# Syphilis

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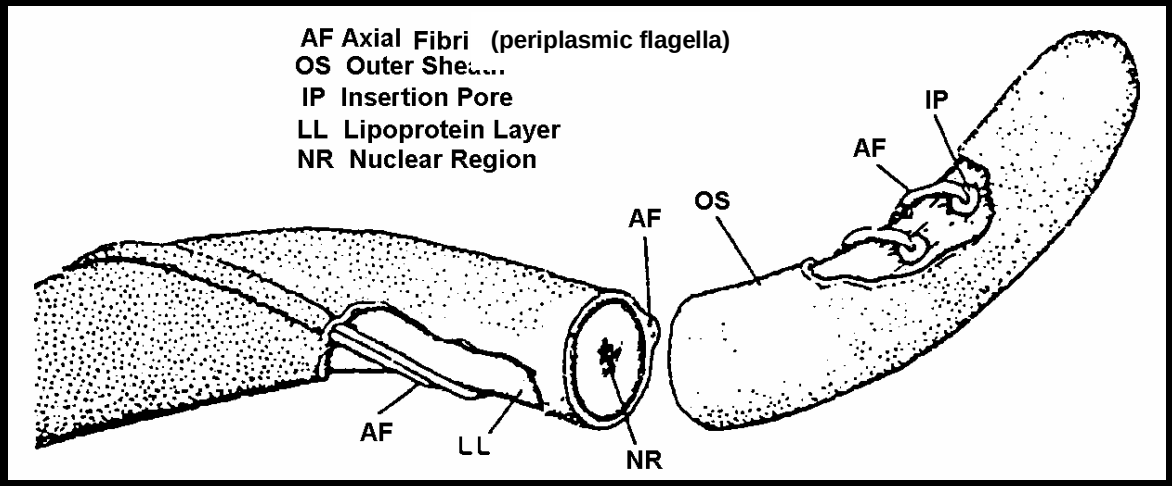
# Syphilis: Etiology and Pathogenesis

- *1st* step of invasion is attachment to epithelial, fibroblastlike and endothelial cells
- Corkscrew motility via periplasmic flagella (flagella not exposed on the surface) transverses junctions between endothelial cells
- Induces production of matrix metalloproteinase-1 (MMP-1) in dermal cells which breaks down collagen
- Enters lymphatics and bloodstream, disseminates following nutrient gradients (chemotaxis)



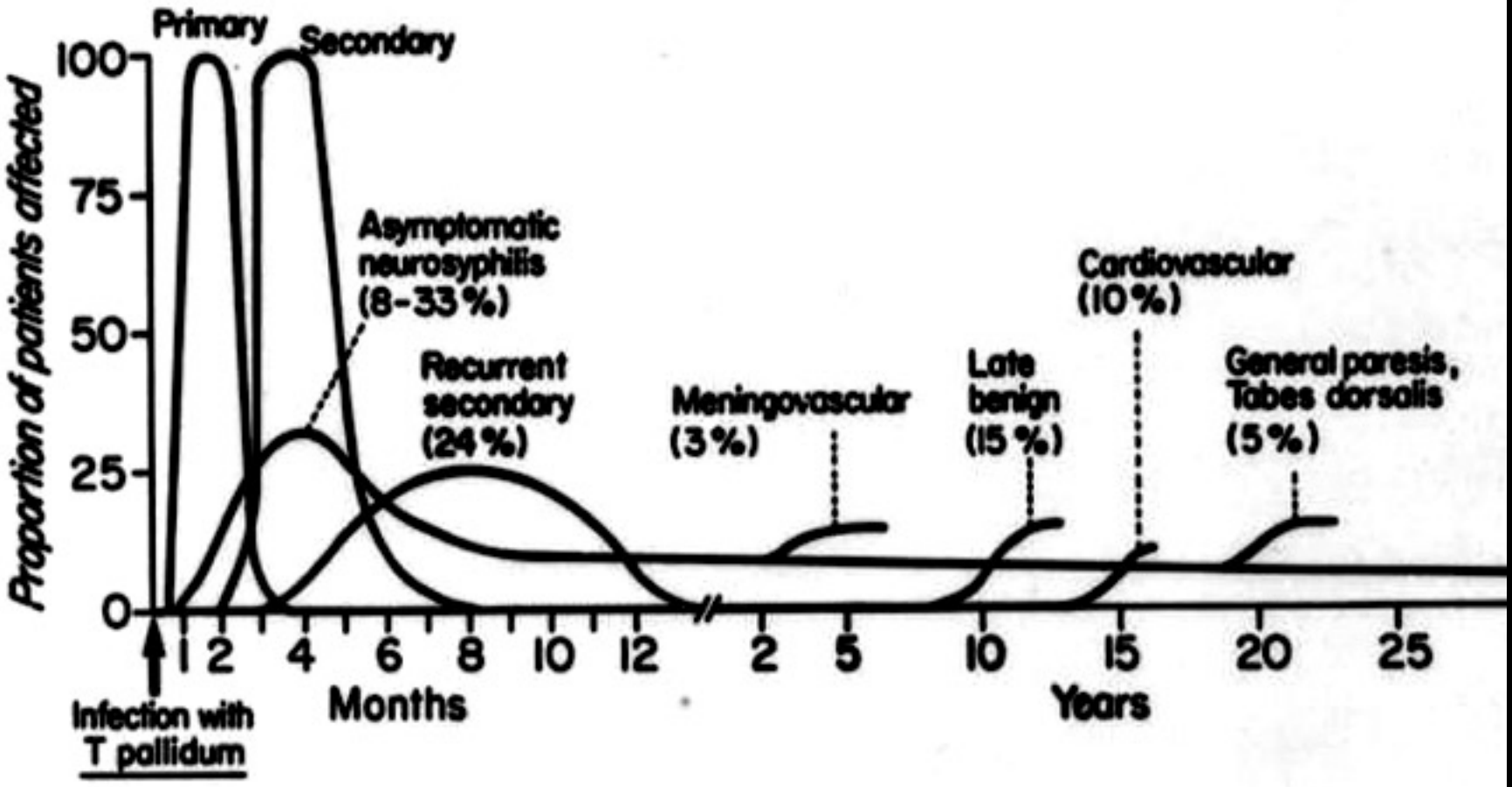

Pathogenic treponemes are motile and possess periplasmic flagella (axial fibrils) anchored at each end of cell that extend back towards the opposite pole of the cell. Motility is a potential virulence factor.

The double membrane cell envelope appears similar to that of a typical gram negative in EM. However, the outer membrane (or outer sheath) lacks LPS and may contain only treponemal rare outer membrane proteins (TROMPS).

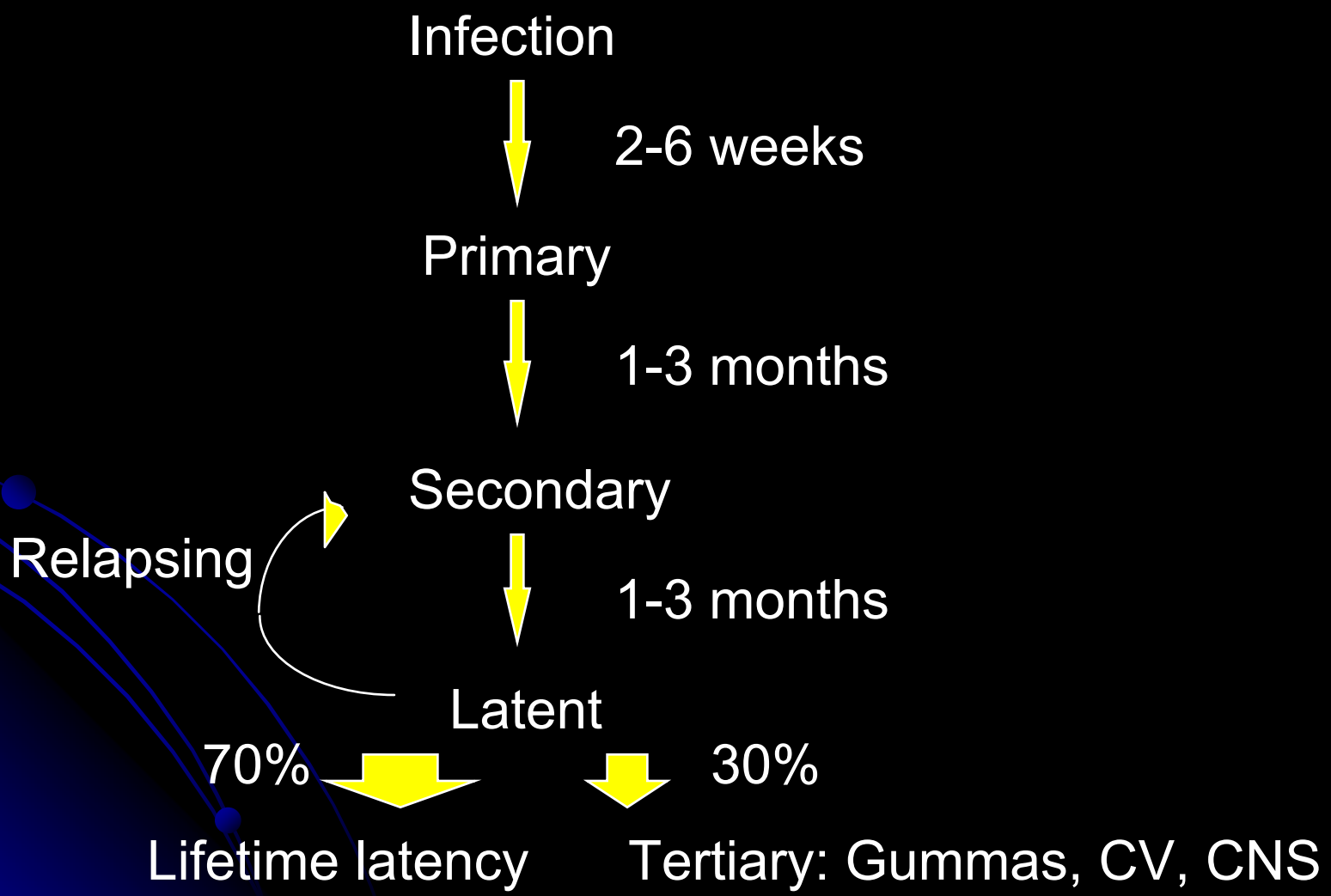
# Ab response

- *T.pallidum* antigens continually stimulate B cells
- Ab response specific for lipids on *T.pallidum* surface, lipoproteins and flagellar proteins
- Ab inhibitory to establishment of infection but not sufficient to kill *T.pallidum* and prevent infection

