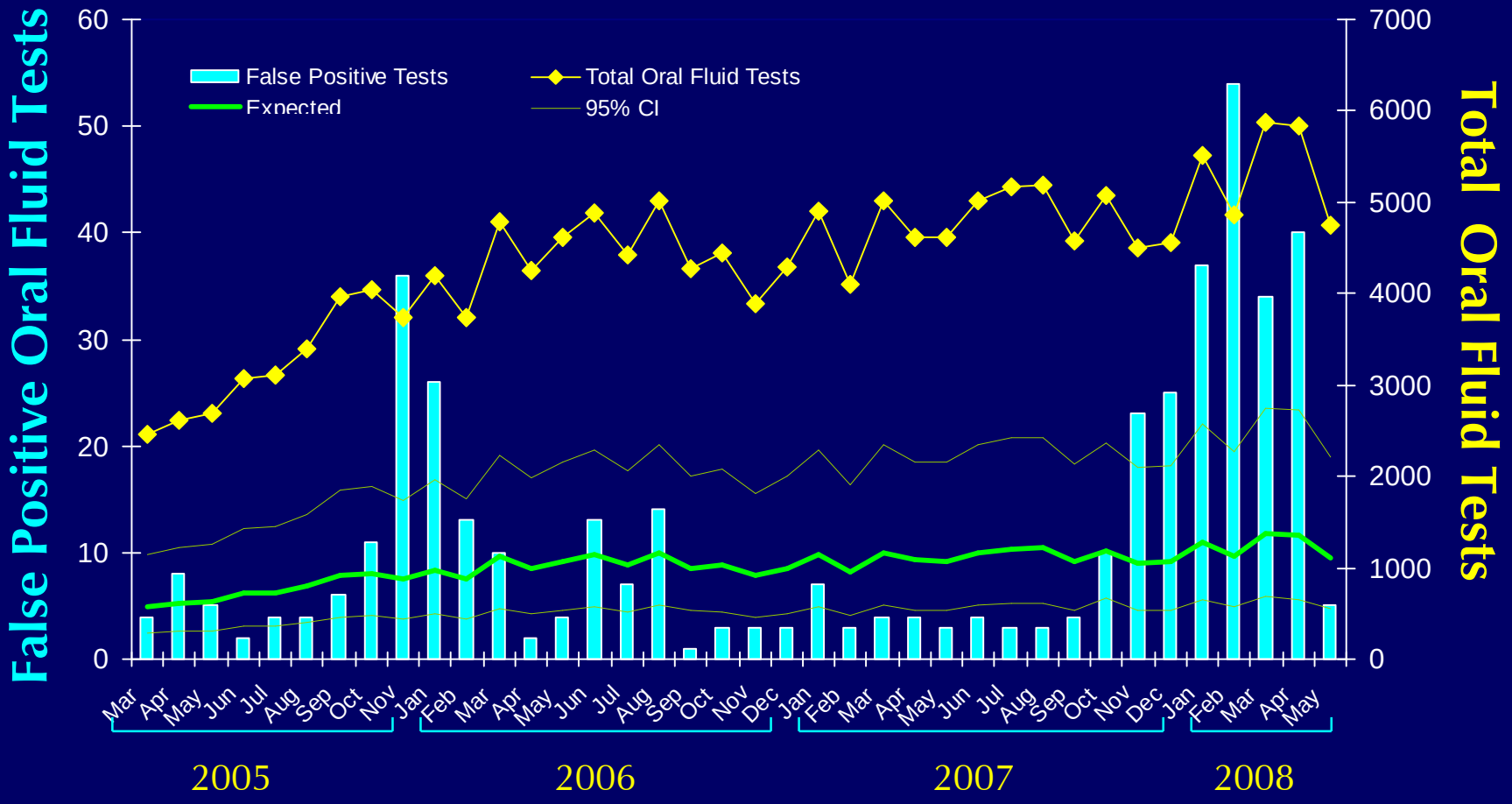
			3-test combination	
Test1	Test2	Test3	sensitivity	specificity
GS HIV-1/2+O	Abbott	Vir HIV-1 + O	99.8	99.6
GS HIV-1/2+O	Vir HIV-1 + O	Abbott	99.8	99.6
Abbott	Vir HIV-1 + O	GS HIV-1/2+O	99.8	99.6
GS HIV-1/2+O	Abbott	Procleix	99.4	99.6
GS HIV-1/2+O	Procleix	Abbott	99.4	99.6
Abbott	Procleix	GS HIV-1/2+O	99.4	99.6
OraQuick	Reveal	Uni-Gold	98.7	100.0
OraQuick	Uni-Gold	Reveal	98.7	100.0
Reveal	Uni-Gold	OraQuick	98.7	100.0

Strategy 3. Initial Oral Fluid Rapid HIV Test



*If using an HIV-1 only rapid test, Negative for **HIV-1 antibodies only**

False Positive Oral Fluid Rapid Tests
New York City STD Clinics 2005-2008



- MMWR June 20, 2008

Finger Stick Blood after OF Reactive

NY City STD Clinics, March 2005- April 07

- 133,832 oral fluid rapid tests
  - 1720 (1.2%) reactive
    - 1664 with confirmatory results
    - 368 false positive (PPV 77%)
  - 1194 with immediate finger stick, same test
    - 850 concordantly reactive on OF and fingerstick
      - 840 confirmed positive (PPV 98.9%)
    - 344 OF-reactive, finger stick negative
      - 1 positive by WB

- MMWR June 20, 2008

Proposed Algorithms

December 2007 HIV Diagnostics Conference

www.hivtestingconference.org

Discussion Topics

- What do settings want from POC?
- What do clinicians want from laboratories, e.g.:
  - "Preliminary positive" EIA results?
- Context-specific issues, e.g.:
  - Pregnancy, diagnosis, etc.
- What data do we need?

Change

The only people who like change…

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention

Acute HIV and STI Co-Infection

Peter Leone, MD
Associate Professor of Medicine
University of North Carolina
Medical Director
North Carolina HIV/STD Prevention and Care

nc department of health and human services

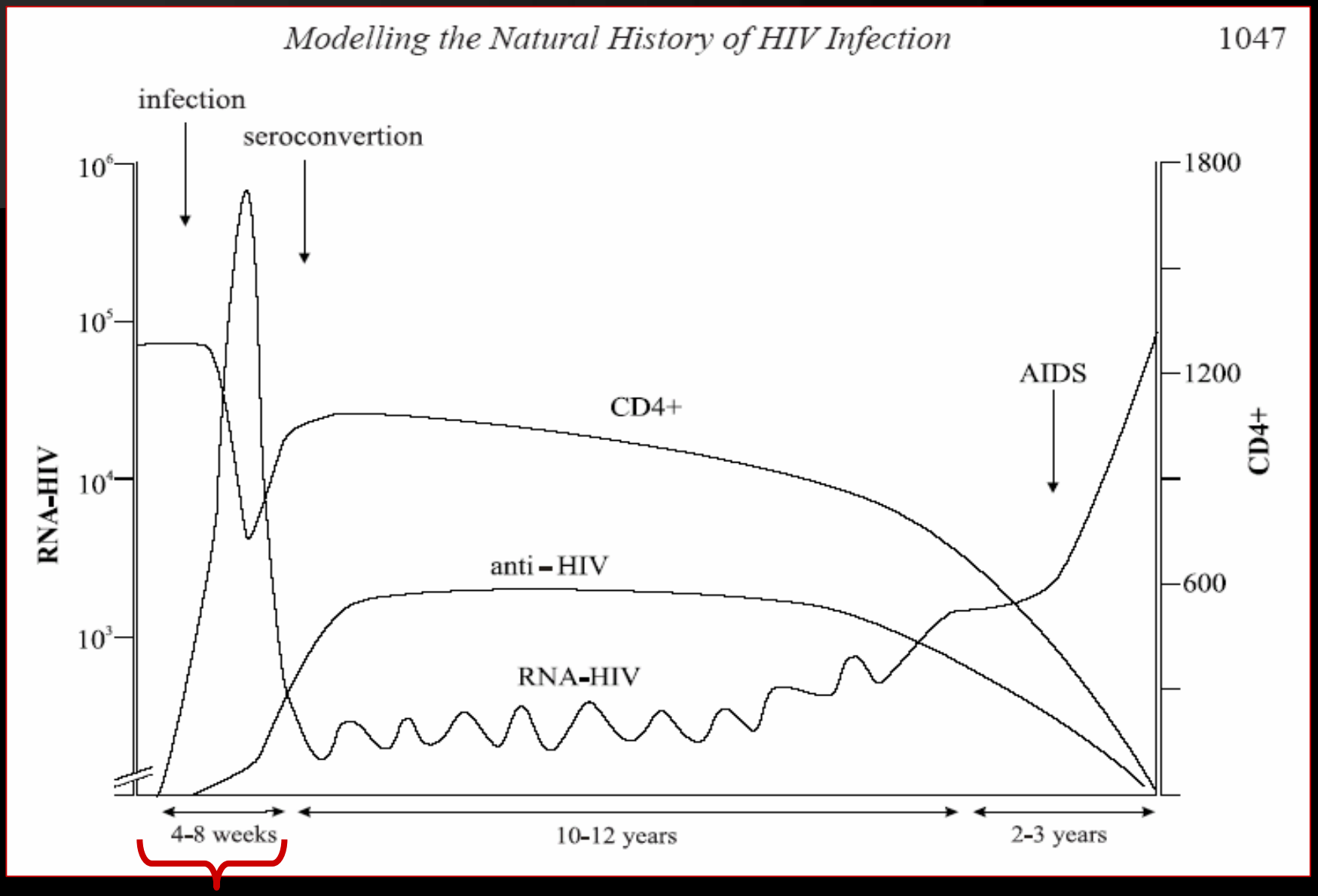
UNIVERSITY OF NORTH CAROLINA • CENTER FOR AIDS RESEARCH •

Definition of Acute HIV Infection

- Time period following infection with HIV during which HIV virus can be detected in blood but antibodies to HIV are not

OR

- Window period when routine HIV antibody tests (EIAs) are negative but HIV virus can be detected in blood

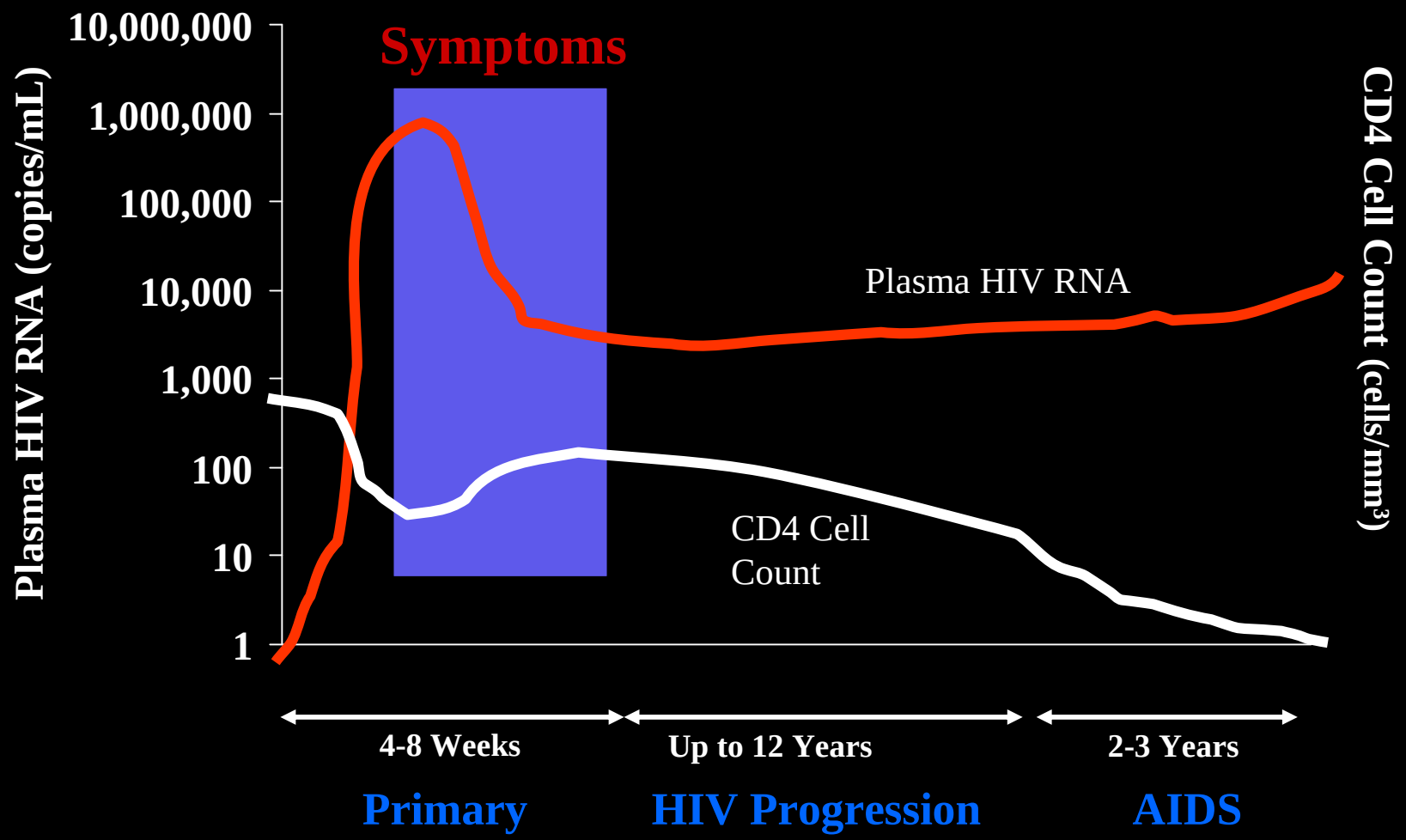


Couthino et al., Bulletin of Mathematical Biology 2001

Detecting Acute HIV Infections

How do we pick-up Acute HIV infection if routine antibody tests are negative?

Primary HIV Infection: Pathogenesis



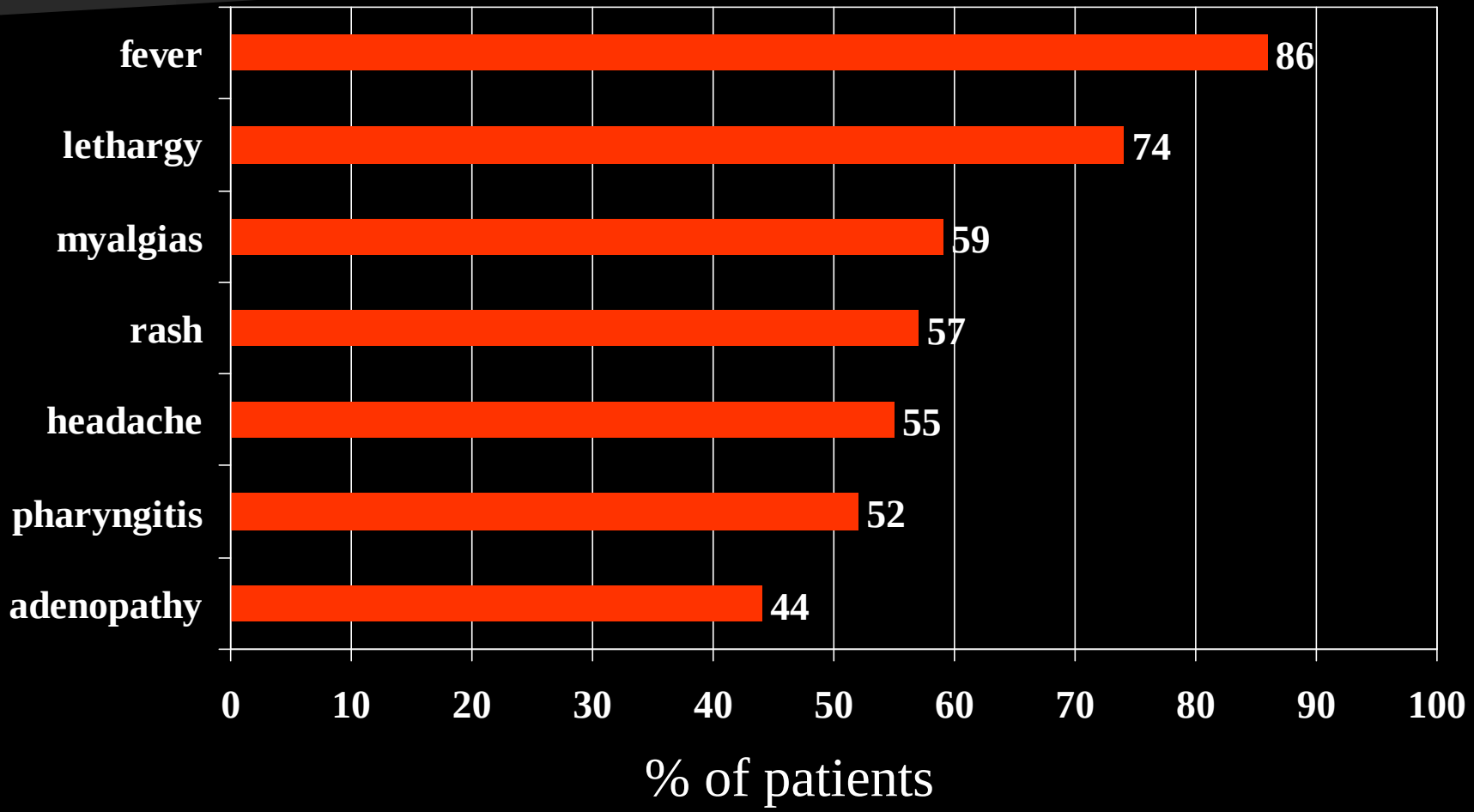
Acute Retroviral Syndrome

- 40-90% of new HIV infections are symptomatic
- Signs and symptoms typically begin 1-4 weeks following the exposure
- Symptoms can last from days to several weeks, but usually <14 days

Pilcher C et al. N Engl J Med 2005;352:1873-1883
Kahn JO, Walker BD. N Engl J Med. 1998;339:33-39
Schacker T, et al. Ann Intern Med. 1996;125:257-264

Common Signs & Symptoms

Study of 160 patients with primary HIV infection in 3 countries



Vanhems P et al. AIDS 2000; 14:0375-0381.

Acute HIV and Symptoms

	Schacker	*Kinloch-de Loes*	*NC STD*
Fever	93%	87%	48%
Fatigue	93	26	37
Pharyngitis	70	48	30
Headache	55	39	26
Rash			15
GI Symptoms			37

Schacker TW, et al., AIM 1996 125:257-64

Common Mis-diagnoses

- Mononucleosis
- Rocky Mountain Spotted Fever
- Strep throat
- Influenza
- “Viral illness”
- Secondary syphilis

AHI with Retroviral Symptoms STD Sites

Factor	Total (N=27)	
	No.	%
Any symptoms **at any time**	20	74%
Any symptoms **at testing**	11	40.7
Any symptoms **after testing**	11	40.7

How do we pick-up Acute HIV infection if patients don't have symptoms?

Screen

Window Periods for HIV Tests

HIV test	Assay method	"Window period" estimates, weeks[a]	"Window period" reduction, days[b]
First-generation EIA	Viral particles used to bind patient HIV Ab, detected by marker conjugated to anti-human Ab	~6	...
Second-generation EIA	Same as first-generation EIA except uses purified HIV Ag or recombinant virus	~4–6	10
Third-generation EIA	"Antigen sandwich": synthetic peptide used to bind patient HIV Ab followed by marker conjugated to additional HIV Ag; able to detect IgM	~3–4	6
Fourth-generation EIA	Uses third-generation EIA methodology plus monoclonal Ab to p24 Ag to detect patient p24 Ag	~2	5
Pooled HIV NAT	First combines multiple individual samples into one common pool, then uses PCR or other amplification techniques to detect patient viral nucleic acids	<1–2	3
Individual HIV NAT	As above, except that samples are tested individually rather than diluted by pooling	<1–2	3

Stekler J. et al CID 2007

Advantages of p24 Ag and 4th generation EIAs

- Current '4th generation' EIAs can detect both p24 Ag and antibody on a single assay
- Could theoretically be used as a confirmatory assay for both positive and negative antibody test results.
- p24 Ag EIAs nearly as sensitive as HIV RNA testing for acute HIV infeciton
- Sensitivity of 4th generation EIAs is now equivalent to neat p24 assays
- Not POC test

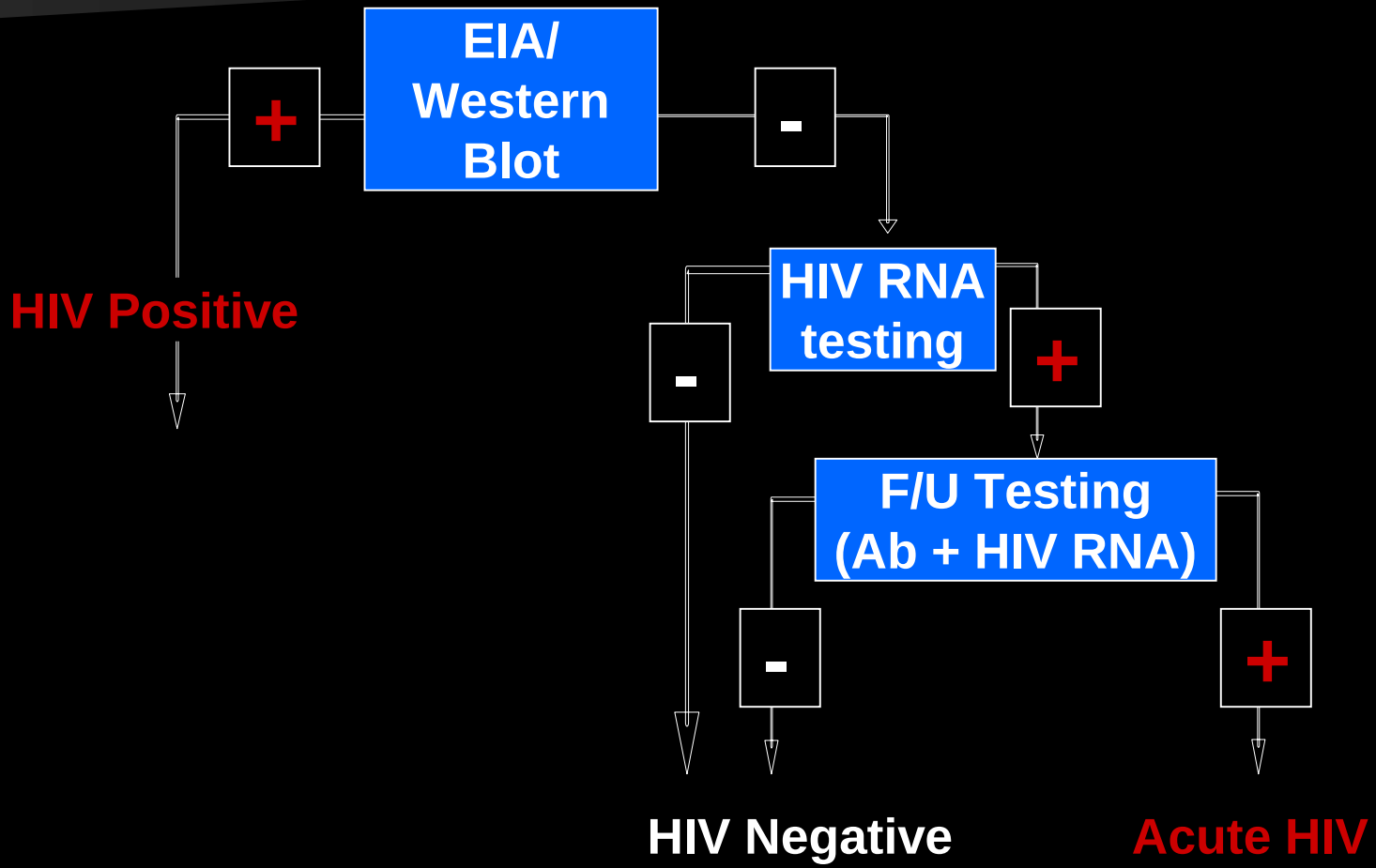
New Technologies

- 4th gen EIAs are a simple, low tech alternative for high prevalence and incidence settings
- Emerging rapid NAATs have the potential to revolutionize HIV testing:
  - Would make AHI diagnosis available in developing world where HIV burden is greatest
  - Would remove remaining barriers to expanding HIV testing to high risk (EDs, urgent cares, primary care) settings
- However: bars for cost and specificity remain high

Our approach to Screening for AHI
Specimen pooling

- Advantages
  - Seamless (almost) incorporation into HIV testing
  - Reduced cost
  - No real change in specificity
  - Universal application
- Disadvantages
  - Requires large testing volume
  - Small loss in sensitivity
  - Logistics
  - Time to Dx and locating patient

