

## Deriving Incidence Estimates from Cross-sectional Measures

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HPTN NL PI

## Cross-sectional incidence testing in HIV prevention trials

Identify populations at high risk of HIV infection

Evaluate prevention interventions using a single, cross-sectional incidence endpoint

Are current laboratory approaches for cross-sectional HIV incidence assessment robust enough for use in clinical trials?

## Assays for acute HIV infection

Ag or RNA pos - Ab neg  
Well-accepted

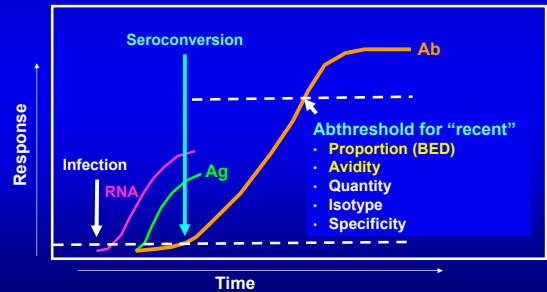
Small window period  $\Rightarrow$  huge study size  
Pooled HIV RNA testing is complex  
Sensitivity varies (pool size, assay cutoff)

Abbott HIV Ag/Ab COMBO assay  
High throughput, rapid, simple  
Detected 61.9% acute samples  
vs.  $\approx$ 71% predicted with pooled HIV RNA testing (pools of 100, 50 c/ml assay)

J AIDS (2009) 52:121-4

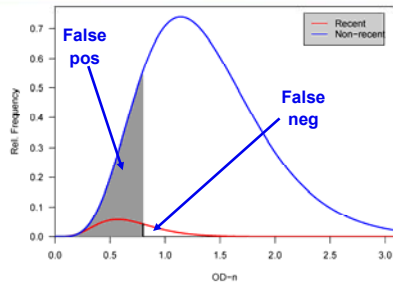
## Assays for recent HIV infection

Traditional approach: Use serologic assays to differentiate between recent and chronic infection

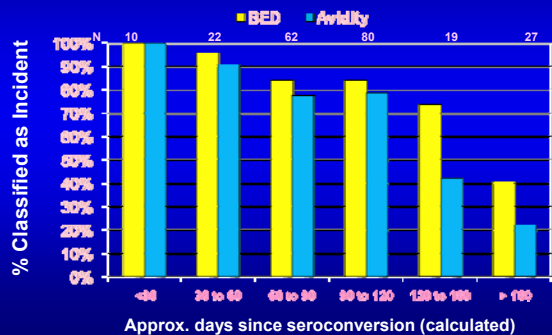


## Misclassification (BED)

Misclassification rate can be  $\gg$  incidence rate



## Misclassification-False Negatives EXPLORE



## Misclassification: False Positives ALIVE

488 chronically-infected IDUs  
2-6 years after HIV infection  
50 (10.2%) misclassified as recent by BED

### Risk factors for misclassification

VL <400  
CD4 <50

NS: Gender, age, sample year (1994-1999),  
years after SC (<=> 4.5 yrs), ART, HSV-2 status

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## Cross-sectional survey JHU ED

Mature epidemic (many HIV+ > 6 yrs)

↑% with low CD4

↑% with viral suppression  
(ARVs + natural suppression)

Viral suppression (VL <400 c/ml)

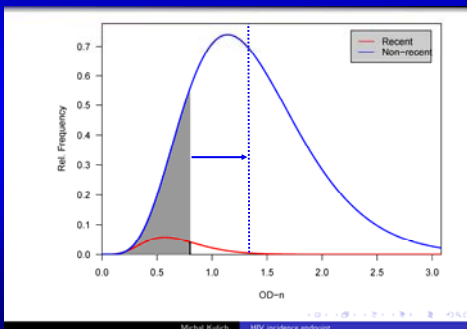
2001=20%

2007=32.7% → 9% with no ARVs

BED estimated incidence for 2007 was 3.5%  
Other data suggests that the true value is ~0.3-0.6%

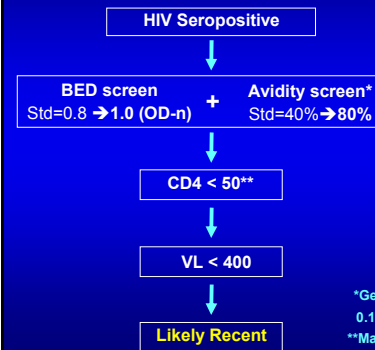
Laeyendecker CROI 2009 #1045

## Does it make more sense to use serologic as screening assays for recent infection?



Michal Katsch HIV incidence endpoint

## HPTN NL multi-assay algorithm



\*Genetic Systems HIV-1/HIV-2 + O EIA  
0.1M diethylamine (chaotropic agent)  
\*\*May need a higher CD4 cutoff if non-B

## HPTN NL multi-assay algorithm

	BED	Alg1	Alg2	Alg3	Avid	Alg4	Alg5	Alg6
BED	<0.8	<0.8	<0.8	<0.8		<1.0	<1.0	<1.0
Avid					<40%	<80%	<80%	<80%
CD4			>200	>200		>200	>50	>50
VL			>400	>400		>400	>400	>400
<b>EXPL n=144, sens</b>								
<100 days	88.7				79.3	88.7		
≤ 1 yr	79.3				65	77.9		
<b>ALIVE n=488, spec</b>								
2-6 yrs post infection	89.8	93.5	94.3	97.6	99.0	97.0	99.2	99.0

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## Key points

In clinical trials, we need to detect differences between  
very small numbers (e.g., 2% vs. 1%)

Incidence estimates must be "precise"

HIV incidence estimates are strongly influenced by  
misclassification of chronics as recent

The frequency of misclassification can vary depending  
on the population studied

AIDS, ARVs, natural suppression, HIV subtype, etc.

## HPTN NL approach

Combine data from two serologic assays  
Use serologic assays for screening only (↑ cutoffs)  
Combine serologic assays with other measures  
Currently: BED screen, avidity screen, CD4, VL

We have analyzed numerous and diverse cohorts  
We are now using modeling to optimize our testing algorithm  
Further validation will include testing of blinded panels  
We continue to consider other assays/algorithms that may further improve the precision of HIV incidence estimates

## Acknowledgments

Oliver Laeyendecker

Study Teams

EXPLORE, ALIVE and JHU ED

NIAID – NIMH - NIDA