

## Acute HIV

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## Acknowledgements

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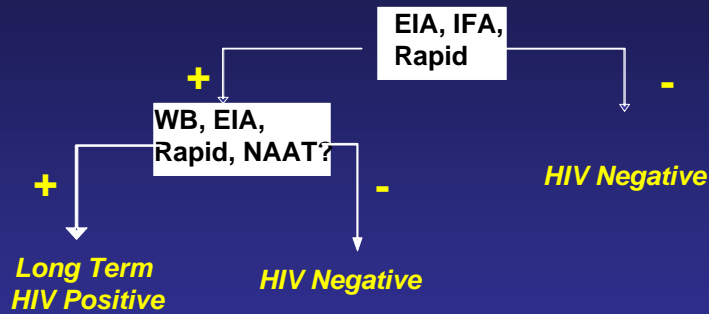
## Unrecognized HIV

- 30% or more of patients remain ignorant of their HIV status until after onset of AIDS (Blair JAIDS 2002)
- HIV incidence is stable or increasing (CDC 2005)
- Fastest increase among African Americans, women and rural residents in the US South
- The reasons behind this increase are very poorly understood

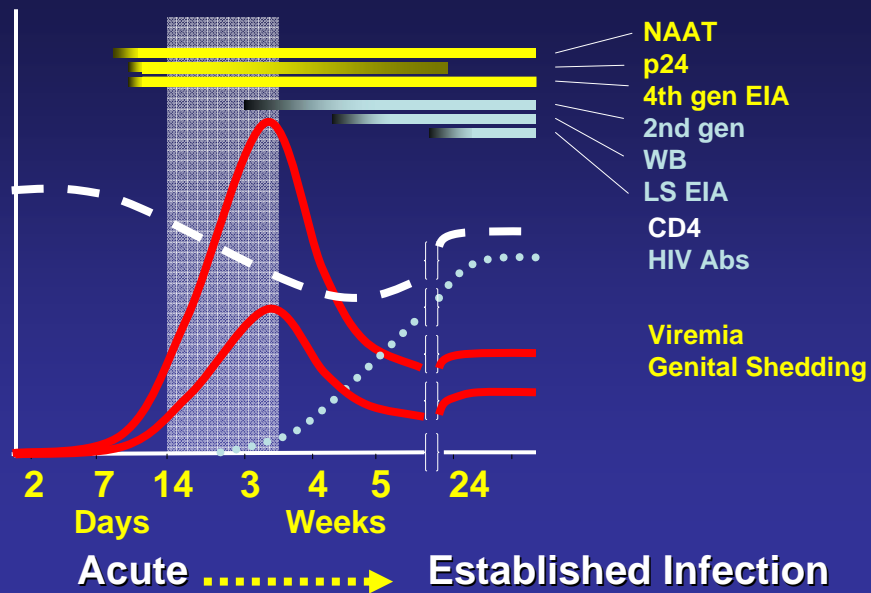
## Rapid Antibody Testing

- Makes testing feasible in non-traditional settings
  - Highly effective for outreach situations (needle exchange, bathhouse testing, “street-corner” outreach)
- Increases receipt of positive HIV test results
  - Where HIV results notification not in place
- Might increase requests for HIV testing
- Is not preferred in many established testing settings

## The strategy to identify HIV antibody positive individuals



## Screening Tests & Acute Viremia

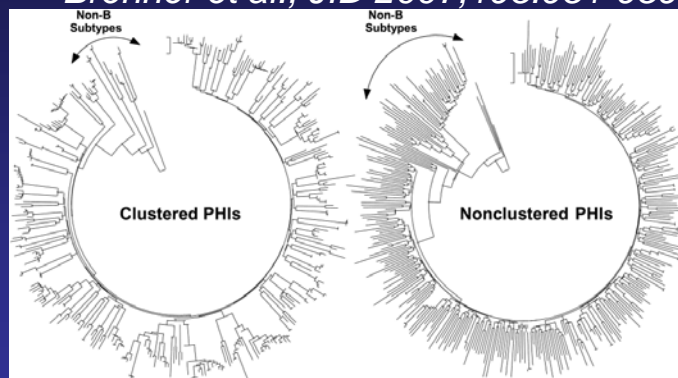


## Transmission in AHI, per partnership

<u>STUDY</u>	<u>Per-partner attack rate</u>	<u>Ave.exposure</u>
• Wawer JID 2005	10/23 (43%)	20 weeks
• Pilcher CROI 2006	6/12 (50%)	10 weeks
• Brooks AIDS 2006	3/13 (23%)	'single' acts