STAT Testing Protocol

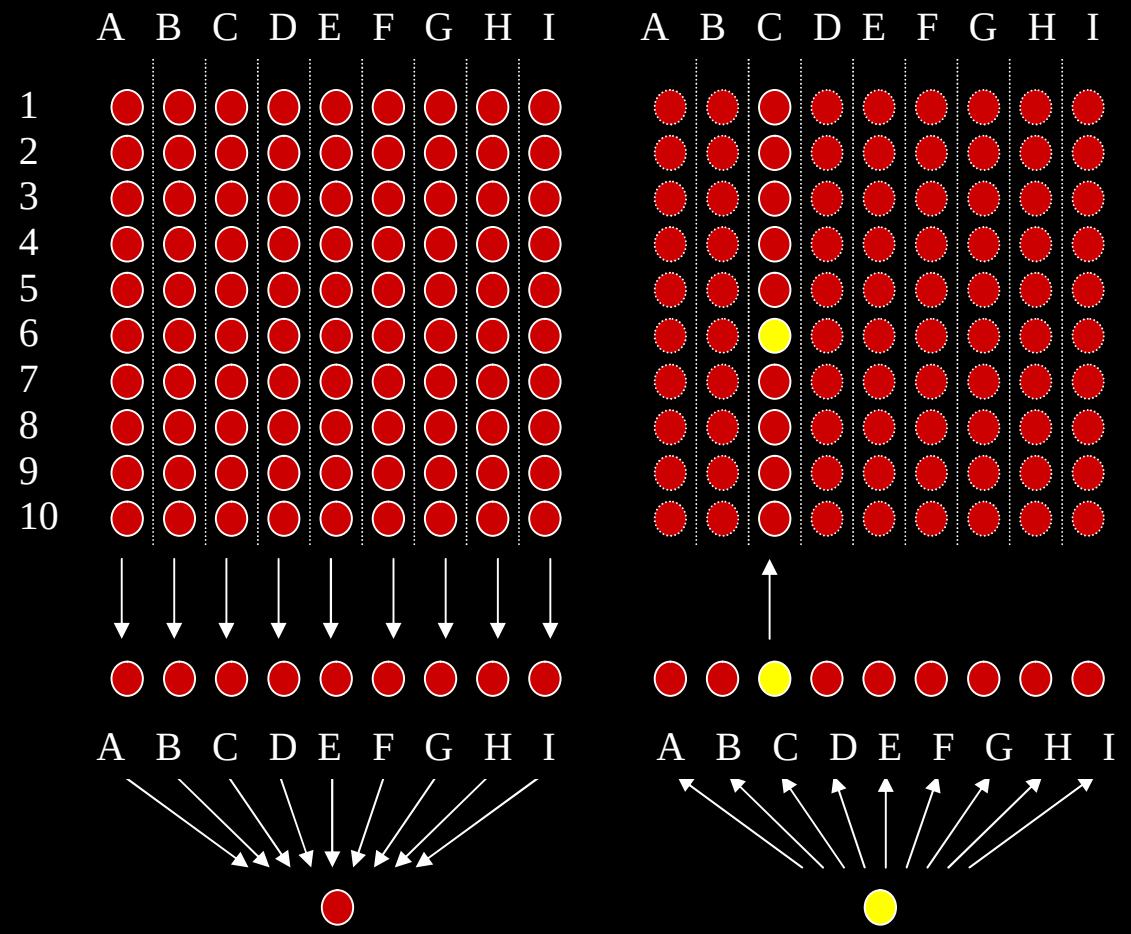


Pooling and HIV RNA testing

90 individual HIV antibody negative specimens

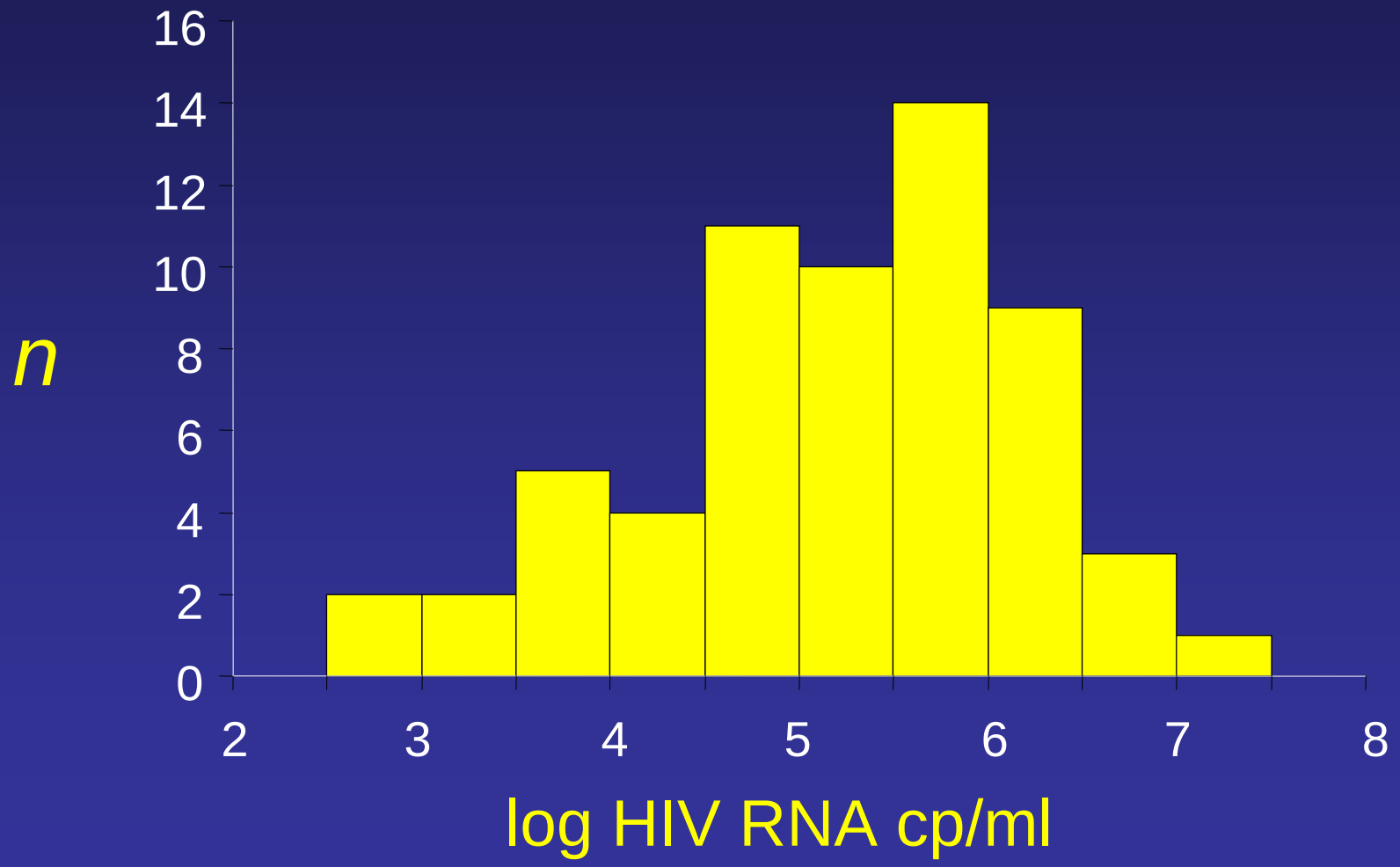
9 intermediate pools (10 specimens)

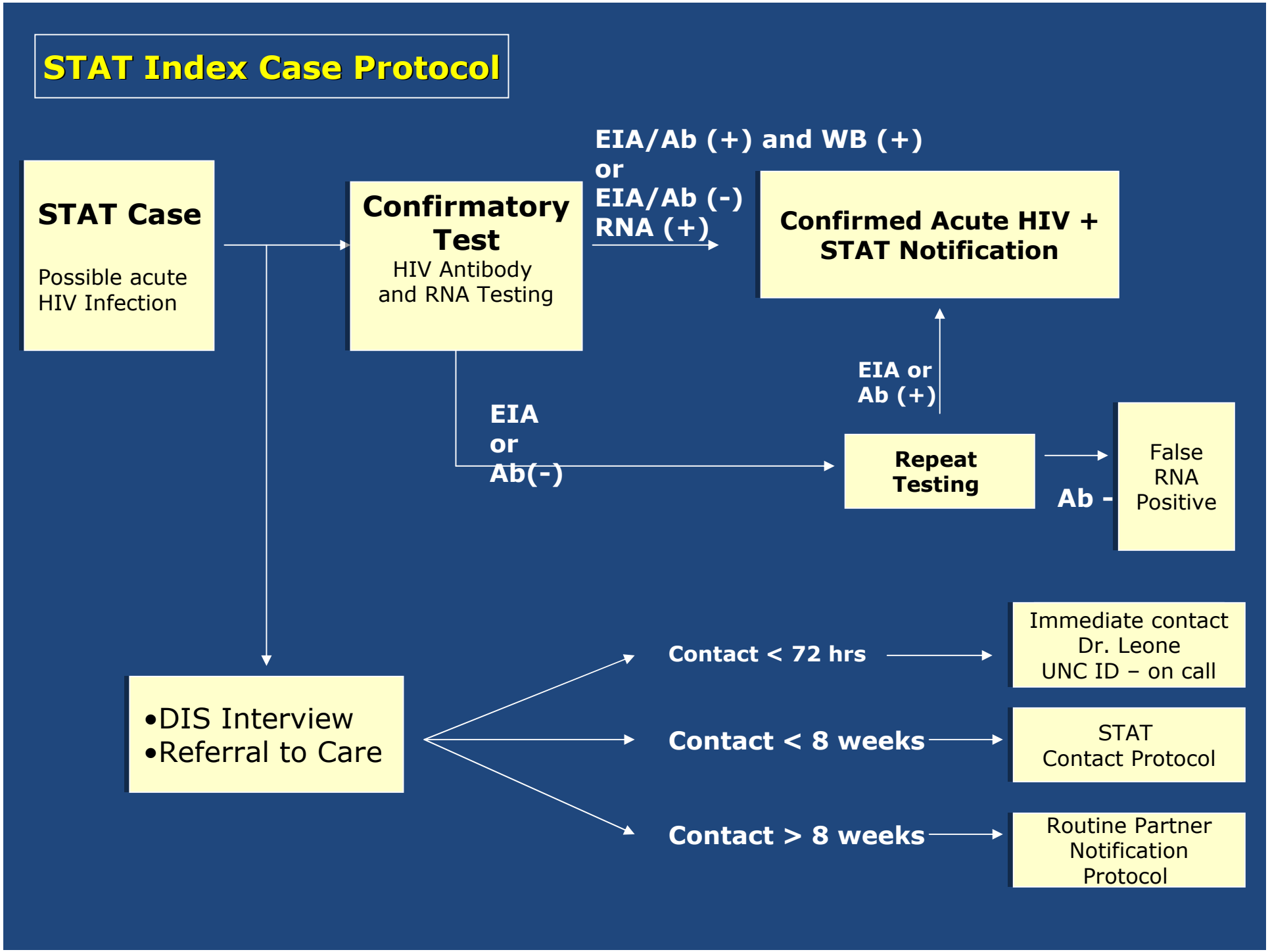
1 master pool (90 specimens)



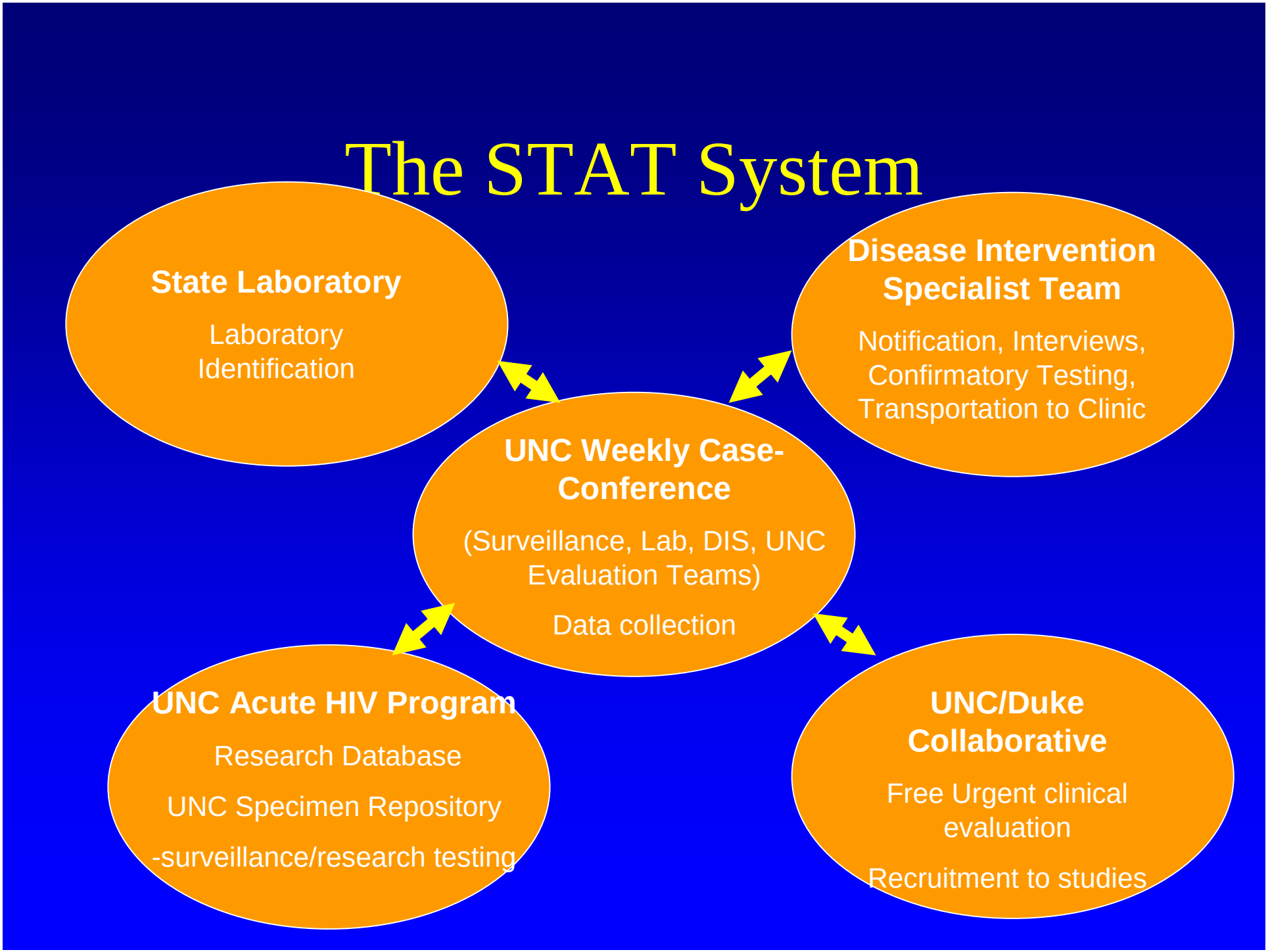
Distribution of Viral Loads in Ab Negative VCT Specimens

NC Testing Data 2002-2005 (n=58)




STAT Index Case Protocol
STAT Case
Possible acute HIV Infection
Confirmatory Test
HIV Antibody and RNA Testing
EIA/Ab (+) and WB (+)
or
EIA/Ab (-)
RNA (+)
Confirmed Acute HIV + STAT Notification
EIA or Ab (+)
EIA
or
Ab(-)
Repeat Testing
Ab -
False RNA Positive
•DIS Interview
•Referral to Care
Contact < 72 hrs
Immediate contact Dr. Leone UNC ID – on call
Contact < 8 weeks
STAT Contact Protocol
Contact > 8 weeks
Routine Partner Notification Protocol

The STAT System



PCR Testing of Pooled Sera to Identify Acute HIV Infection (seronegative, PCR positive)

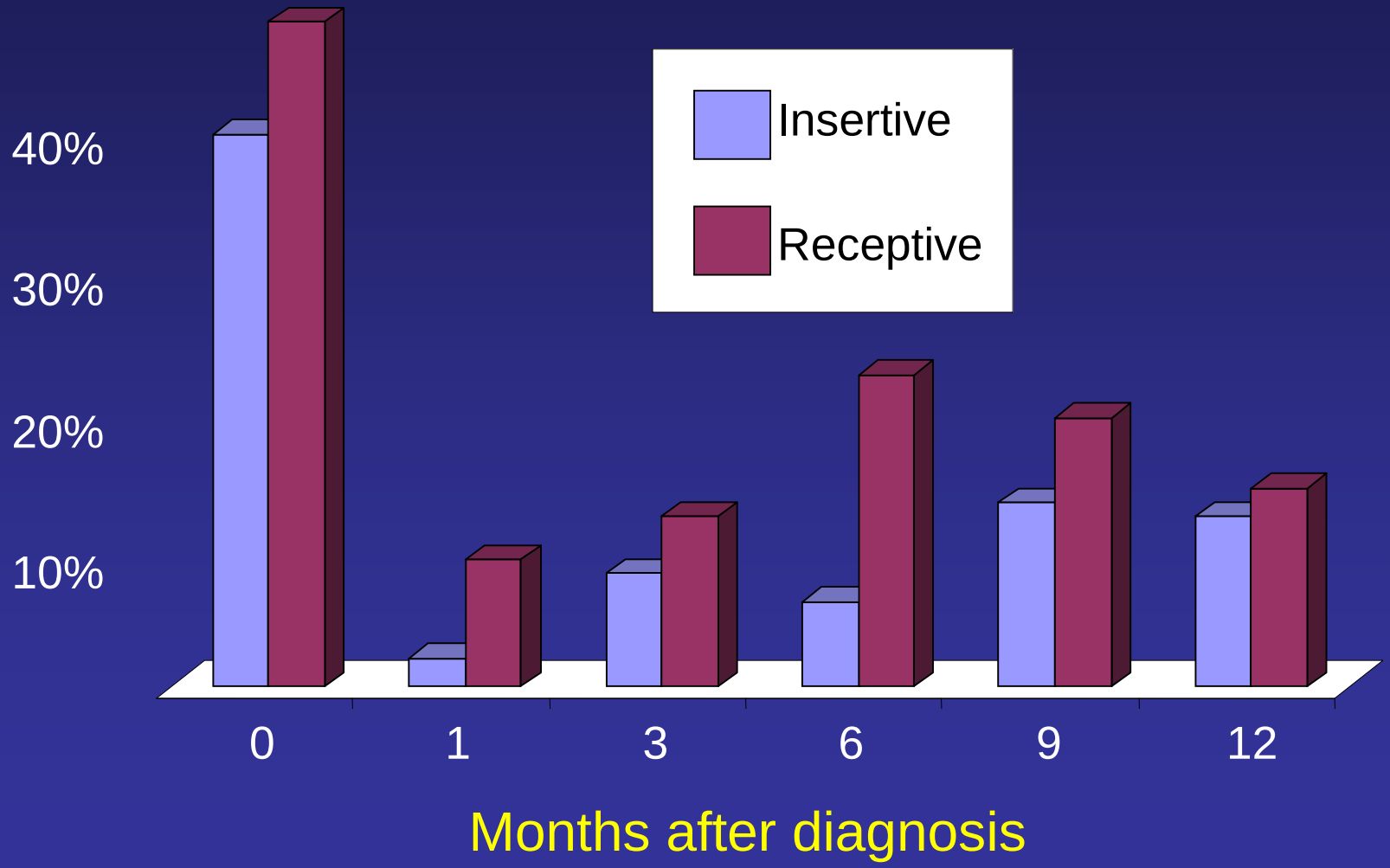
Pooled HIV RNA Testing: Yields

Program	Population	Prevalence HIV RNA+/EIA-	Increase in Testing Yield
New York City	NYC 3 STD Clinics		15%*
North Carolina	All persons tested for HIV via North Carolina DOH	23/109,250 (0.02%)	4%
Public-Health Seattle & King County	Men who have sex with men tested through PHSKC	21/5995 (0.35%)	13.5%
San Francisco	SF STD Clinic Patients	11/2722 (0.40%)	10.5%
Los Angeles	Men tested in 3 STD Clinics	1/1698 (0.06%)	7.1%
Maryland (not Baltimore)	STD clinics	0/15000	0
Atlanta	STD clinics, community testing and drug treatment	4/2128 (0.19%)	5%
Washington DC	STD clinic	6/1553 (0.39%)	10%

Source: ISSTDR, 2007 25% in the Chelsea STD clinic

MSM Seroconverters reporting UAI with HIV -/unknown status partners

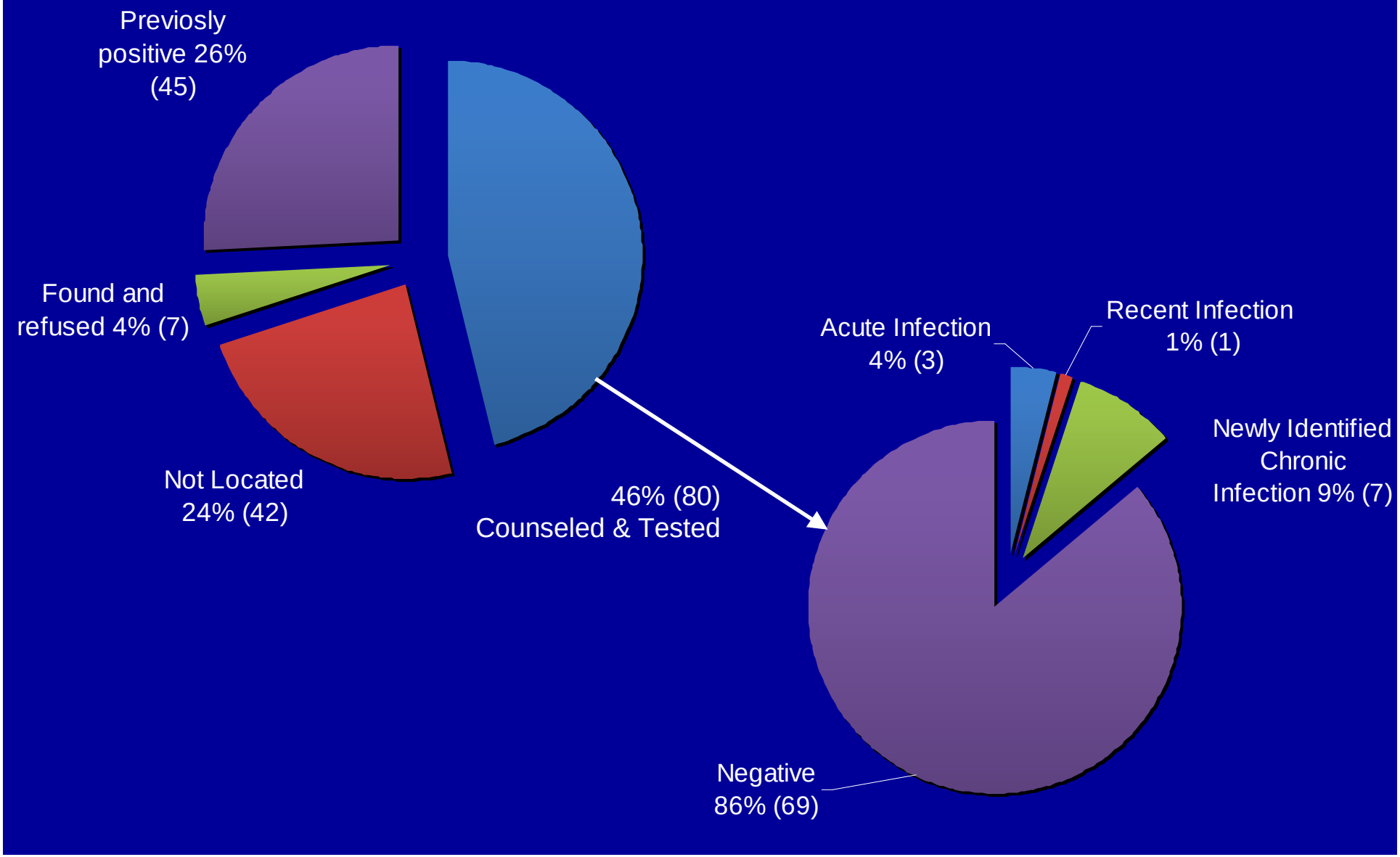
HIVNET Vaccine Prep. Cohort: Colfax GN AIDS 2002

