MEASURING HIV INCIDENCE:

APPROACHES & CHALLENGES

VOCABULARY

HIV PREVALENCE

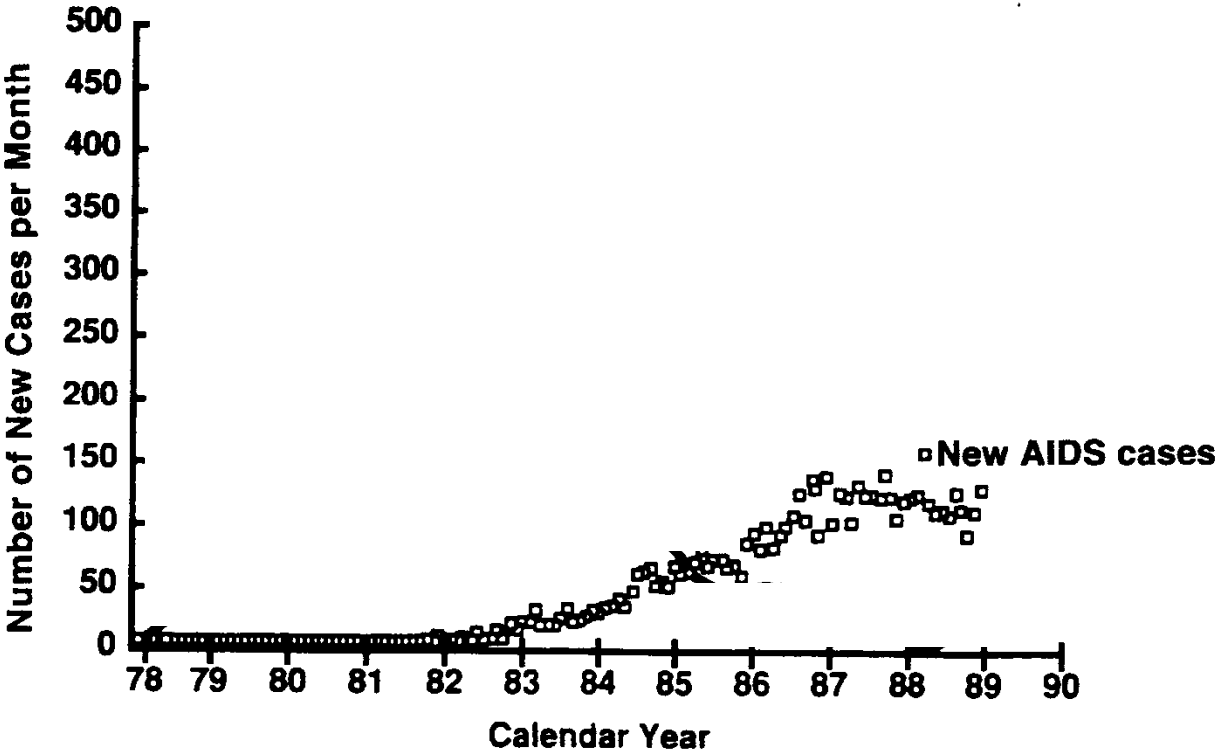
HIV INCIDENCE

U.S. Centers for Disease Control 2008

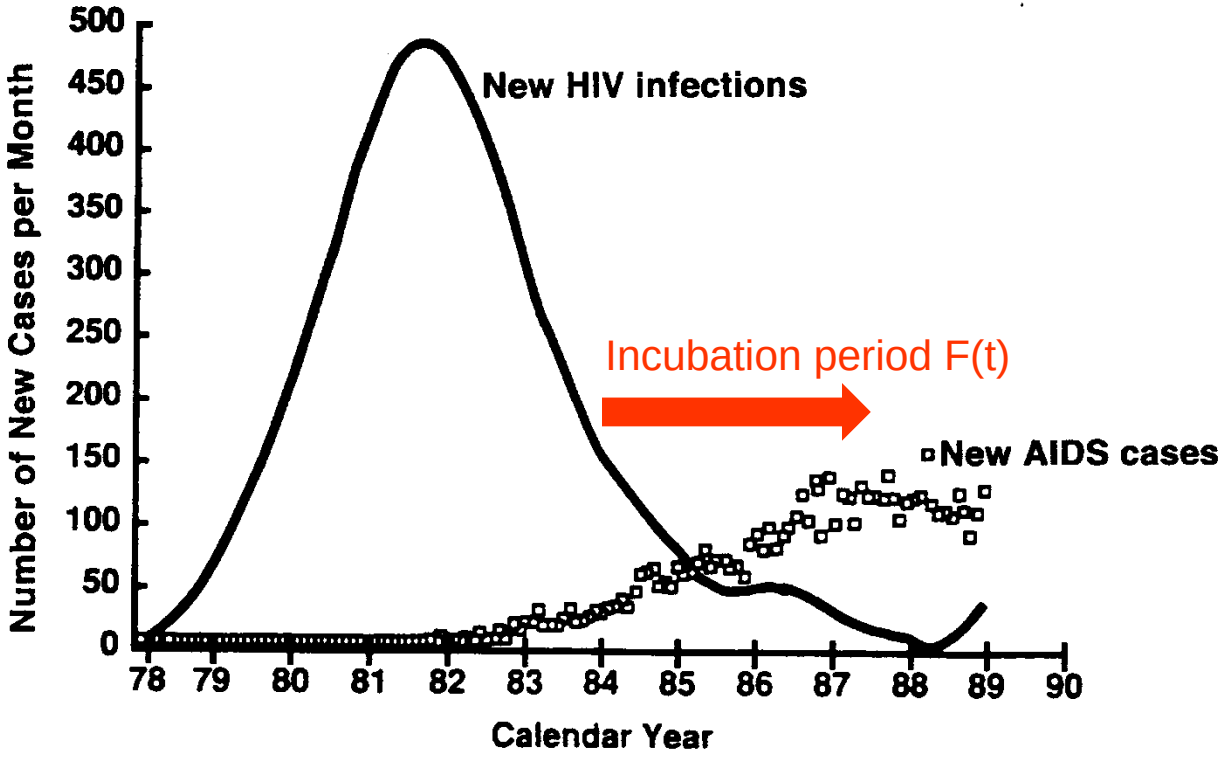
HIV PREVALENCE = 1.1 MILLION

HIV INCIDENCE= 56,000

HIV PREVALENCE


Number of New Cases per Month
500
450
400
350
300
250
200
150
100
50
0
78
79
80
81
82
83
84
85
86
87
88
89
90
Calendar Year
New AIDS cases

i


Number of New Cases per Month
500
450
400
350
300
250
200
150
100
50
0
New HIV infections
Incubation period F(t)
New AIDS cases
78
79
80
81
82
83
84
85
86
87
88
89
90
Calendar Year

