



# CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA



CAPRISA IS A UNAIDS  
COLLABORATING CENTRE  
FOR HIV PREVENTION RESEARCH

## HIV incidence estimation for prevention trials

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# Overview

- Importance of HIV incidence estimations for prevention trials?
  1. Using risk factors to identify high risk populations
  2. Using mathematical models on HIV prevalence data from cross-sectional studies
  3. Laboratory methods to identify recent HIV infection
  4. Estimating incidence from cohort studies
  5. Extrapolating incidence from other trials in the same population
- Summary & Conclusion

# Why is estimation of HIV incidence for HIV prevention trials important?

- Key **effectiveness** endpoint in all microbicide and other prevention trials
  - Want to have adequate power & reduce risk of inconclusive trial result
- Key **safety** endpoint in all microbicide trials
  - Experience from COL-1492 and CS trials
    - HIV incidence showed harm before any other variable
    - Phase I and II trials showed COL-1492 & CS to be safe but HIV incidence in effectiveness studies showed harm
    - No other correlate of safety besides HIV found yet

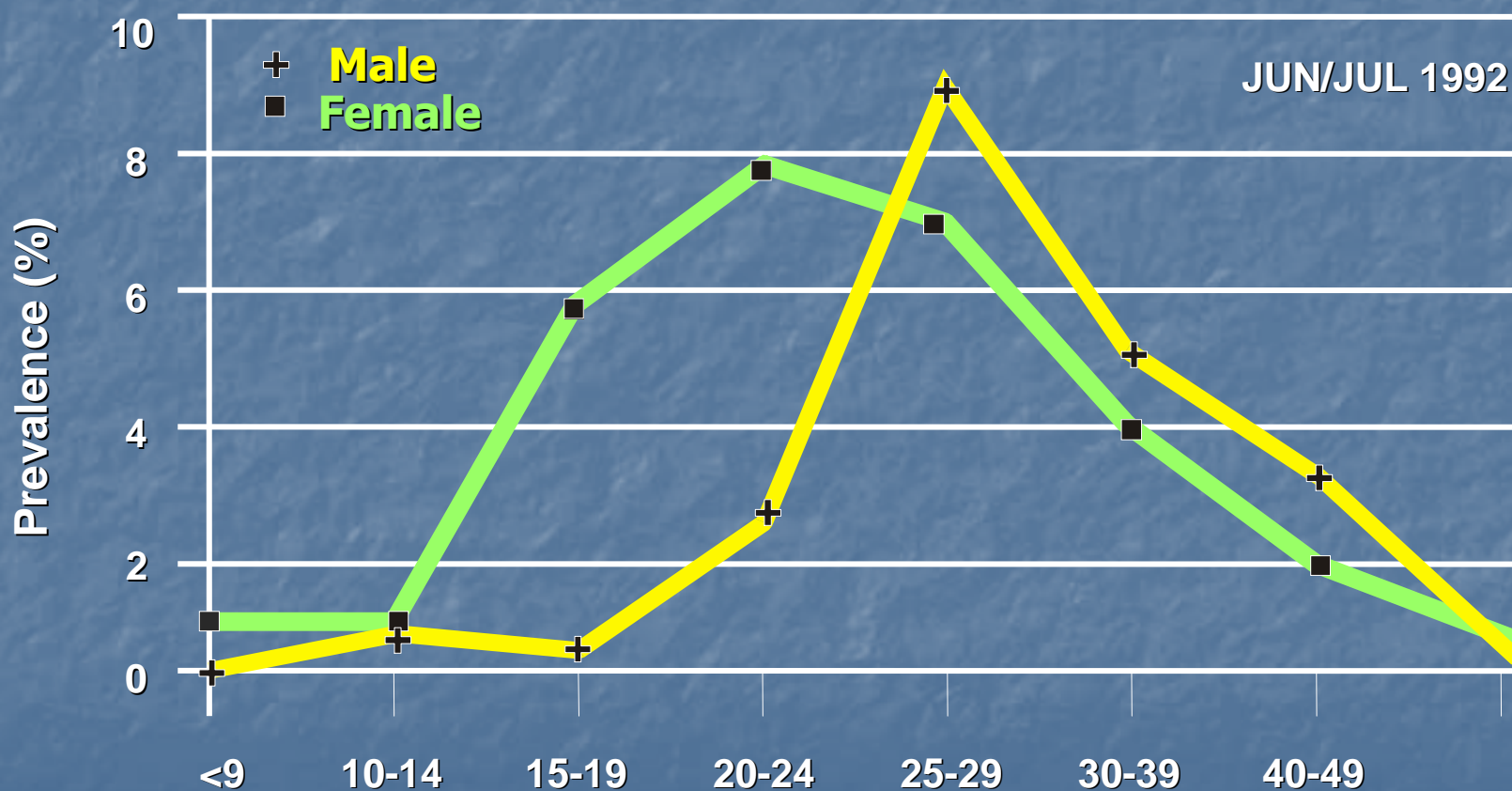
# 1. Using risk factors

to identify

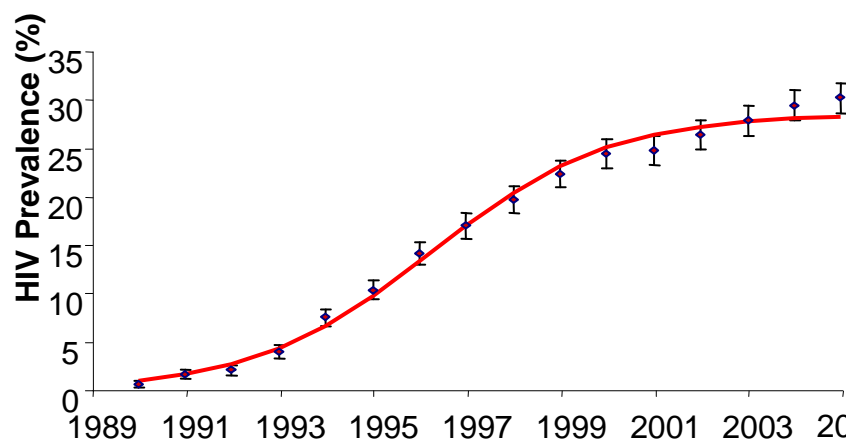
high HIV incidence populations

- Risk factors + HIV prevalence only hint, at best, that there may be high incidence
- Crude & Unreliable
- Not a quantitative measure of incidence

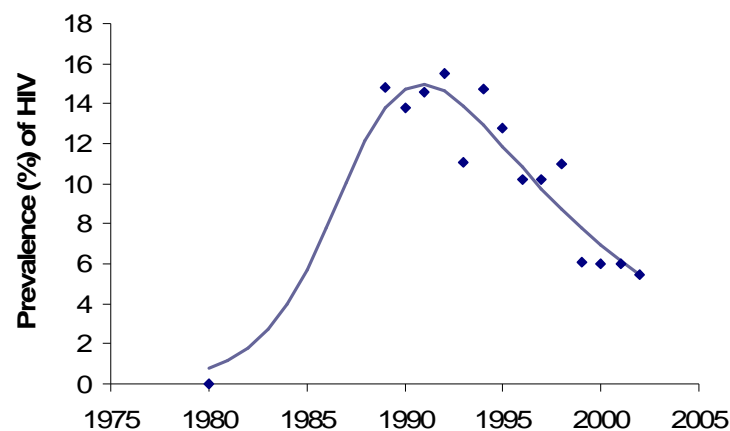
# Selecting study populations for microbicide trials on risk factors such as age and gender



# Selecting study sites & populations for microbicide trials based on stage of HIV epidemic



South Africa



Uganda

Source: Abdool Karim SS & Abdool Karim Q (eds). HIV/AIDS in South Africa  
Uganda curve fitted to UNAIDS data on [www.unaids.org](http://www.unaids.org) (Epi fact sheets)

**2. Using mathematical models  
on HIV prevalence data  
from cross-sectional studies**

# Mathematical models

- **Dynamical models, use data on time trends in age-specific prevalence of HIV infection**
  - makes assumptions about age dependence and
  - survivorship function for HIV infected people
- **Demographic models, mostly investigate the demographic consequences of HIV - for use in life insurance, health and pension applications**