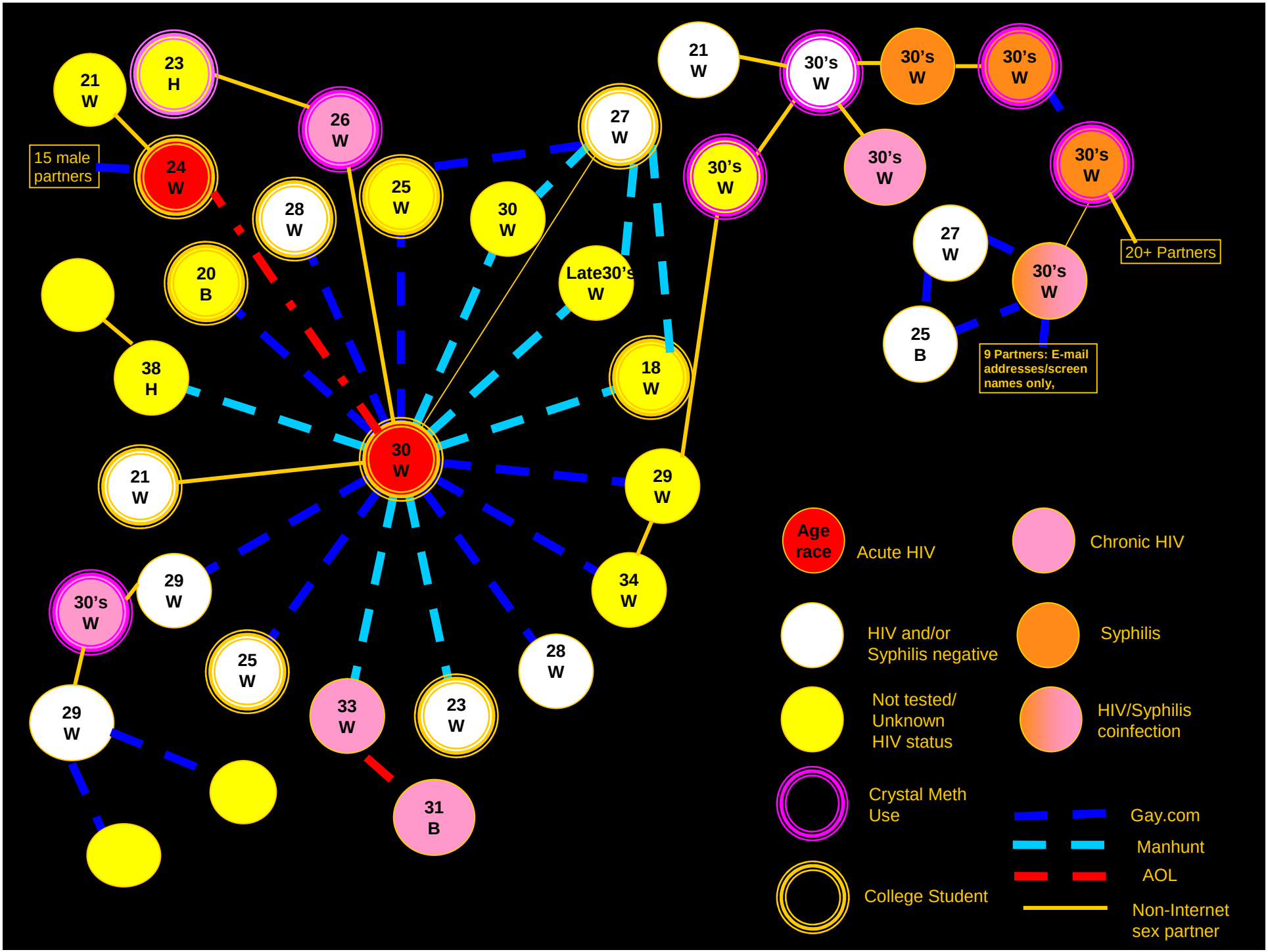


Screening and Tracing Active Transmission (STAT) Program

- From 2003-2006, 79 cases identified
  - 3 not located
  - 1 refusal for PCRS
- 269 partners (from 75 AHI patients) identified within an 8-week exposure window
  - 174 (65%) named
    132 (76%) located
  - 95 (35%) anonymous

STAT PCRS Outcomes (2003-2006)




21 W
23 H
26 W
27 W
21 W
30's W
30's W
30's W
15 male partners
24 W
25 W
30 W
30's W
30's W
28 W
20 B
Late30's W
27 W
30's W
20+ Partners
25 B
9 Partners: E-mail addresses/screen names only,
38 H
18 W
30 W
21 W
29 W
34 W
30's W
29 W
25 W
28 W
33 W
23 W
29 W
31 B
Age race
Acute HIV
Chronic HIV
HIV and/or Syphilis negative
Syphilis
Not tested/ Unknown HIV status
HIV/Syphilis coinfection
Crystal Meth Use
College Student
Gay.com
Manhunt
AOL
Non-Internet sex partner

AHI Testing and STI in North Carolina

Sandi McCoy, PhD, MPH

Study Population

Nov. 2002 – Oct. 2006, n=75

Characteristic	N (%)
Age (years)	
≤ 25	33 (44.0)
26-35	20 (26.7)
≥36	22 (29.3)
Race or ethnic background	
White, non-Hispanic	20 (26.7)
Non-White	55 (73.3)
Gender and risk behavior	
MSM	39 (52.0)
Heterosexual male	17 (22.7)
Female	19 (25.3)
Testing Location	
HIV Counseling and testing site	17 (22.7)
STD Clinic	36 (48.0)
Other type of clinic	22 (29.3)

STI Co-infections

- 23 clients (31%) had a concurrent STI

STD Type	N	(%)	Men (n=13)		Women (n=10)	
Gonorrhea	9	(39)	7	(54)	2	(20)
Trichomoniasis	5	(22)	0	(0)	5	(50)
Syphilis	4	(17)	4	(31)	0	(0)
Herpes	3	(13)	2	(15)	1	(10)
Chlamydia	3	(13)	1	(8)	2	(20)
Bacterial vaginosis	-	-	-	-	3	(30)
GUD, unspecified	1	(4)	1	(8)	0	(0)

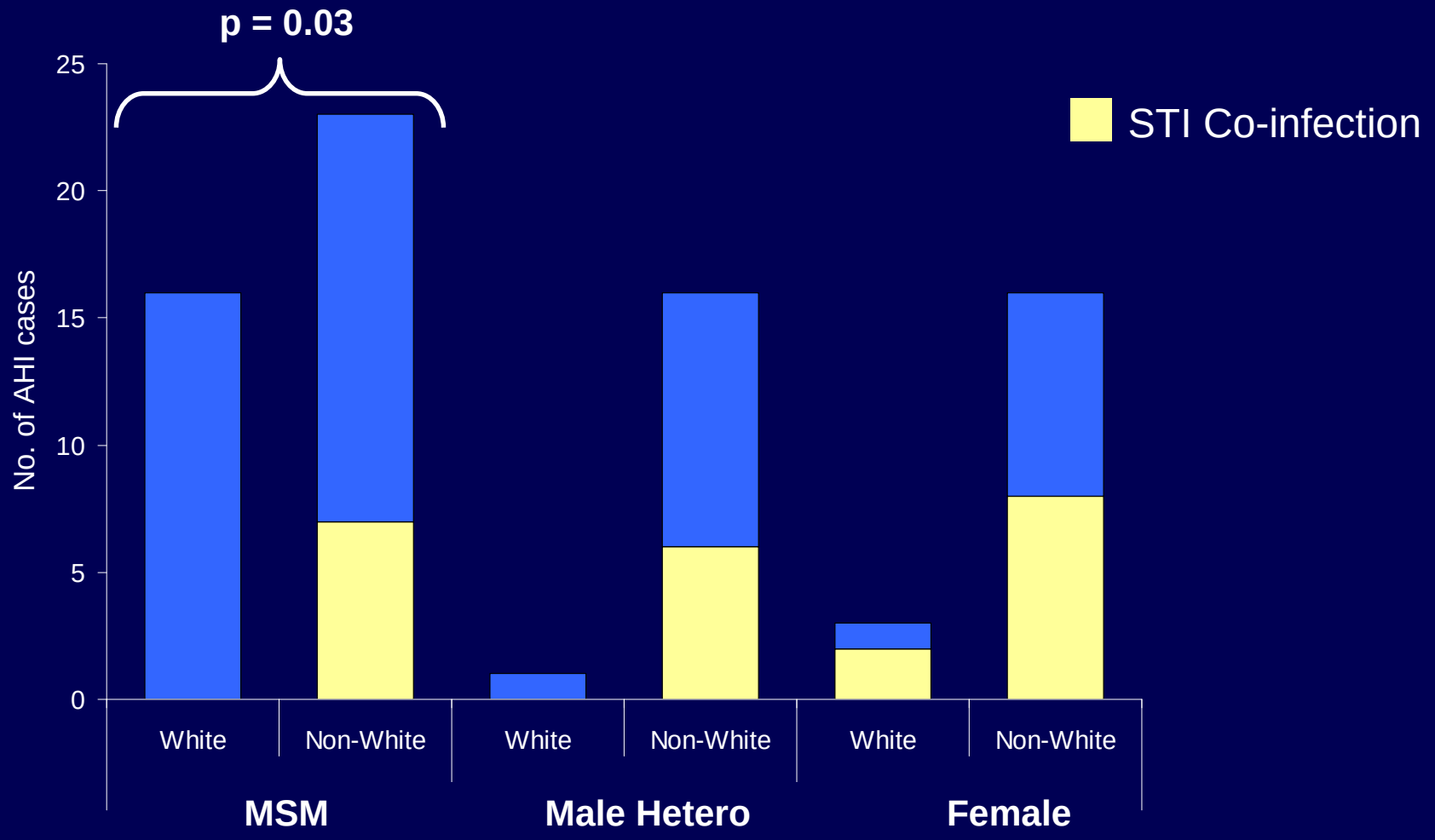
Factors Associated with STI Co-infection

Characteristic	Prevalence (95% CI)	PR (95% CI)
Age (years)		
≤ 25	39.4% (22.9, 57.9)	1.97 (0.74, 5.21)
26-35	20.0% (5.7, 43.7)	*Referent*
≥36	27.3% (10.7, 50.3)	1.36 (0.45, 4.14)
Race or ethnic background		
White, non-Hispanic	10.0% (1.2, 31.7)	*Referent*
Non-White	38.9% (25.9, 53.1)	3.89 (1.00, 15.10)
Gender and risk behavior		
MSM	18.0% (7.5, 33.5)	0.34 (0.15, 0.76)
Heterosexual male	35.3% (14.2, 61.7)	0.67 (0.31, 1.45)
Female	52.6% (28.9, 75.6)	*Referent*
Testing Location		
HIV Counseling and testing site	35.3% (14.2, 61.7)	*Referent*
STD Clinic	36.1% (20.8, 53.8)	1.01 (0.66, 1.55)
Other type of clinic	18.2% (5.2, 40.3)	0.52 (0.17, 1.54)
Symptoms at or before testing		
Yes	24.4% (12.9, 39.5)	0.61 (0.31, 1.20)
No	40.0% (22.7, 59.4)	*Referent*

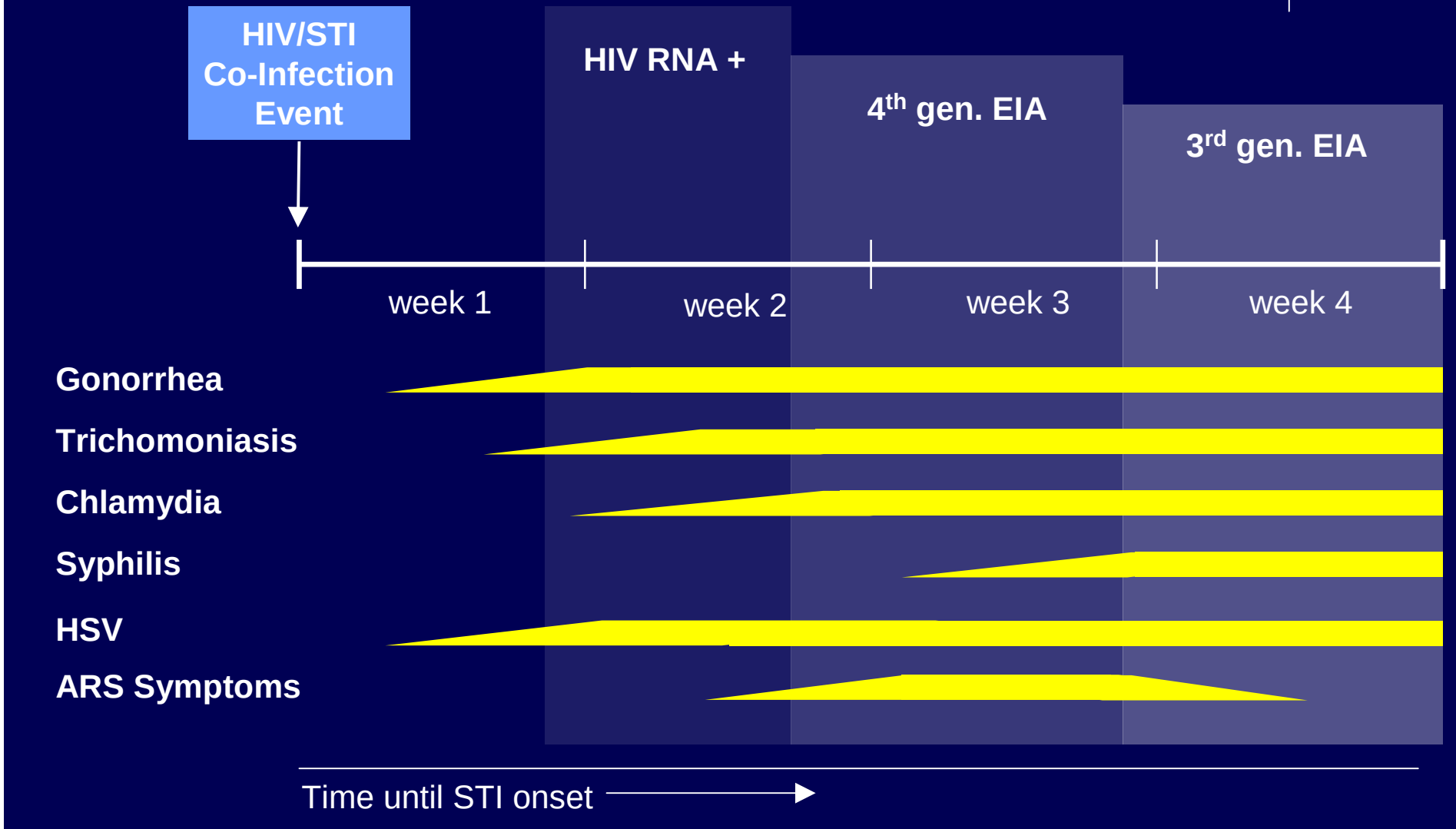
Factors Associated with STI Co-infection

Characteristic	Prevalence (95% CI)	PR (95% CI)
Age (years)		
≤ 25	39.4% (22.9, 57.9)	1.97 (0.74, 5.21)
26-35	20.0% (5.7, 43.7)	*Referent*
≥36	27.3% (10.7, 50.3)	1.36 (0.45, 4.14)
Race or ethnic background		
White, non-Hispanic	10.0% (1.2, 31.7)	*Referent*
Non-White	38.9% (25.9, 53.1)	3.89 (1.00, 15.10)
Gender and risk behavior		
MSM	18.0% (7.5, 33.5)	0.34 (0.15, 0.76)
Heterosexual male	35.3% (14.2, 61.7)	0.67 (0.31, 1.45)
Female	52.6% (28.9, 75.6)	*Referent*
Testing Location		
HIV Counseling and testing site	35.3% (14.2, 61.7)	*Referent*
STD Clinic	36.1% (20.8, 53.8)	1.01 (0.66, 1.55)
Other type of clinic	18.2% (5.2, 40.3)	0.52 (0.17, 1.54)
Symptoms at or before testing		
Yes	24.4% (12.9, 39.5)	0.61 (0.31, 1.20)
No	40.0% (22.7, 59.4)	*Referent*

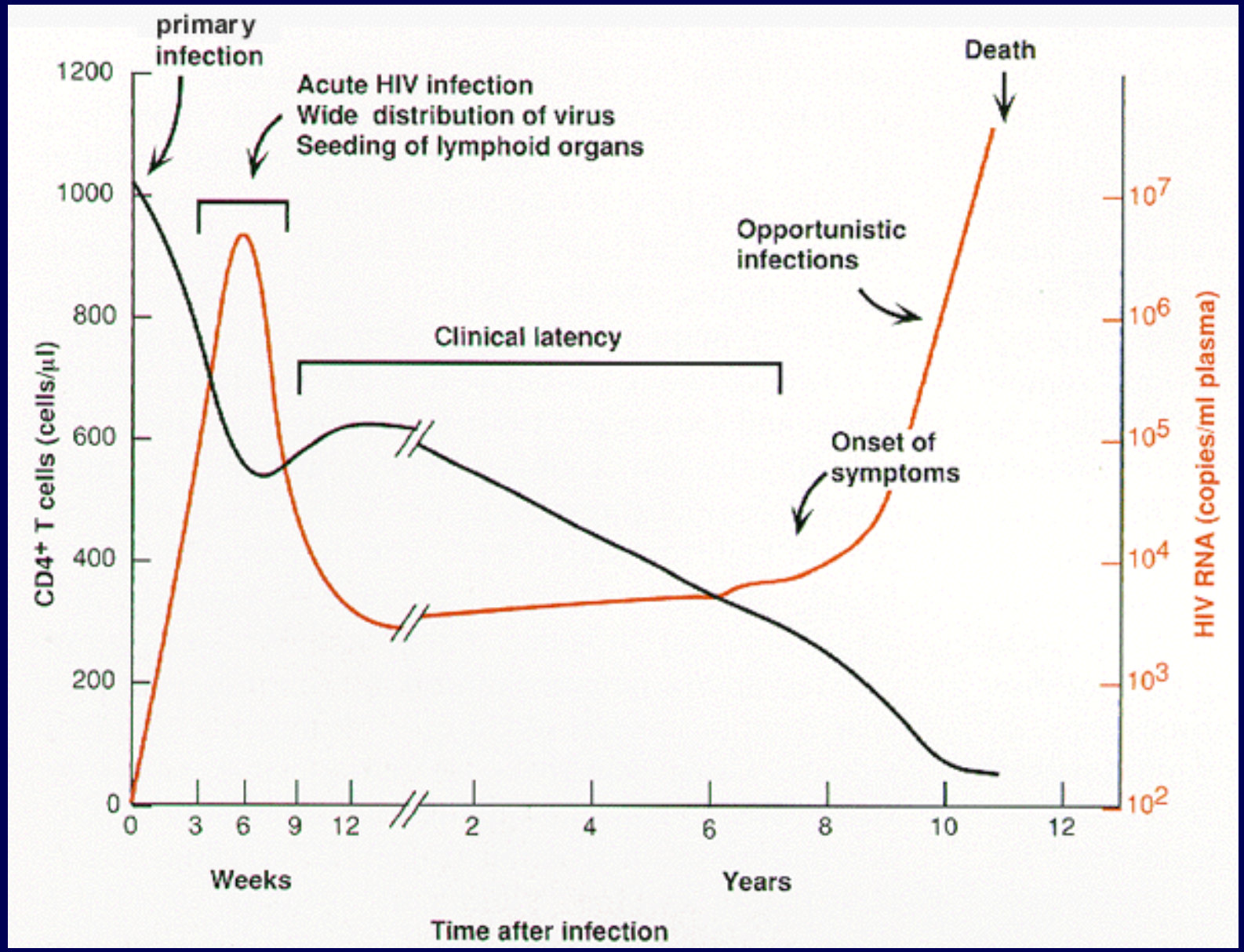
STI Co-infections by Race, Gender, and Risk Category



Potential impact of STI co-infection on detection of AHI

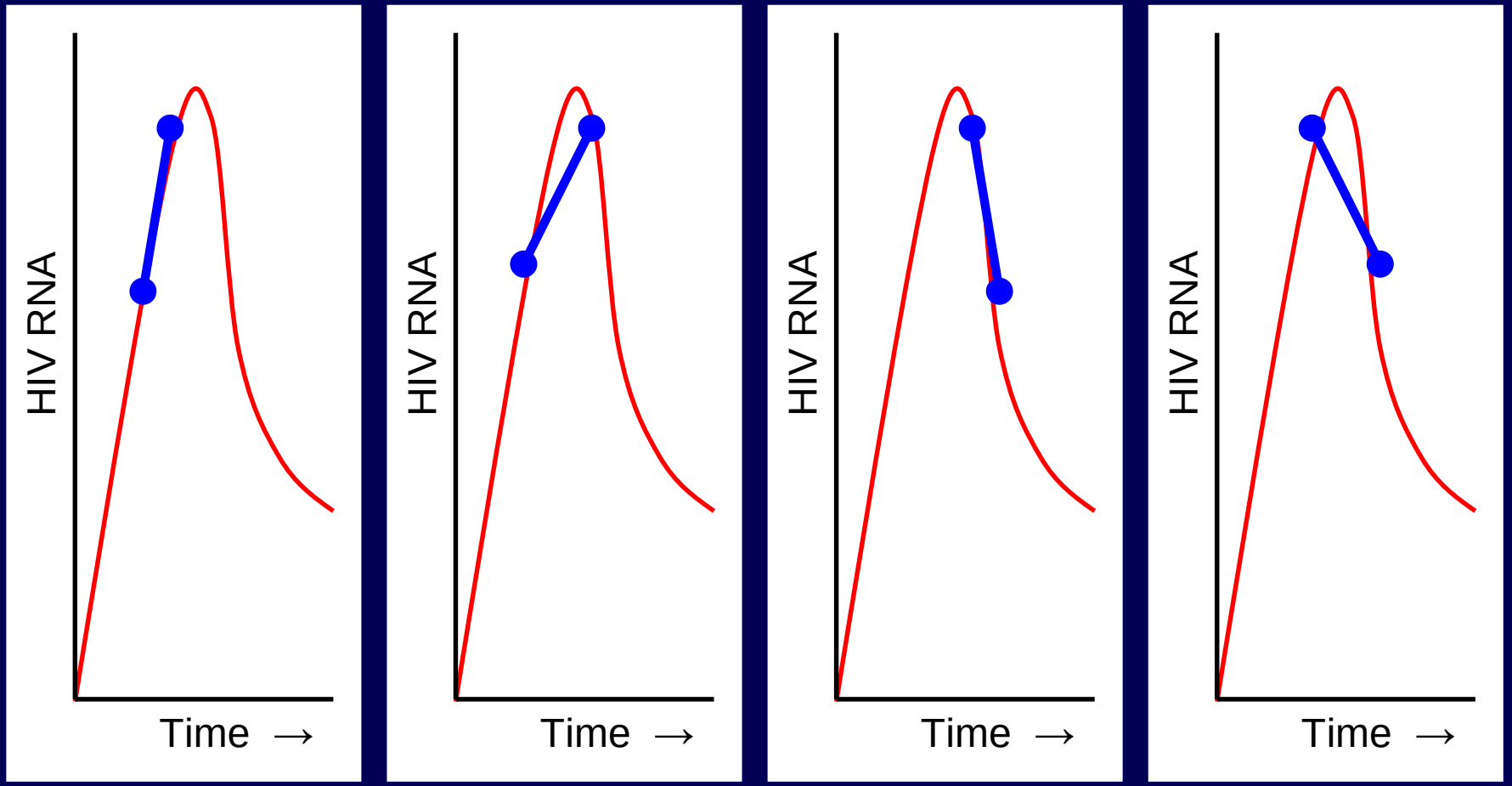


Acute HIV Infection



Slide adapted from Fauci A, *Ann Intern Med* 1996;124:654-663.