BACK-CALCULATION

DECONVOLUTION

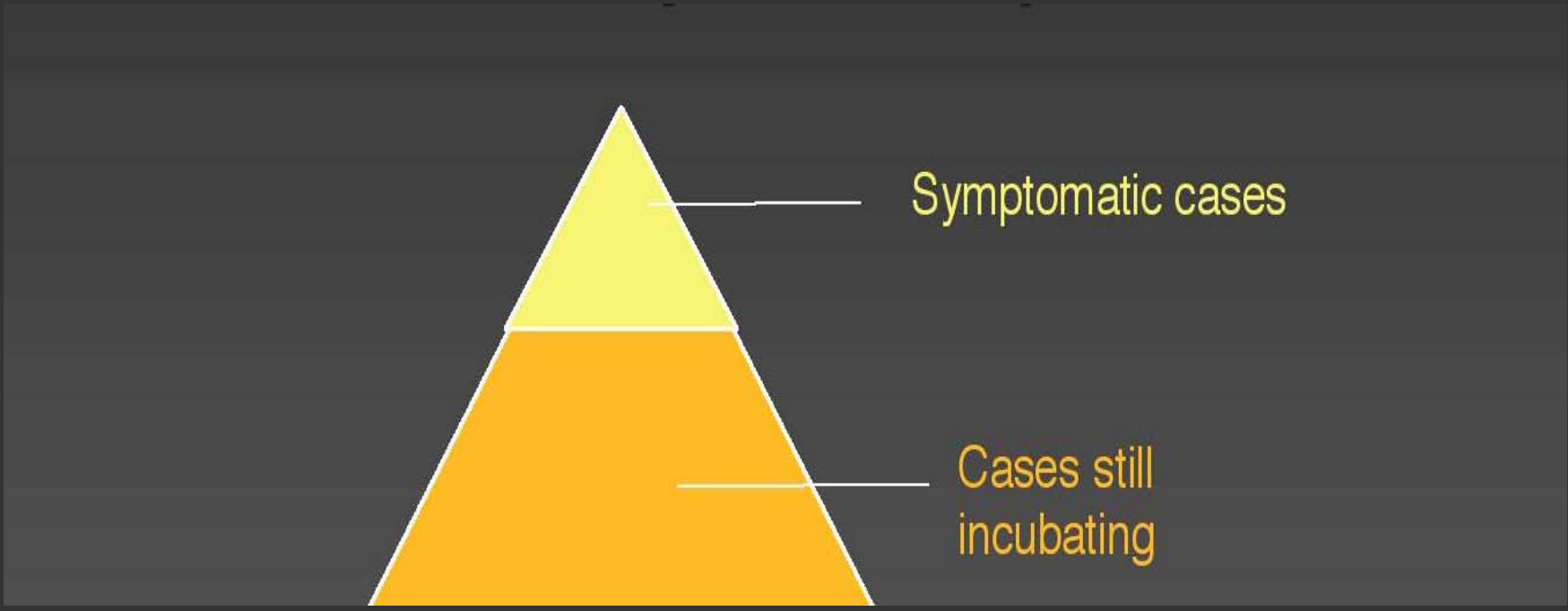
AIDS DX DATE = HIV INFECTION DATE + INCUBATION

$$E(y_i) = \int_0^{t_i} I(s) F(t_i - s) - F(t_{i-1} - s) ds$$

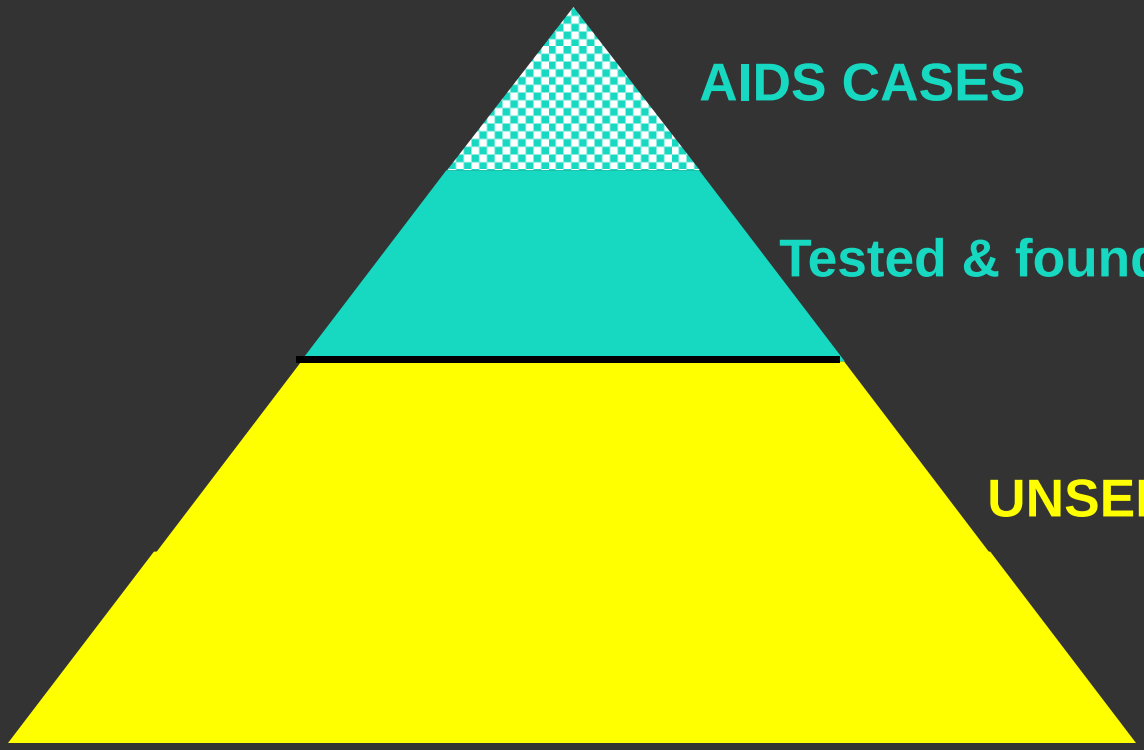
$$E(\mathbf{y}) = \boldsymbol{\beta}\mathbf{Z}$$

