Defining Recent HIV Infection for TDR Surveillance

Chunfu Yang, DVM, PhD
Team Lead of Molecular Diagnostics and Surveillance
International Laboratory Branch
DGHA, CGH
CDC, USA
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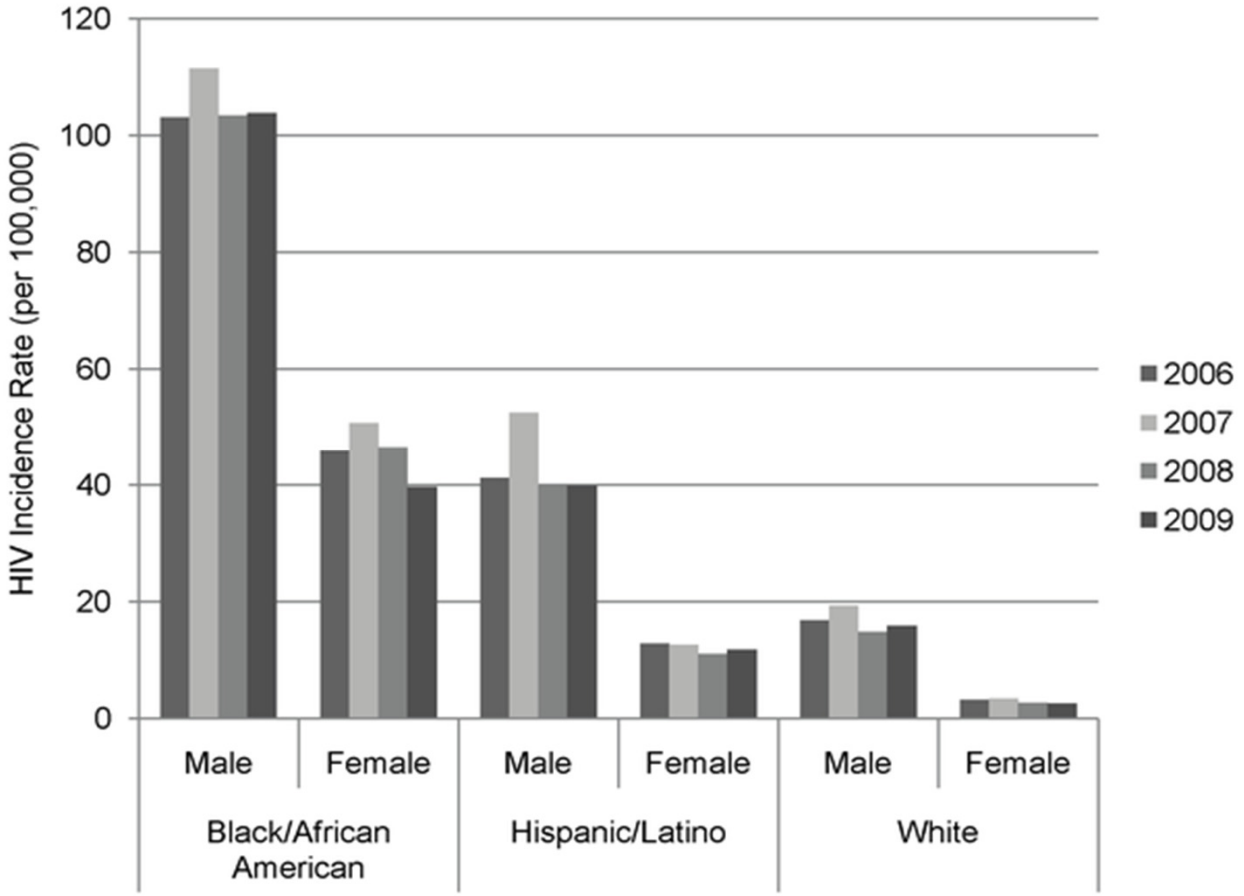
Identify HIV incidence for TDR

- **Direct Methods:**
  - Prospective longitudinal cohort method: Costly and impractical for surveillance purposes
- **Indirect Methods: Laboratory-based cross-sectional methods**
  - **Serologic**
    - BED-CEIA (Parekh et al. ARHR, 2002)
    - MAA (Multi-Assay Algorithm, Laeyendecker et al. JID, 2013)
    - LAg Avidity EIA (Duong et al. PLoS One, 2012
    - BioRad 1/2+O Avidity (Masciotra et al. CROI 2010, Abs# 937)
    - V3 IDE (Barin JCM 2005)
    - Vitros LS (Keating JCM 2012)
    - Abbott AzSYM HIV1/2 Avidity (Suligoi JAIDS 2003)
    - Bio-Plex Multi-abalyte (Curtis ARHR 2012)
  - **Nucleic Acid**
    - HRM (High-resolution melting assay, Cousins et al. PLoS ONE, 2011)
    - Sequence-based
      - Base ambiguity (Kouyos CID 2011)
      - Hamming distance-Q10 (Park AIDS 2011)