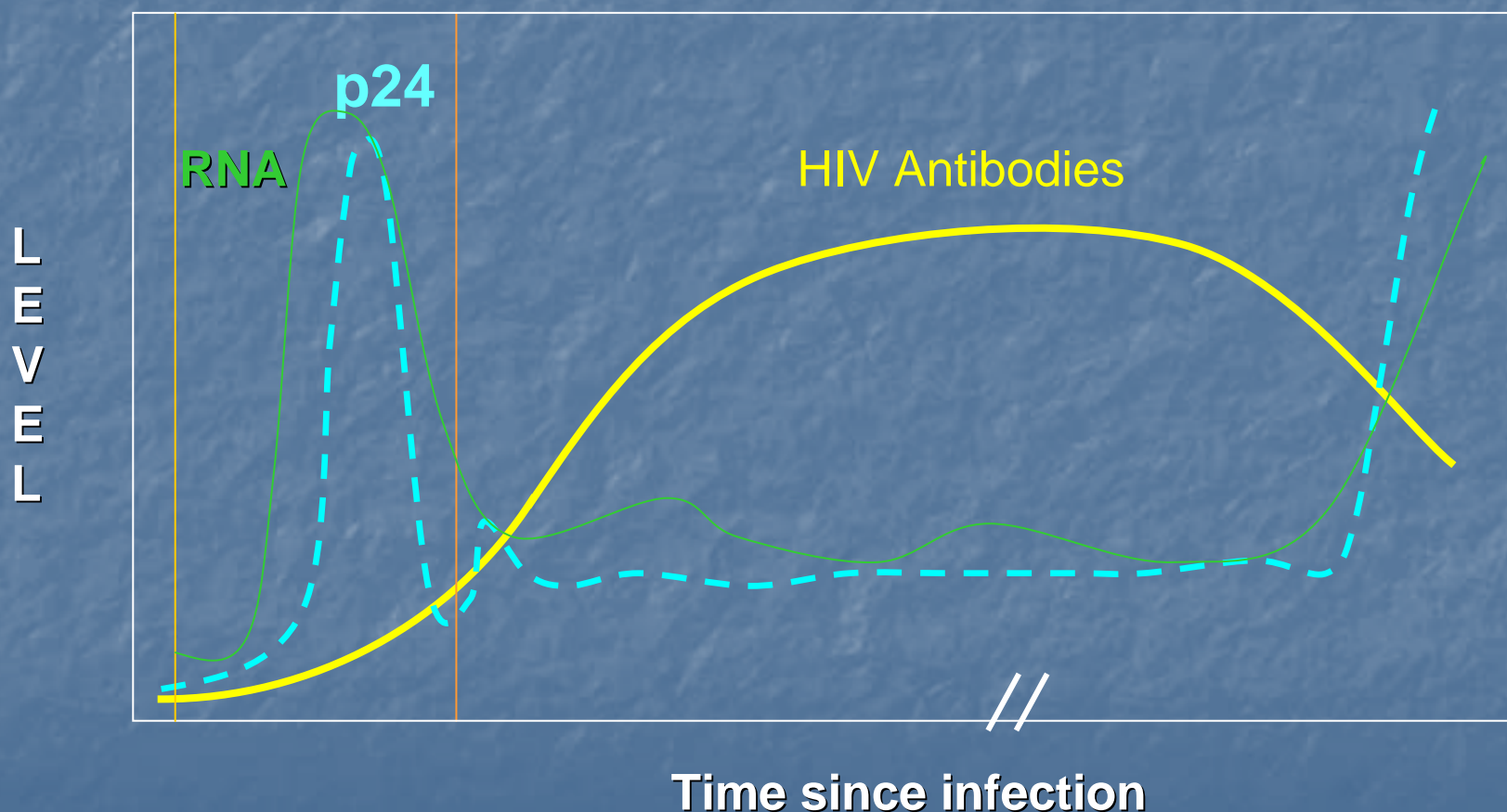
# **3. Laboratory methods to identify recent HIV infection**