$$\text{var}(\mathbf{y}) = \sigma^2 E(\mathbf{y})$$

BACK-CALCULATION: ICEBERG EFFECT

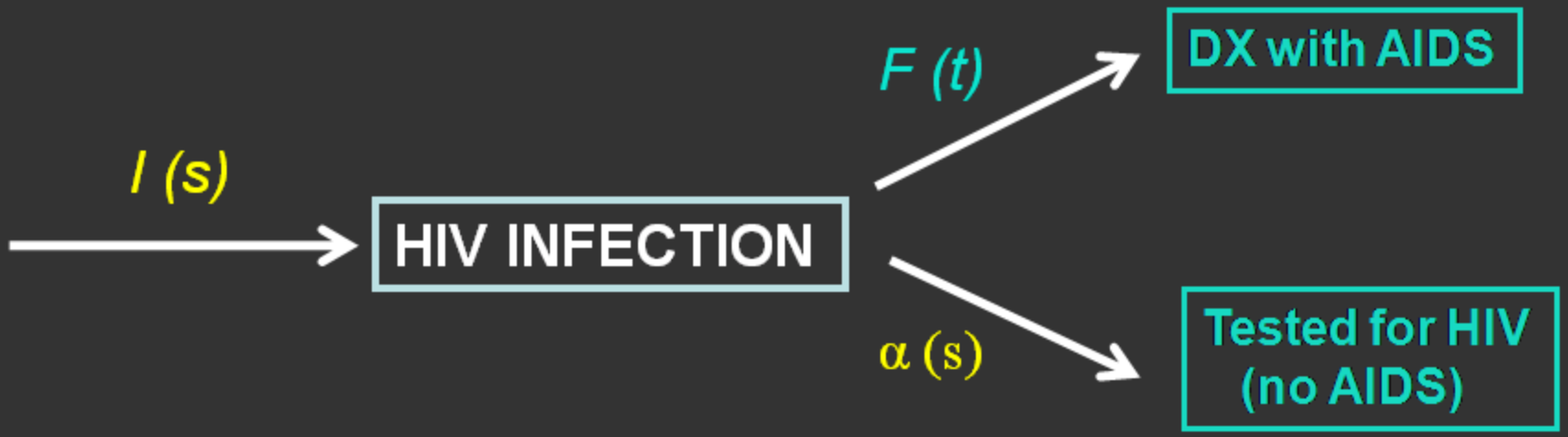


BACK-CALCULATION: ICEBERG EFFECT



EXTENDED BACK-CALCULATION

DECONVOLUTION
Rhodes (2008), Hall et al (2008)



US HIV PREVALENCE

U.S. HIV PREVALENCE=1.1 million (*JAMA*, 2008)

- STATISTICAL DECONVOLUTION
- UNCERTAINTIES
  - INCUBATION PERIOD
  - COMPLETENESS OF CASE REPORTING
  - PARAMETRIC MODEL FOR $\alpha(s)$, $I(s)$
  - RECENT INFECTIONS

CURRENT HIV INCIDENCE

MEASURES THE LEADING EDGE OF THE EPIDEMIC

- COHORT STUDY
- CROSS-SECTIONAL BIOMARKER APPROACH

CURRENT HIV INCIDENCE

COHORT STUDY

$$\textit{Incidence} = \frac{\textit{incident infections}}{\textit{person time}}$$

ISSUES

Assembling cohort is difficult
Counseling may reduce HIV risk
Incidence is changing over time
Selection bias: who returns for follow-up?