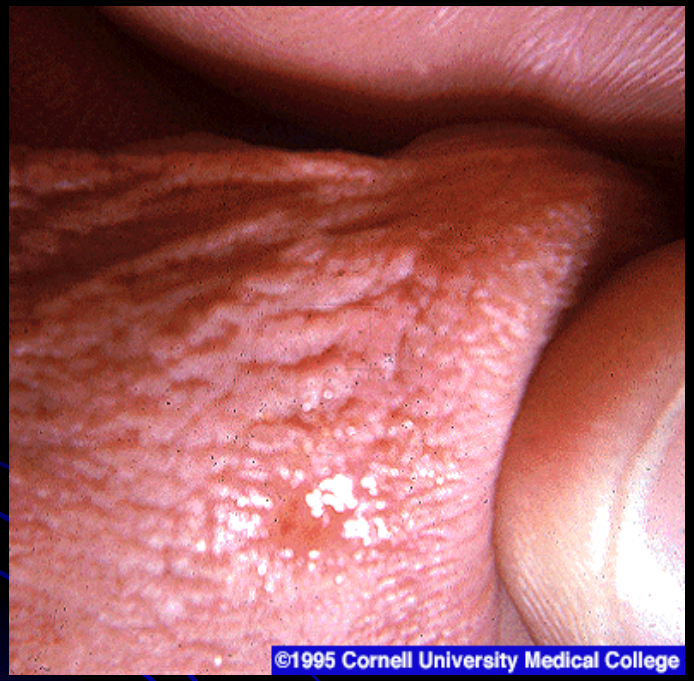
# CLINICAL COURSE OF UNTREATED SYPHILIS



# Syphilis: Clinical Disease
# Rule of 3s



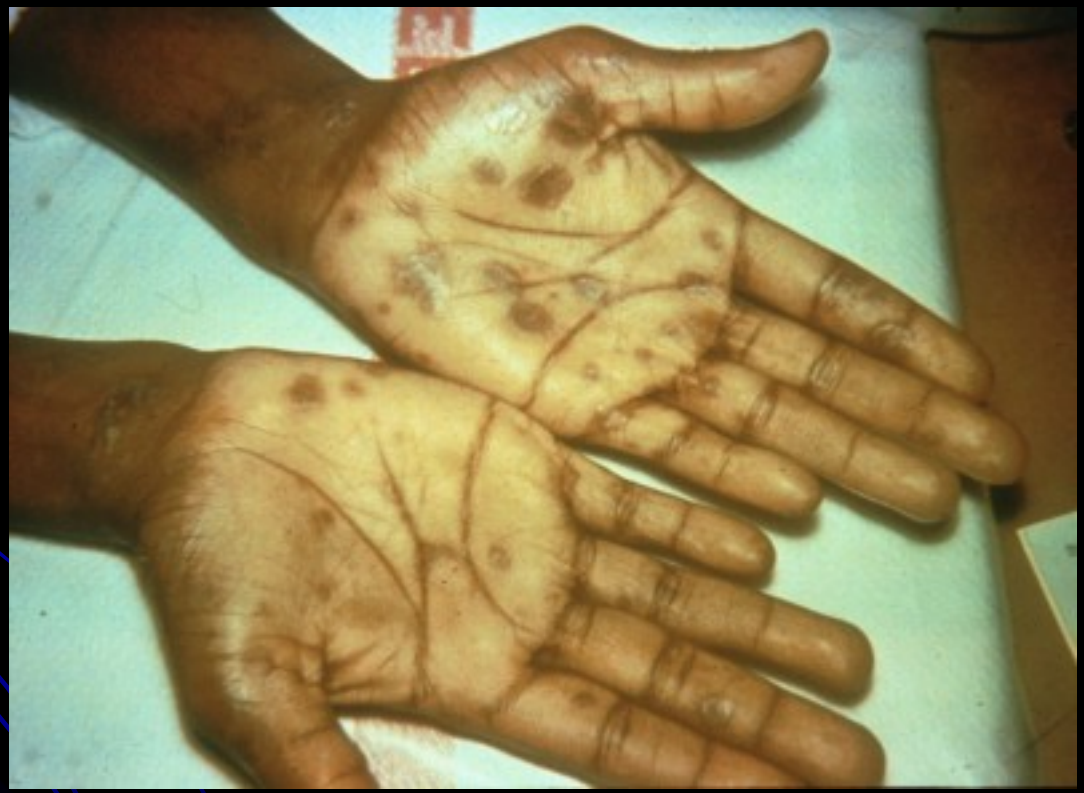
# Syphilis:  Primary Stage



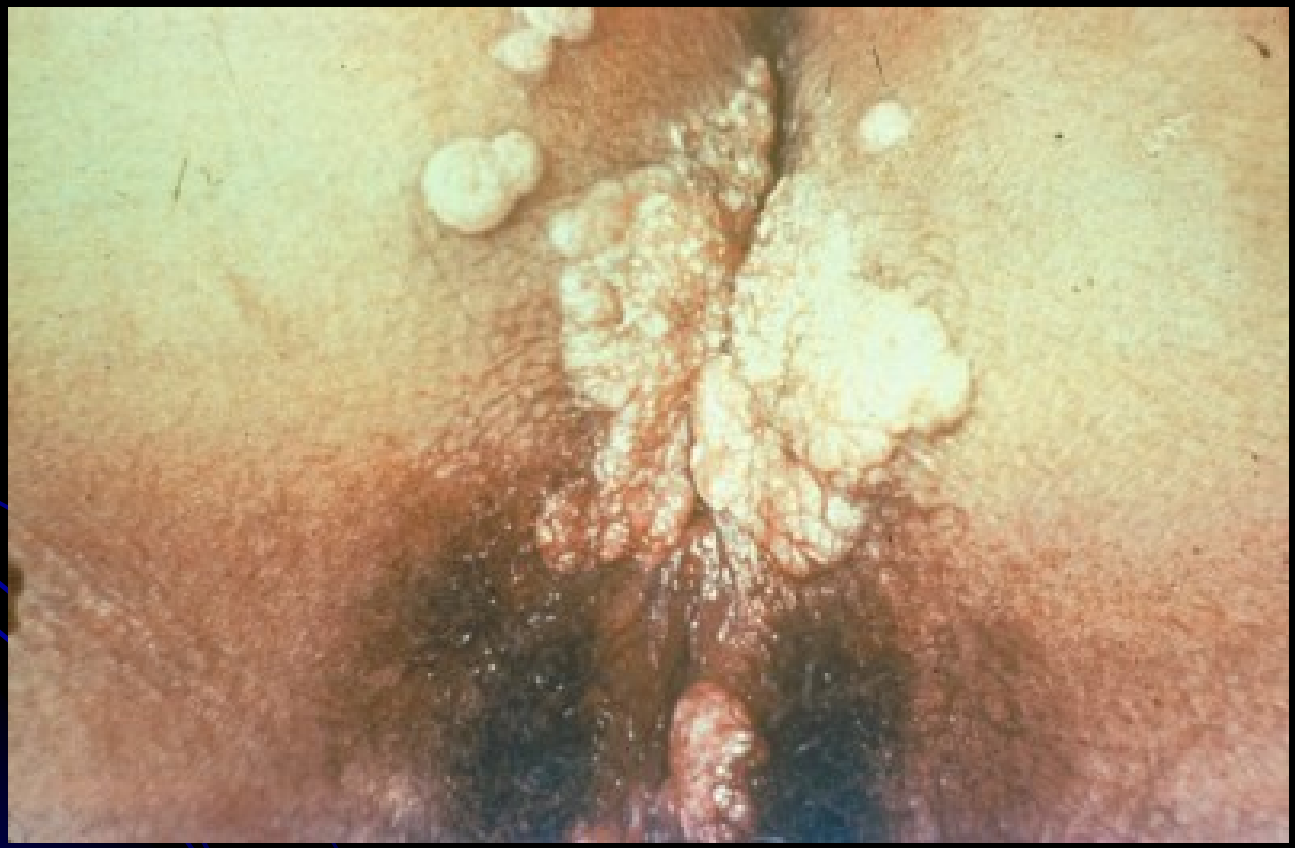

- 10-60 day incubation
- Painless chancre
  - resolves in 1-6 weeks
- May go undetected
- Heals in 4-8 weeks
- Anogenital skin and mucous membranes
  - lips, tongue, buccal mucosa, tonsils, fingers

# Secondary syphilis

# Secondary syphilis



# Secondary syphilis - condyloma lata



# Syphilis and HIV Co-infection: A win, win, lose relationship

*Syphilis affects HIV*

- Transiently increases serum viral load
- Decreases CD4 cell counts
- Facilitates HIV transmission/acquisition

*HIV affects syphilis*

- Early neurological manifestations
- Increased risk of serological failure

***HIV-infected individuals and their partners lose!***

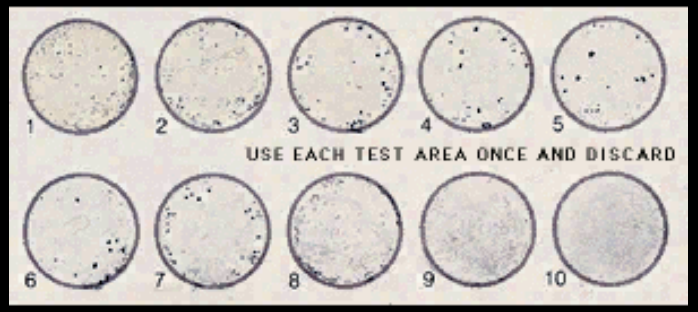
# Diagnostic Points

- A positive darkfield or Direct Fluorescent Antibody (DFA) test of lesion exudate or tissue is a DEFINITIVE DX

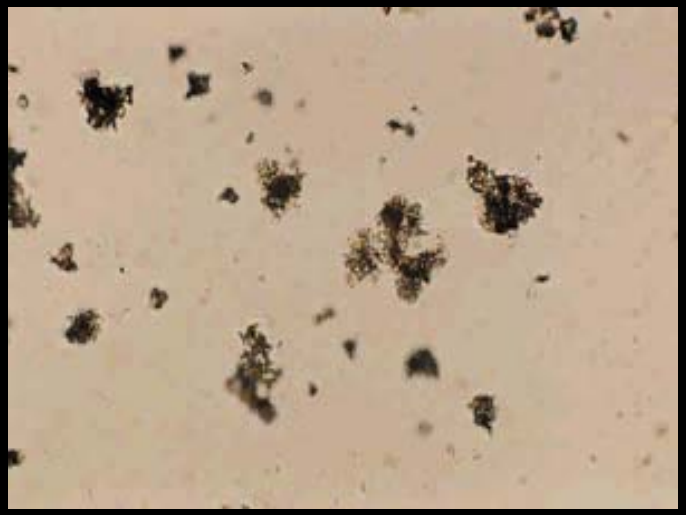
- Presumptive DX:
  + nontreponemal test (VDRL/RPR) AND
  + confirmatory treponemal test (FTA-ABS)

# Screening Tests for Syphilis Nontreponemal tests

- RPR Card Test: read directly




- VDRL Test: read via microscope



# Serologic Tests for Syphilis

| Test | Sensitivity by stage of untreated syphilis | | | | Specificity |
|---|---|---|---|---|---|
| | Primary | Secondary | Latent | Late | |
| VDRL | 74-87% | 100% | 88-100% | 37-94% | 96-99% |
| RPR | 77-100% | 100% | 95-100% | 73% | 93-99% |
| TRUST | 77-86% | 100% | 95-100% | | 98-99% |
| MHA-TP | 69-90% | 100% | 97-100% | 94% | 98-100% |
| FTA-ABS | 70-100% | 100% | 97-100% | | 98-100% |

# Lab Tests for Syphilis

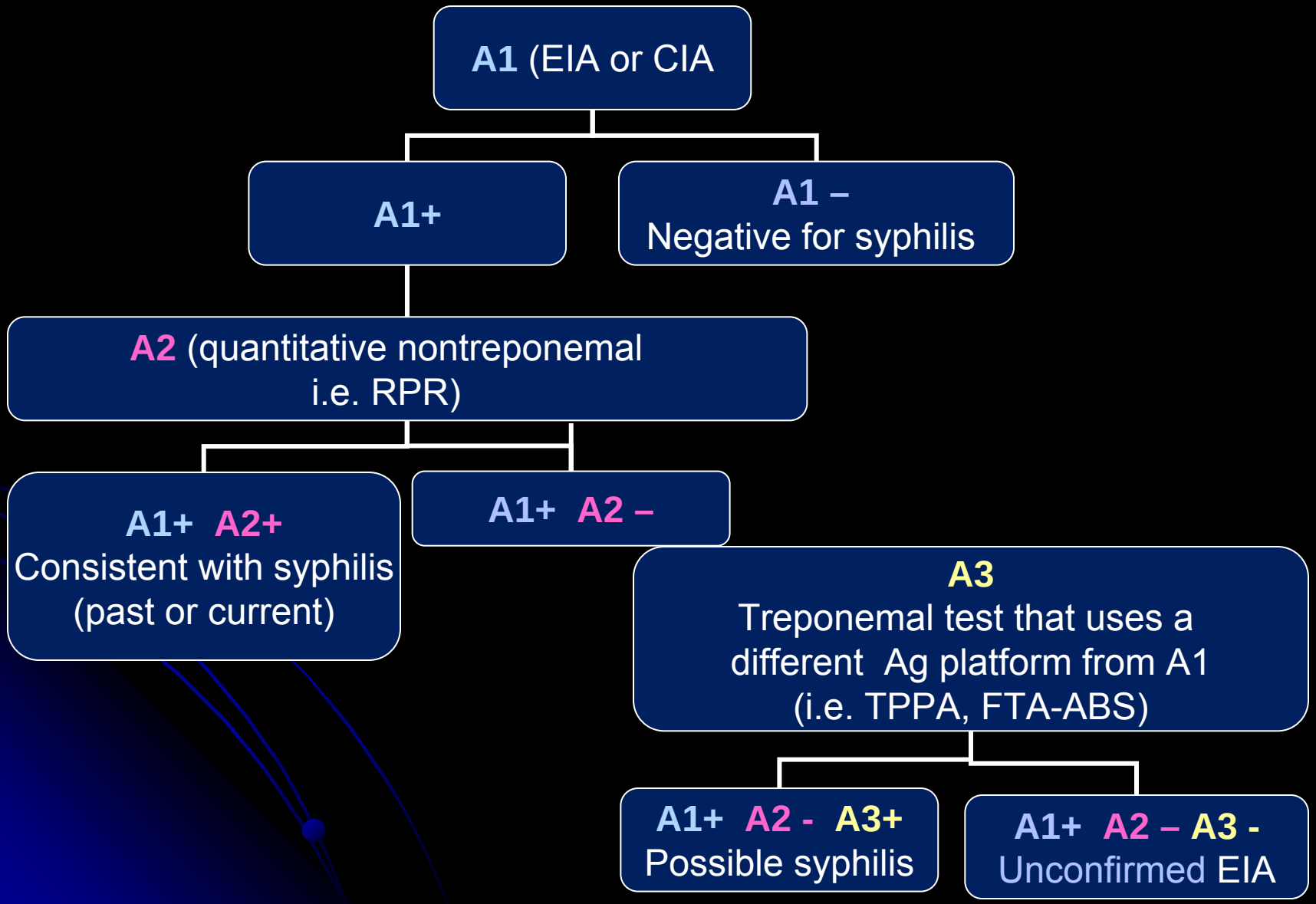
Treponemal serologic tests

- TP-PA and FTA-ABS
- Use to **confirm** positive nontreponemal tests
- Positive or negative only (titers not useful)
- Generally stay positive for life
- Seroreversion in 15% of patients treated for early primary syphilis

# Syphilis Laboratory testing and the EIA dilemma

- Two licensed tests for screening and confirmation
  - Trinity Captia Syphilis G (sonicated treponemes)
  - Trepchek G (cloned antigens)
- Increased use of  treponemal EIA for screening; clinical management problems
- Quantitative non-treponemal testing to guide patient management; if test is negative, perform a second treponemal test to determine reactivity

# Recommendations for laboratory syphilis testing algorithm with treponemal EIA (or CIA) as initial test



# Biggest question?

- How to interpret a positive treponemal, but negative non-treponemal result!
  - Treatment?
  - Contact investigation?
  - Reporting?