Acute HIV Infection



Logistic Regression of HIV RNA Slope (1=increasing slope, 0=decreasing)

Characteristic	Mean HIV RNA (log_{10} copies/mL)	OR (95% CI)
Gender and risk behavior		
MSM	5.4 (5.0, 5.7)	1.20 (0.29, 4.93)
Heterosexual male	4.9 (4.3, 5.6)	1.20 (0.23, 6.39)
Female	5.1 (4.6, 5.6)	*Referent*
Race or ethnic background		
White, non-Hispanic	5.4 (5.0, 5.9)	*Referent*
Non-White	5.1 (4.8, 5.4)	1.72 (0.38, 7.85)
Testing Location		
HIV Counseling and testing site	5.0 (4.5, 5.5)	*Referent*
STD Clinic	5.3 (4.9, 5.7)	0.19 (0.04, 0.94)
Other type of clinic	5.1 (4.7, 5.6)	0.36 (0.07, 1.88)
STI Co-Infection at diagnosis		
Yes	4.9 (4.4, 5.4)	1.30 (0.36, 4.72)
No	5.3 (5.0, 5.6)	*Referent*
Symptoms at or before testing		
Yes	5.3 (5.0, 5.6)	3.02 (0.78, 11.66)
No	5.1 (4.6, 5.5)	*Referent*

Conclusions

- Co-infection with HIV and another STI is common
  - Likely prevalent infections or co-acquisition events – potentially facilitating HIV transmission
  - Most common among heterosexual men & women
  - Co-infection mirrors STI disparities in North Carolina
- STI symptoms are an important indicator of HIV risk, *even in non-STD clinic settings*
  - Acute HIV could be missed with many bacterial STI
  - STIs could be missed with AHI
- Co-infection had no effect on timing of testing

Limitations

- Small sample size
- Testing site subject to misclassification
- Selection bias: public testing sites, diagnostic bias
- Serum viral load slope as a proxy for timing of testing
- HIV RNA bias downward

Acute HIV and North Carolina
STAT

Integration of STD/HIV Screening: Novel Approaches & Strategies for HIV Case Detection

Kees Rietmeijer, MD, PhD

Denver Public Health Department

46th Annual Meeting of IDSA

Washington, DC

Friday, October 24, 2008

Background

- Diagnosis of HIV infection is the cornerstone of HIV prevention
- 25% of persons with HIV are unaware of their status and they may be responsible for up to 50% of new infections
- CDC recommends universal testing for all persons 13-64 years who interact with the health care system
- Given risk overlap and epidemiologic synergies between HIV and other STI, HIV screening is particularly critical in STD clinic settings

National STD Clinic HIV Testing Needs Assessment

- Purposes:
  - To ascertain the status of HIV test implementation in STD clinics in the U.S.
  - To determine facilitators and barriers to HIV test implementation at the local, state, and national levels
  - Based on the above, and careful review of the literature, to establish a “best practice” guidance for HIV testing in categorical STD clinics

HIV Testing in STD Clinics 2008 Needs Assessment

- Comprised of STD clinic survey followed by in-depth interviews with key informants
- Collaborative effort National Network of STD/HIV Prevention Training Centers (NNPTC) with support from CDC
- Conducted by the NNPTC HIV Testing Workgroup under leadership from the California PTC (Chris Hall, PI)

HIV Testing Survey Methods

- Survey was conducted online using SurveyMonkey
- A list of U.S. clinics available from the CDC was updated and expanded by the regional PTCs
  - 744 STD clinics were identified
  - 579 were surveyed
  - 251 responded (representing 43 states)
    - 181 (72%) were categorical STD Clinics
    - The remainder of the clinics offered STD services but were not primarily STD clinics (e.g., family planning/reproductive health clinics, adolescent health clinics, etc.)

HIV Testing Survey
Preliminary Results

- >98% of clinics offer HIV testing
  - Median 70 tests per month (range 0 – 1,750)
- Type of test
  - Conventional: 90%
  - Rapid: 46%; of these:
    - 78% offer rapid test to all clients
    - 32% use risk algorithms to prioritize rapid testing
  - HIV RNA pooling: 14%

HIV Testing Survey
Preliminary Results

- Confidential vs Anonymous testing
  - 62% Confidential
  - 38% Confidential and Anonymous
- Test practices
  - 33% of clinics offer HIV testing to all patients
  - 57% use some form of risk assessment to target testing
- Opt-In vs Opt-Out
  - 25% of clinics test all new STD patients for HIV unless they opt out
  - Of remaining clinics, 85% require documentation of written consent

HIV Testing Survey
Preliminary Results

- Median HIV positivity rate: 1% (range 0% – 13%)
- 97% of STD clinics have a linkage to care protocol for those testing HIV+ and 63% of clinics follow up to see if the newly HIV diagnosed patient attended their first appointment
- 95% of STD clinic report offering partner counseling and referral at time of positive HIV result delivery

HIV Testing Survey

- Facilitators
  - 75% of responding clinics reported that testing had increased in recent years – reasons:
    - New CDC recommendations
    - Increased staff awareness
    - Increased promotion of availability of testing
  - Key informants indicated:
    - Benefits of testing outweigh barriers
    - Transition from standalone STD clinic to integrated STD/HIV clinic
    - Increased staff awareness
    - Enhanced cooperation between STD and HIV disease investigators, avoiding duplication of efforts
    - "Integration of HIV testing with STD and reproductive health services improves clinic logistics by saving time"
      - Requires changes in clinic logistics

HIV Testing Survey

- Barriers
  - Budget cuts and unreliable funding streams
  - Lack of adequate staffing
  - Data collection requirements are too burdensome
  - Patient demand for alternate types of test
  - Clinic flow
  - Patient worries about confidentiality and anonymity

Normalizing HIV Testing in the Denver STD Clinic

Denver Metro Health Clinic

- Largest STD clinic and HIV testing facility in Rocky Mountain region
- Provides:
  - confidential HIV testing in the STD clinic
  - confidential and anonymous testing in the HIV counseling and testing site integrated in the clinic
- In 2006:
  - ~16,000 visits
  - 11,300 HIV tests
  - 119 HIV diagnoses: ~50% of new HIV infections in the Denver Metro area; ~30% in Colorado.

HIV Testing at Denver STD Clinic
Before November 2003

- General consent for all procedures and testing, except HIV testing, obtained at registration
- HIV testing offered by clinician during the clinic visit, based on risk assessment
- Blood drawn for syphilis and HIV (if accepted) testing during the clinic visit
- HIV test used: standard EIA

HIV Testing at Denver STD Clinic After November 2003

- November 2003: Rapid HIV testing (OraQuick) offered
  - First as optional alternative to standard EIA
  - Routine after July, 2004
- May 2004: Change in testing logistics
- March 2005: Introduction electronic medical record and switch from opt-in to opt-out HIV testing

HIV Testing at Denver STD Clinic
Change in Testing Logistics

- To avoid adding another 20 minutes to the visit, prior to clinic encounter:
  - Draw RPR blood before clinician sees patient
  - Offer HIV testing routinely
  - Obtain additional consent
  - Use RPR blood draw to collect extra tube for rapid HIV test

Evaluation

- HIV testing acceptance and HIV test positivity was evaluated for 4 time periods:
  - Period 1: The year before introduction of rapid testing
    - December 2002 – November 2003
  - Period 2: The 6 months following introduction or rapid testing, before logistical adjustment in the clinic and discontinuation of the standard test
    - December 2003 – May 2004
  - Period 3: The 10 months following logistical adjustment, but before introduction of the electronic medical record and opt-out testing
    - June 2004 – March 2005
  - Period 4: The 6 months following opt-out testing
    - April 2005 – September 2005

Evaluation

- Inclusion/Exclusion criteria
  - New problem visits
  - RPR performed
  - Previously known HIV+ excluded
- Main outcome: HIV/RPR ratio
  - RPR used as the gold standard of routine testing

Impacts of Rapid Testing

Denver Metro Health Clinic

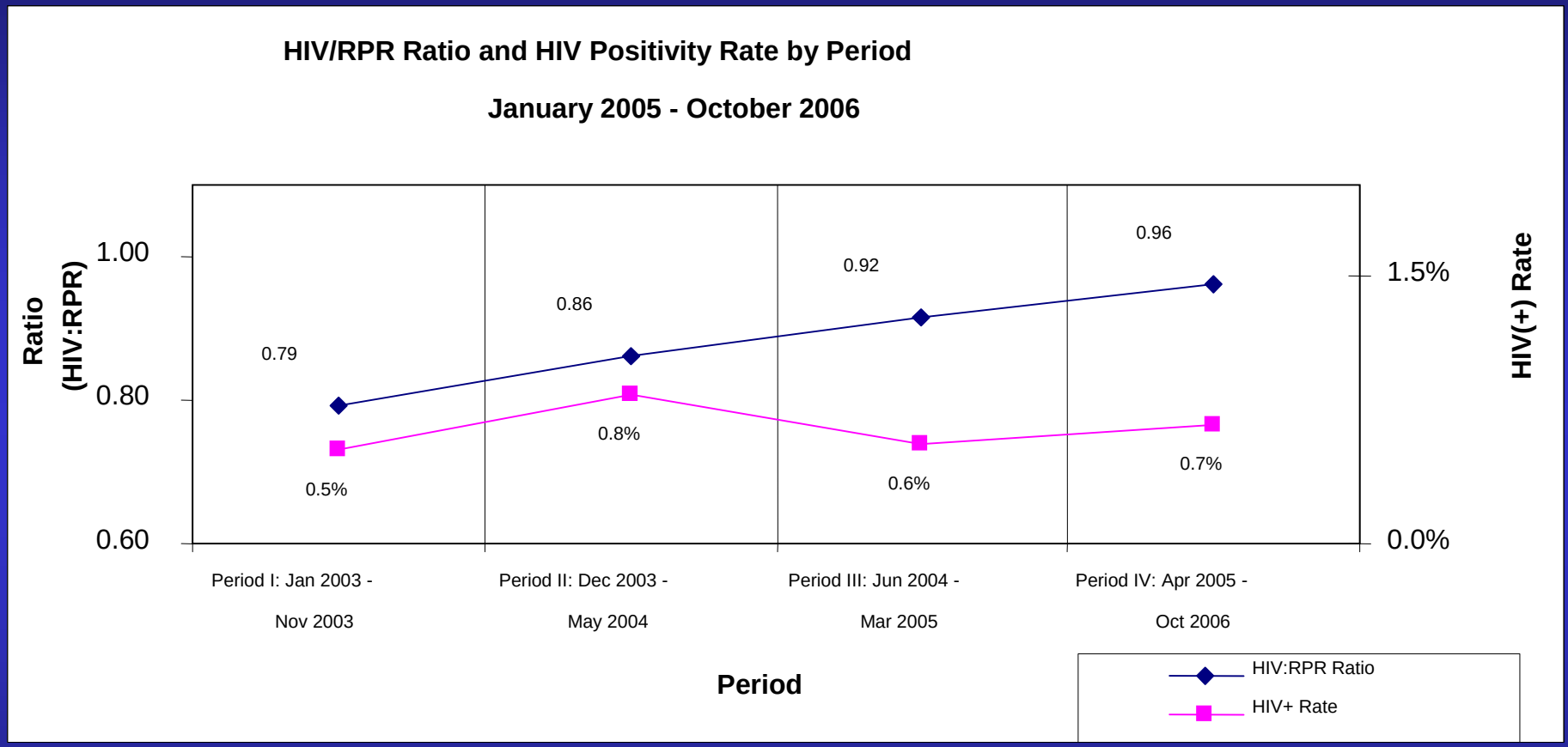
Percentage of patients who received their positive test results:

Before:

66%

After:

100%


HIV/RPR Ratio and HIV Positivity Rate by Period
January 2005 - October 2006
Ratio (HIV:RPR)
1.00
0.80
0.60
HIV(+) Rate
1.5%
0.0%
0.79
0.86
0.92
0.96
0.5%
0.8%
0.6%
0.7%
Period I: Jan 2003 - Nov 2003
Period II: Dec 2003 - May 2004
Period III: Jun 2004 - Mar 2005
Period IV: Apr 2005 - Oct 2006
Period
HIV:RPR Ratio
HIV+ Rate

Conclusions

- HIV Testing appears to be offered in majority of U.S. STD clinics
- Testing policies and techniques vary:
  - Universal vs. risk algorithms
  - Opt-in vs. Opt-Out
  - Rapid test vs. traditional EIA
  - HIV RNA pooling conducted in minority of clinics

Conclusions

- Enhancing HIV testing uptake at the Denver STD clinic proved to be principally a matter of logistics and convenience:
  - Rapid HIV Testing
  - Change in clinic logistics to avoid lengthier visits
  - Offer HIV testing on a routine basis rather than as part of risk assessment
  - Opt-out testing was a “natural” step in logistical adjustments, but had a small effect on testing uptake

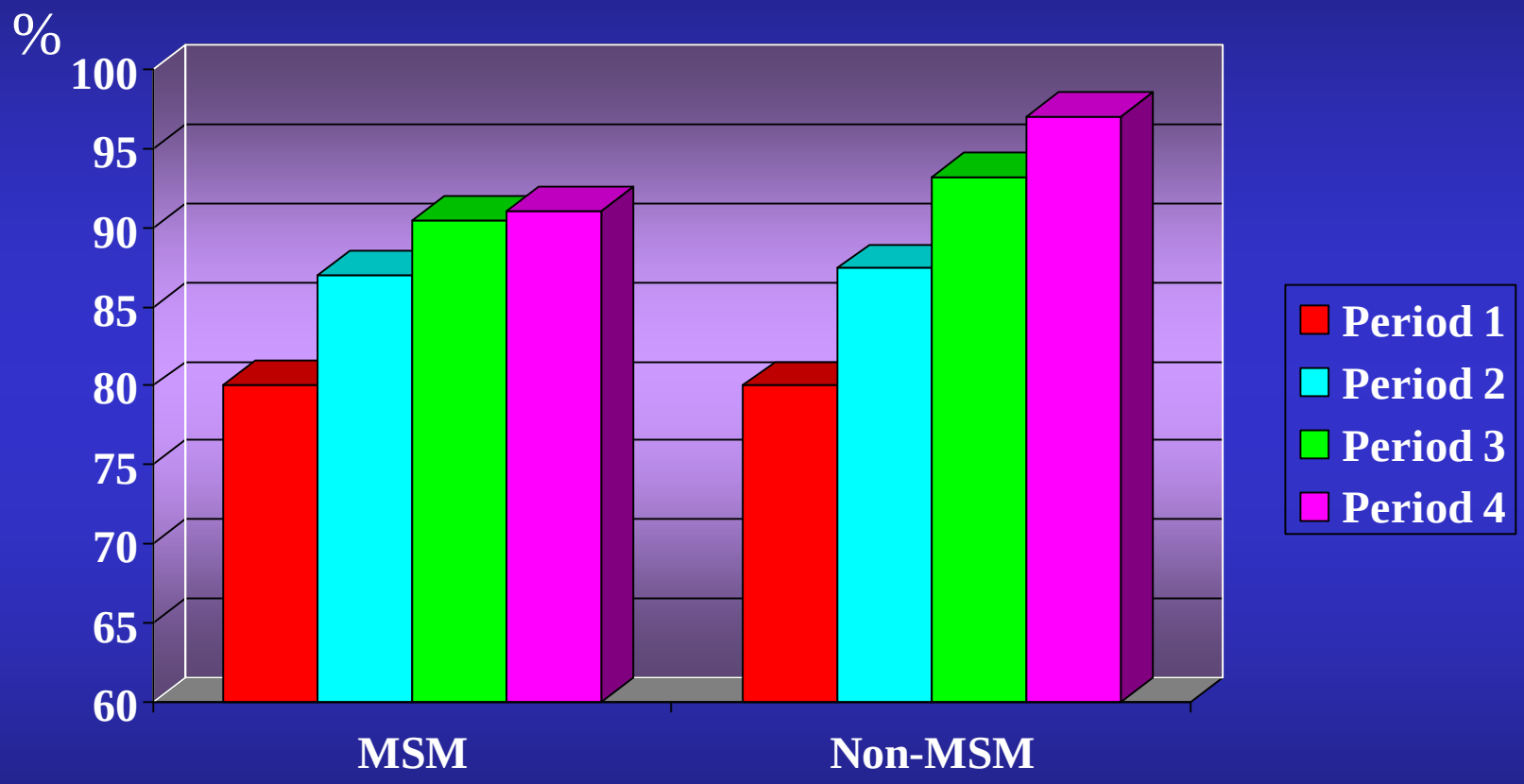
Conclusions

- Issues that appear not to influence testing uptake:
  - Stigma
    - STD clinic is already a stigmatized environment
  - Testing acceptance
    - Most patients expect HIV testing to be part of the STD clinic testing protocol
    - Acceptance among clinicians may play a larger role
  - Specific HIV consent
    - Opt-out testing only marginally improved testing acceptance rates, especially among non-MSM

Acknowledgements

- California Department of Public Health, STD Control Branch:
  - Chris Hall and Ann Oldervoll
- Denver Department of Public Health, STD Control Program:
  - Christie Mettenbrink
  - Julie Subiadur
  - Dean McEwen
  - Lesley Brooks

HIV Testing Acceptance



Period 1: Before introduction of rapid testing
Period 2: Following Period 1, before logistical adjustments
Period 3: Following Period 2, before opt-out consent
Period 4: After Introduction of opt-out

What About Counseling?

- Concern:
  - Traditional (2-visit) testing provides the opportunity for 2-session (pre- and post-test) counseling
  - In a multi-site, randomized, controlled study (Project Respect), 2-session counseling (1 week apart) was associated with a 30% reduction of sexually transmitted infections at 6 months and 20% at 3 months*

*Kamb et al. JAMA 1998;280:1161-7

What about Counseling?

- Rapid testing provides pre- and post-test counseling at the same visit
- Is this as effective as when the sessions are separated by a week?

What About Counseling?

- Project Respect-2*:
  - STI at12 months:
    - 19.1% in the rapid group
    - 17.1% in the standard group
    - Difference (~10%) not statistically significant
  - STI incidence higher in standard group among:
    - Men (RR 1.34; 95% CI 1.06-1.70)
    - MSM (RR 1.86; 95% CI 0.92 – 3.76)
    - No STI at baseline (RR 1.21; 95% CI 0.99 – 1.48)

*Metcalf et al. Sex Transm Dis 2005;32:130-8

Concerns

- Coercion
- Inadvertent testing due to mislabeling of blood specimens
- PEMS
- Effects on prevention counseling by clinicians
  - Of particular concern in STD clinics where most are at higher risk for non-HIV STD's and where prevention counseling is most effective in reducing incident/recurrent STD's
- Linkage to care
- Linkage to "prevention services"
- Cost issues

Solutions?

- De-link counseling from testing
  - STD clinicians should be trained to develop client-centered skills, not as a an add-on counseling within the encounter, but rather as a way of communicating with the client
- Develop innovative prevention strategies
  - Prevention case management (PCM) and PCM-”light” (long-term follow-up with known positives)
  - Prevention for known HIV-infected individuals visiting STD clinics – ongoing PCRS?
  - Prevention counseling in HIV care settings
- Role of the STD/HIV Prevention Training Centers

Genital HSV Infection:

Interactions with HIV
Updates and Implications

Connie Celum, MD, MPH

Departments of Global Health and Medicine

University of Washington

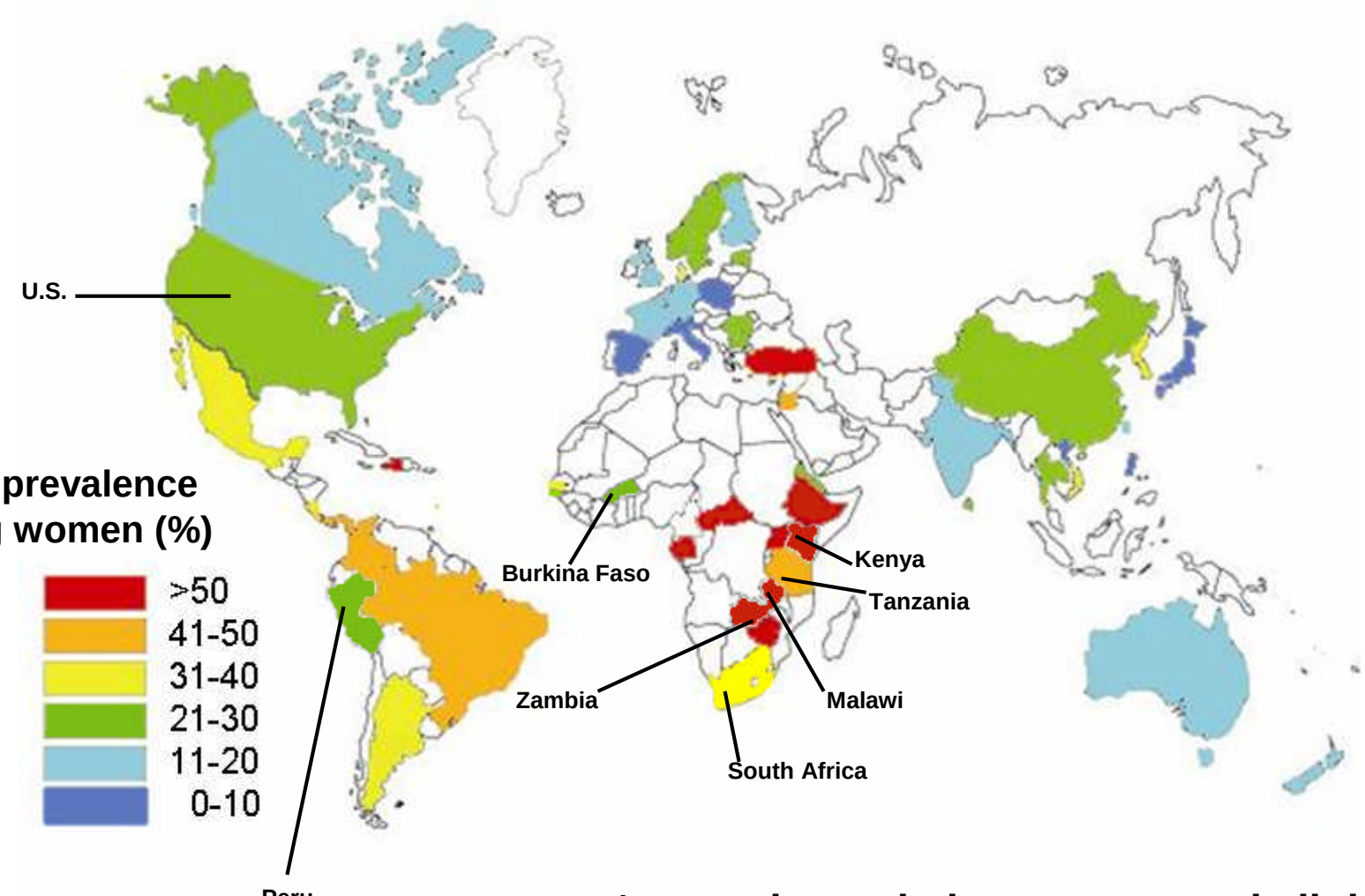
Overview

- HSV-2 Overview
- HSV-2 as a risk factor for HIV acquisition
- Design & Results of Mwanza & HPTN 039 Trials
- HSV-2 and HIV Infectiousness and Disease Progression
- Proof-of-concept studies to reduce systemic and mucosal HIV with HSV-2 suppression

Herpes Simplex Virus-2: “Primer”

- Highly prevalent globally
  - 22% of sexually active adults in US
  - 60% of HIV-negative MSM in Peru
  - 50-70% of HIV-negative women in southern Africa
  - >80% in HIV-infected men and women globally
- Most common cause of genital ulcer disease (GUD) globally
- 80-90% of HSV-2 + persons do not report prior GUD
- After counseling, most recognize genital herpes
- Majority shed HSV-2 in the genital tract, even if previously unrecognized genital lesions → thus, are infectious