CURRENT HIV INCIDENCE

BIOMARKER APPROACH

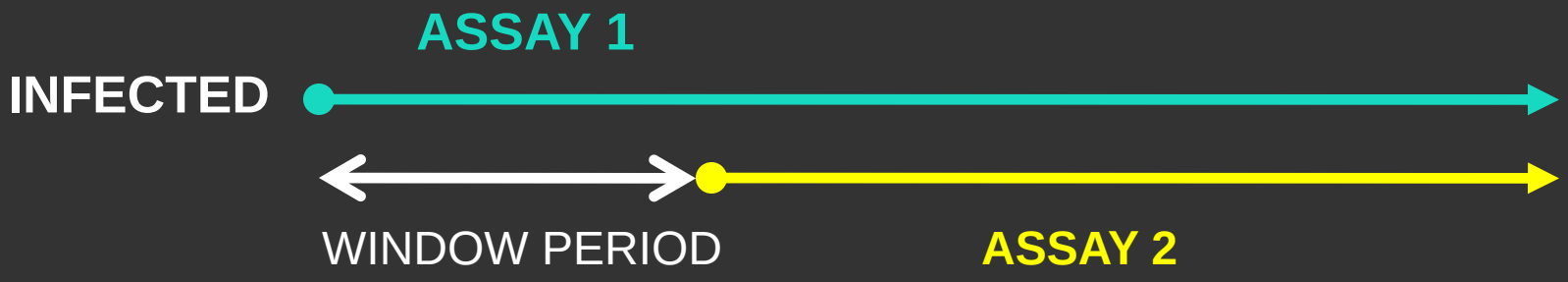
- CROSS-SECTIONAL SAMPLE

- COLLECT BIOMARKERS OF RECENT INFECTION AT BASELINE

- SNAPSHOT APPROACH

BIOMARKER APPROACH

BIOMARKER APPROACH



S(t) *window period survival distrb.*
μ *= mean window period*

BIOMARKER APPROACH

$$P(Window) = \int_0^\infty g(t)\,S(t)\,dt$$

$$\approx g \int S(t)$$

$$= g\mu$$

μ= mean window period
g=pdf of window entry times

BIOMARKER APPROACH

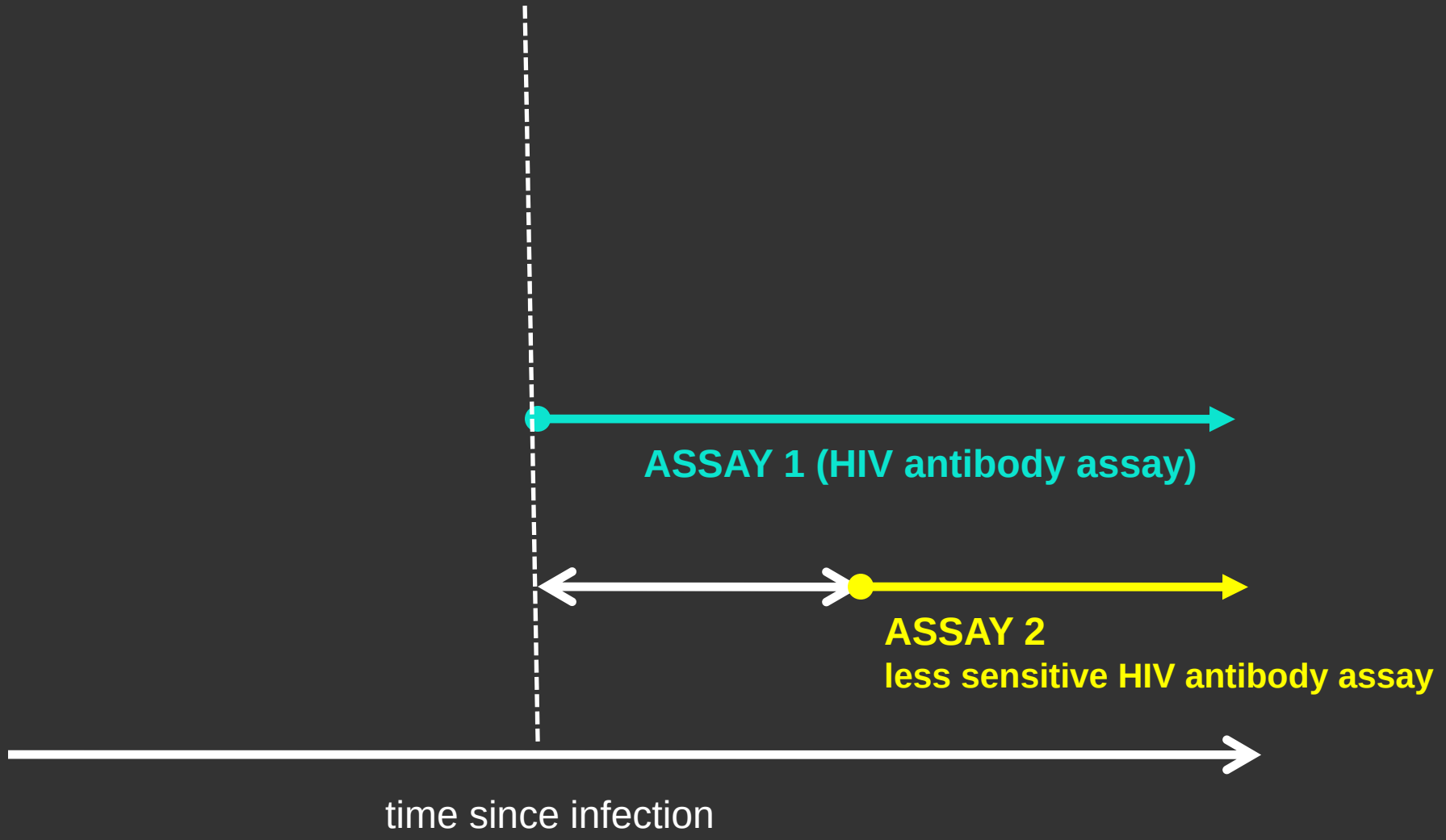
PROPORTION IN THE WINDOW = INCIDENCE X μ

$$\hat{I} = \frac{x}{N\mu}$$

X= # in window : assay 1 +, assay 2 -
N= # assay 2 –

- CROSS-SECTIONAL SAMPLE
- NO FOLLOW-UP!
- **SNAPSHOT** ESTIMATOR

ANTIBODY BIOMARKERS



BIOMARKERS FOR RECENT INFECTION

DETUNED ASSAY*	μ=129 days
BED ASSAY*	μ=156 days

*Need to assay only those HIV antibody +

NEW U.S ESTIMATE OF HIV INCIDENCE

56,300 ANNUAL NEW HIV INFECTIONS IN U.S.
***JAMA* 2008**

- BASED ON CROSS-SECTIONAL BIOMARKER APPROACH (BED ASSAY)
- ESTIMATE PROBABILITY PERSON GETS HIV TEST
- 19 EXTRAPOLATED TO 50 STATES

BIOMARKER APPROACH

U.S.
EUROPE
INDIA
THAILAND
CARIBBEAN
AFRICA

CONTROVERSY

CDC

"The BED biomarker assay is the preferred approach for calculating HIV incidence in the U.S."

UNAIDS

"Does not recommend the BED assay for determining incidence"

ZIMBABWE
ZVITAMBO STUDY OF NEW MOTHERS

BIOMARKER ESTIMATE =2 X HIGHER THAN COHORT
Hargrove (2008)

•Follow-up bias?

• “False recents”
McWalter and Welte (2009)
Wang and Lagakos (2009)

BIOMARKER APPROACH: THEORY

INCIDENCE NOT CONSTANT ?