# Syphilis

## Primary, Secondary, Early Latent

Recommended regimen

- Benzathine Penicillin G, 2.4 million units IM

*Penicillin Allergy**

- Doxycycline 100 mg twice daily x 14 days

# HIV Testing Overview

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# New CDC Recommendations

**In health care settings:**

- HIV screening is recommended in all health care settings, after notifying the patient that testing will be done unless the patient declines (opt-out screening)

- Persons at high risk for HIV infection should be screened for HIV at least annually

- Separate written consent for HIV testing is not required. General consent for medical care is sufficient to encompass consent for HIV testing

- Prevention counseling need not be conducted in conjunction with HIV testing

# Rationale for Revising Recommendations

- Many HIV-infected persons access health care but are not tested for HIV until symptomatic
- Effective treatment available
- Awareness of HIV infection leads to substantial reductions in high-risk sexual behavior
- Inconclusive evidence about prevention benefits from typical counseling for persons who test negative
- Great deal of experience with HIV testing, including rapid tests

# Hurdles or Pitfalls to Expanded HIV testing

- State law requiring counseling and proof of informed consent
- No linkage to care
- No proof of informed consent
- Inadequate counseling before or after test
- Poor  understanding of HIV law and institutional policies

Hanssens C CID 2007:45 (Suppl 4).

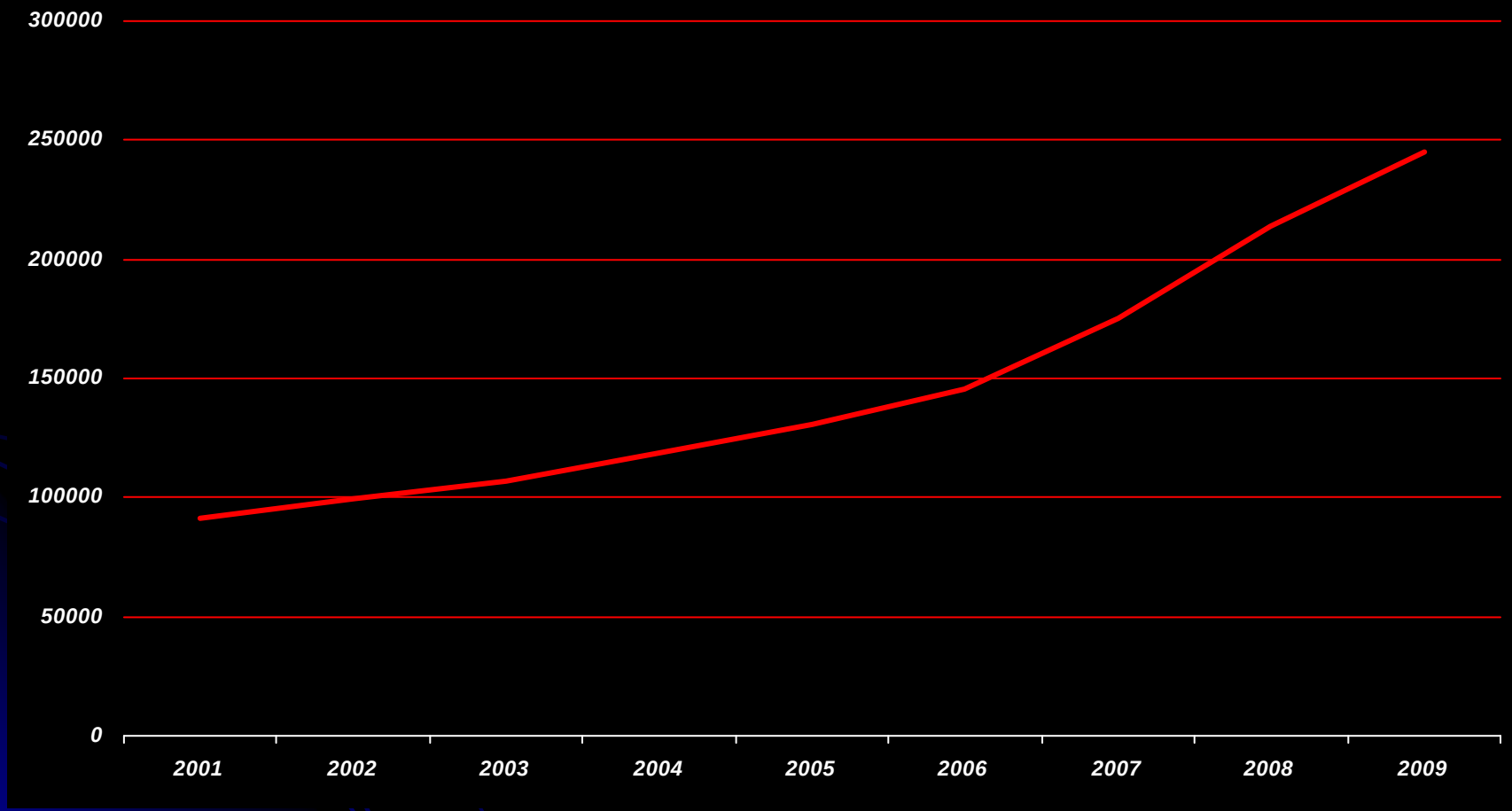
# Changes to NC Administrative Code Nov. 1, 2007

- Opt-out HIV screening in medical settings and for prenatal and STD visits
- Pre-test counseling not required
- Post-test counseling required only for positives
- HIV tests at first prenatal visit and 3rd trimester
- Mandatory HIV test at L&D for all women for whom HIV status is unknown and in infant if test not obtained from mother

# The North Carolina Integrated Response to HIV Prevention and Treatment

"….the objective of improving HIV care provision in central North Carolina through the transformation of the current, disjointed, HIV testing and care delivery system into a single structure where testing and care are linked. The coupling of testing and provision of care is necessary in order for patients to benefit from treatment and prevention messages."

# HIV Tests North Carolina DHHS Laboratory



# North Carolina Opt-out testing

- Only one major medical center with change in testing requirements
  - risk management is barrier
- Emergency Departments: Although waiving of separate written informed consent at UNC, continue with limited testing in ED
  - cost of test
  - commitment of emergency department

  limited staffing
- STD Clinics

# NC Delay to Testing

- Over one-quarter of patients reported delayed seeking an HIV test for over 4 years.
- Patients who reported HIV infection in more recent calendar years had a shorter duration of testing delay.

Self-reported HIV testing delay in North Carolina

# Barriers to initiation of testing: Patients

The lack of perceived vulnerability to HIV acquisition could be broadly divided into three themes:

- people who did not recognize their behavior as risky
- people who viewed their behavior as very low risk
- people who felt like exposure to HIV was unlikely, regardless of behavior

Few identified benefits of seeking an HIV test

S.I. McCoy, et al. 2009

# Barriers to initiation of testing: Access to Health Care

- Most participants accepted testing when it was offered, suggesting that routine screening may increase the numbers of people tested and de-stigmatize the testing process.

- For expanded HIV testing  programs to have impact, people living with unrecognized HIV infection must have contact with the healthcare system.

- In the Southeast, HIV infection is often a disease of the rural and poor; new strategies to improve health care access will be a necessary precursor for any increased screening to reach the groups most in need.

# Missed opportunities for diagnosis

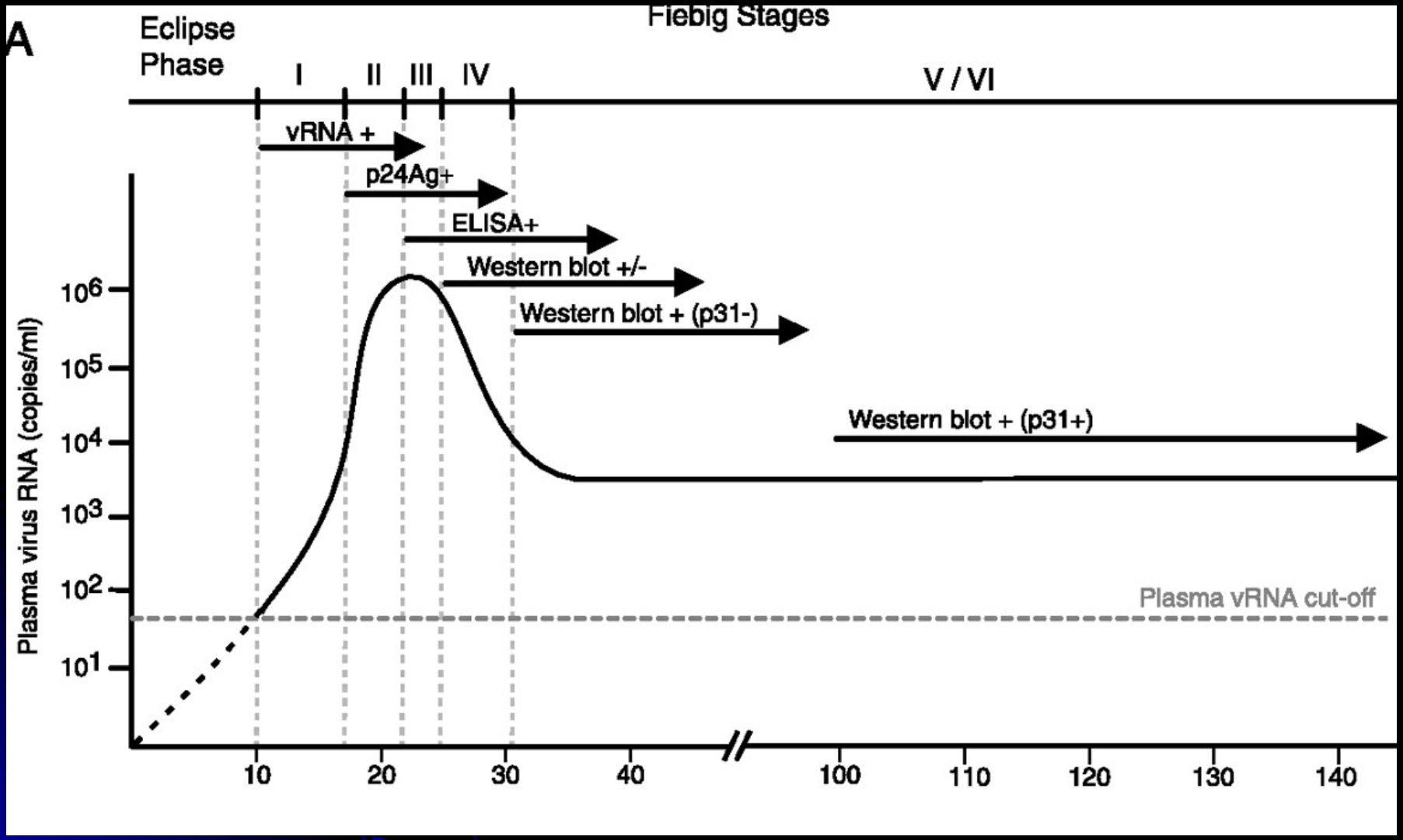
- In South Carolina, there were 4,315 cases of HIV reported between 2001-2005*
  - 41% had AIDS diagnosis within 1 year of HIV diagnosis
  - 16.5% had AIDS diagnosis within 30 days
  - Of 1,748 late testers, 1,303 had a health care visit(s) from 1997-2005
    - Number of health care visits with no HIV test: 7,988 (average 4 per person)
    - Visits with diagnosis that should trigger HIV testing: 1,711
    - No risk at visit: 6,277