## Epidemiologic Linkages using Phylogenetic Analysis: Quebec

*Brenner et al., JID 2007;195:951-959*

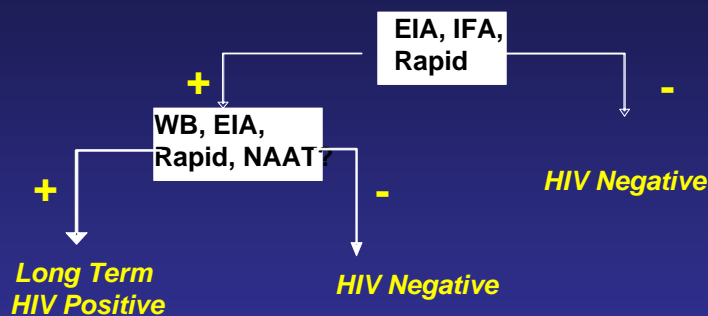


- N=593 PHI, 135 naïve CHI; 660 exp. CHI
- PHI: PHI clusters **293/593 (49.4%)**
- PHI: CHI **61/593 (10.2%)**

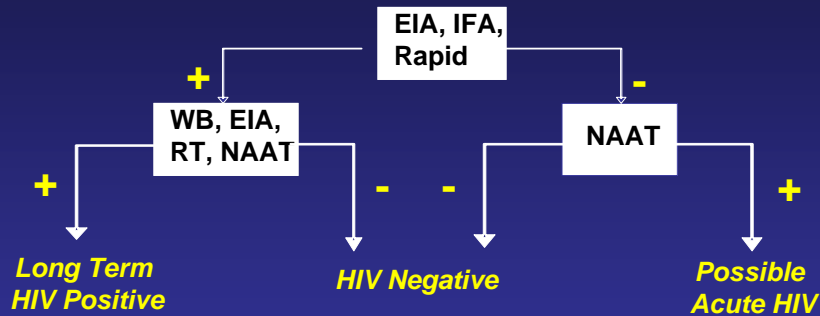
## Rationale for Acute HIV Intervention

- Transmission in acute HIV infection can contribute a substantial proportion of new infections
- High immediate risk of infection (25-50%) for contacts to acute HIV infection
- Large, immediate (albeit short-term) reductions in transmission risk behavior

## The strategy to identify HIV antibody positive individuals



## An alternative strategy: detect 'all detectable HIV infections'



## Poor clinical sensitivity (89-98%) of antibody assays in diverse general testing populations

STUDY	AHI Prevalence	% HIV+ missed by Ab
• Pilcher, C NEJM 2005 (NC)	.0002	4%
• Priddy, F CROI 2005 (Atlanta)	.002	6%
• Stekler J, AIDS 2005 (Seattle)	.002	6%
• Klausner J, NEJM 2005 (SF)	.004	11%
• Patel, P JAIDS 2006 (LA)	.006	7%
• Stevens, W IAS 2005 (Jo-burg)	.010	2%
• Pilcher, C AIDS 2004 (Malawi)	.024	5%

## Central challenges for 'window period' screening tests: Cost and Specificity

<u>Assay</u>	<u>Cost</u>	<u>Sp</u>
bDNA (Bayer)	\$\$\$	95.4 (91.4, 97.5)
RT-PCR(COBAS)	\$\$\$	99.7 (99.2, 99.9)
TMA (qualitative)	\$\$	99.8 (99.6, .99.9)
HIV p24 EIA (P-E)	\$	99.6 (98.7, 99.9)

Source: Roche, Gen-Probe: package inserts  
 bDNA: Hecht et al AIDS 2003  
 p24 Ag: Fiscus et al JID 2006

## AHI prevalence is relatively low: PPV as a Function of Specificity

Population, (AHI Prev)	NC VCT (0.0002)	Seattle MSM (0.002)	Malawi STD (0.02)
Sp=99.5	0.04	0.29	0.80
Sp=99.9	0.17	0.67	0.95
Sp=99.99	0.67	0.95	0.995