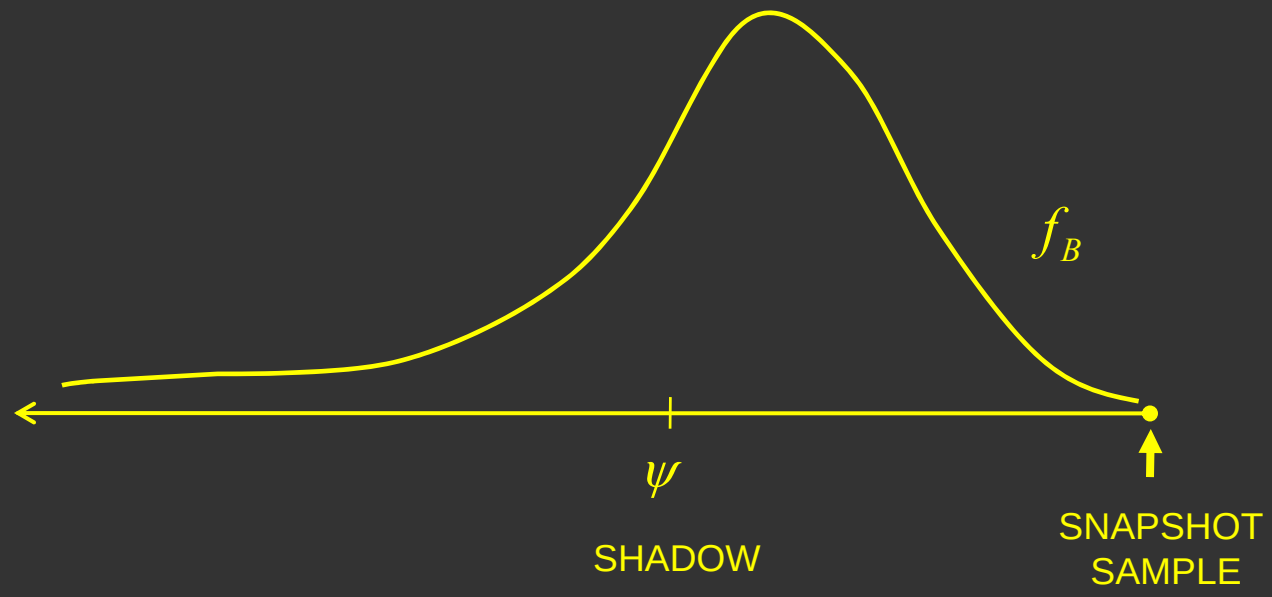
$$\hat{I} \rightarrow \bar{I} \approx \int_0^{\infty} I(t) f_B(t) dt$$

$$f_B(t) = \frac{S(t)}{\mu} = \textit{backward recurrence density}$$

$$\psi = \int t f_B(t) = = \int t \frac{S(t)}{\mu} dt$$

$$\bar{I} \approx I(\psi) + \frac{I''(\psi) V}{2}$$

KAPLAN AND BROOKMEYER, *OPERATIONS RESEARCH*



SHADOW ψ = mean of backward recurrence

$$\overline{I} \approx I(\psi)$$

$$\psi = \int t f_B(t) = = \int t \frac{S(t)}{\mu} dt = \mu\left(1 + CV^2\right)$$

SHADOWS

SHADOW DEPENDS ON MEAN AND CV OF WINDOW

SHADOW (years)

Mean window (yrs)	Coefficient of variation .50	1.0	2.0	3.0
.25	.16	.25	.63	1.25
.50	.31	.50	1.25	2.50
1.00	.63	1.00	2.50	5.00
1.50	.94	1.50	3.75	7.50

ACCURACY ?

- BIAS & VARIANCE

- ACCURACY OF ASSAY FOR HIV INCIDENCE:
  MEAN WINDOW (μ)
  SHADOW (CV, μ)

- BIG μ OR SMALL μ?
  TRADEOFF : BIAS VS VARIANCE

ISSUES
WITH BED/DETUNED ASSAY METHOD

- **ELITE CONTROLLERS**
  - LONG TAILS OF *S(t)*
  - LOW VIRAL LOADS

Brookmeyer, “On the Statistical Accuracy of Biomarker Assays for HIV Incidence,” J. AIDS, 2010

ISSUE
ELITE CONTROLLERS: MIXTURE MODEL

- FAST PROGRESSORS THROUGH WINDOW = γ
- SLOW PROGRESSORS THROUGH WINDOW $= 1-\gamma$
  (e.g. elite controllers)

$$S(t) = \gamma S_1(t) + (1-\gamma) S_2(t)$$

$$shadow = \frac{\mu_1^2\left(1+CV_1^2\right)\gamma + \mu_2^2\left(1+CV_2^2\right)(1-\gamma)}{2\left(\mu_1\gamma + \mu_2(1-\gamma)\right)}$$