* CDC MMWR Weekly Report Dec. 1, 2006

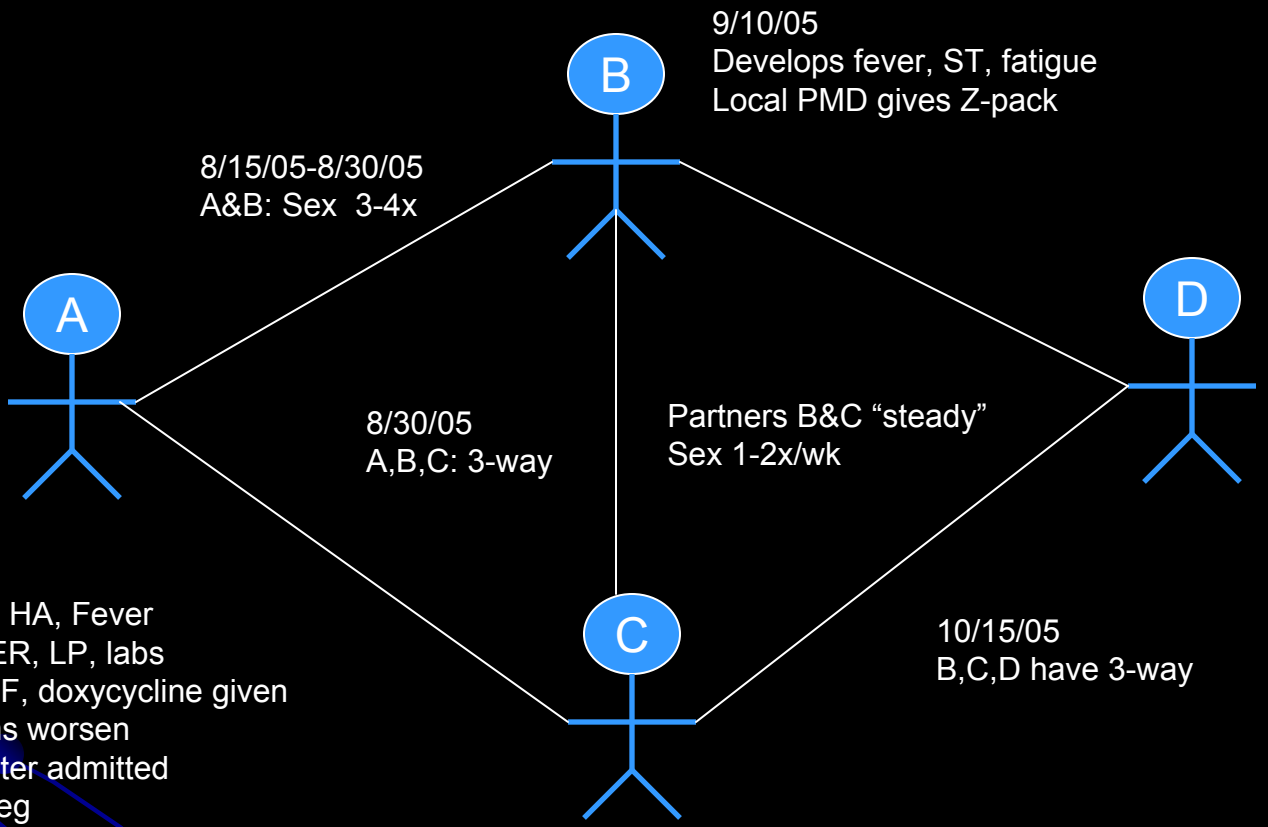
# CONCLUSION

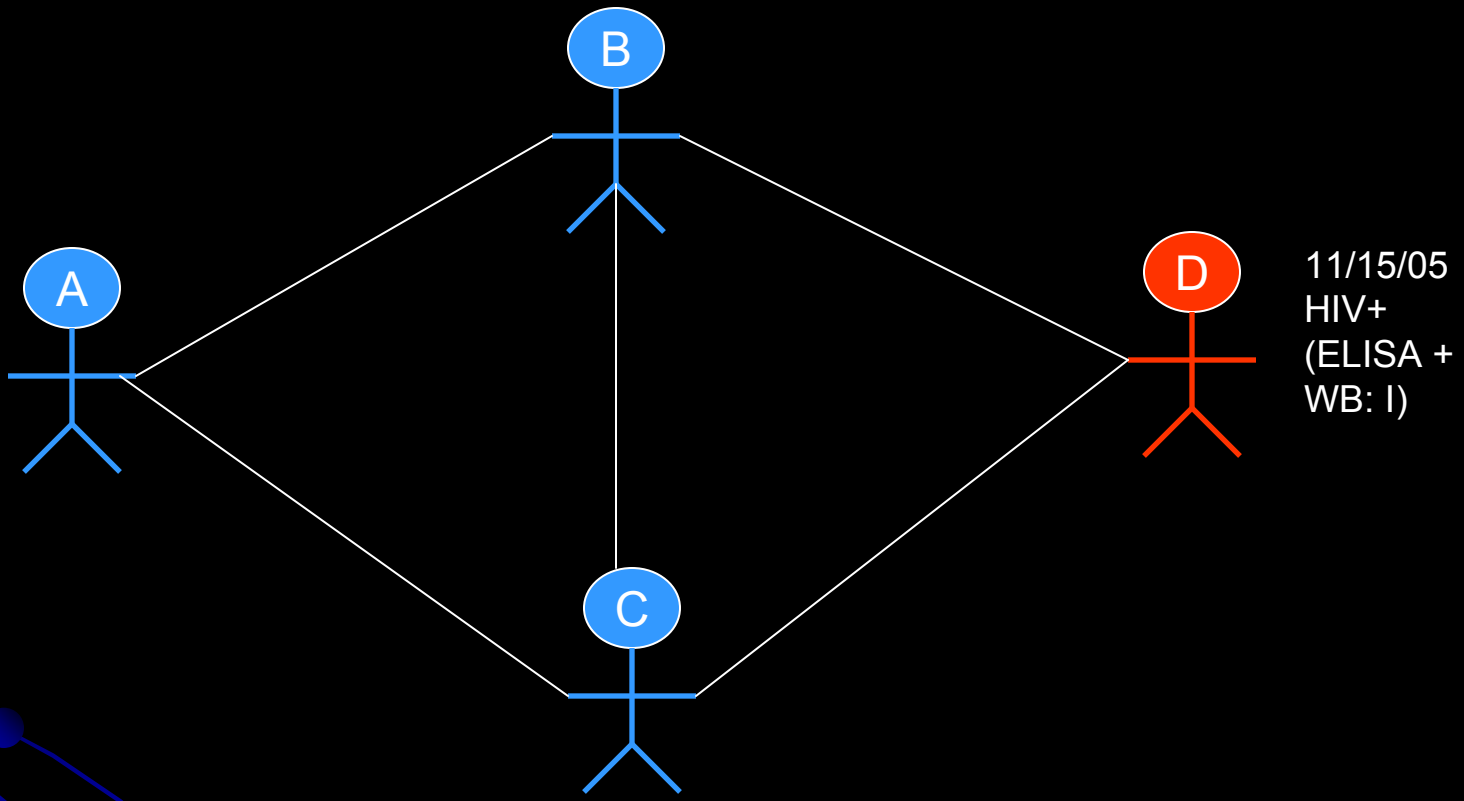
- Increased awareness of the importance of HIV testing among high risk populations and their providers is  essential
- Find the intersection
- Opt-out testing can increase testing
- Systems of care that reduce time from infection to care initiation need to be a priority
- A large proportion of patients who suspect that they have been infected with HIV delay testing for several years