# RNA group testing of Ab- specimens circumvents cost and specificity

Pilcher, CD et al. JAMA 2002;288:216-221

Individual specimens



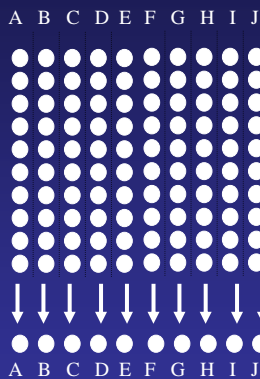
Pools of 10

## Pooling schema

Individual specimens

N=100

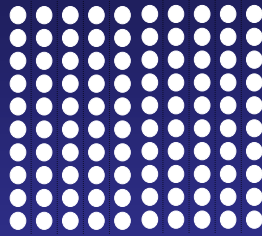
10 Pools of 10



## 2-Stage Pooling

Individual specimens  
N=100

A B C D E F G H I J



10 Pools of 10

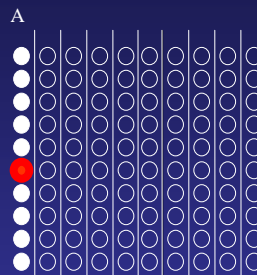


1 Screening Pool



## Resolution Testing

Individual testing on 10 specimens



10 pools of 10 screened



20 Screening Pools Tested

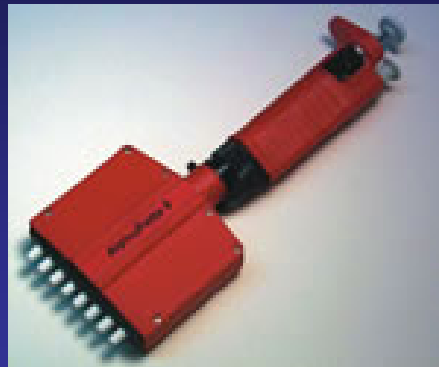


N=2000





## Hand pooling



12-Channel AlphaPette Pipettor

## HIV Testing in NC

Pilcher, CD et al. NEJM 2005 May 5;352:1873-83

- Antibody tests missed 4% of all cases because clients were **acutely HIV infected** and **antibody negative**
- Positive predictive value of a positive NAAT screen was 90%
- Central RNA testing gave high cost-efficiency (\$3.63/test, including testing and case followup) and
- Notification, interview and partner counseling were used for rapid disease intervention

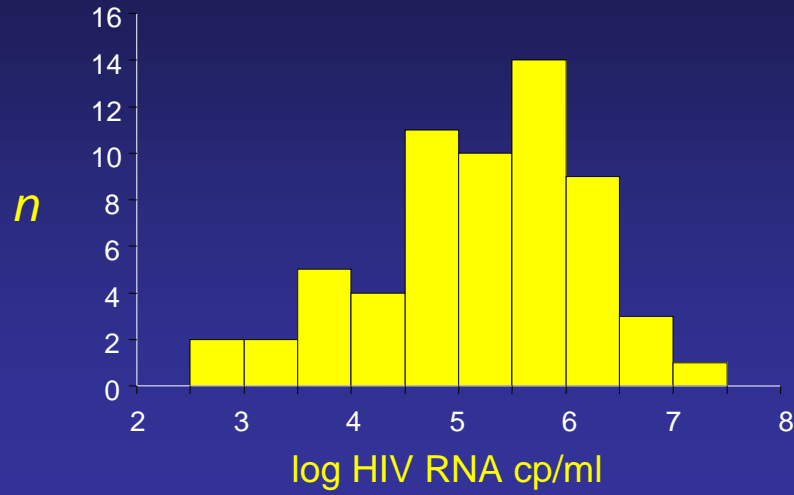
## Pooling with a Hand Pipettor and a Trough for US VCT\*

<u>Assay Specificity</u>	<u>PPV with no pooling</u>	<u>PPV using a 10:1 "minipool"</u>
0.99	.02	0.61
0.995	.04	0.85