## **3a. Assays for HIV infection before the presence of HIV antibodies**

- p24 antigen assay
- Nucleic acid amplification

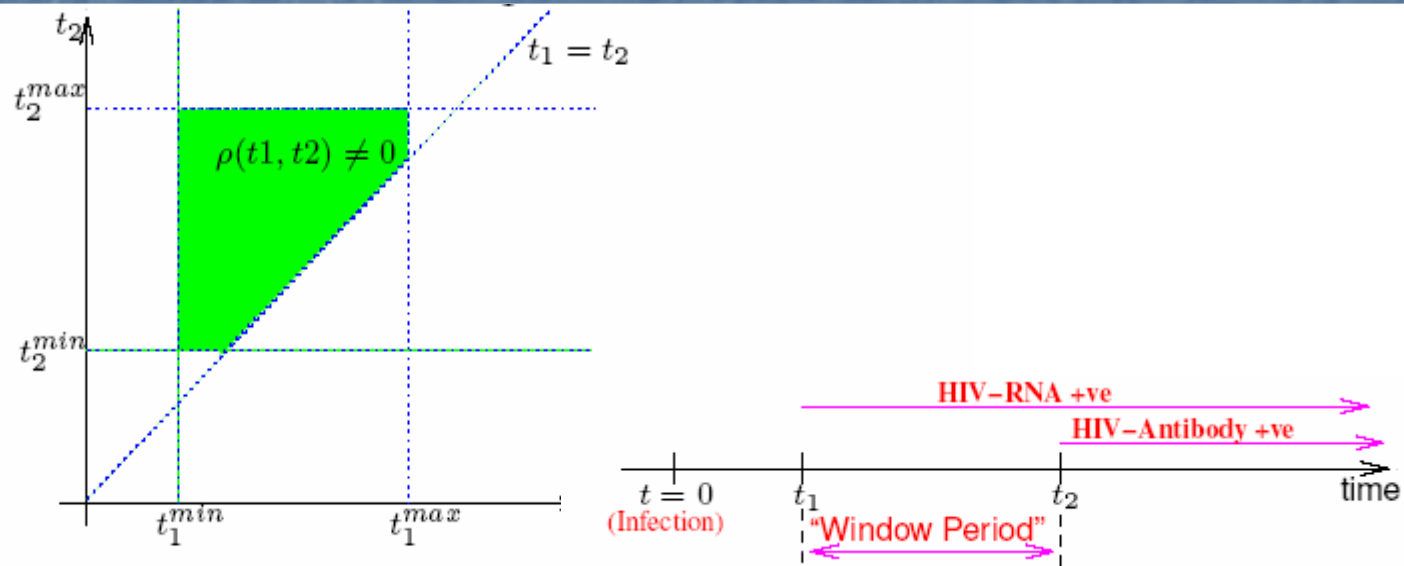
# Estimating HIV incidence from prevalence using laboratory methods: Natural Course of HIV Infection

Infection      seroconversion



# Estimating HIV Incidence from window period prevalence

Let  $(t_1; t_2)$  be the distribution of times individuals take to reach the detection thresholds of the 2 assays



$$R = \int_{-t_2^{max}}^0 \int_0^{-t} \int_{-t}^{t_2^{max}} i(t) N_s(t) \rho(t_1, t_2) dt_2 dt_1 dt \quad (2)$$

# RNA PCR pooling to estimate incidence from cross-sectional HIV prevalence studies

## ▪ Advantages

- RNA PCR highly sensitive and specific – accurate

## ▪ Disadvantages

- HIV antibody tests are becoming more sensitive – reducing the duration of the window period
- Costly – need many pooled PCRs to identify one window period PCR+ Ab- specimen
- Need to confirm that HIV Ab is negative – not a false negative. Even a small Ab false –ve rate makes a big impact on estimate of incidence
- Variations in duration of window period