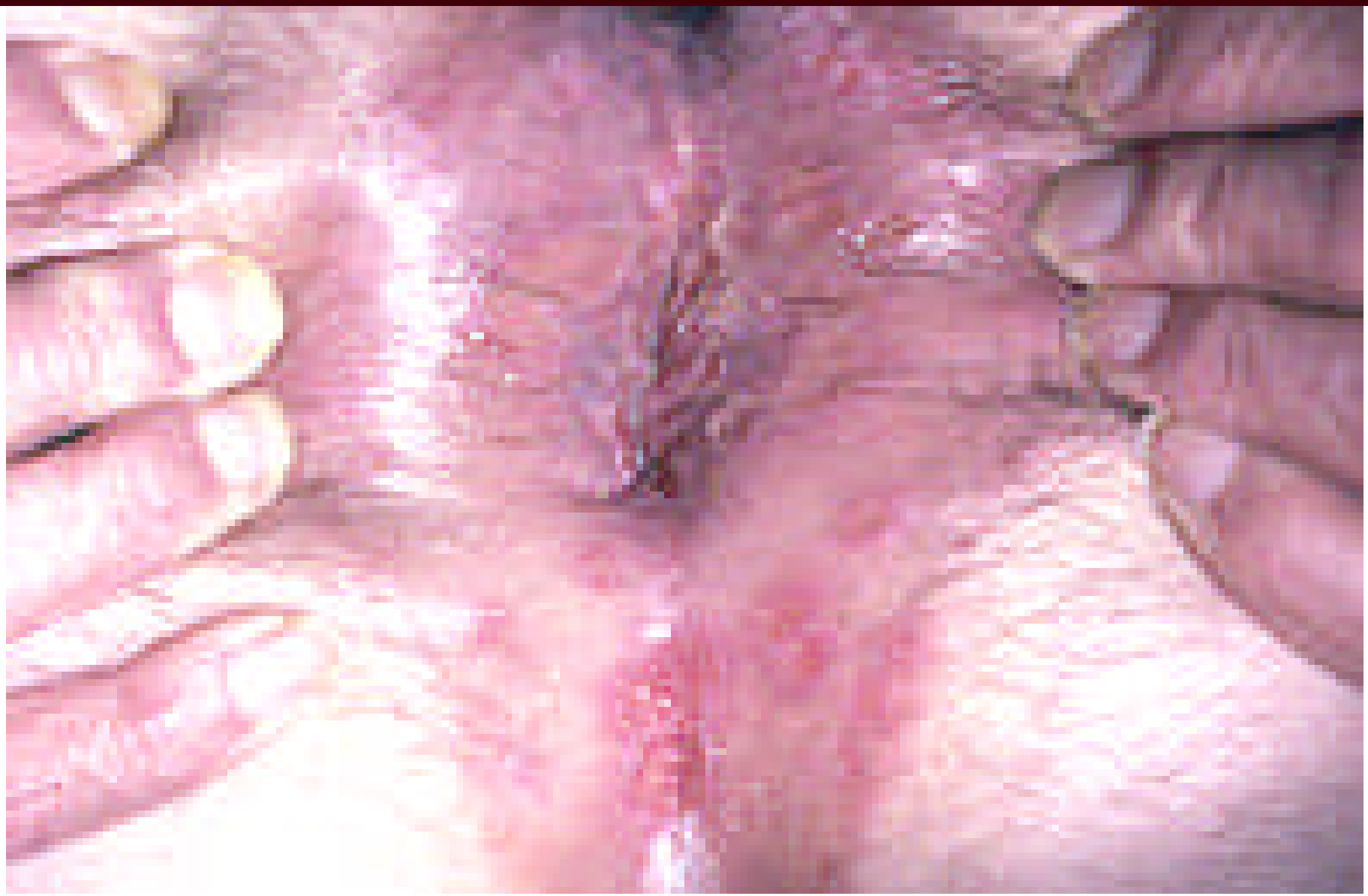
HSV-2 Prevalence Among Women*



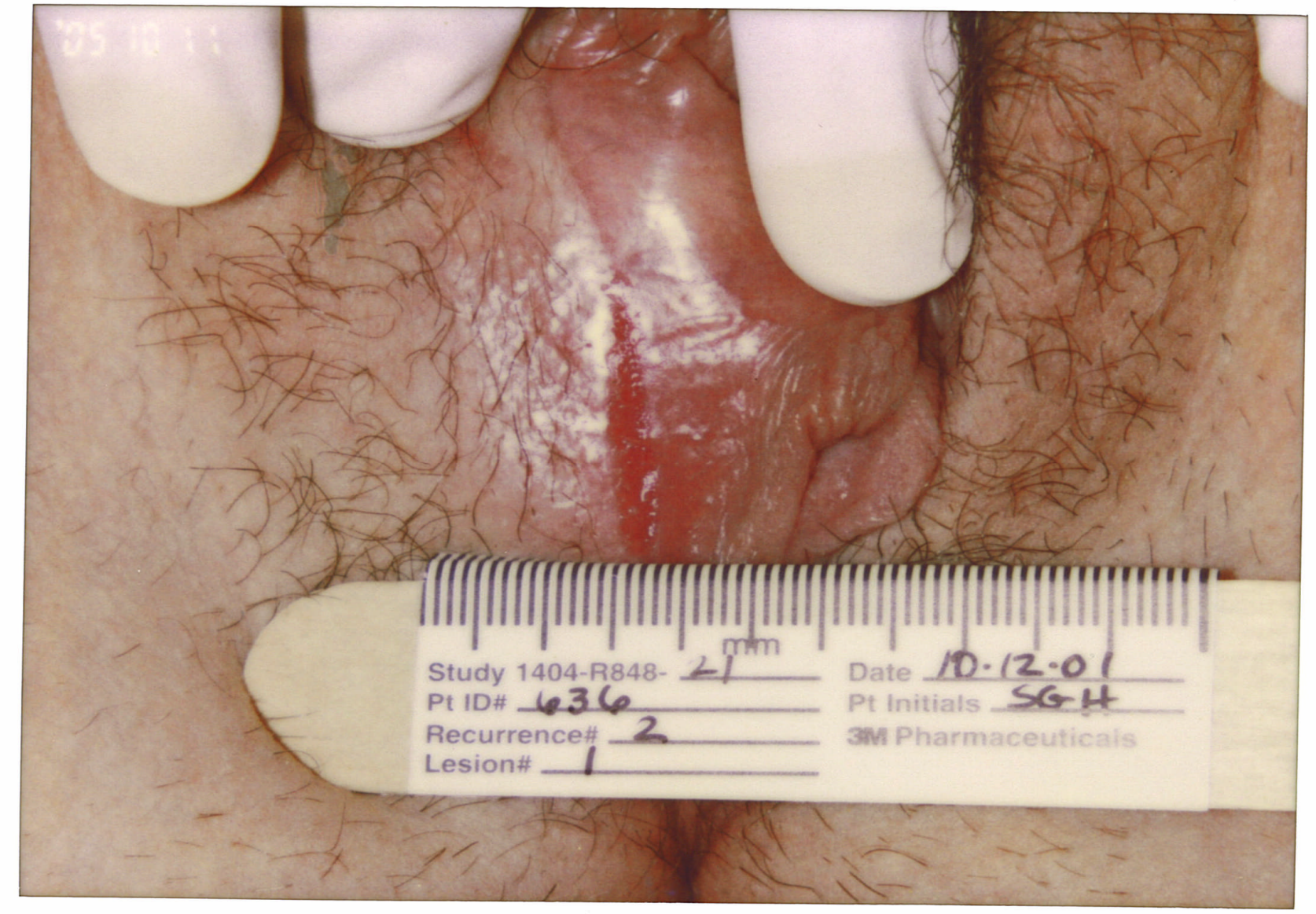
***general population or antenatal clinics**

Modified from Corey *JID* 2007;195:1242; Nagot, *STI* 2004;80:124; Konda *STD* 2005;32(9);534; Weiss *Herpes* 2004;11(S1):24A

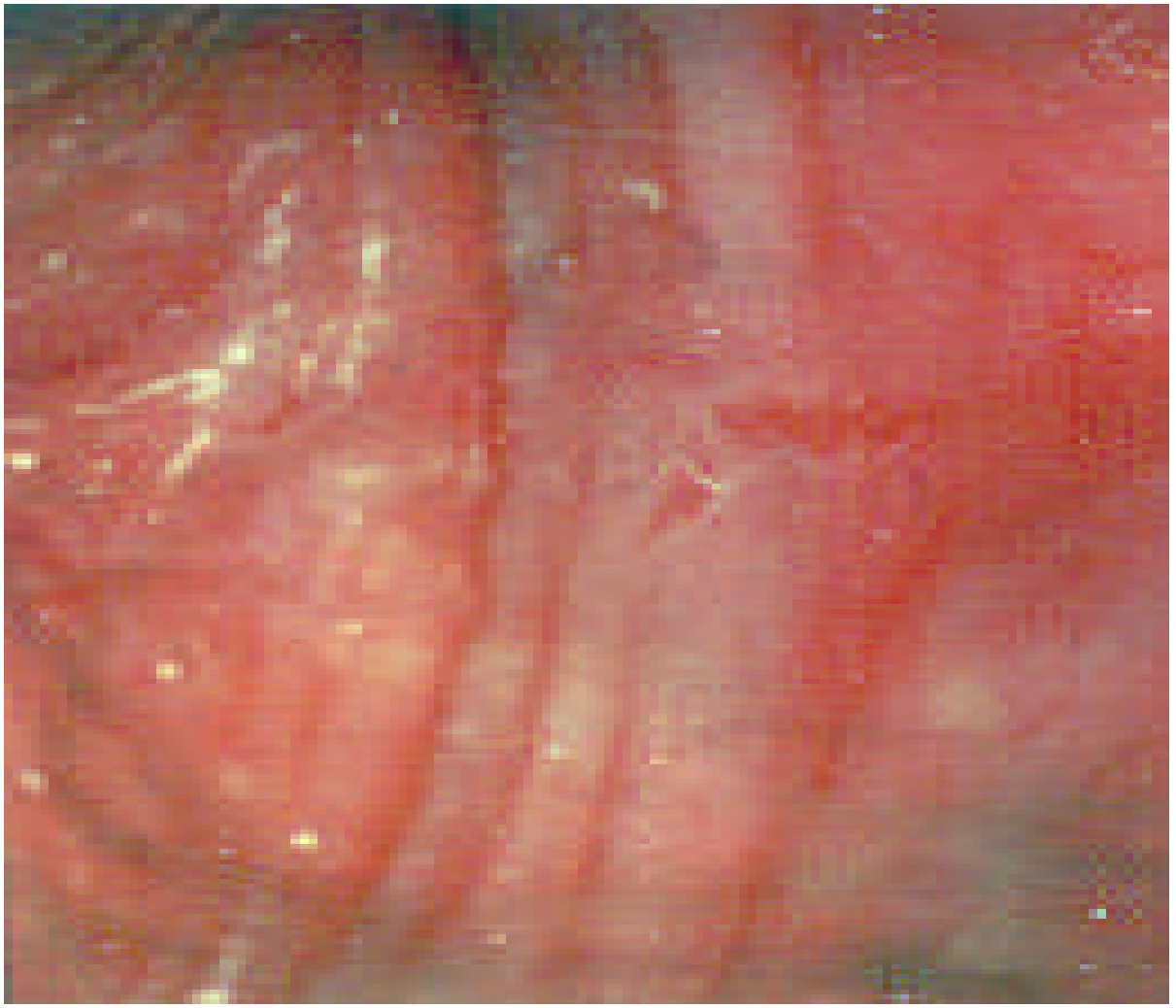
Bilateral HSV-2 in Primary HSV-2



Recurrent HSV-2 presenting as fissure

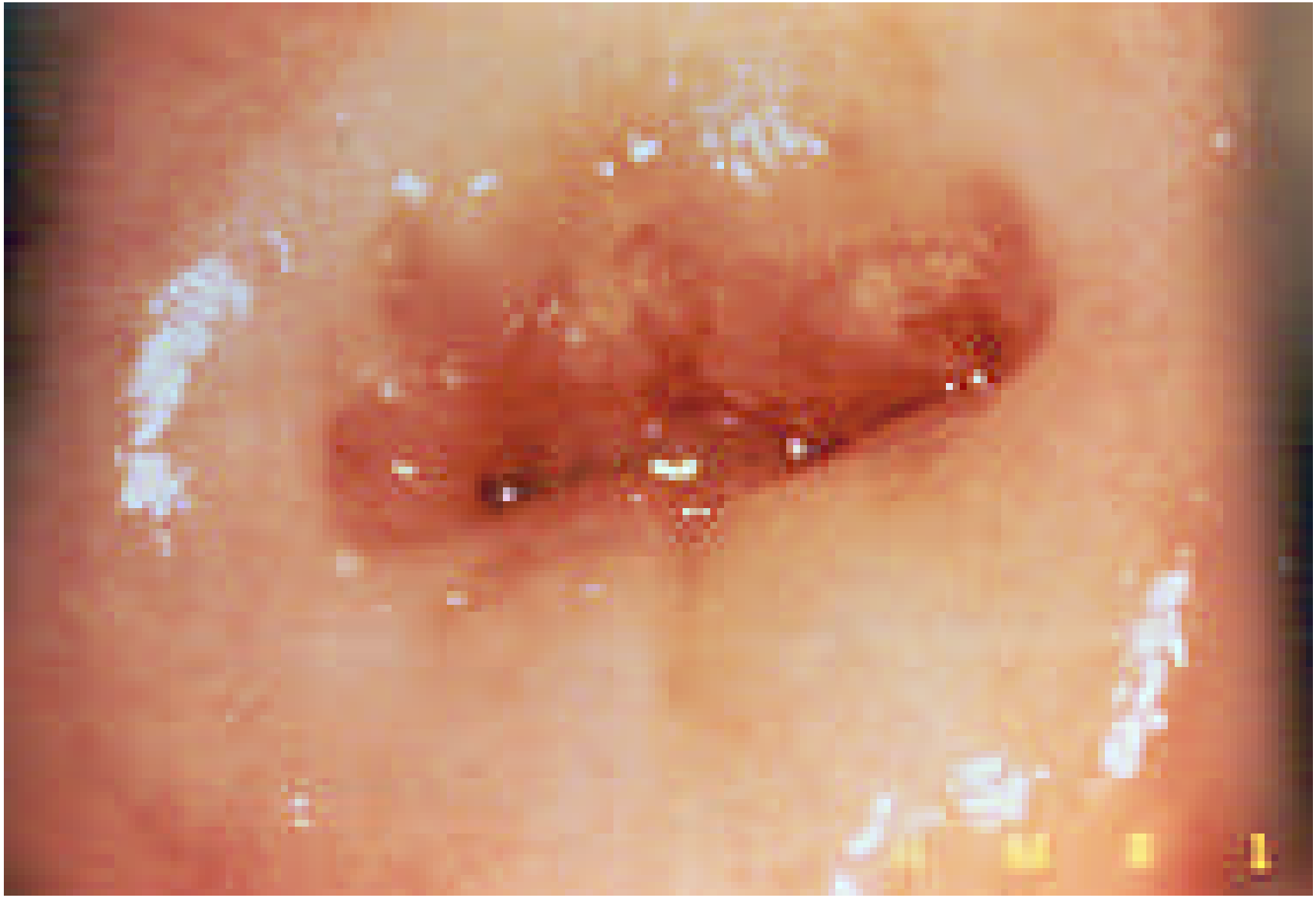


Protean manifestations of Genital Herpes in HIV-negative persons

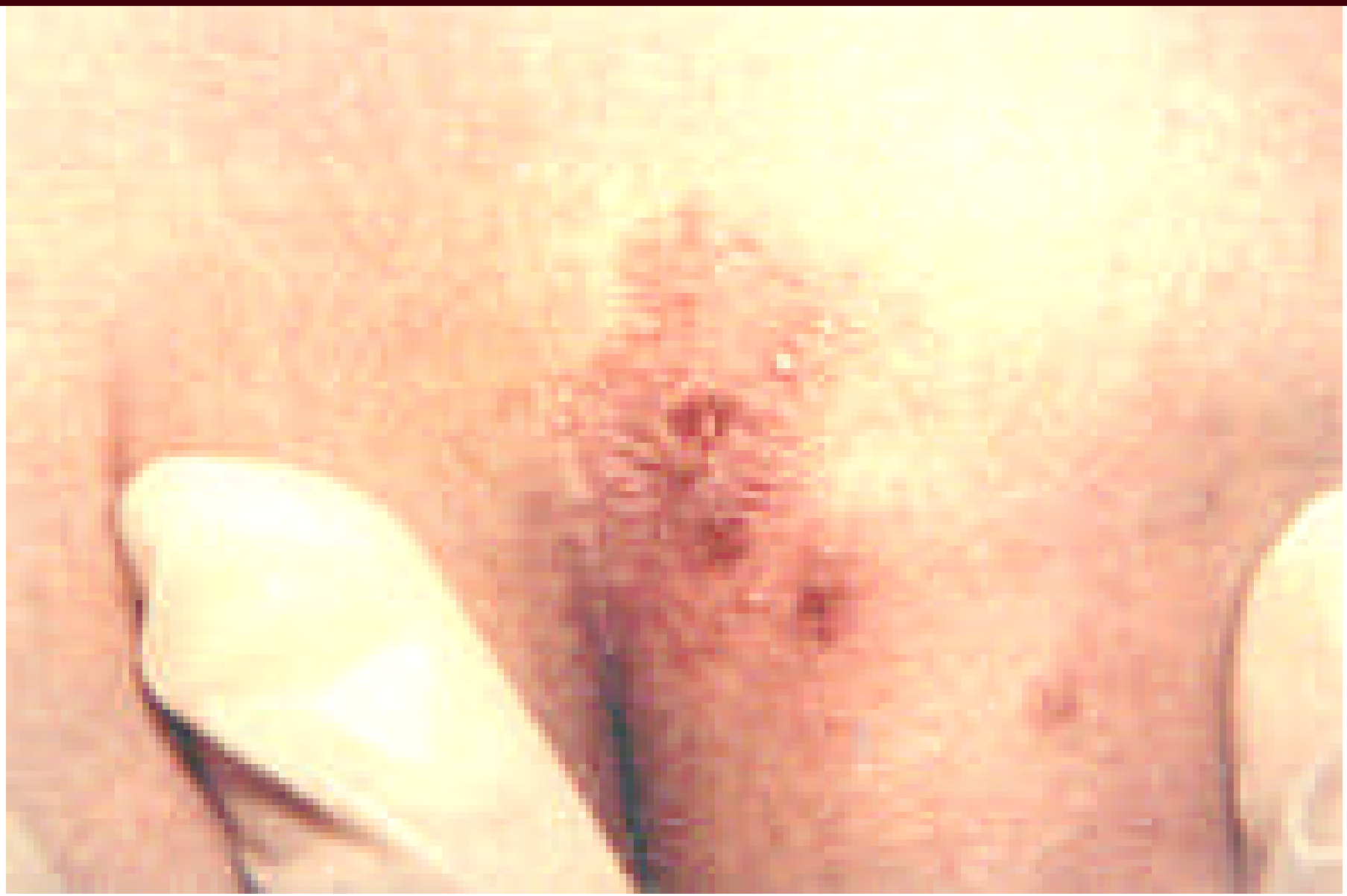


HSV-2 fissure mis-diagnosed as candida

HSV-2 cervicitis (seen in primary HSV-2)



Recurrent Gluteal HSV-2



Rapidly Cleared Episodes of Herpes Simplex Virus Reactivation in Immunocompetent Adults

Karen E. Mark,[1,4] Anna Wald,[1,2,3,4] Amalia S. Magaret,[3,4] Stacy Selke,[3] Laura Olin,[3] Meei-Li Huang,[3] and Lawrence Corey[1,3,4]

Table 2. Characteristics of herpes simplex virus (HSV) shedding episodes.

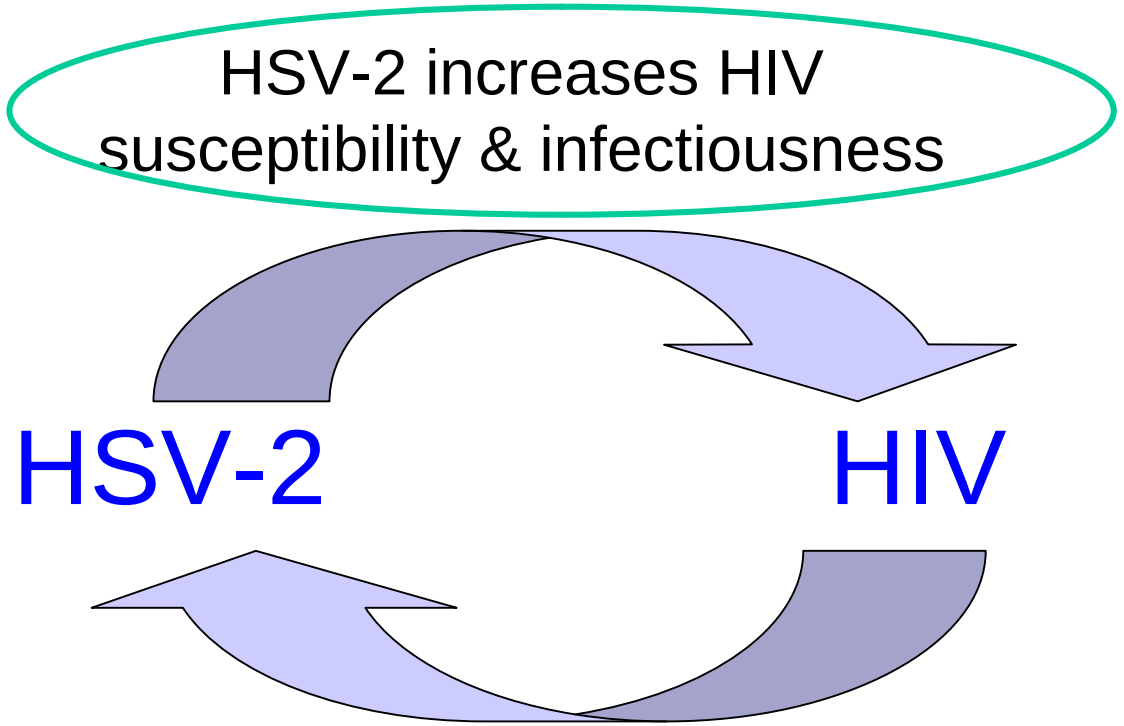
Characteristic	Genital shedding episodes (n = 72)	P
HSV reactivation duration		
Overall, median (range)	13 h (4 h to 17 days)	
≤12 h, no. (%), episodes	35 (49)	
≤6 h, no. (%), episodes	17 (24)	
HSV level, median (range), copies/mL		
At episode onset	$10^{3.5}$ ($10^{2.2}$–$10^{7.5}$)	
In last positive sample	$10^{3.3}$ ($10^{2.2}$–$10^{5.8}$)	
HSV level at episode onset, median, copies/mL		
By episode duration		<.001
>12 h	$10^{4.2}$	
≤12 h	$10^{3.1}$	
By sex		<.0001
Women	$10^{4.5}$	
Men	$10^{3.2}$	

- Estimated average of 18 reactivations/year

HSV-2 Suppression for HIV Prevention:

- Not what we expected for HIV Acquisition
- Results re HIV Transmission & Disease Progression: mid-2009

HSV-2 & HIV: Epidemiologic Synergy & Double Trouble



HSV-2 increases HIV susceptibility

- **Epidemiologic Data**
  - Longitudinal studies which adjusted for age & sexual behavior (n=18)
  - Prevalent HSV-2 infection and HIV acquisition
    - Men RR 2.7 95% CI 1.9-3.9
    - Women RR 3.1 95% 1.7-5.6
    - MSM RR 1.7 95% CI 1.2-2.4
  - 38-69% of new HIV infections in ♀ & 8-49% in ♂ due to prevalent HSV-2 (Freeman AIDS 2006)

- **Biologic Plausibility**
  - HSV-2 causes macro- & microscopic ulcerations
  - HSV-2 reactivation is frequent: 20% of days HSV PCR+ in HIV-negative persons (Mark ISSTDR 2007)
  - ⇑ cervical CD4 T cells & immature dendritic cells in HSV-2 seropositive women (Rebbapragada AIDS 2007)

- Need proof of concept trials to demonstrate whether can reduce effect of HSV-2 on HIV susceptibility & HIV infectiousness

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

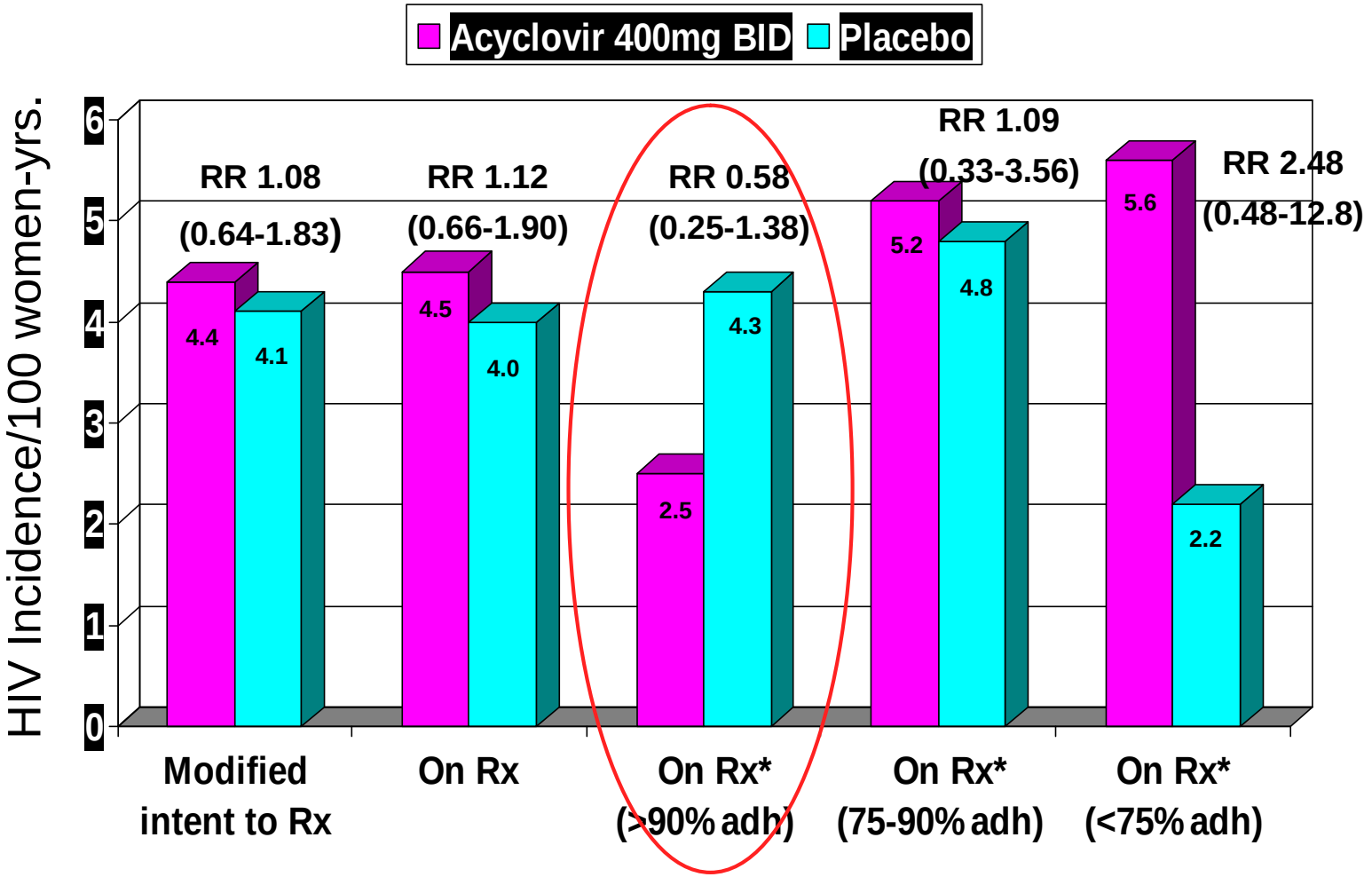
Effect of Herpes Simplex Suppression on Incidence of HIV among Women in Tanzania