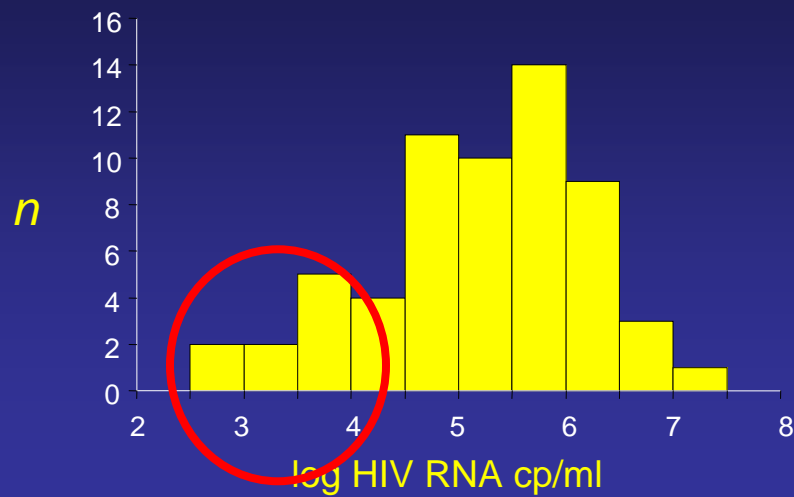
\* 2 truly RNA positive specimens per 10,000

What is the effect of specimen pooling on clinical sensitivity?

## Distribution of Viral Loads in Ab Negative VCT Specimens NC Testing Data 2002-2005 (n=58)



Low viral load specimens occur...but are rare



### Relationship between analytical sensitivity and clinical sensitivity, given VL distribution

LL, cp/ml	Ab- HIV N=58	Se (Ab-)	All HIV N=1437	Se (all)
1000	56	96.5	1435	99.9
3000	54	93.1	1433	99.7
5000	52	89.6	1431	99.6
10000	49	84.5	1428	99.4
Ab only	0	0	1379	95.9

### The Requirement for Analytical Sensitivity is Less Stringent than for VL Monitoring

- To be recommended as part of (all) general HIV testing, a NAAT would likely need ~95% detection at viral loads the equivalent of 5,000 to 10,000 HIV RNA copies per mL
- Better sensitivity required for effective analysis of pooled specimens

## Summary: Pooling vs. Individual NAAT

- **Pooled screening** (even with 'minipools') makes testing possible by reducing costs and improving predictive value
- More complex=more efficient
- **Single specimen NAAT screening** should be reserved for situations where the pre-test likelihood of acute HIV infection is  $\geq 1\%$  (e.g., suspected AHI, ED/urgent care screening)

## Cost-effectiveness: Decision Tree Analysis

- The expected savings from averting new HIV cases offset 22% of the testing costs
- Overall cost per QALY of \$4,345
- Conclusion: the program appears to be well below the cost effectiveness threshold of \$50,000 which is often used as an indicator of good public health investment opportunities in the US.

## Cost-effective...but still \$\$\$

- It is clearly cost-effective in terms of prevention when added to standard antibody testing algorithms for HIV voluntary counseling and testing
- However, new 2006 CDC Guidelines recommend 'routine testing' of low risk persons as part of primary health care

## Effectively targeting NAAT in NC

- Over 2 years, at 135 public testing sites in NC, 325 acute and recent infections were identified among 224,124 testing clients (66% females, 4% MSM)
- Only 1/3 acute clients had HIV symptoms at testing
- There were no cases in 48 of 100 counties
- If NAAT were used only in HIV C&T, STD, prison, and field visit sites in counties with  $\geq 1$  case, 95.4% of acute cases identified testing only 54.0% of the population with NAAT
- Testing only in STD clinics identified 40.1% of cases while testing 41.4% of the population.

## Targeting is necessary; but be wary of preconceptions

- It is possible to construct a targeting algorithm for NAAT testing based on knowledge of local geographic and individual risk factors associated with having recent infection
- “Detuned” test results can be used to develop NAAT targeting criteria
- A priori assumptions about who to test with NAAT are likely to be incorrect (i.e., limiting testing to “high risk” clinics, or to symptomatic clients would be counterproductive)

## Pregnancy and Vertical Transmission

*K. Patterson, et al. 13<sup>th</sup> CROI*

- 6 (3.4%) of 475 HIV+ women were antibody negative
- Four (25%) of these 16 acute cases were in fact pregnant at testing.
- Two were tested in Prenatal/OB testing sites, where they represented 2 of 45 (4.4%) all new infections detected.
- All pregnant, acutely HIV infected women were located, counseled and initiated on antiretroviral therapy. All 4 infants were delivered uninfected.
- During this same period, at 6 infants were born HIV infected in NC. The mothers of 3 had been HIV antibody negative early in pregnancy.