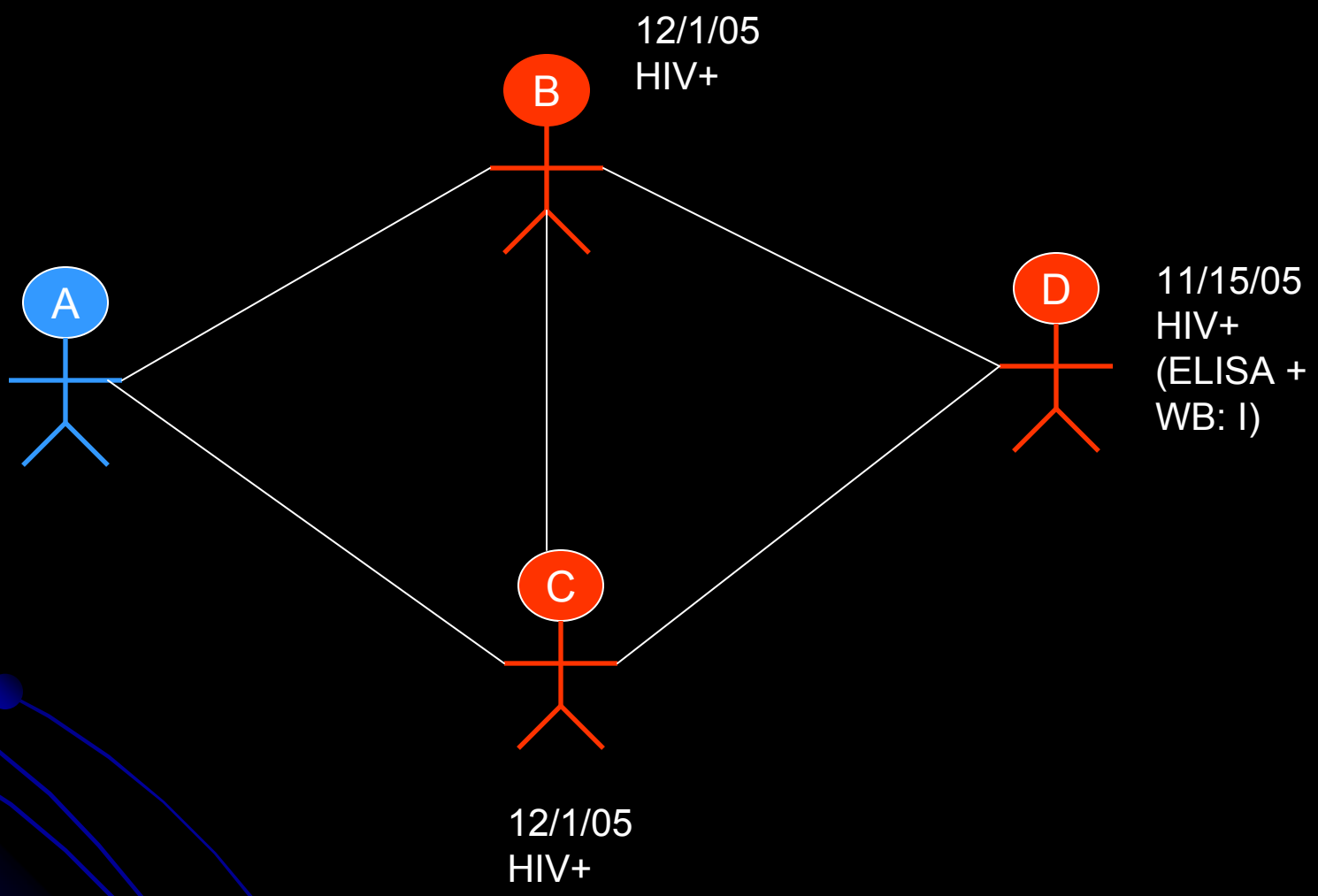
# Fiebig Classification

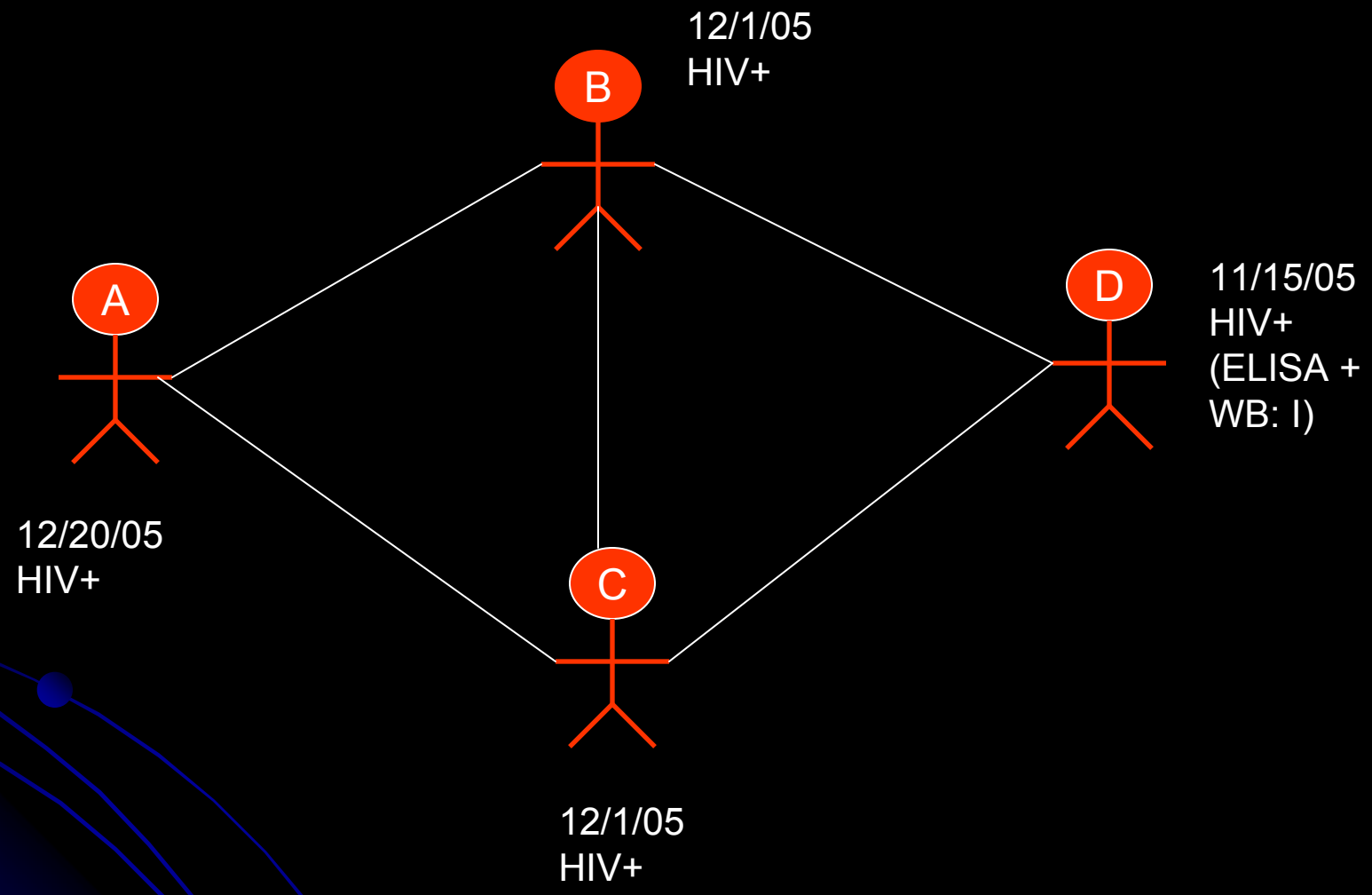



Fiebig et al, AIDS. 2003;17:1871-9.


B
9/10/05
Develops fever, ST, fatigue
Local PMD gives Z-pack
8/15/05-8/30/05
A&B: Sex 3-4x
A
D
10/28/05
Develops fever, ST,
oral ulcers, thrush
Antibiotics given
Requests HIV test
8/30/05
A,B,C: 3-way
Partners B&C “steady”
Sex 1-2x/wk
7/28/05
Develops HA, Fever
Went to ER, LP, labs
DX: RMSF, doxycycline given
Symptoms worsen
2 Days later admitted
HIV Ab neg
Discharge Aseptic meningitis
Possible RMSF
C
10/15/05
B,C,D have 3-way
9/30/05
Develops fever, LAD,ST
Local PMD gives Z-pack


B
A
D
C
11/15/05
HIV+
(ELISA +
WB: I)


12/1/05
HIV+
B
A
D
11/15/05
HIV+
(ELISA +
WB: I)
C
12/1/05
HIV+


12/1/05
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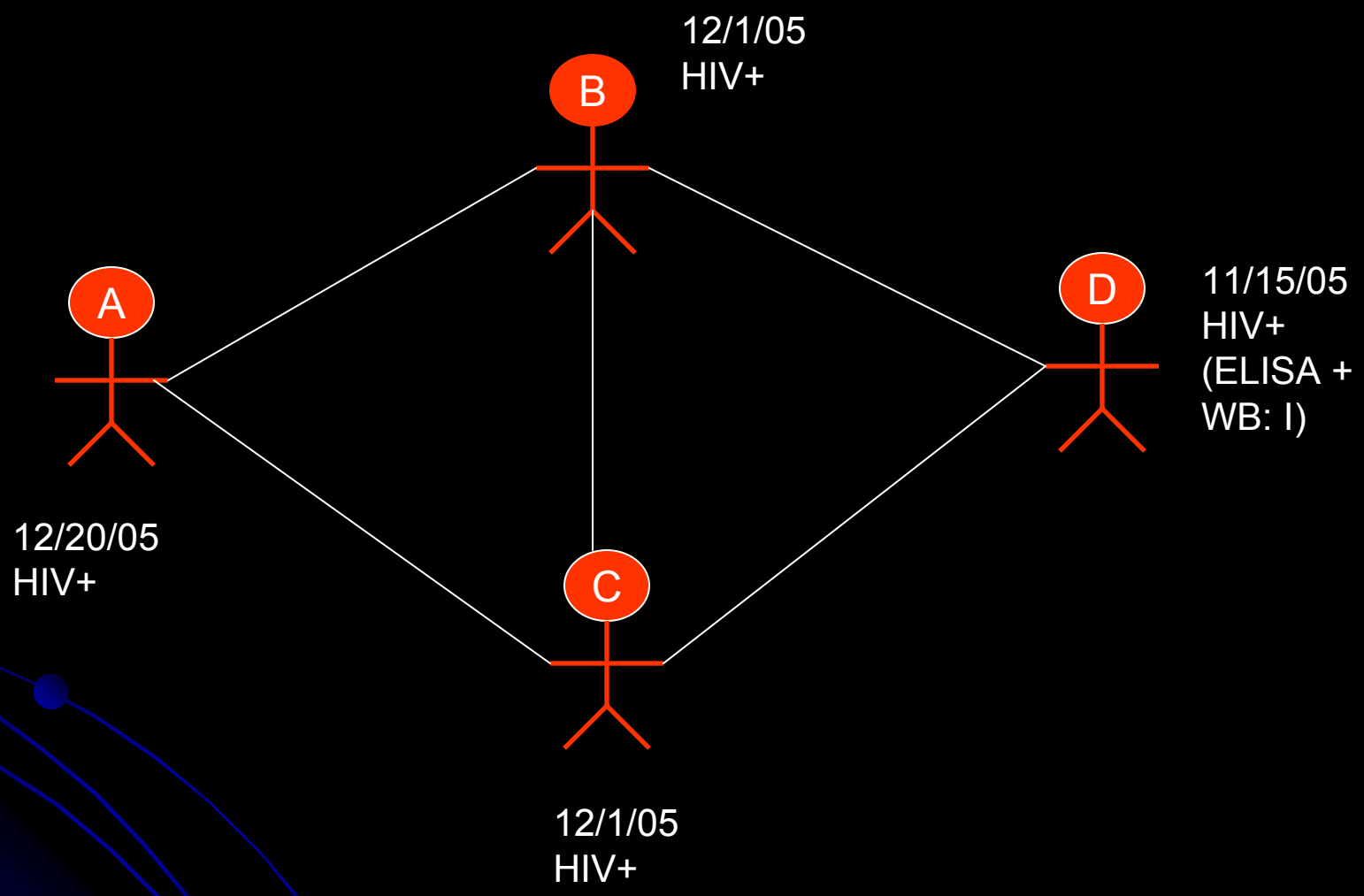
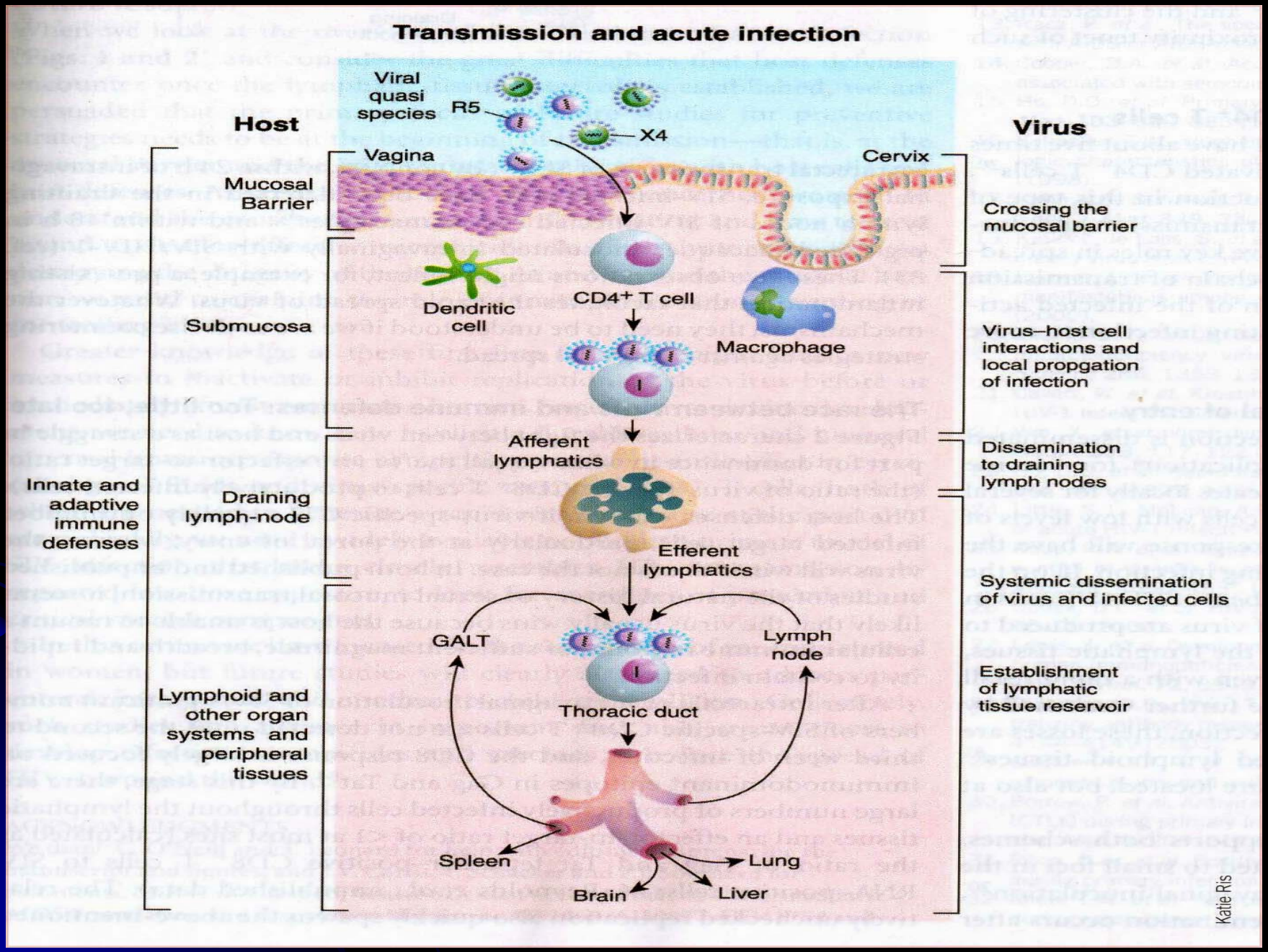
HIV+




*6 infections could have been avoided if acute HIV infection considered at first presentation*


Transmission and acute infection
Host
Virus
Viral quasi species
R5
X4
Vagina
Cervix
Mucosal Barrier
Crossing the mucosal barrier
Dendritic cell
CD4+ T cell
Macrophage
Submucosa
Virus–host cell interactions and local propgation of infection
Afferent lymphatics
Dissemination to draining lymph nodes
Innate and adaptive immune defenses
Draining lymph-node
Efferent lymphatics
Systemic dissemination of virus and infected cells
GALT
Lymph node
Thoracic duct
Lymphoid and other organ systems and peripheral tissues
Establishment of lymphatic tissue reservoir
Spleen
Lung
Brain
Liver
Katie Ris