Deborah Watson-Jones, M.D., Ph.D., Helen A. Weiss, Ph.D., Mary Rusizoka, Dip.Med., John Changalucha, M.Sc., Kathy Baisley, M.Sc., Kokugonza Mugeye, Dip.Med., Clare Tanton, M.Sc., David Ross, M.D., Ph.D., Dean Everett, Ph.D., Tim Clayton, M.Sc., Rebecca Balira, M.Sc., Louise Knight, M.Sc., Ian Hambleton, Ph.D., Jerome Le Goff, M.Sc., Ph.D., Laurent Belec, M.Sc., Ph.D., and Richard Hayes, D.Sc.*

NEJM 2008

- Randomised, double-blind, placebo-controlled trial of acyclovir 400mg bid. vs placebo
- Women working in bars & other high-risk venues recruited
- 12-30 months follow-up, mobile clinics, quarterly visits
- HIV acquisition in 821 HIV-negative women

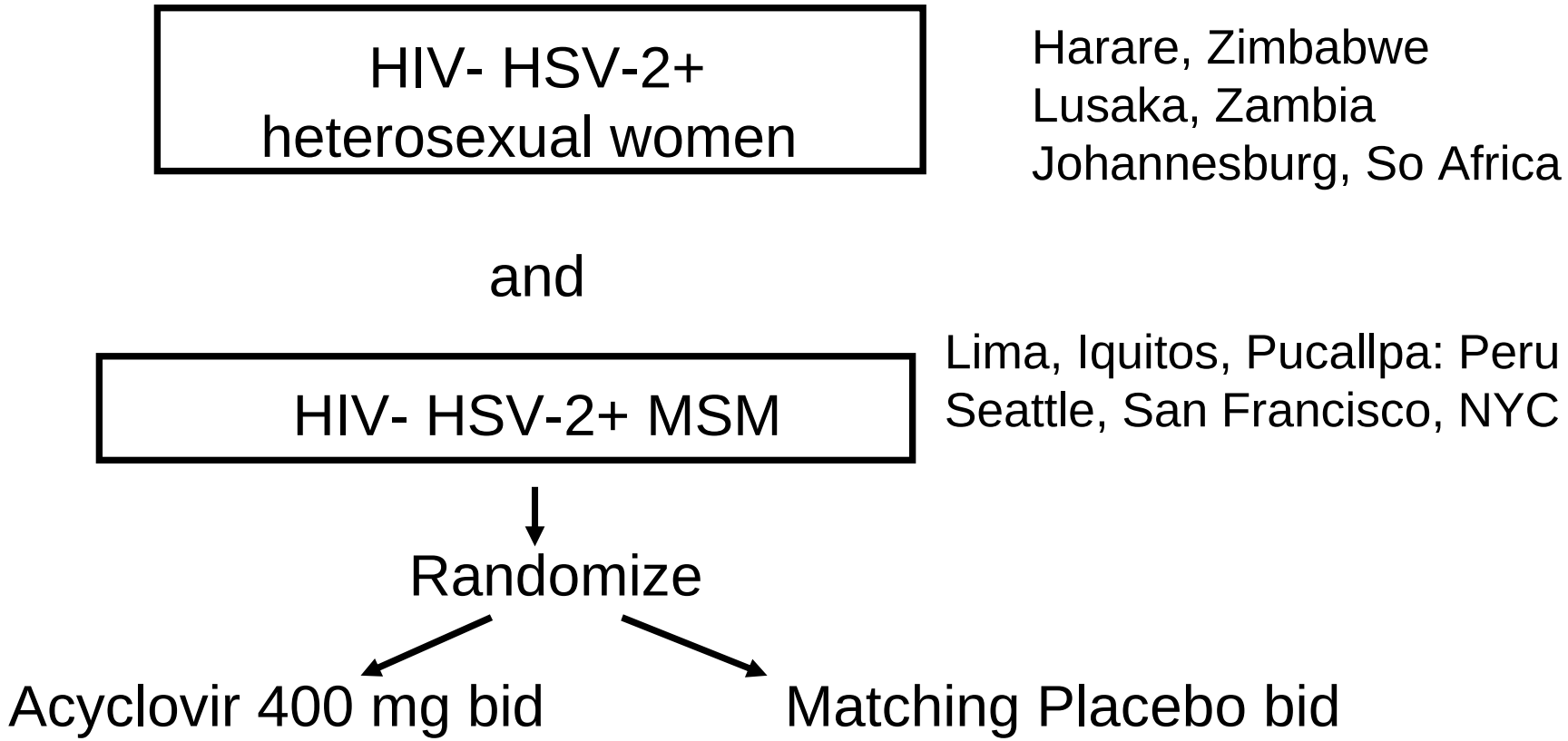
No Reduction in HIV Incidence with HSV-2 Suppressive Therapy in HSV-2^{+}/HIV^{-} Women in Mwanza, 2004-'06



* Test for trend with adherence p=0.10

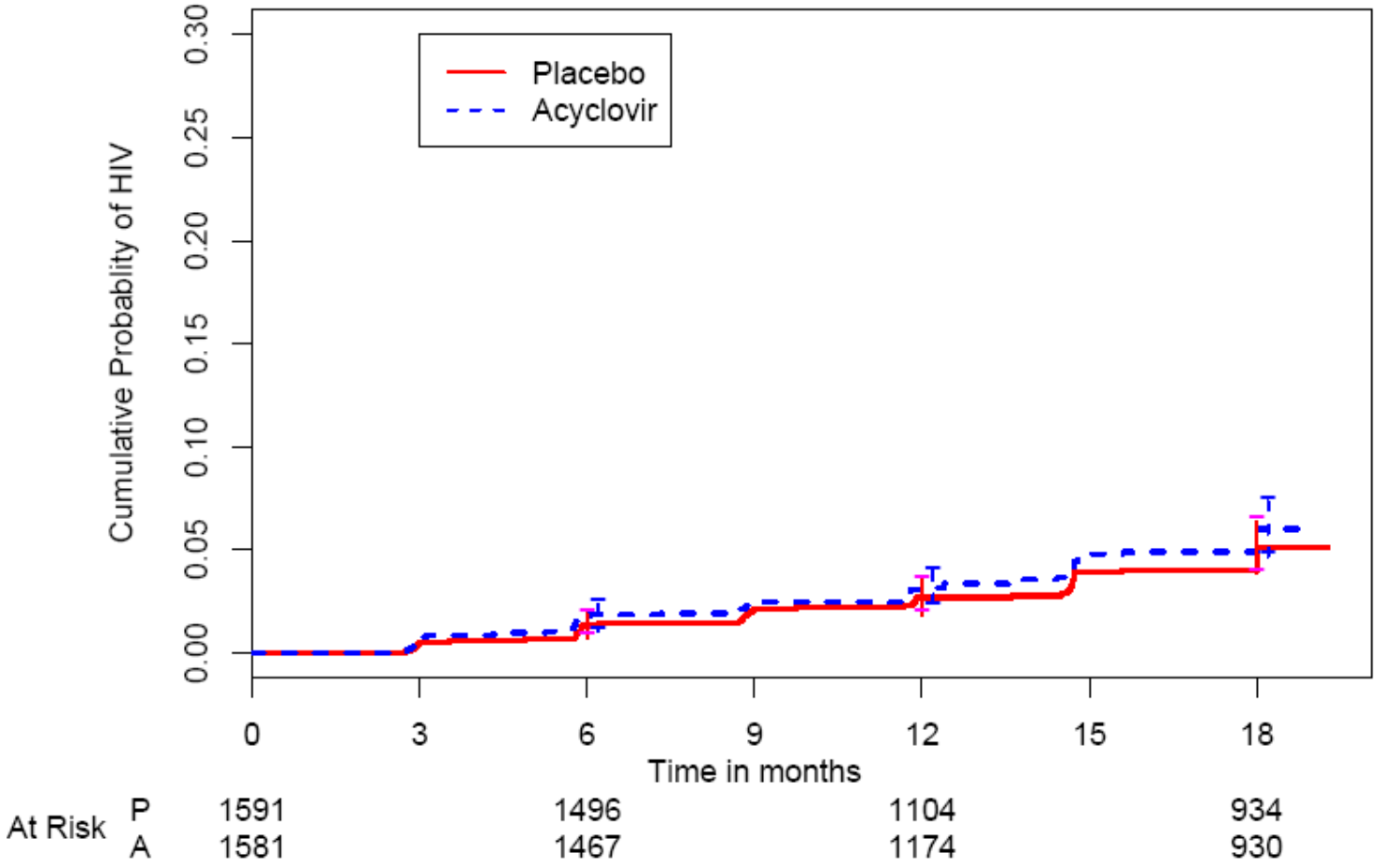
Source: Watson-Jones et al. *NEJM* 2008;358:1560-71.

HPTN 039: HSV-2 suppressive therapy to prevent HIV acquisition, N = 3252



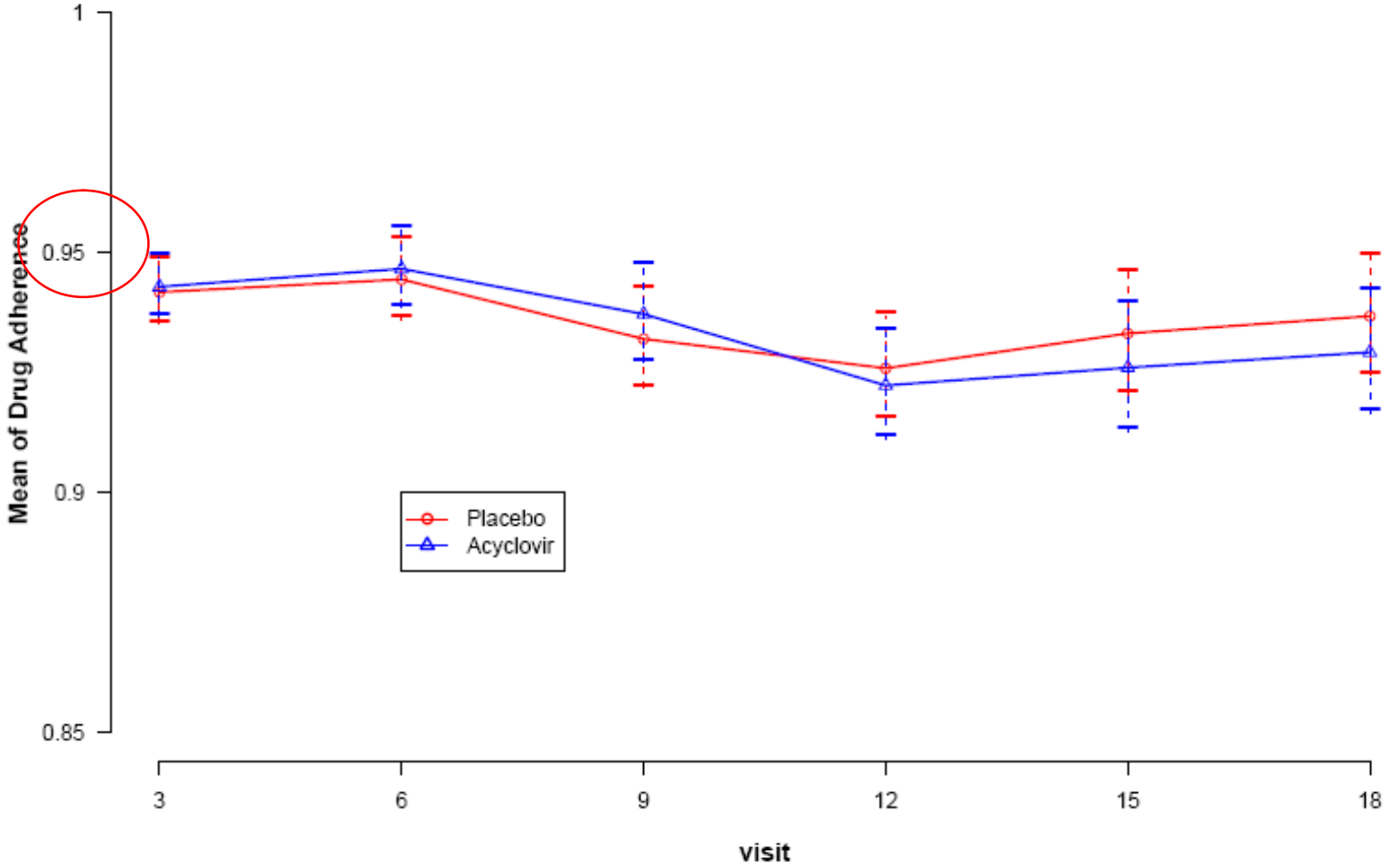
1° endpoint: HIV infection

HPTN 039: Time to HIV by study arm



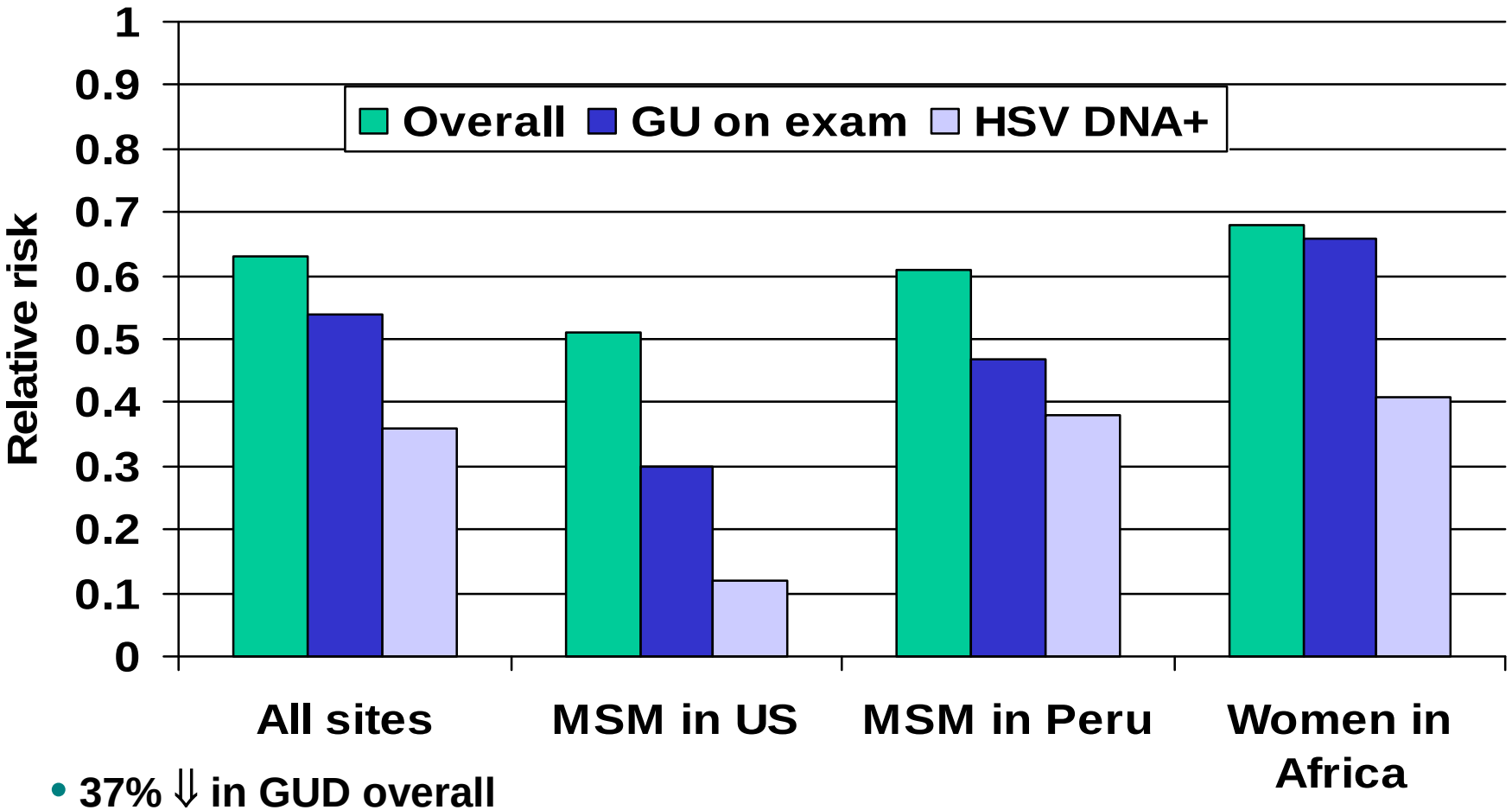
Overall HR 1.16 (95% CI 0.83-1.62); p=0.39

HTPN 039: Mean quarterly adherence by pill count & self-report by treatment arm



Consecutive missed doses (≥6) reported at <4% of visits

HPTN 039: Relative risk of GUD in acyclovir compared with placebo arm



- 37% ⇓ in GUD overall
- 64% ⇓ in HSV PCR + GUD & significant regional differences

HIV Prevention Trials Network

HPTN 039: Conclusions

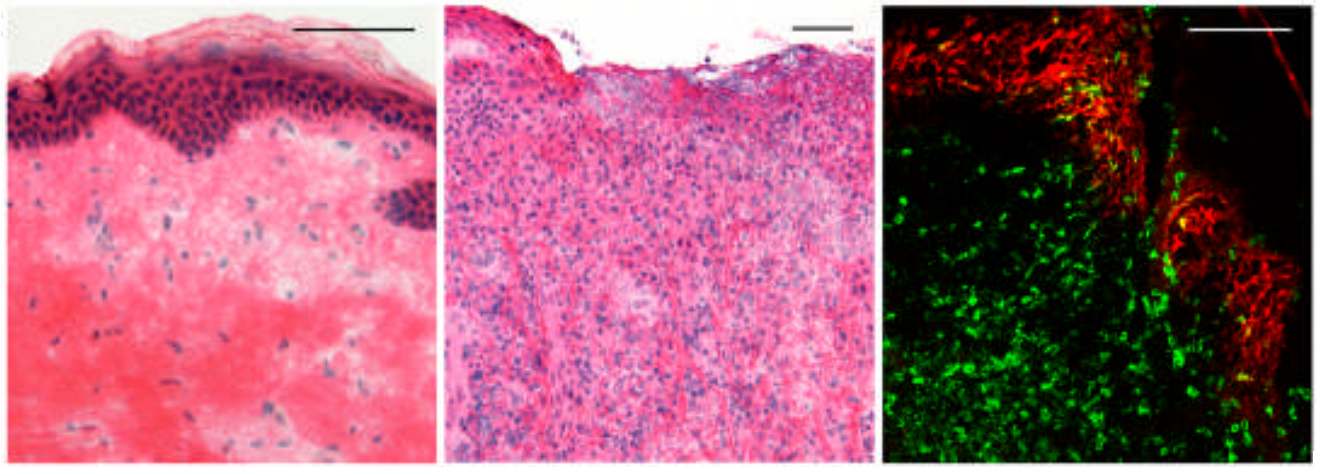
- Acyclovir 400 mg bid did not reduce risk of HIV acquisition among high-risk HSV-2 seropositive women & MSM
- Adherence to study drug was excellent
- Acyclovir 400 mg bid was safe and well-tolerated; largest trial ever of HSV-2 suppression
- Suppressive acyclovir led to a significant reduction in incidence of genital ulcers
- Surprising, disappointing, & important result for HIV prevention
- Is lack of efficacy related to the concept or the intervention?

Possible Interpretations of HPTN 039

- HSV-2 is not a risk factor for HIV
  - Due to confounding? (plethora of epidemiologic data)
- HSV in Africa responds less well to acyclovir
  - Less decrease in GUD & HSV quantity in GUD than in prior trials
  - Are acyclovir pharmacokinetics or susceptibility a factor?
  - Was adherence overestimated by pill count & self-report?
  - Other etiologies of genital ulcers (trauma) important?
- We have underestimated HSV-2 in terms of frequency of reactivation & genital immune response
  - Need higher doses, new HSV drugs or combination therapy?
  - Need interventions to shut down genital immune response to HSV?

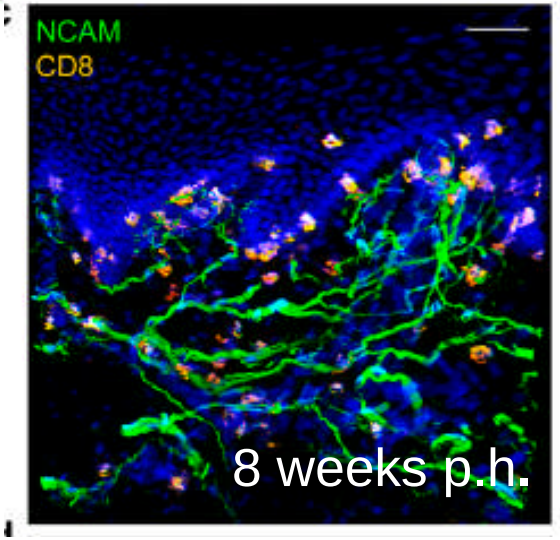
Mucosal immune response to HSV

- Lymphocytes & dendritic cells infiltrate genital mucosa during HSV reactivation

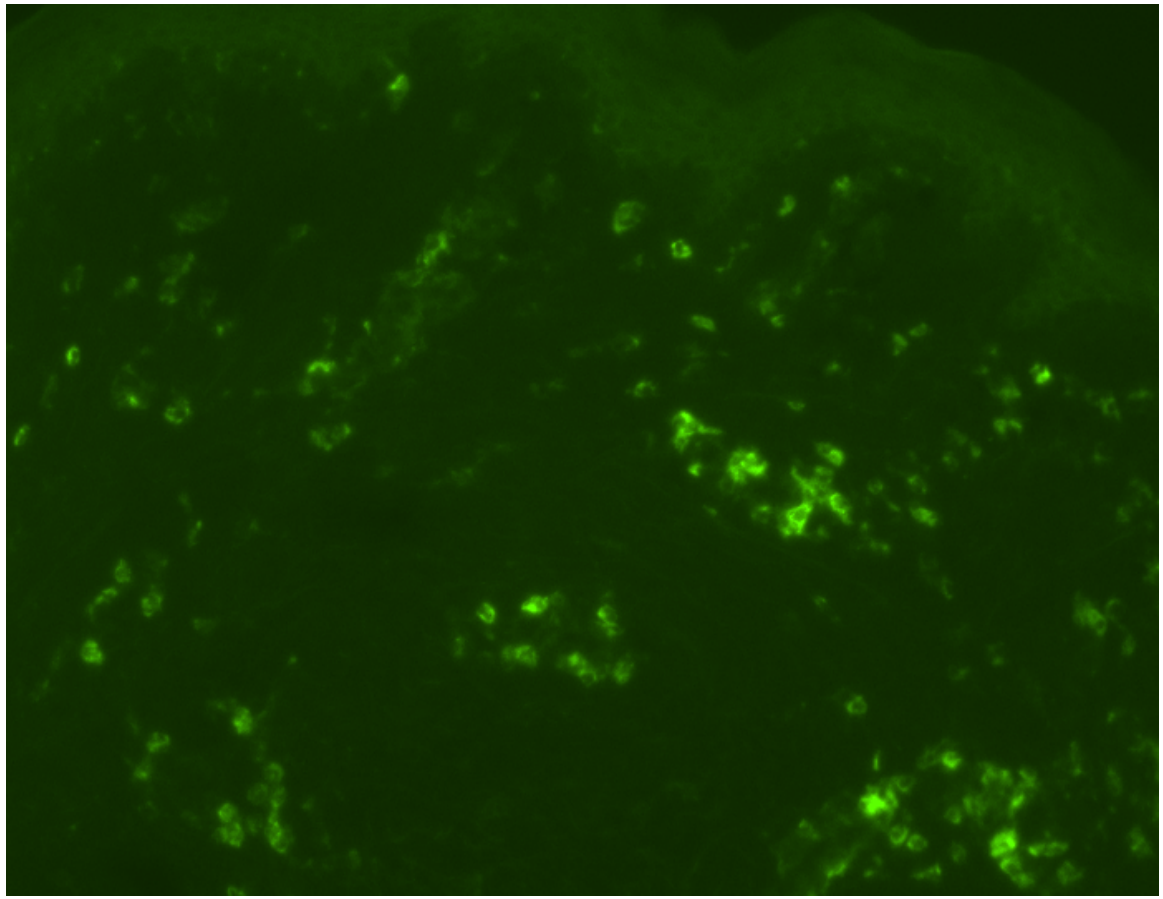


- CD8 cells at peripheral nerve endings in genital skin <u>persist</u> after HSV reactivation (right)