MIXTURE MODEL: ELITE CONTROLLERS

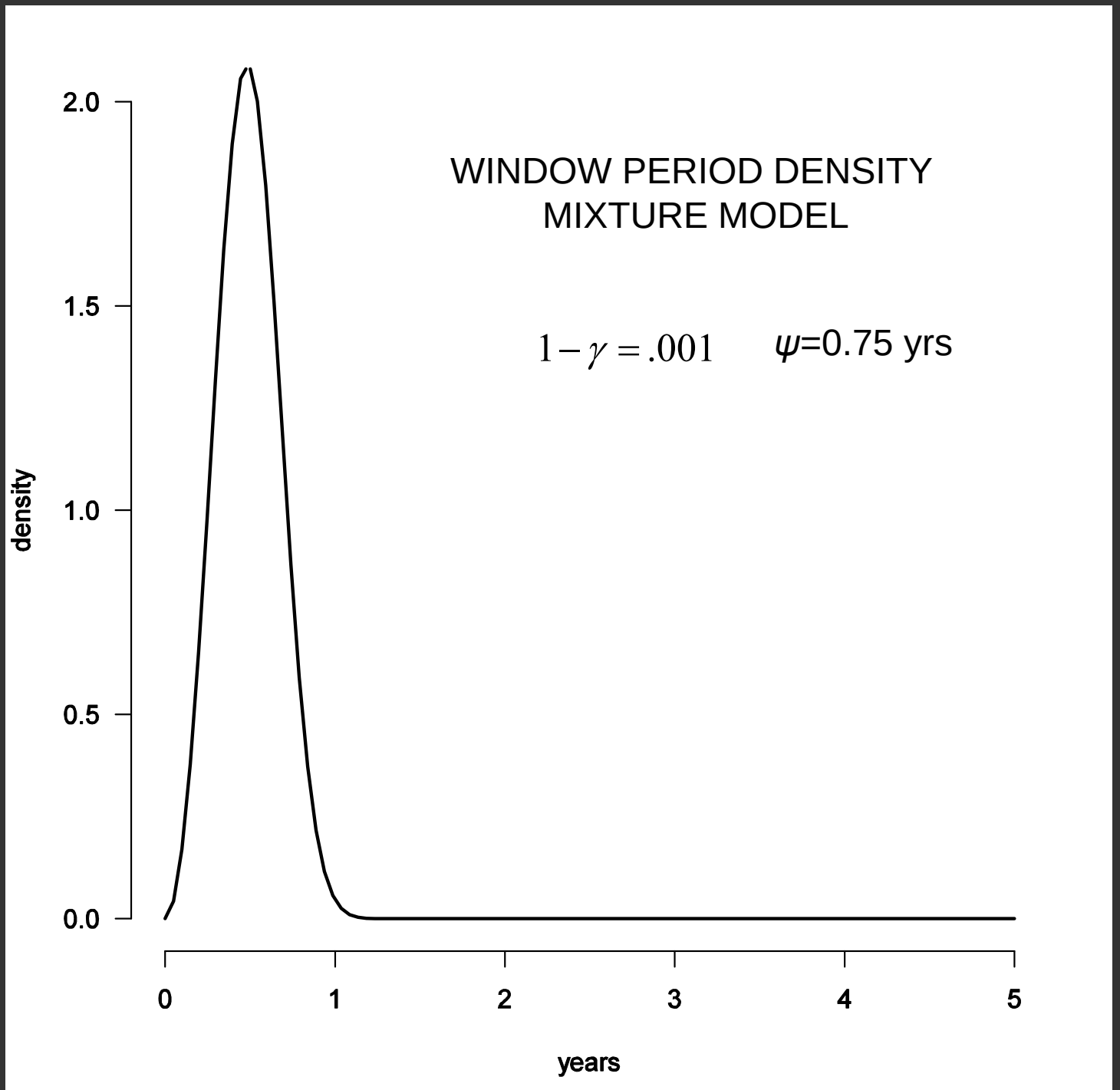
$$S(t) = \gamma S_1(t) + (1-\gamma) S_2(t)$$

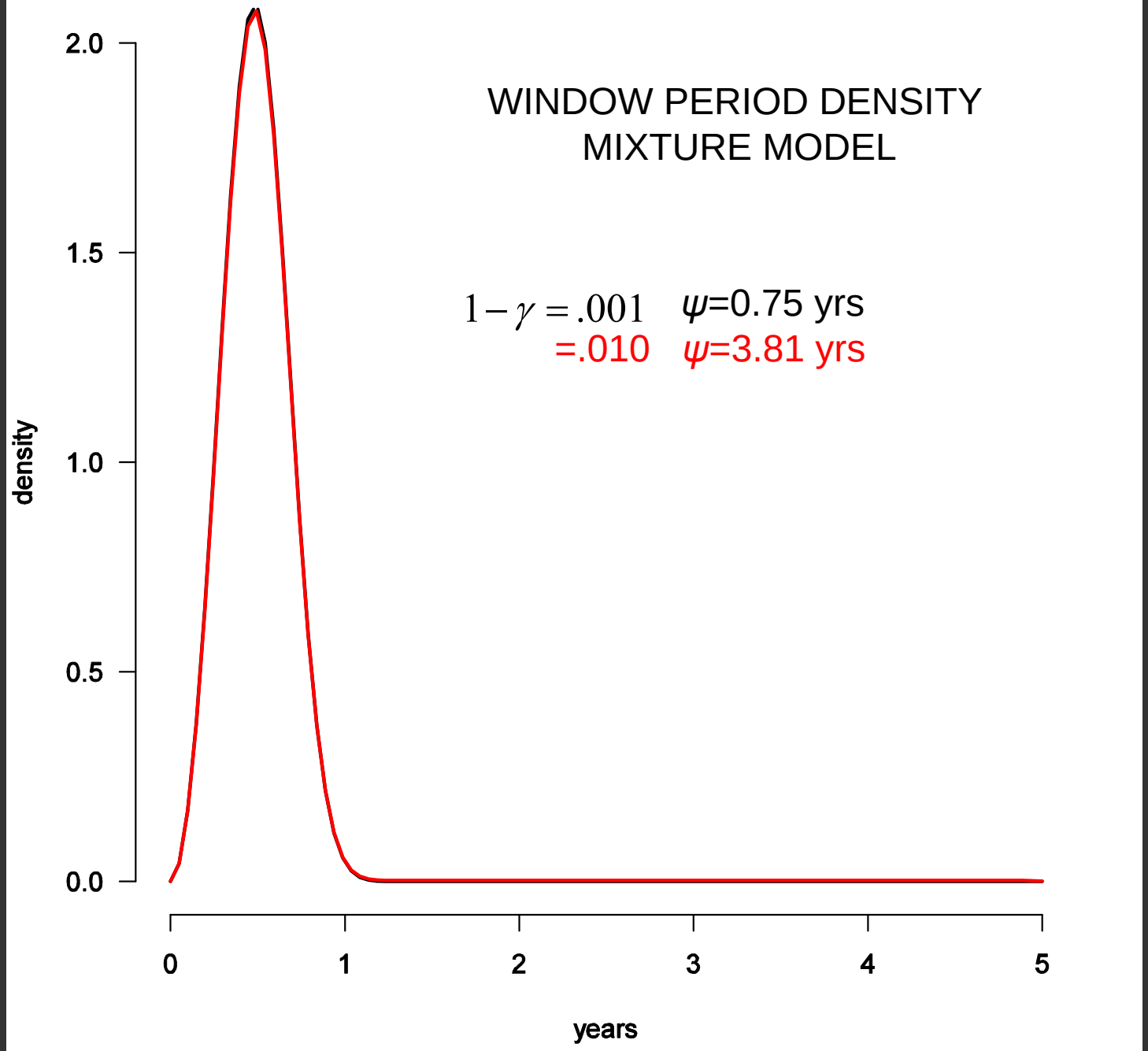
μ_1=0.5 yrs
weibull cv_1=.36

μ_2 =20 yrs
weibull cv_2=.50

$1-\gamma$	μ yrs	Shadow yrs
.000	0.50	0.28
.001	0.52	0.75
.005	0.60	2.33
.010	0.70	3.81
.015	0.79	4.91
.020	0.89	5.77