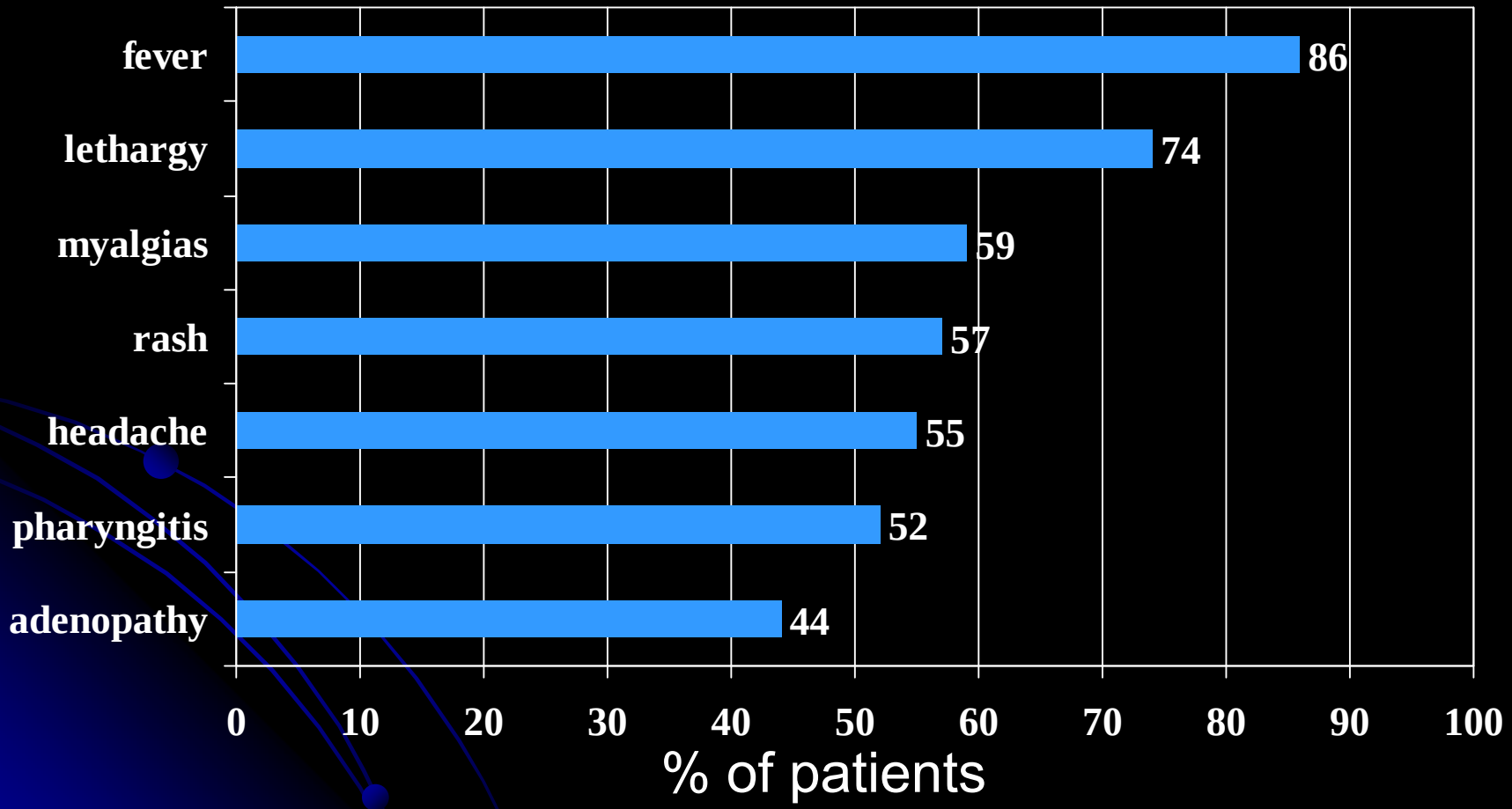
# Acute Retroviral Syndrome

- 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 Syndrome and Medical Evaluation

- 78% (25/31) with symptoms 3 mo. prior to 1st positive test
- 65%( 20/31) sought medical evaluation
- 50% (10/20) went to ED or Urgent Care
- 20% (4/20) went to private MD
- 30% (6/20) Dx bacterial infection
- 30% (6/20) Dx viral syndrome
- 15% (3/20) Dx AHI
- 18.8% (6/31) aware of AHI prior to Dx

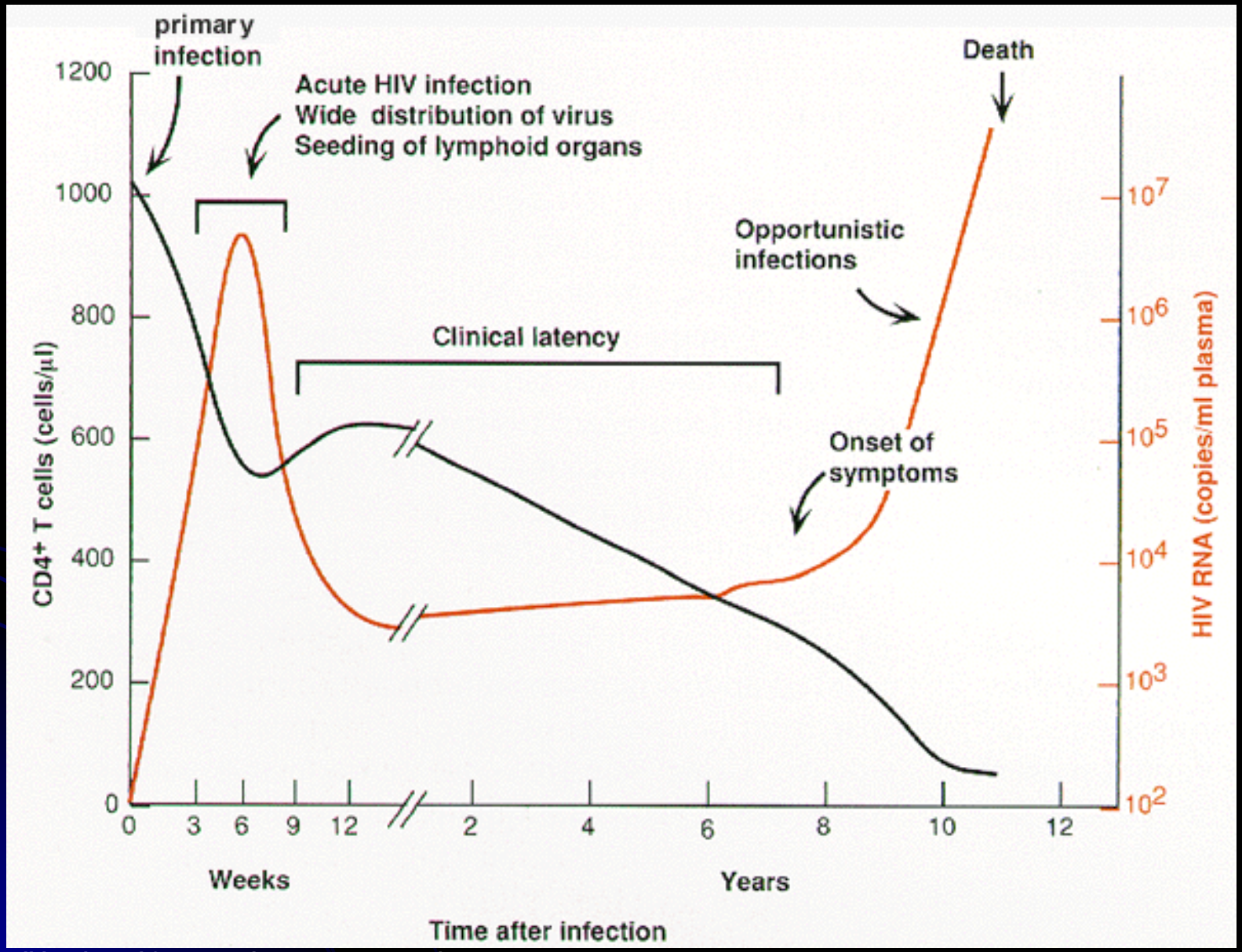
# Lack of Recognition of AHI by Patients

This lack of awareness was in three primary domains:

- The signs and symptoms of an acute retroviral syndrome
- The different HIV testing technologies
- Heightened infectiousness during AHI, when HIV antibody test is likely to be negative

Remien RH, et al. AIDS Behav (2009) 13:1046–1053

# Acute HIV Infection




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

# 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

# Rationale for Acute HIV Diagnosis

- Most infectious period and Dx often missed
- Individual perspective
  - Improve prognosis with acute treatment????
    - Lowering of viral set point
    - Preservation of CD4 T cells
    - Decrease in rate of progression
    - Long-term control of HIV viremia
    - Viral eradication
  - Early entry into care
  - Short-term behavioral change results in large benefit
  - Management of STIs

# Rationale for AHI Diagnosis

Public Health

- Recognize previously missed infections
- Avoid transmission to partners with risk reduction
  - 10-100 fold increased transmission risk x 3-6 months
  - May be responsible for 14-50% of all transmission of HIV
  - Quebec AHI/PHI <10% of infection but ~50% transmission
- Networks – leading edge of transmission

-Identify transmission networks for intervention

-Prevent secondary transmission by contact tracing and counseling to modify risk behaviors

- Geographic focus

Brenner BG, et al, JID 2007:195

# HIV-1 Transmission, by Stage of Infection

**T. Déirdre Hollingsworth, Roy M. Anderson, and Christophe Fraser**

**Table 2. Calculation of the basic reproduction number ($R_0$), according to the contribution from each stage of HIV-1 infection, under 2 extremes of sexual behavior.**

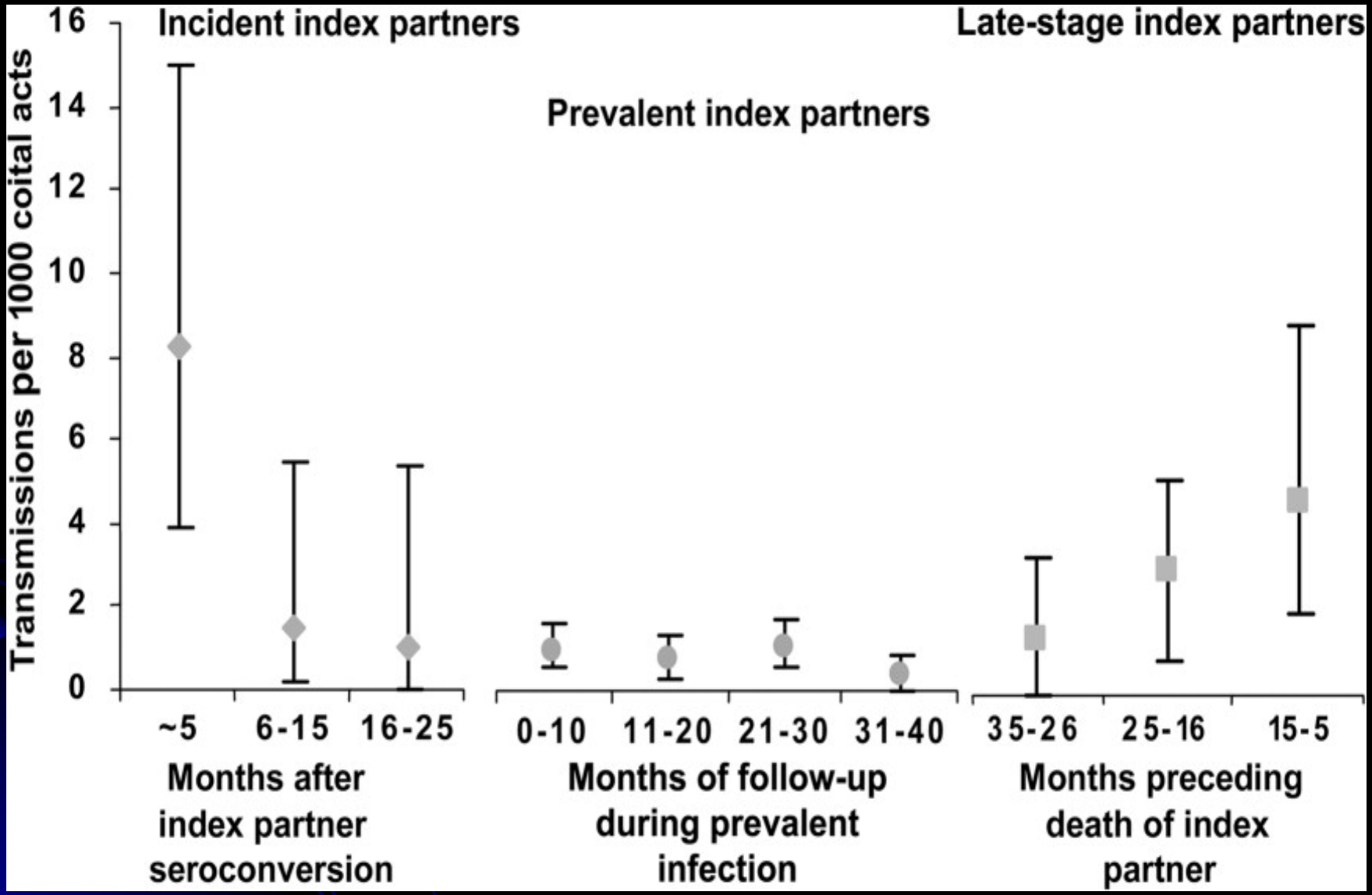
| Infection stage | Hazard of transmission ($\beta$) per person-year | Duration of high infectiousness ($d$)/interval between seroconversion and death[a] (%), mean, years | No. (%) of new transmissions, by sexual behavior[b] | |
|---|---|---|---|---|
| | | | Serial monogamy | Random mixing |
| Primary | 2.76 | 0.24/10.2 (2) | 0.10 (9) | 0.67 (31) |
| Asymptomatic | 0.106 | 8.38[c]/10.2 (82) | 0.77 (71) | 0.91 (42) |
| AIDS | 0.760 | 0.75[d]/10.2 (16) | 0.21 (20) | 0.57 (27) |
| $R_0$ | . . . | . . . | 1.09 (100) | 2.15 (100) |

[a] The mean interval between seroconversion and death (10.2 years) was adopted from the report by Morgan et al. [48].