Jie Zhu, JEM, 2007



CD4 cells in biopsy of genital skin from a person with GUD after 8 weeks of suppressive antiviral therapy



- Green fluorescence indicates CD4+ cells
- Are these HSV specific lymphocytes?
- Is mucosa among HSV-2 negative persons different?
- May need more potent viral and/or immunologic tools to reduce persistent genital immune response to HSV-2 reactivation

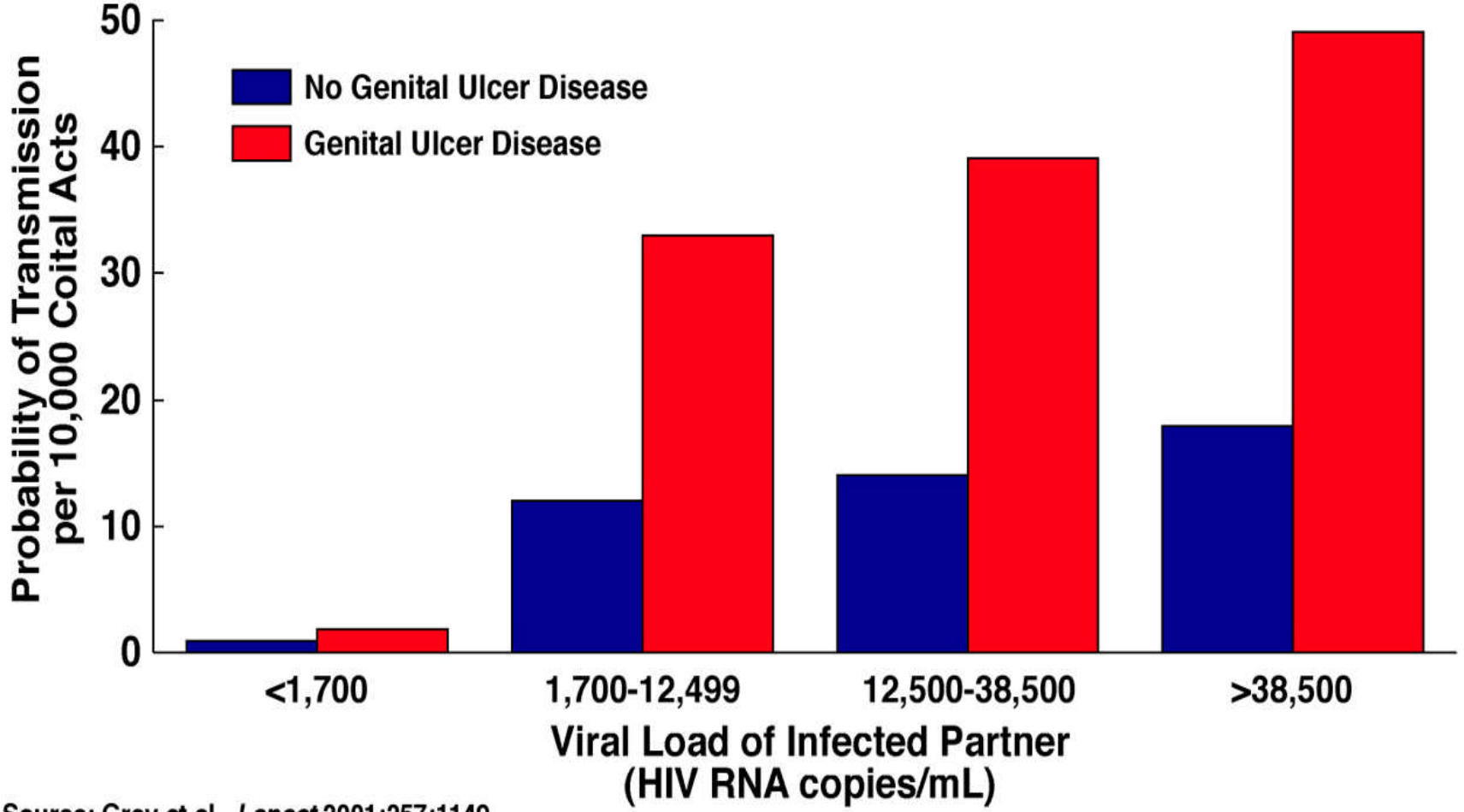
Research Priorities re HSV-2 and HIV

- HSV-2 interacts with HIV through different mechanisms
- Should complete studies that are testing different hypotheses
  - HIV transmission & disease progression (Partners in Prevention)
- Biology of HSV-2 in HIV-negative & HIV-positive persons
  - Genital immune activation & persistence
  - Significance of short bursts of HSV shedding
- HSV drugs
  - New targets (helicase inhibitors), longer duration of activity
- HSV vaccines

Biologic plausibility for HSV-2 & HIV transmission

- Metaanalysis: ACV plus mono or dual NRTIs reduced mortality (Ionniadis JID 1998)
- HSV-2 reactivation among HIV positive persons is high (PCR+ >30% of days)
- Extensive, long-lasting lesions if CD4 <200
- High amounts of HIV in lesional fluid
- ↑ plasma & genital HIV during asymptomatic HSV reactivation
- Mechanisms: Early HSV proteins upregulate HIV replication, pro-inflammatory cytokines

Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda



Source: Gray et al., *Lancet* 2001;257:1149

Proof-of-concept Trial: HSV Treatment To Reduce HIV Infectiousness

- Concept: Use antiviral therapy as a probe to measure effect of HSV-2 on:
  - Genital HIV shedding and transmission: HIV infectiousness
  - Plasma HIV levels: HIV disease progression

- Episodic vs suppressive therapy
  - Episodic is cheaper & easier than suppressive therapy
  - HSV-2 shedding often asymptomatic

- Partners in Prevention trial is a direct assessment of impact of HSV-2 suppression on HIV transmission

Trials of Episodic Therapy for GUD on HIV Infectiousness

Setting	Ghana & Cen African Rep.	Malawi	South Africa
PI	**Belec, Gresenguent**	**Phiri**	**Paz Bailey, Lewis**
Patients	**441 Women**	**500 Women and Men**	**600 Men**
Intervention	**Acyclovir 400 mg TID x 5d**	**Acyclovir 800 mg BD x 5d**	**Acyclovir 400 mg TID x 5d**
Primary Outcome	**HIV shedding (ulcer healing)**	**Ulcer healing (HIV shedding)**	**Ulcer healing (HIV shedding)**
Follow-up	**1 month**	**1 month**	**1 month**
Results	**Shortened lesion if higher CD4, no effect on HIV**	**Shortened lesion by 1 day**	**Shortened lesion by 2.5 days, 0.4 log ⇓ HIV shedding**

Pilot Studies of HSV Suppression on Plasma & Genital HIV

- **Burkina Faso: 140 HIV/HSV-2 co-infected women, CD4>250** (Nagot NEJM 2007)
  - **Valacyclovir 500mg bid or placebo for 12 wks**
  - **⇓ 0.5 log in plasma & trend towards ⇑ effect with higher CD4 and over time**

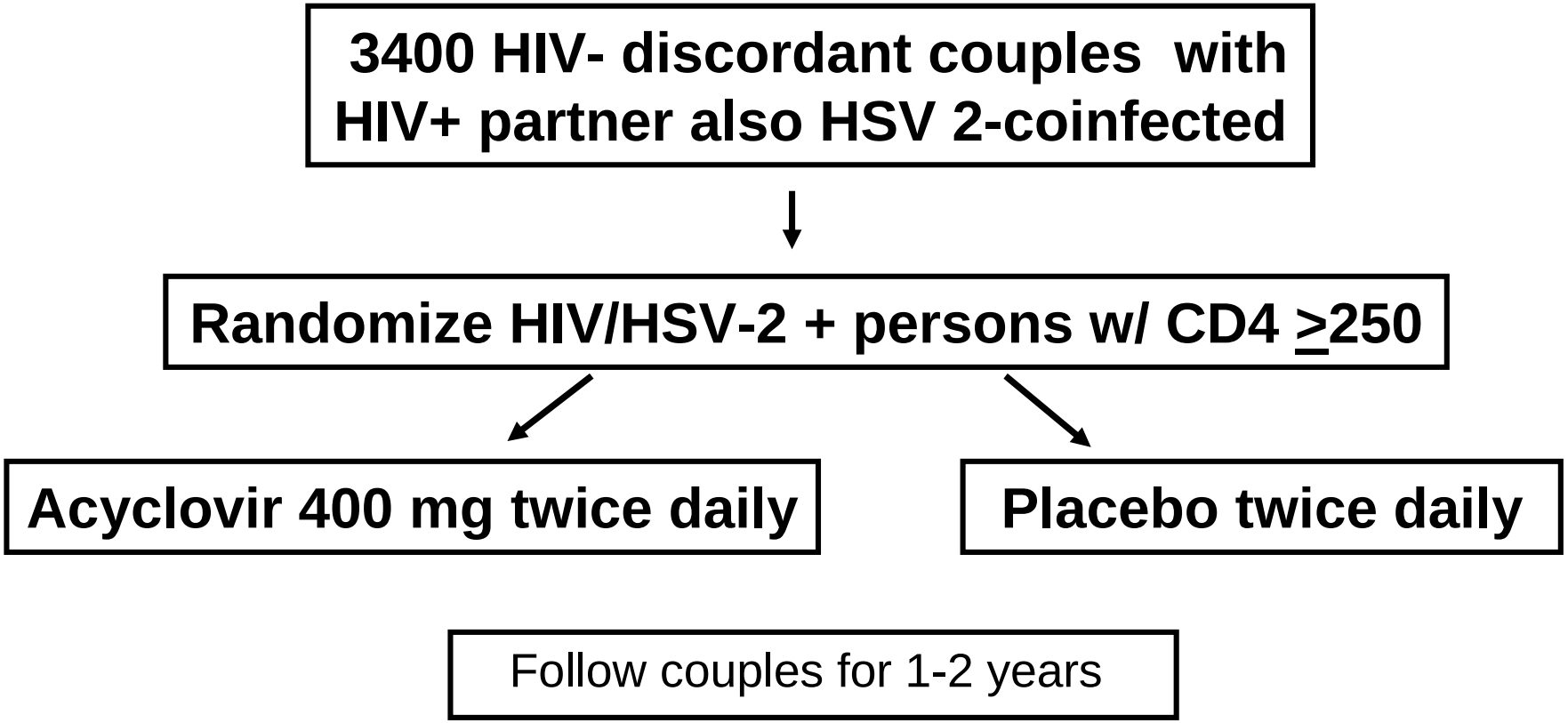
- **South Africa: 300 HIV/HSV-2 co-infected women, CD4 >250, not on HAART**
  - **Acyclovir 400 mg bid or placebo for 12 wks**
  - **⇓ 0.4 log in plasma**

- **Peru: 20 HIV HIV/HSV-2 co-infected men, CD4 >250, not on HAART** (Zuckerman JID 2007)
  - **Cross-over trial: Valacyclovir 500mg bid and placebo for 8 wks**
  - **⇓ 0.3 log in plasma, rectal secretions, semen⇑ effect with higher CD4**

- **Peru: 20 HIV/HSV-2 co-infected women, CD4 > 250, not on HAART** (CROI 2008)
  - **Cross-over trial: Valacyclovir 500mg bid and placebo for 8 wks**
  - **⇓ 0.3 log in plasma, cervical secretions**

- **Thailand: 67 HIV/HSV-2 coinfected women, CD4>250, not on HAART** (CROI 2007)
  - **Cross-over trial: Acyclovir 800 mg bid**
  - **⇓ 0.5 log in plasma**

Partners in Prevention:
HSV-2 Suppression to Prevent HIV Transmission



1° endpoint: HIV infection in HIV-negative partner

(estimated 4% in placebo arm)

Partners in Prevention Objectives

- Primary objective:

  Assess HIV transmission to HIV-neg partners

  - Hypothesis: HSV-2 suppression will decrease HIV transmission by 50%

    (in context of prevention services & bacterial STI treatment)

- Secondary Objectives:

  Effect of HSV-2 suppression on …

  - HIV disease progression (time to HAART, CD4 <200, death)
  - HIV levels in blood and genital tract and CD4 count
  - Incidence of asymptomatic & symptomatic genital herpes
  - Changes in sexual behavior
  - Incidence of herpes zoster (shingles)
  - Per-contact transmission rates for covariates (gender, HIV levels, CD4, circumcision, STIs)

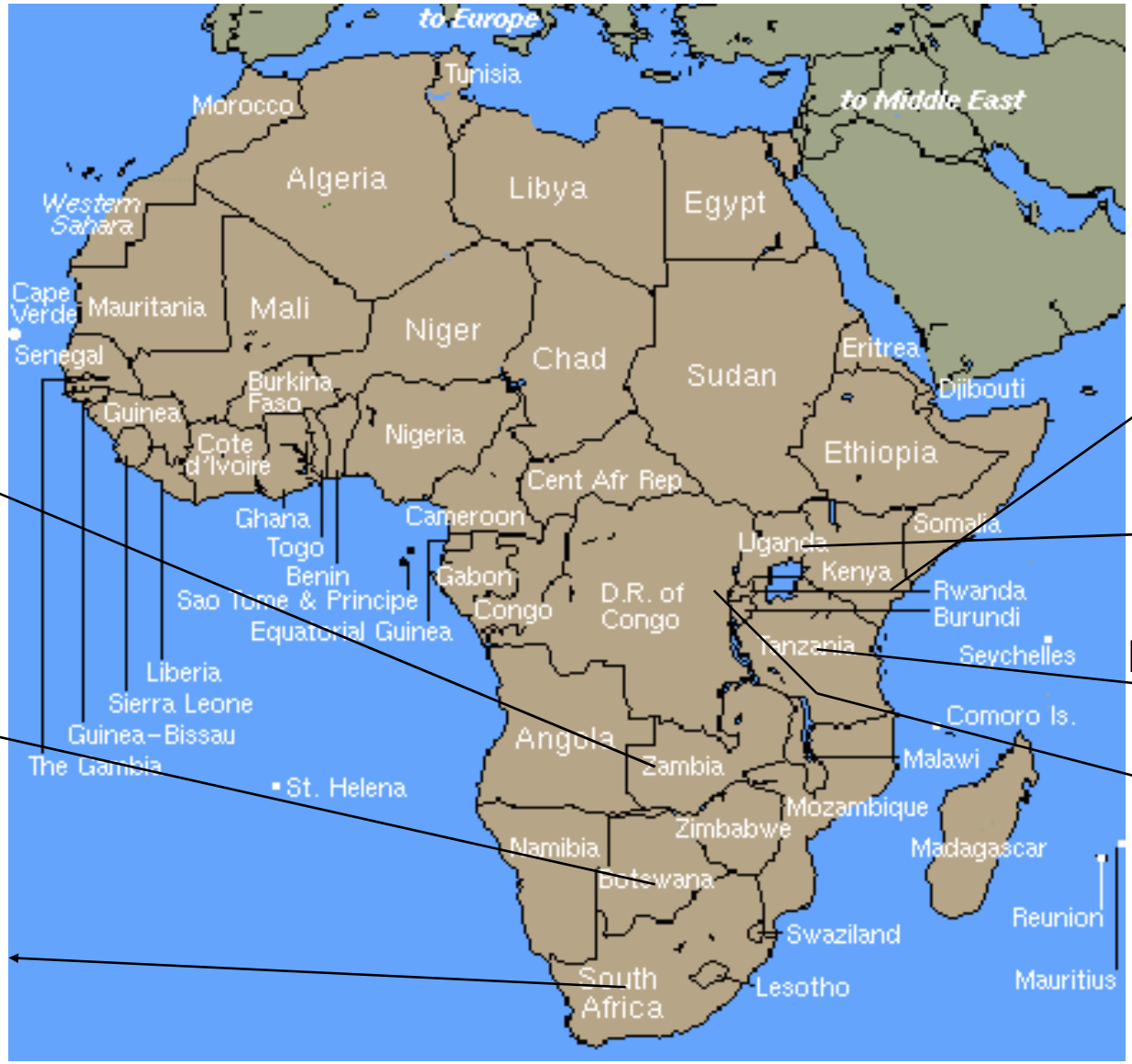
HIV discordant couples: Significance & Challenges

- Most direct way to evaluate interventions on infectiousness
- HIV transmission in Africa often occurs within HIV discordant couples in stable partnerships
- For each couple in which one partner is HIV-positive, ~50:50 chance their partner is HIV-discordant
- However, most couples are not aware of their HIV discordancy
  - HIV disclosure by HIV+ is low (~ 20%) due to stigma
  - Men are reluctant to be tested for HIV
  - Small proportion (~10%) test for HIV as couples
- Requires large community outreach & VCT effort

Prevention trials with couples to reduce infectiousness are the most challenging!

- Deliver intervention to the infected & follow the susceptible for transmission
  - Requires twice the participants & visits
- Limited experience with recruiting HIV discordant couples
- Sites found effective recruitment strategies
  - Have exceeded total HIV discordant couples published in the literature (2000) over 20 yrs
  - Develop couples' VCT program
  - Public health benefits
- Ancillary studies
  - Nested case-control studies of genetic, virologic & immunologic determinants of HIV transmission

14 Sites for HSV-HIV Transmission Trial



Nairobi, Thika
Eldoret, Kisumu
Kenya (4)

Lusaka, Kitwe,
Ndola, **Zambia (3)**

Kampala, **Uganda**

Moshi, **Tanzania**

Gaborone,
Botswana

Kigali, **Rwanda**

Soweto, Orange
Farm, Cape Town
S. Africa (3)

Partners in Prevention

Partners in Prevention Achievements

- ~50,000 couples of unknown HIV status counseled and tested for HIV in 14 African sites in 2 yrs
  - Represents a public health intervention
- Screened ~6600 HIV discordant couples
- Enrolled 3408 couples— Largest cohort of HIV-discordant couples
  - Will provide invaluable data on risk factors for HIV transmission
- Retained 91% (HIV-) & 93% (HIV+) partners at 1 year
- Dispensed 96% of study drug: ~80% took >90% of pills
- On track with endpoints; study finishes early 2009

Summary

- HSV-2 is important to diagnose: highly prevalent, often minimally symptomatic, and increase HIV susceptibility & infectiousness (HSV-2)
- Use HSV-2 serologic testing (eg Focus EIA) for screening & diagnose
- Likely need better interventions for reducing HSV-2 effect on increased HIV susceptibility
- Substantial biologic plausibility and pilot data indicate HSV-2 suppression may have clinical and public health benefits for HIV+ persons
- Stay tuned for Partners in Prevention results: HSV-2 suppression on HIV transmission & disease progression in 2009

Time has come for HSV Control Programs

- Public awareness of HSV-2
- Provider training & motivation
- HSV-2 serologic testing
  - Opt out? Co-pay?
  - Targeted populations (eg MSM, minority women, pregnant women)
- Pilot different strategies for counseling HSV-2+ persons
- HSV suppression in HSV-2 serodiscordant couples
- Priorities: HSV vaccines, ? HSV suppression in HIV+ persons

IHMF Recommendations re HSV-2 screening & treatment in HIV-infected persons

- HSV-type specific testing should be offered to all HIV+ patients
  - Clinical benefits; possibly public health benefits
- Suppressive antiviral therapy is safe and effective in people co-infected with HSV-2 & HIV
- Suppressive therapy should be offered
  - Greatest benefit in HIV-positive patients with frequent clinical HSV-2 reactivation and those with advanced immune suppression

Summary: HSV type-specific serologies

- Focus HerpeSelect-2 ELISA or Kalon
  - Most cost-effective test for screening
  - Sufficiently sensitive (96%) for clinical diagnosis
- Specificity of Focus HerpeSelect-2 ELISA may be an issue for screening, particularly in Africans
  - Often due to cross-reacting HSV-1 antibodies
  - Use of increased index value (3.5) improves specificity to ~95%
- Biokit may be good alternative to Western blot for confirmation & can be done

CDC STD Treatment Guidelines
Genital Herpes in HIV+

First episode (same as HIV-)

- Acyclovir 400 mg TID or 200 mg 5x/d x 7-10 d
- Famciclovir 250 mg TID x 7-10 d
- Valacyclovir 1.0 g BID x 7-10 d

Episodic Treatment of Recurrences

- Acyclovir 400 mg TID or 800 mg bid x 5-10 d
- Acyclovir 200 mg 5x/d x 5-10 d
- Famciclovir 500 mg bid x 5-10 d
- Valacyclovir 1 gm bid x 5-10 d

Suppressive Treatment

- Acyclovir 400-800 mg bid/tid
- Famciclovir 500 mg bid
- Valacyclovir 500 mg bid

“ I have discovered the secret that after climbing a great hill, one only finds that there are many more hills to climb.”

Nelson Mandela

Shoes worn by clinical trial investigators;

it’s a long road

Acknowledgments: HPTN 039

- Anna Wald, co-chair
- Larry Corey, co-investigator
- Jim Hughes, Statistician
- Site PIs:
  - Jorge Sanchez, Abner Ortiz, Martin Casapia (Peru)
  - Stewart Reid, Sinead Delaney-Moretlwe, Frances Cowan (Africa)
  - Susan Buchbinder, Jonathan Fuchs, Beryl Koblin (US)
- Site Staff
- HPTN: Ward Cates, Scott Rose, Sam Griffith, Kathy Hinson, FHI
- Data management: Jing Wang, Marla Husnik, Carol Antone, Karen Patterson, Alicia Young, Tom Perdue, SCHARP
- Central Laboratory: Estelle Piowar-Manning (Johns Hopkins); Anne Cent, Rhoda Morrow, Meei-li Huang, & Bob Coombs (UW)
- DSMB
- IRBs
- Community Advisory Boards
- Sponsor: Division of AIDS, NIAID, NIH
- Study Participants

Acknowledgments: Partners in Prevention

"It takes a team to design & implement clinical trials"

Coordinating Center:

- Co-Investigators: Anna Wald, Larry Corey, Julie McElrath, Jared Baeten
- Program Management: Linda Barnes
- Regional Directors: Nelly Mugo, & Andrew Mujugira, Patrick Ndase
- Clinical Monitors: Marothodi Semenya, Hilda O'Hara, Apollo Odika
- Coordinating Center Operations: Meighan Krows, Heena Shaw, Khris Kline, Dana Panteleeff, Margaret Warner Lubin, Ellen Wilcox
- Biostatisticians/Data Management: Jim Hughes; Amalia Meier, Richard Wang, Erin Kahle, Lara Kidoguchi, Kim Nelson
- Fiscal/Admin Linda Barnes, Darcie Somera, Carlos Flores, Becky Karschney, Matt Leidholm, Toni Maddox, Alice Rose, Troy Sexton, Calvin Tran, Christy Wilson
- Central Repository: Justin Brantley, Shauna Durbin, Vikram Nayani

Coordinating Center Contractors:

- Site Laboratory Oversight: Wendy Stevens, Clinical Lab Services, Univ of Witswaterstrand
- HIV-1 Retrovirology Labs: Bob Coombs, Joan Dragavon; Jane Kuypers, Reggie Sampoleo
- HSV-2 Virology Lab: Rhoda Ashley, Anne Cent
- HIV Virology (Endpoint Analysis) Lab: Jim Mullins, Mary Campbell
- Data Management Contractor: Darryl Pahl & Lisa Ondrajeck

DSMB

Funding: Bill & Melinda Gates Foundation

Partners in Prevention Site Investigators

- Nairobi: J Kiarie, C. Farquhar, G. John-Stewart
- Kisumu: E. Bukusi, C. Cohen
- Eldoret: E. Were, K. Fife
- Thika: N. Mugo
- Tanzania: R. Manongi, S. Kapiga
- Kampala: A. Ronald, E. Katabira
- Kigali: E Karita, S. Allen
- Soweto/PHRU: G. Gray, G. DeBryn, J. McIntyre
- Orange Farm/RHRU: S. Delaney & H. Rees
- Cape Town: D. Coetzee
- Gaborone: J. Makhema , M. Essex
- Lusaka, Ndola & Kitwe: B. Vwalika, M. Inambao, W. Kanweka, S. Allen

- And above all: thanks to HIV discordant couples in Africa who screened and participated in the trial

Syphilis Management Issues in HIV-infected Individuals:

What's new in 2008?