Brookmeyer, "On the Statistical Accuracy of Biomarker Assays for HIV Incidence, *J. AIDS*, 2010


WINDOW PERIOD DENSITY
MIXTURE MODEL
$1-\gamma = .001$
ψ=0.75 yrs
density
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
years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1.5
1.0
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4
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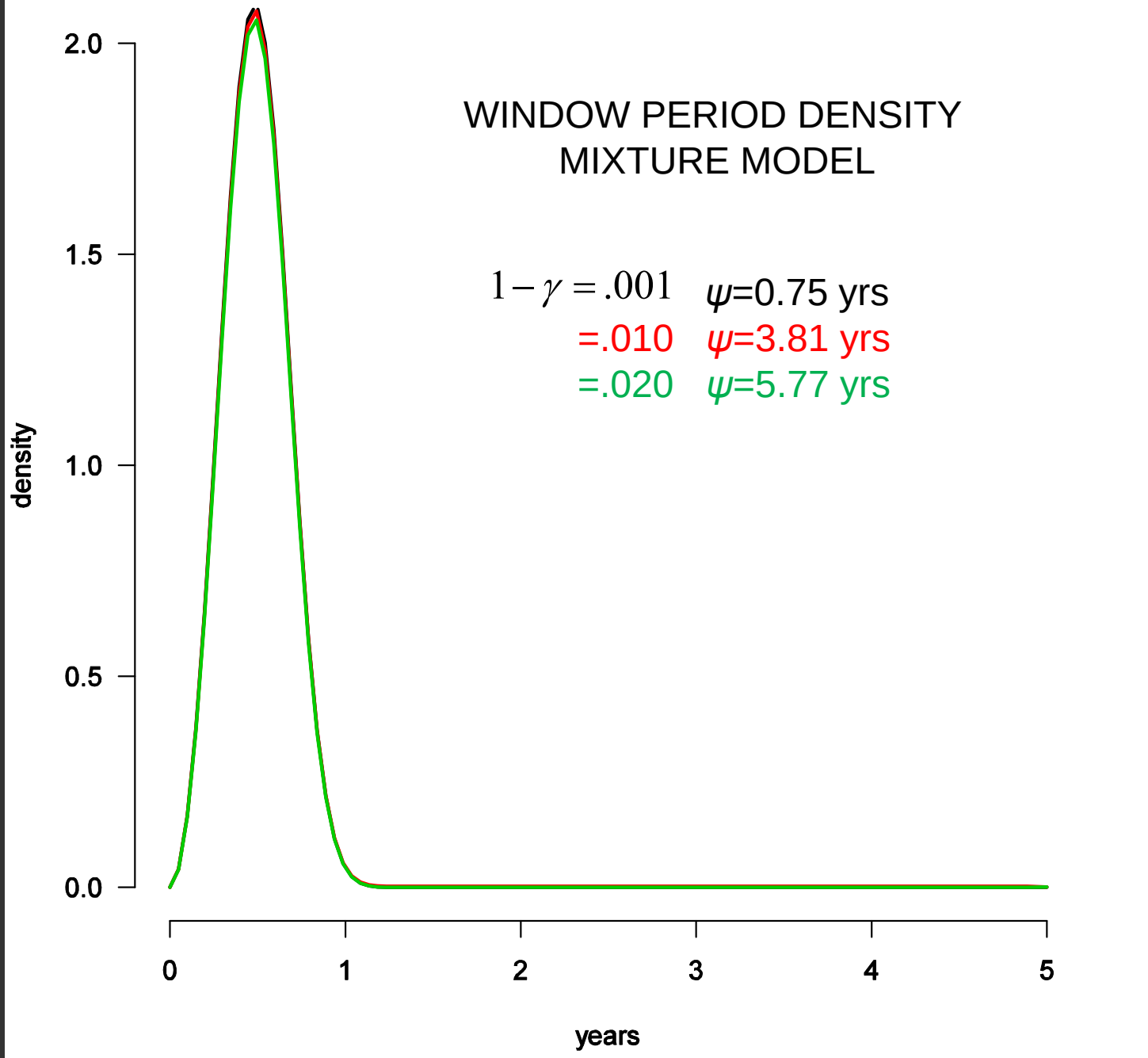
years


WINDOW PERIOD DENSITY
MIXTURE MODEL
$1-\gamma = .001$ ψ=0.75 yrs
=.010 ψ=3.81 yrs
=.020 ψ=5.77 yrs
density
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
years

ZIMBABWE CONTROVERSY

- Biomarker incidence higher than cohort estimate in study of new mothers

- A shadow of 2+ years is produced with only 0.5 % elite controllers.

- HIV Incidence :
  Pre-partum vs post partum period
  Counseling/behavior change