[b] The formula for calculating the number of new transmissions in a scenario of serial monogamy is $\beta cd/(\beta + c + 1/d)$, where $c$ is 1.25 partner changes/year. The formula in a scenario of random mixing is $\beta d$ (appendix).

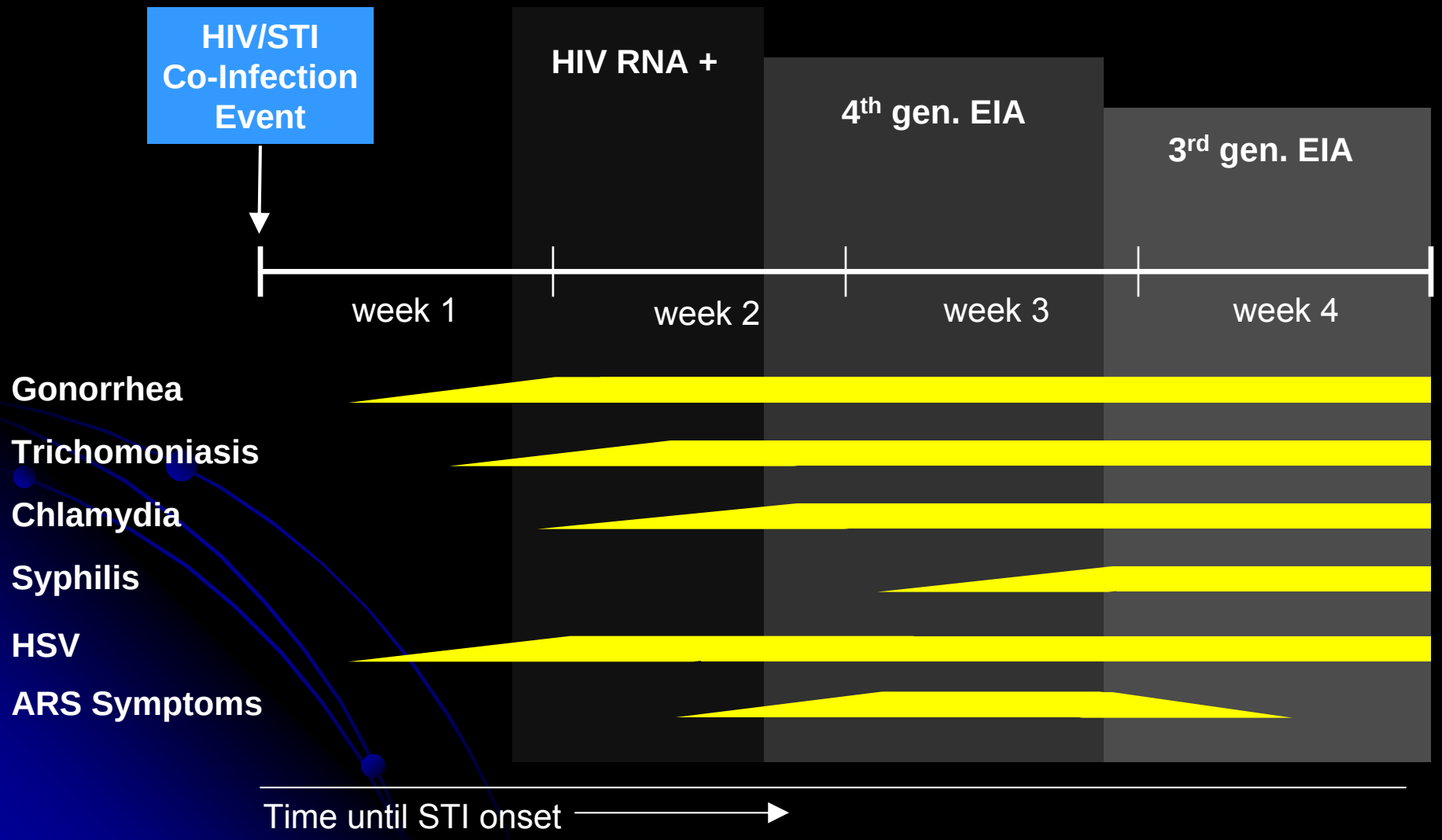
[c] $d$ was calculated by subtracting the mean durations of the periods of high transmissibility during primary infection (0.24 years) and AIDS (0.75 years) and the mean duration of zero transmission risk before death (0.83 years) from the mean interval between seroconversion and death (10.2 years).

[d] $d$ corresponds to the period 10–19 months before death during which $\beta$ was greatest for this infection stage. $\beta$ was zero during the 10-month period immediately before death.




Wawer, et al, JID 2005, 191:1403

# Potential impact of STI co-infection on detection of AHI



# 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

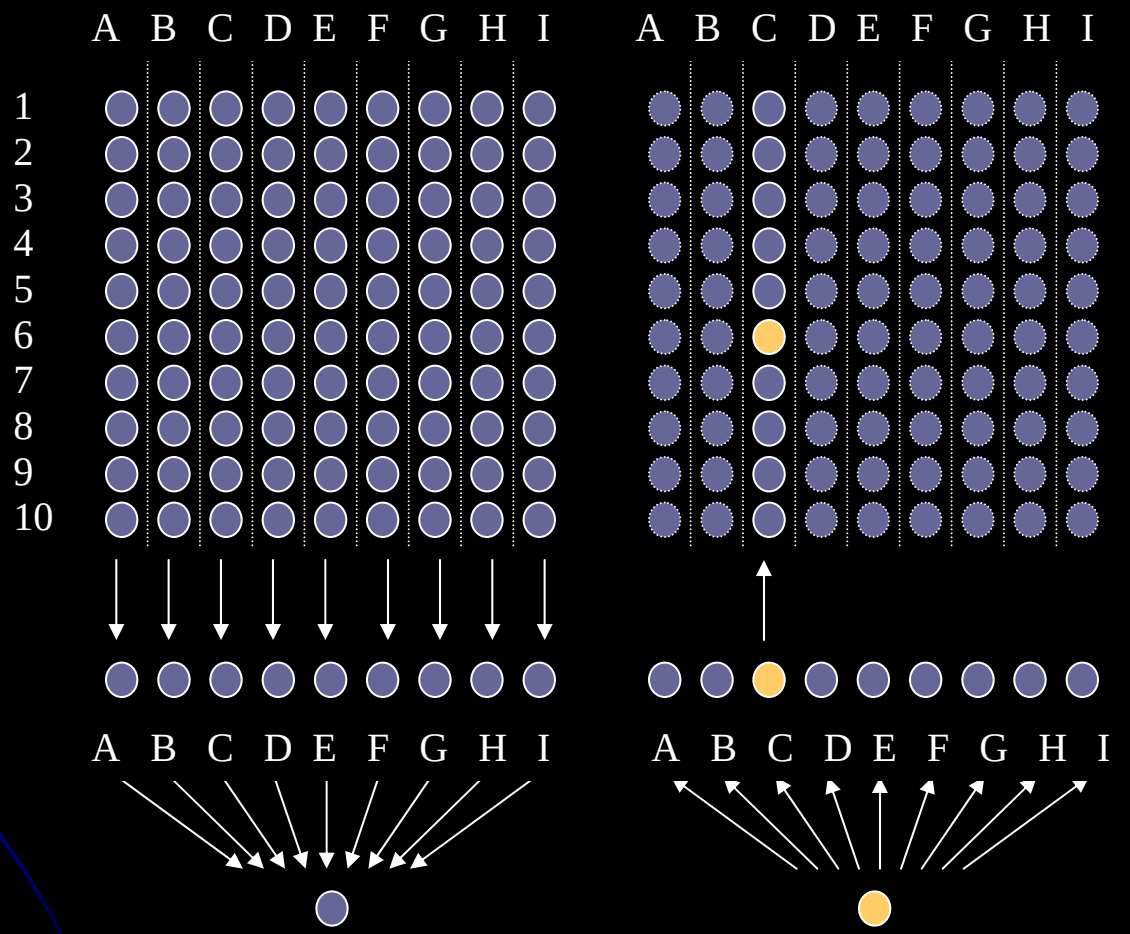
# North Carolina Screening for AHI
# Specimen pooling

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 locate patient
- False positives/lab errors

# Pooling and HIV RNA testing

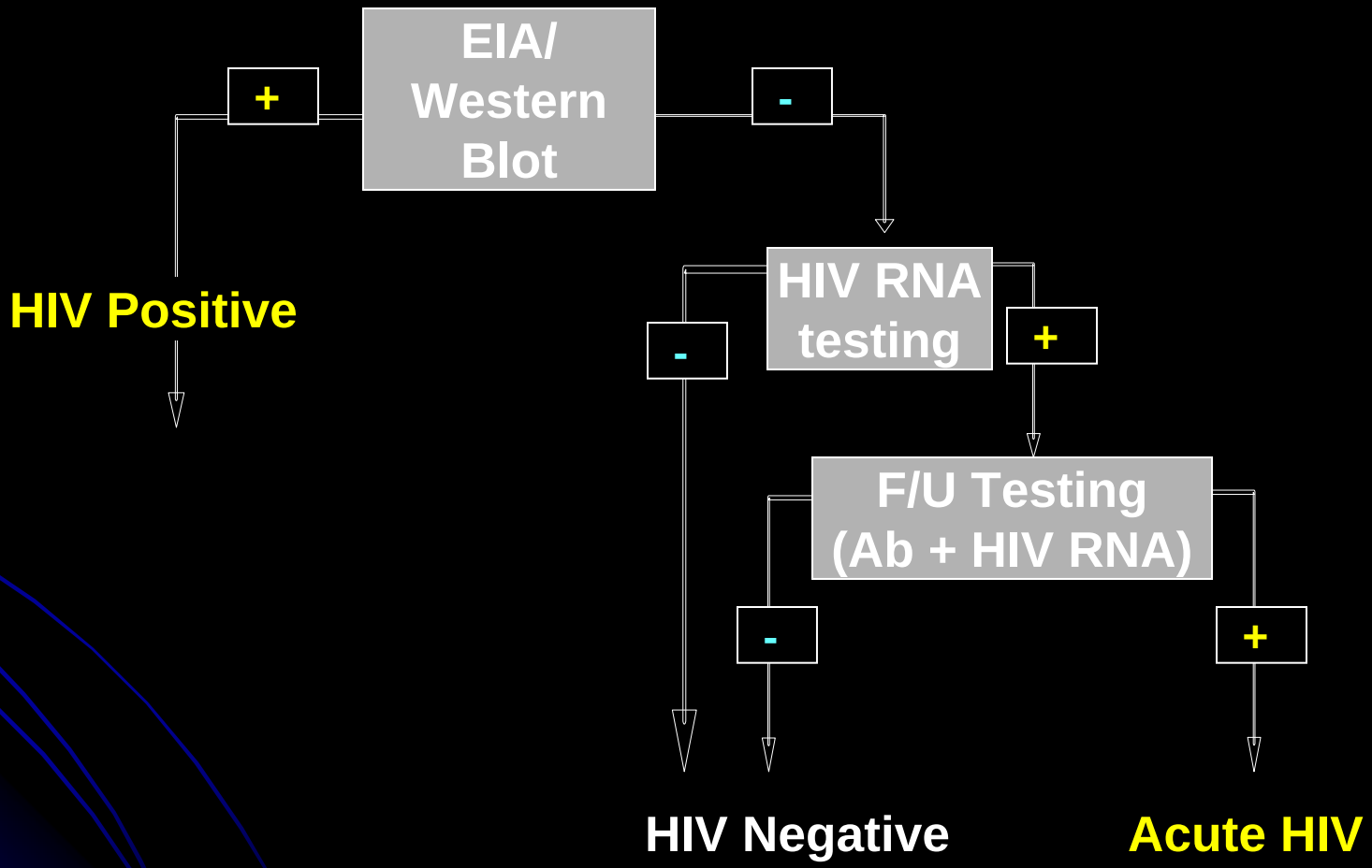
90 individual HIV antibody negative specimens