Gail Bolan MD
Chief, STD Control Branch
CA Department of Public Health
October 24, 2008

Overview of Syphilis Management Issues 2008

- New screening algorithm
  - Reversal of the screening and confirmatory test order
- Neurosyphilis management dilemmas
  - Follow-up of treated cases
- Early syphilis management dilemmas
  - When to LP
  - How much penicillin
- Missed Opportunities

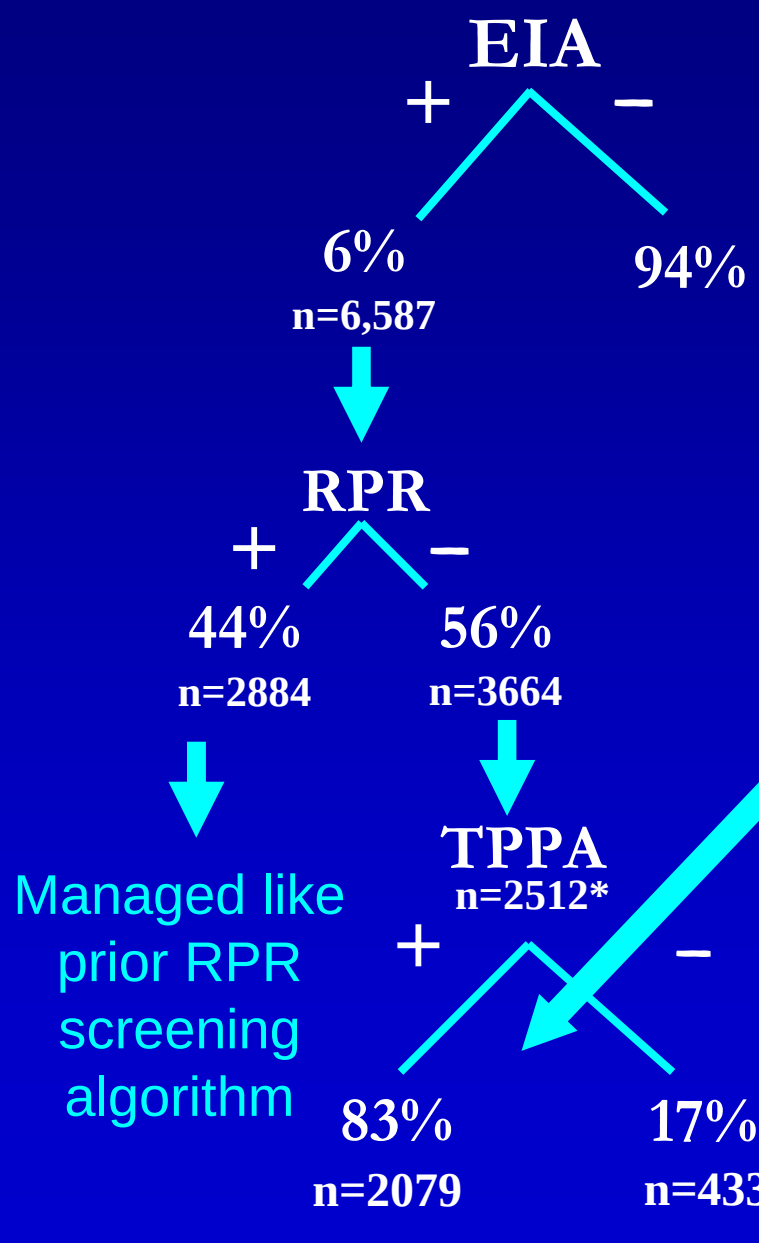
Screening for Syphilis

- Non-treponemal tests confirmed by treponemal test
  - RPR and VDRL
  - TP-PA and FTA-abs
- Enzyme immunoassay tests (EIA/CLIA)
  - Treponemal tests
  - Automated lab procedure
  - Specificity questions
- Targeted screening recommendations
  - MSM, corrections, STD clinics, clients with other STDs
  - Prenatal screening at first visit, third trimester, at delivery

Treponemal EIA/CLIA Tests

- Treponemal tests FDA cleared for clinical use
  - Captia, Trep-Chek, Trep-Sure, Liaison
- Can be used for screening but if positive then need quantitative reflexive RPR/VDRL for clinical management
- Both IgM and IgG tests available
  - No clinical value of IgM in adult early latent syphilis diagnosis
- Advantages
  - No prozone, low cost, automated, and less lab occupational hazard (pipeting)
- Disadvantages
  - Limited utility as a screening test in previously treated patients and the neonate

EIA Screening in New York



- 3 laboratories
- 116,822 specimens
- 3.1% EIA+ / RPR–

What are these?

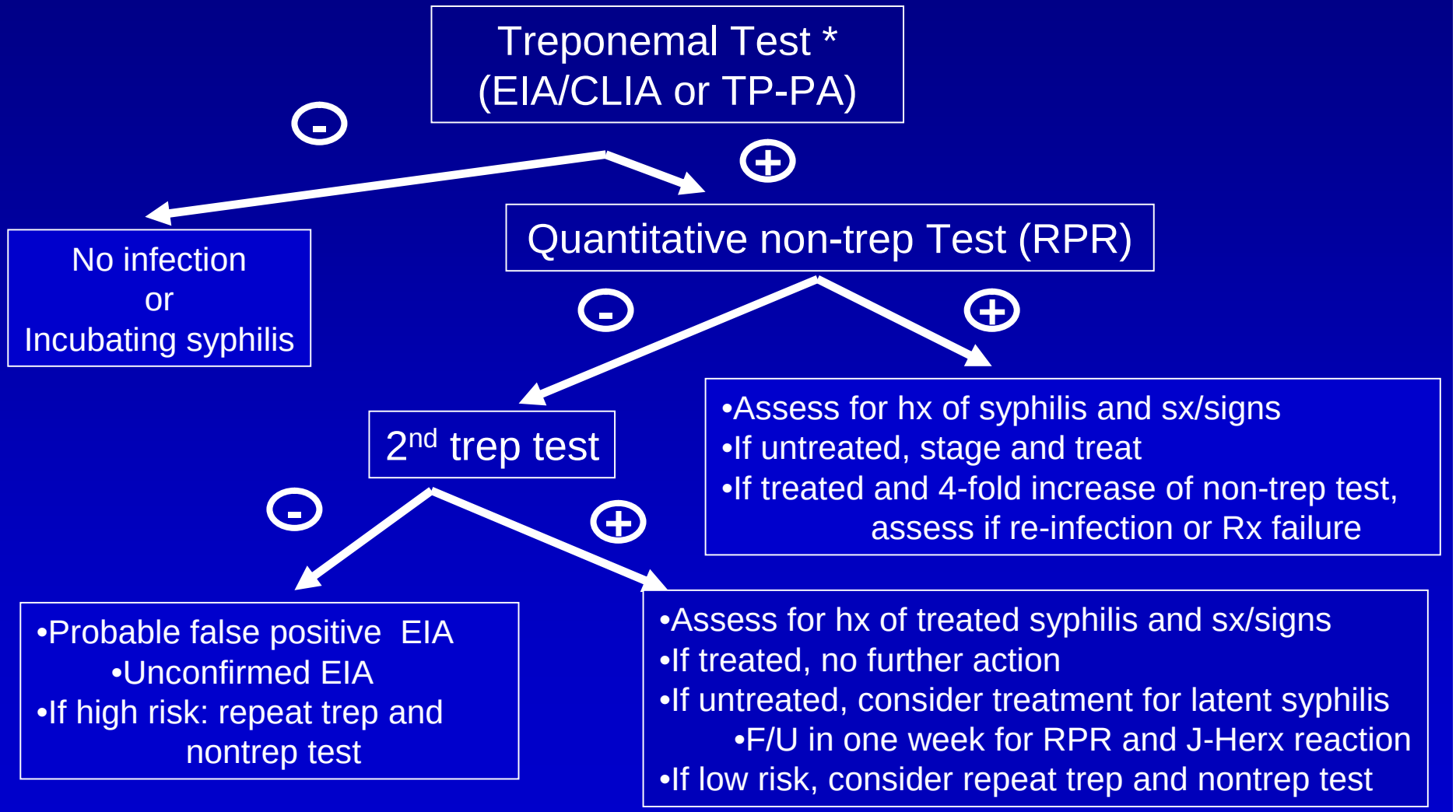
1) Old, untreated syphilis
2) Old, treated syphilis
3) Early syphilis
4) False positives

False Positive EIA or False Negative TPPA

* not all labs reflexed to a second treponemal test

Adapted from Selvam, CDC 2008

California EIA/CLIA Testing Algorithm-Draft



* Not useful if history of treated syphilis or neonatal

Normalization of Serum RPR Predicts Normalization of CSF Abnormalities

Table 2. Normalization of CSF measures in patients whose serum rapid plasma reagin (RPR) titer had normalized by the time of each visit.

	Time after neurosyphilis treatment, months					
	4		7		13	
Variable	PPV	NPV	PPV	NPV	PPV	NPV
CSF WBC count	39/43 (91)	23/28 (82)	56/61 (92)	5/8 (62)	60/62 (97)	1/3 (33)
CSF protein concentration	18/39 (46)	21/25 (84)	27/52 (52)	4/7 (57)	30/40 (75)	2/3 (67)
CSF VDRL titer	30/32 (94)	21/26 (81)	46/51 (90)	3/5 (60)	50/53 (94)	1/1 (100)
Meningitis[a]	20/25 (80)	10/12 (83)	29/33 (88)	2/3 (67)	30/33 (91)	0/1 (0)
Eye disease[b]	12/14 (86)	6/9 (67)	17/20 (85)	2/3 (67)	20/21 (95)	NA

Marra, CID 2008

When is an LP indicated?

The CDC 2006 criteria for CSF examination are the following:

- Neurologic or ophthalmic symptoms/signs
- Evidence of tertiary disease
- HIV infection with late latent or latent of unknown duration
- Treatment failure
- **Some experts recommend a CSF exam in:**
  - **Patients with latent syphilis and an RPR titer ≥ 1:32**
  - **HIV-infected patients with CD4 count ≤ 350**

Proposed Criteria for Performing LP in HIV-Infected Patients with Newly Diagnosed Syphilis

Stage of Syphilis	CD4-Cells	Recommendation
Primary or early latent with RPR ≤ 1:32	≥350 <350	No LP Consider LP
Any stage with RPR >1:32	Any	Consider LP
Late-latent or syphilis of unknown duration	Any	LP indicated
Positive RPR/confirmatory test with neurologic or ophthalmic symptoms and/or signs	Any	LP indicated

Source: AIDS Clinical Care, 2003 Vol. 15, No 2

Evidence for CSF Examination if RPR ≥ 1:32 or CD4 count ≤ 350

- One study of 326 patients with syphilis referred for LP because they met the 1993 CDC criteria- *Marra et al, JID 2004; 189:369-76*
  - 125/326 had symptoms of syphilitic meningitis or ocular syphilis
  - 65/125 with Sx NS met the laboratory case definition of NS
    - Positive CSF VDRL or
    - CSF WBCs > 20 cells/*u*L
- Lab diagnosis of NS was not more common in patients with Sx NS

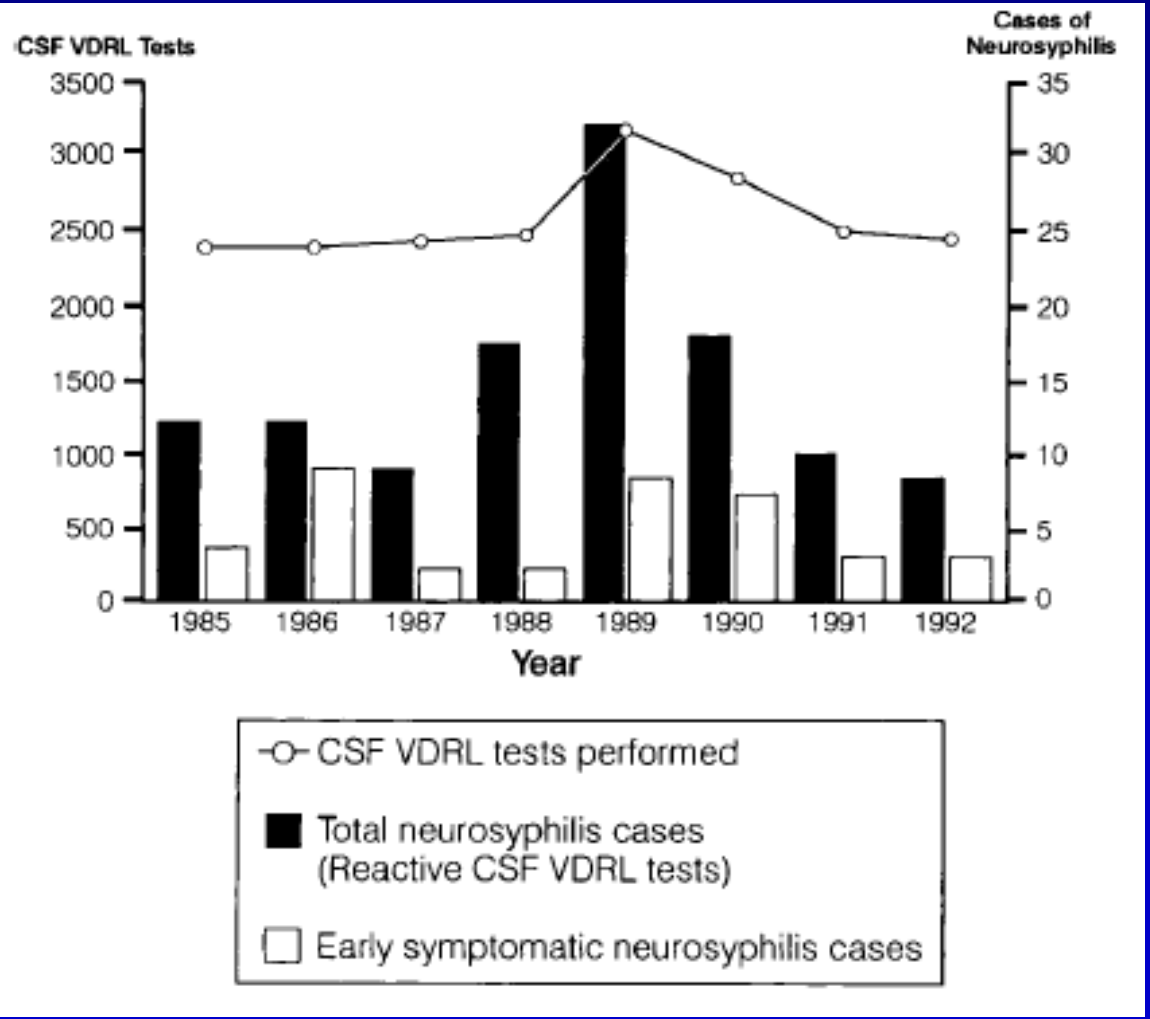
Questions Regarding the Recommendation for LP if RPR ≥ 1:32 or CD4 count ≤ 350 ?

- Who are the patients affected by this recommendation?
  - HIV negative aSx patients with latent syphilis and RPR ≥ 1:32
  - HIV positive aSx patients with early latent and RPR ≥ 1:32 and/or with early syphilis and CD4 ≤ 350
- How large is this group and how common is aSx NS?
- What is the clinical benefit of treating aSx NS in this group?
- What is the cost and potential negative consequences of the recommendation?
- Why change the LP criteria based on one study after years of conventional treatment of many patients and very limited number reported adverse neurologic events after treatment?

Serologically Defined Treatment Failure in an Observational Cohort, 1991-1994

	3 Months	6 Months	12 Months
Total Patients (n=553)	23 % (364)	17% (329)	13% (281)
Syphilis Stage & HIV infection			
Primary			
HIV +	17% (18)	22% (8)	14% (14)
HIV -	6% (66)	5% (59)	8% (53)
Secondary			
HIV +	36% (42)[a]	23% (35)	19% (32)
HIV -	15% (141)	10% (121)	6% (96)
Early Latent			
HIV +	40% (15)	19% (16)	13% (15)
HIV -	49% (78)	35% (77)	29% (69)

Neurosyphilis during the AIDS Epidemic, San Francisco, 1985 - 1992



Case # 1

4/27/06	HIV-infected men with serum RPR 1:512, Rx BIC 2.4 mu x 3 despite ocular Sx
6/6/06	Dx uveitis, RPR 1:128, LP 6/21/06- CSF VDRL 1:16, WBCs 5
	Rx IV PCN 3 mu q 4hrs x 14 days out patient
10/4/06	RPR 1:256, Rx BIC 2.4 mu x 3, ocular Sx resolved
12/6/06	RPR 1:128
1/1/07	Doxycycline 100 BID x 3 months
1/30/07	RPR 1:256, LP- CSF VDRL 1:8, WBCs 12
5/16/07	RPR 1:128
7/7/07	Rx IV PCN x 14 days in patient
8/1/07	RPR 1:32
11/7/07	Seizure, RPR 1:64, W/U negative, LP 11/26/07- CSF VDRL 1:4, WBCs 4
12/31/07	RPR 1:32
1/29/08	Rx IV PCN 3mu 2 4 hrs x 3 months, LP (3/24/08)- CSF VDRL 1:2, WBCs 5
4/09/08	RPR 1:64, LP (4/28/08)- CSF 1:2, WBCs 9

What is the recommended treatment for early syphilis in HIV infected adults?

- Recommended Regimen
  - Benzathine PCN G (L-A) 2.4 million units IM single dose
    - Do not use other PCN formulations!
      - E.g. PCN G (C-R)


MMWR
Morbidity and Mortality Weekly Report
Weekly March 11, 2005 / Vol. 54 / No. 9
Inadvertent Use of Bicillin® C-R to Treat Syphilis Infection — Los Angeles, California, 1999–2004

- Alternative Regimens
  - Doxycycline 100 mg PO bid x 14 days (inferior)
  - Ceftriaxone 1 g IV or IM daily x 8-10 days (inferior)
    - Do not use azithromycin


Macrolide Resistance in *Treponema pallidum* in the United States and Ireland

Sheila A. Lukehart, Ph.D., Charmie Godornes, B.S., Barbara J. Molini, M.S., Patricia Sonnett, B.S., Susan Hopkins, M.D., Fiona Mulcahy, M.D., Joseph Engelman, M.D., Samuel J. Mitchell, M.D., Ph.D., Anne M. Rompalo, M.D., Christina M. Marra, M.D., and Jeffrey D. Klausner, M.D., M.P.H.

Bicillin® L-A for Syphilis
Error in Los Angeles County

- In March 2004, the Los Angeles Gay & Lesbian Center notified county health officials that it has given the wrong medication to about 300 syphilis patients seeking treatment since 1999
- Clients were administered the penicillin formula Bicillin® C-R instead of the long acting penicillin formula Bicillin® L-A (benzathine penicillin G)
- The formula given to center clients contains only half the dose of benzathine penicillin G that CDC recommends for treatment of syphilis

Follow-up and Serologic Response after Treatment for Early Syphilis

- Follow-up titers should be compared to the nontreponemal titer obtained on day of treatment
- Primary, secondary and early latent syphilis
  - Examine at ~1-2 weeks to confirm improvement of symptoms (1^o and 2^o)
  - Repeat titers at:
    - 3, 6, 9, 12, and 24 months for HIV-infected
    - 6, 12 and 24 months for HIV negative
  - Expect fourfold decrease in serology within 6-12 months
  - Serologic response is slower in HIV-infected patients

Management of Suspected Syphilis Treatment Failures

- Treatment failure is defined as:
  - Slow resolution or relapse of mucocutaneous signs
  - Sustained (greater than 2 weeks) fourfold increase in nontreponemal titers
    - Reinfection may be difficult to rule out
  - Failure of nontreponemal titers to decrease fourfold
- Management of treatment failure includes:
  - LP to rule out neurologic site of infection
  - Benzathine Penicillin G 7.2 million units (2.4 mu weekly x 3)
  - Follow serofast titers annually but additional therapy/repeat LP not warranted
  - Fluctuating high titers have been observed in HIV-infected patients

Case # 2

A 30 year-old HIV-infected men presented to an urgent care center with a painful, erythematous rash on his groin. He was treated with ketoconazole. Six days later, he returned to the clinic with a rash over 50% of his body and an RPR test was ordered. One week later, he returned again because the rash was not getting better and another serologic test was ordered. Three weeks after he was originally seen the local health department received a lab report of RPR 1:8 and reactive TP-PA.

Case # 3

A 40 year old HIV-infected male sees his doctor because of rash on his buttocks. Three weeks later, he returns to the provider, this time with rash over his full body and scalp, in addition to the unresolved rash on buttocks. His provider believes the rash to be herpes zoster and treats with Valacyclovir. One week later, he returns to the provider because rash is not healing. Having done independent web-based research, patient requests a syphilis test. An RPR was order and the titer was 1:128, no treponemal confirmatory test was done. Provider reports positive result to health department within two days but the lab never reported the positive result.

Case # 4

A 34 year-old theology student presented to the student health center with reddish, crusted lesions on his penis. He was treated with fungal cream. One week later, he returned because the lesions were not getting better and he was prescribed dicloxacillin. Three months later he returned with a rash on his trunk. An RPR test was ordered and he was treated with one shot of Benzathine PCN G.

Question: How many missed opportunities in clinical management occurred in these cases?

1. Two
2. Three
3. Four
4. Five
5. Six

Syphilis Management Issues in HIV Infected Patients

Answer: Five

1. Sexual history taking absent
2. Misdiagnosis of primary and secondary lesions
3. Lack of empiric treatment on initial visit
4. Delayed or absent provider reporting
5. Delayed or absent lab reporting

Missed Opportunities in California, 2003 and 2005
Symptoms: Missed or Misdiagnosed

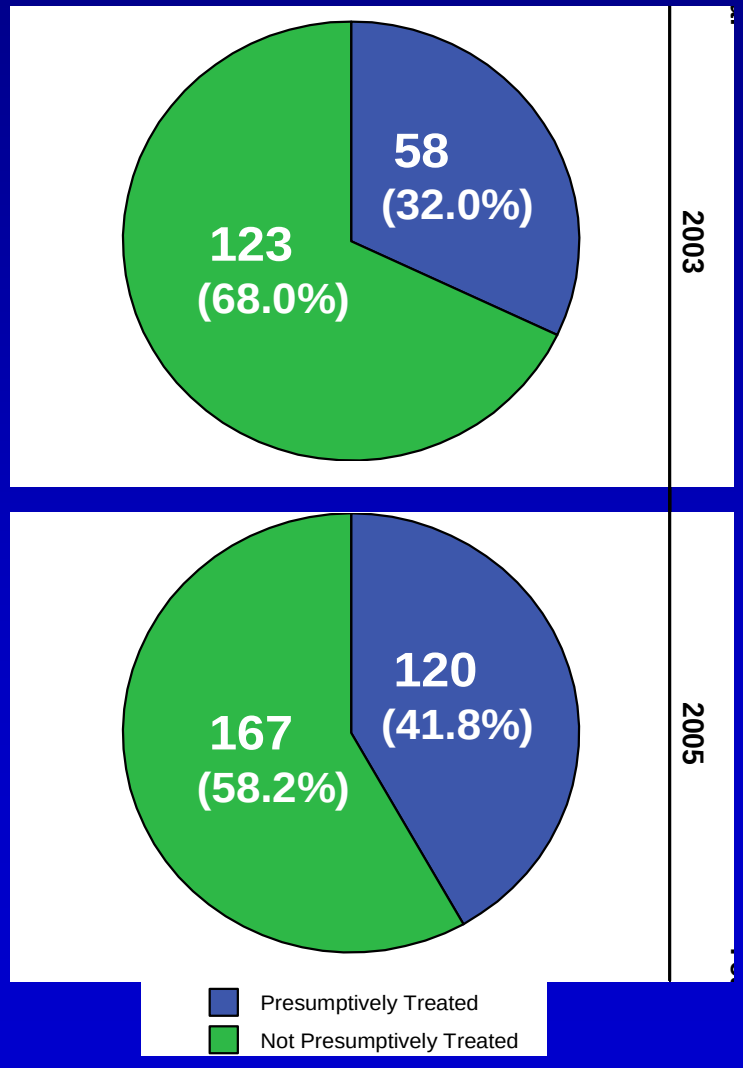
Primary and Secondary Syphilis Cases with Symptoms Present But Missed or Misattributed to a Non-syphilis Etiology

		2003	2005
Yes	N	**32**	**31**
	%	22.1%	14.0%
Total presenting with symptoms		145	221

Statistically significant difference across the two time periods (X^2 yields $p < 0.05$).

Missed Opportunities in California, 2003 and 2005
Lack of Empiric Treatment

No empiric treatment on initial visit for suspected cases of primary and secondary syphilis



"On the Internet, nobody knows you're a dog."

Innovation in Partner Notification

via Internet

Individuals use Web site to notify partners

- anonymous
- free
- referrals for testing provided

http://www.inspot.org

CDC 2006 STD Treatment Guidelines Development

- Evidence-based on 4 outcomes of STD therapy
  - microbiologic cure, clinical cure, prevention of sequelae and prevention of transmission
- Alternative regimens should not be used unless a medical contraindication to a recommended regimens
- Alphabetized unless there is a priority of choice
- Reviewed in April 2005 and published in September 2006 and next meeting April 2009
- www.cdc.gov/std/treatment

Questions?