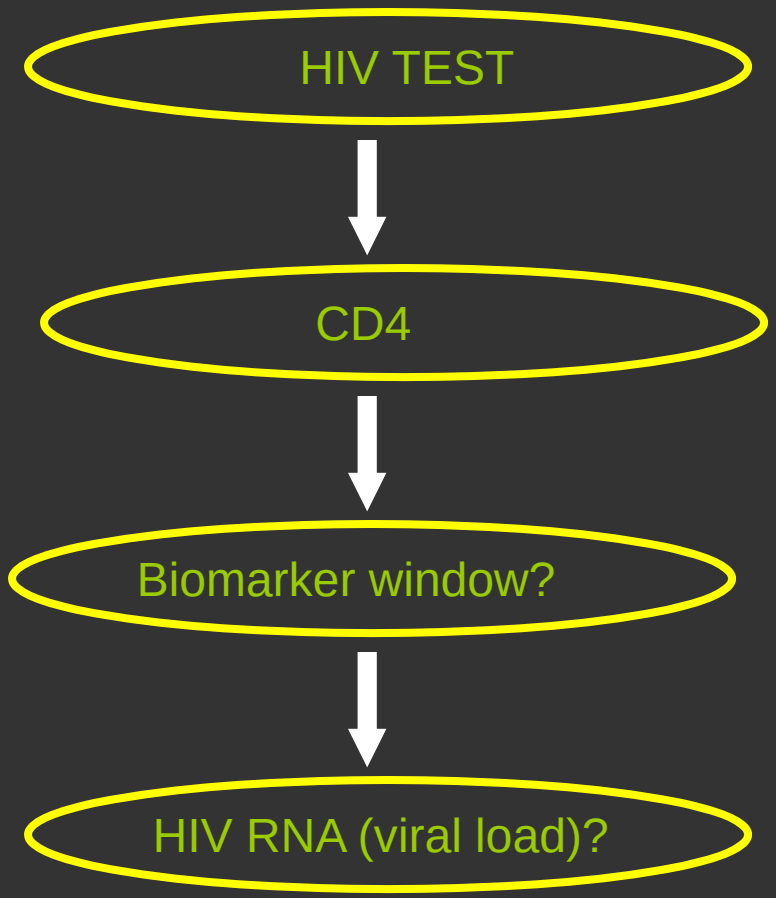
Brookmeyer, AIDS(2009); Brookmeyer,JAIDS (2010)

TINY ALMOST IMPERCEPTIBLE DIFFERENCES IN TAIL BEHAVIOR CAN HAVE HUGE EFFECTS !

SOME SUGGESTIONS

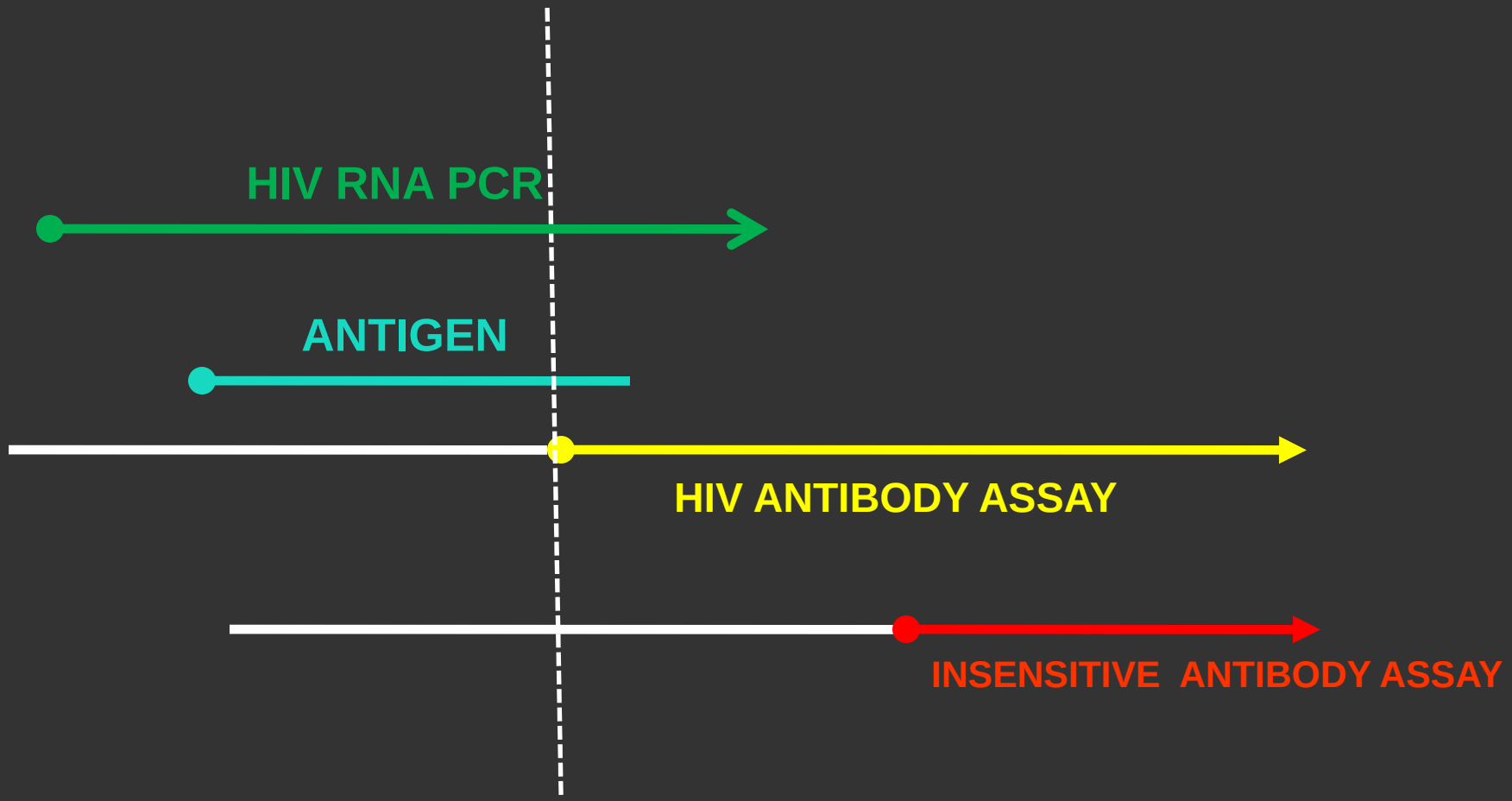
TRIM THE TAILS

WEED OUT ELITE CONTROLLERS, AIDS CASES, ON ART



Laeyendecker et al, 2009

RNA PCR /ANTIBODY BIOMARKER



PERSPECTIVES

- STATISTICAL CONTRIBUTIONS TO MEASURING HIV EPIDEMIC

- INCORPORATE BIOLOGY INTO MODELS

- SMALL CHANGES IN TAILS CAN HAVE BIG EFFECTS!

- ITS NOT ONLY ABOUT A SINGLE NUMBER: TRENDS