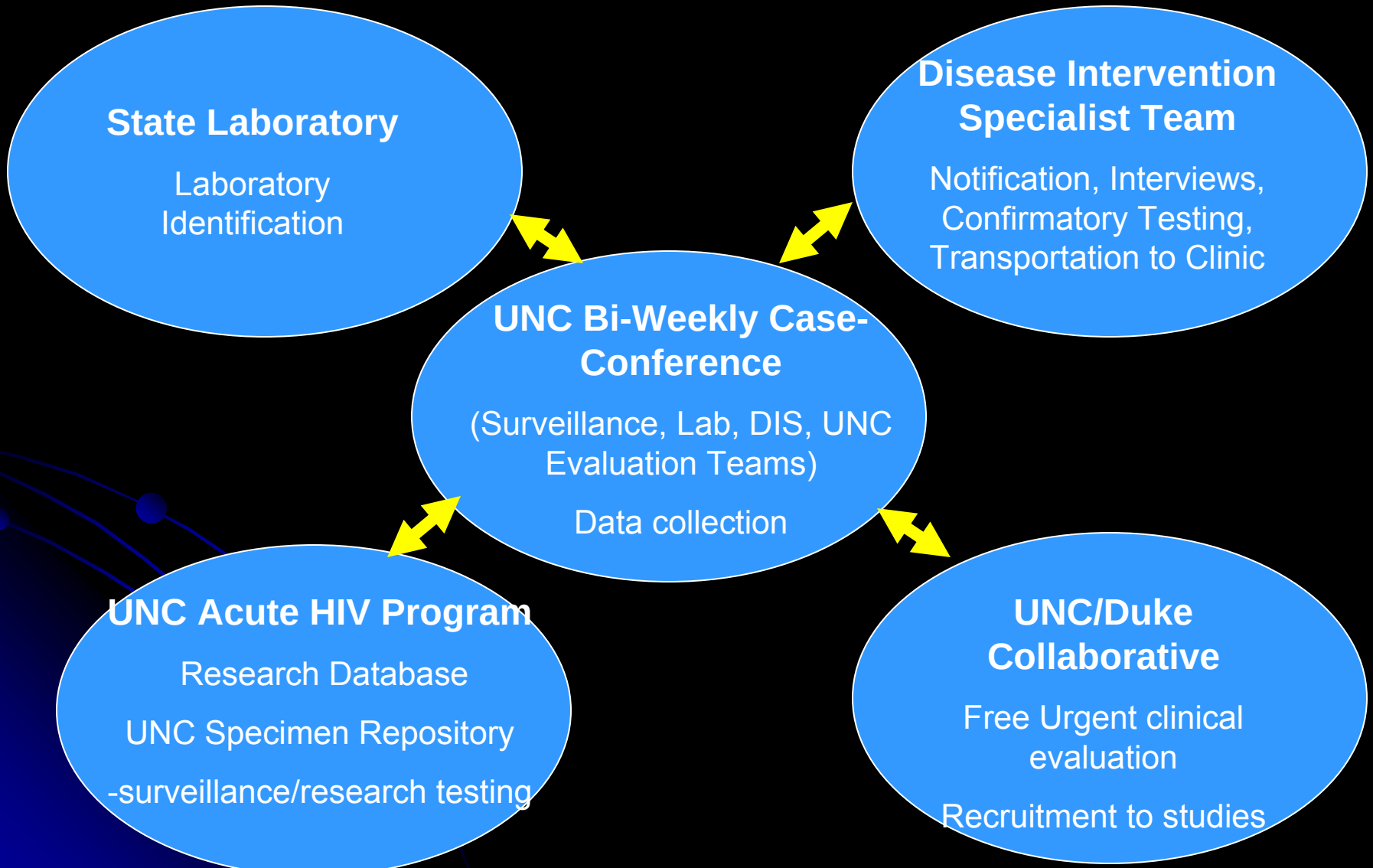

9 intermediate pools (10 specimens)

1 master pool (90 specimens)

# STAT Testing Protocol



# The STAT System



# Advantages of p24 Ag and 4th generation EIAs

- Current '4th generation' EIAs can detect both p24 Ag and antibody on a single assay
- Could be used as the initial HIV screening test
- p24 Ag EIAs nearly as sensitive as HIV RNA testing for acute HIV infection
- Sensitivity of 4th generation EIAs is now equivalent to heat p24 assays

# HIV Testing Algorithms

# A Status Report

A publication from The Association of Public Health Laboratories and The Centers for Disease Control & Prevention

**April 2009**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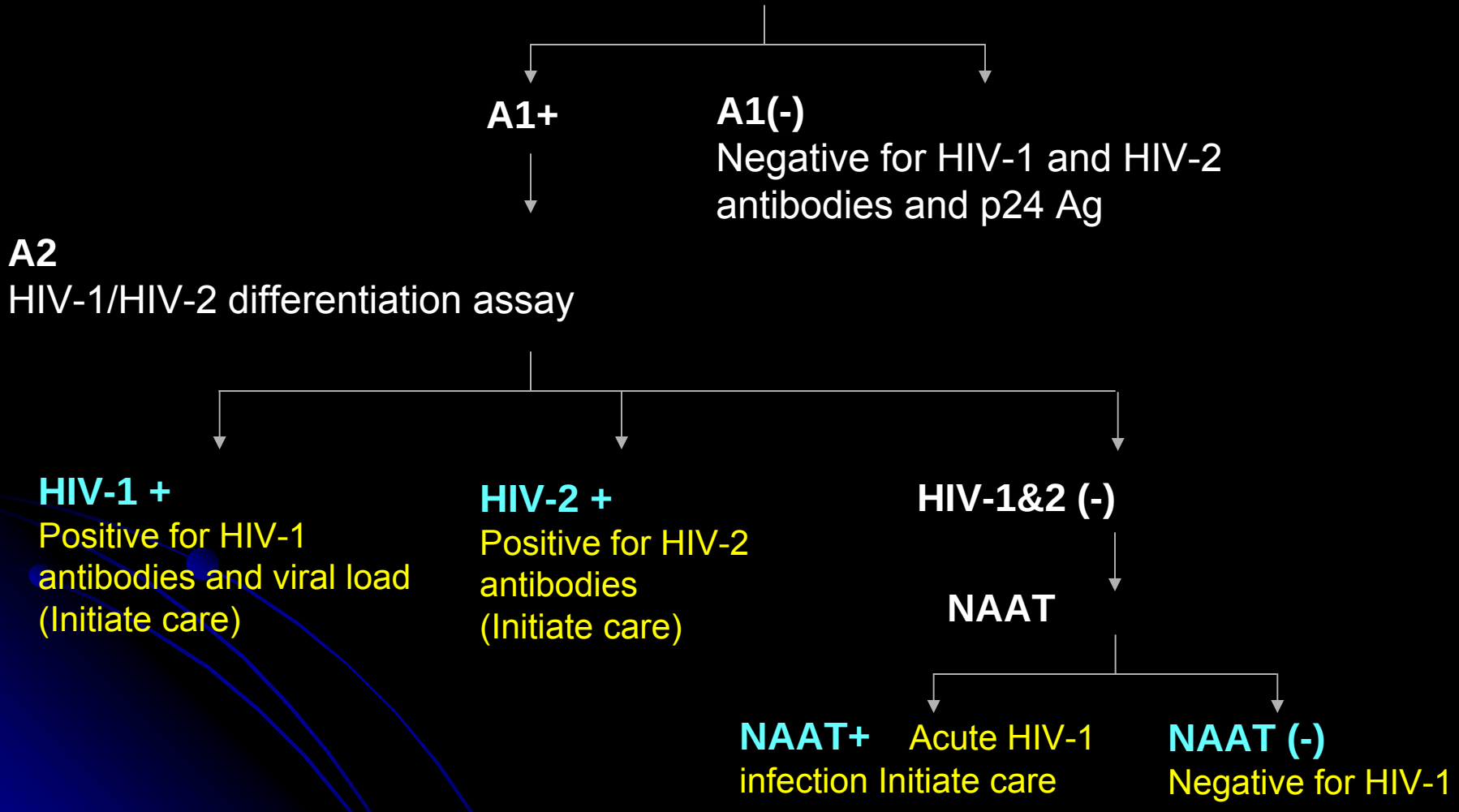
# A1: 4th generation HIV-1/2 assay



# How does a 4th Generation IA ( HIV Ag/Ab Combo) perform on the recent / acute infection panel ?

- Detects 57 / 64 positively (89%)
  - (3rd gen detected 42%)
- Of the 29 “recently infected” specimens: 29/29 (100%)
  - (3rd gen detected 93%)
  - (Uni-gold Rapid: 76%)
- Of the 35 “acute” specimens (RNA pos, completely Ab negative: 28/35 (80%)

# 4th gen HIV Ag/Ab Combo considerations / conclusions

- Can detect infection in antibody-negative individuals
- Viral load cutoff may be about 14,000 – 31,000 RNA copies / ml
- Can be used as a replacement for RNA testing, would detect ~90% of Ab-/RNA+ detected by RNA pooling
- Shorter time to Dx , potential for better PPV,  and lower cost  than RNA pooling

# Confirmatory Testing

- Confirmatory test is essential
- For Western blot:
  - Venipuncture for whole blood
  - Oral fluid specimen
- Follow-up testing of persons with negative or indeterminate Western blot results after 4 weeks
- HIV RNA  or $4^{th}$ gen  test for suspected acute HIV
- A single positive EIA test is not reportable but confirmation is covered under Ryan White for billing

# Rapid HIV Antibody Tests

- Ability to detect acute infection (n=42)
- 3rd generation EIA detected 34% of RNA positive specimens
- Unigold 26%
- Multispot 17%
- OraQuick 2.3%
- Clearview 2.3%
- Western Blot 0%
- Combo assay 80% (n=35)

# Detection of Acute HIV Infection

- Important public health issue
- Identifying AHI may decrease HIV transmission
- Earlier treatment with HAART
- Earlier linkage to care
- Most useful in high risk setting i.e. STD clinic, EDs and MSM populations

# What to consider

- AHI important at individual and population level
- Consider panels for acute viral illness that would include testing for AHI
- 4th generation assays provide faster alternative for Dx AHI
- Important to screen for AHI in STD clinics and with MSM populations

# ACUTE HIV SYNDROME

**If you have an STD, Get Tested for HIV.**

**Early Detection is Best!**

**Learn to Recognize IT. Tell a Friend.**

***Acute HIV is Easily Misdiagnosed.***

***IT CAN BE MISTAKEN FOR COMMON ILLNESSES***

**Common Symptoms of Acute HIV:**

- High Fever
- Rash
- Fatigue
- Swollen Glands
- Sore Throat
- Nausea/Vomiting
- Night Sweats

**Symptoms usually appear about 2 weeks after exposure**

**What Puts You At Risk?**

- Unprotected Sex
- Sharing Needles

**The Acute HIV Program 919-966-8533**

If you suspect you may have Acute HIV, get tested at your Local Health Department or at your doctor's office.

- FREE Screening for acute HIV is done on all HIV tests done through the NC Health Departments
- Screening for acute HIV can be done at your doctor's office – ask for an HIV RNA test in addition to the standard HIV antibody test.

UNC SCHOOL OF MEDICINE

# SPREAD THE WORD - NOT HIV

DUKE UNIVERSITY SCHOOL OF MEDICINE

# Acute HIV and North Carolina STAT