# Estimating HIV incidence : laboratory methods

- P24 antigen - to identify early “window period” infection
- RNA PCR - diagnosing early HIV infections
- Sensitive/less sensitive assay: Based on low Ab levels in early infection
  - Variability in duration of positivity by clade
  - Cannot distinguish early and late stage disease
  - Substantial over-estimation of incidence
- BED capture enzyme immunoassay - Based on anti-HIV IgG to total IgG fraction: OD<0.8 in early infection
  - Unreliable due to variability in the humoral response
  - Over-estimates incidence

# **3. Laboratory methods to identify recent HIV infection**

## **3b. Assays to distinguish early antibody responses from antibodies in established infection**

- Sensitive / less sensitive ELISA
- IgG-Capture BED EIA
- Avidity index (& variations on this)

# Avidity Index

**Based on weakness of Ab-Ag binding in early infection:**

**Avidity Index <80% indicates infection within the last 120 days**

**Similar shortcomings as BED-EIA**

# Laboratory methods to estimate incidence from cross-sectional studies

- **Pros:**

- Quick and easy to do
- Generally cheaper than cohort studies
- Can be done without patient identifiers

- **Cons:**

- Does not simulate trial setting (recruitment, follow-up, interventions)
- Low levels of accuracy - subject to high false positives
- Variability by clades

# 4. Estimating incidence from cohort studies

- Pros:
  - Provides a real measure of incidence
  - Cohort studies can simulate trial setting
  
- Cons:
  - Expensive
  - Time-consuming – incidence may change
  - Since done with small samples – incidence estimates have wide confidence intervals
  - Without the intervention – conditions are different from a clinical trial



# **HIVNET/HPTN 055**

## **HIV Prevention Preparedness Study**

**A Study of the HIV Prevention Trials Network**

**Sponsored by:**

Division of AIDS, US National Institute of Allergy and Infectious Diseases

US National Institute of Child Health and Human Development

US National Institute of Mental Health

US National Institute on Drug Abuse

US National Institutes of Health





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## PROTOCOL

### HIV Incidence Rates in Vulindlela and Durban: A Prevention Preparedness Study<sup>1</sup>

#### **Principal Investigator:**

Professor Quarraisha Abdool Karim

#### **Co-Investigators**

Prof Willem Sturm

Prof Salim S Abdool Karim

# Cohort studies to estimate incidence: Example from Vulindlela cohort

- Enrolled 369 HIV- women in 12 months; 782 screened
- 22 seroconversions in 300 person years (py)
- HIV incidence rate: 7.7 per 100 py  
95% Confidence Interval: 4.3 – 11.1 per 100 py
- Incidence rate changes over time in this cohort:
  - first 6 months post-enrolment: 5.3%
  - second 6 months post-enrolment: 7.1%
  - third 6 months post-enrolment: 9.2%

# 5. Extrapolating incidence from other trials in the same population

- Pros:
  - Estimate of incidence under trial conditions
  - Obtain estimates of trial screen : enrol ratio
  - Obtain estimates of enrolment and retention rates
  
- Cons:
  - Rarely available
  - Incidence may have changed since previous trial
  - Need long-term commitment to sites

# HIV incidence in truck stop sex workers in COL-1492 trial and CAPRISA 002 cohort

Year	HIV Incidence rate per 100 py (95% CI)	Number HIV +
1996/7	16.8 (8–26)	14
1998	18.2 (11–25)	25
1999	20.0 (9– 31)	13
Overall 1996/9	18.2 (13–23)	52
New study: 2004-5	8.2 (4 - 13)	23

Source: Abdool Karim SS, Ramjee G and Gouws E  
 – Data from COL-1492 trial and CAPRISA 002



## In summary...

- The more costly and time consuming methods of estimating incidence are more reliable
- Mathematical models are cheapest and can provide useful insights – limited by assumptions in model
- Laboratory methods have variable accuracy – newer assays like PCR are costly but more accurate
- Cohort data and incidence rates from previous trials are useful – however, need to consider changing epidemics
- Different methods not mutually exclusive – combination of methods more reliable

# Conclusion

Approach to help decide which method of estimating HIV incidence is most appropriate for your HIV prevention trial preparations:

- How important is it to know the incidence rate?
- What margin of error willing to tolerate?
- How long before you need the estimate?
- How much money can you afford to spend to estimate HIV incidence?