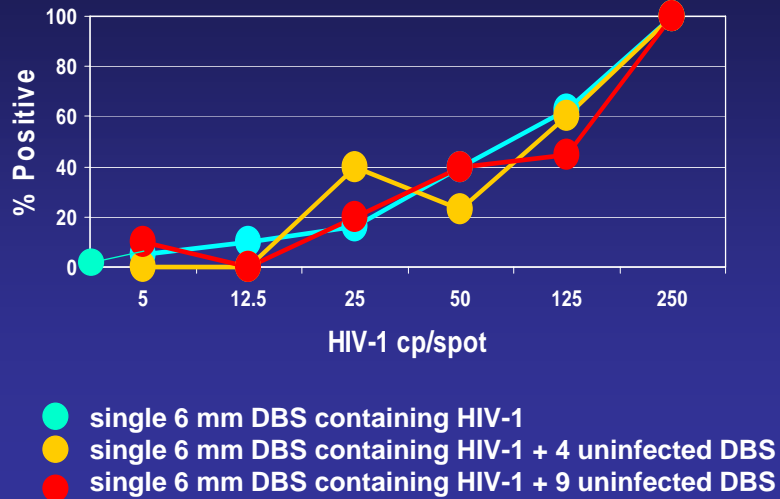
## The Future

- Alternative Specimen types
- The 4<sup>th</sup> Generation EIA
- Rapid NAATs?

## Pooling of Dried Blood Spots

- Elution method needs improvement:
  - Currently we detect ~20% of the total amount present in a DBS
- ~90% detection rate at 50 copies/DBS (from 50  $\mu$ L of whole blood containing 1,000 copies/mL of HIV-1)
- Sensitivity is proportional to the size of the DBS (13 mm vs. 6 mm)  
Pooling of DBS at 1+4 or 1+9 does not affect sensitivity of HIV-1 detection

## Analytical Sensitivity after DBS Pooling—HIV TMA

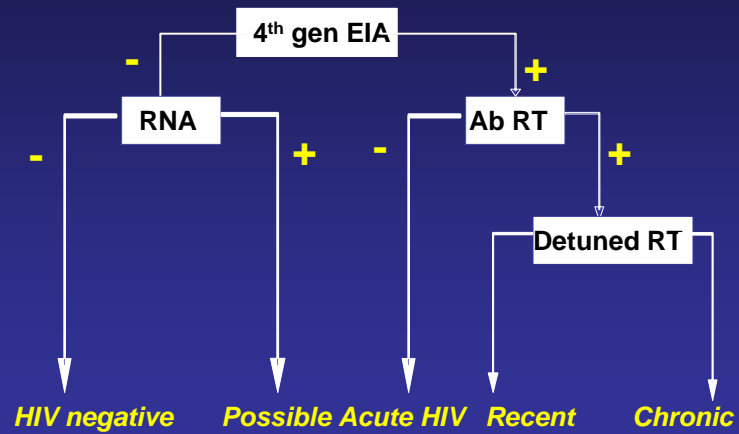


## Projeto AMPLIAR

*University of Caxias do Sul/UCSF*

- Network of 4 large VCT centers in Porto Alegre, Via Mau, and Caxias do Sul, in Rio Grande do Sul state.
- 62% coverage of the South Region's HIV testing population
- All labs use 4<sup>th</sup> generation EIA with Ab confirmation

## AMPLIAR Project Schema: Same-day AHI testing



## Rapid Window Period Tests

- The future....but several years off
  - p24 Ag
  - NAAT

## Conclusions

- For purposes of HIV prevention, assays able to detect antibody-negative infections should be part of the current standard of care
- NAAT may not be reasonable for low-risk 'routine' screening in well patients
- Rational criteria for targeting NAAT need to be elaborated
- 4<sup>th</sup> generation EIAs may present an alternative for diagnosis of acute HIV infection and merit urgent large-scale clinical evaluations

Thank you!!!