STARHS-Serologic Testing Algorithm for Recent HIV Seroconversion

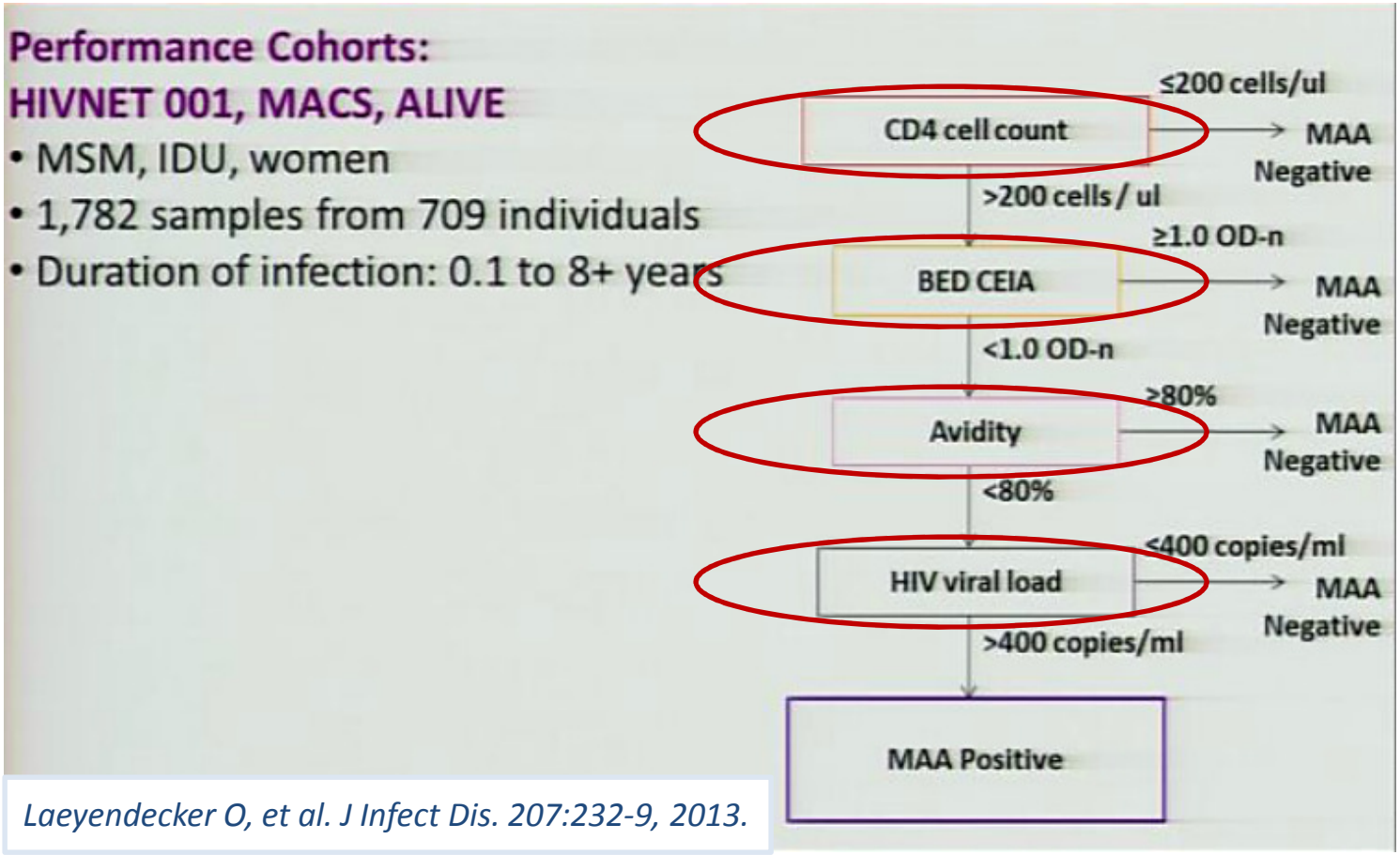
- STARHS, known as a "detuned assay“
- If people initially test HIV-positive using standard EIA tests, but negative on the less sensitive version of the EIA test, BED-CEIA, this indicates that they were probably infected within the past 4-6 m.
- STARHS estimates HIV incidence rates based on:
  1. BED-CEIA test results
  2. Treatment history questions answered by infected people
     - Date of first positive HIV test
     - Date of last negative HIV test, or "No previous HIV testing"
     - Number of negative HIV tests in the 2 years preceding the first positive HIV test.
     - ART histories (for post-exposure prophylaxis, pre-exposure prophylaxis, or medications for Hepatitis B that overlap with HIV, e.g. Epivir). Names of medications and dates started and ended needed.

Rate (per 100,000) of new HIV infections by gender and race/ethnicity – United States, 2006–2009



Prejean et al. Estimated HIV Incidence in the United States, 2006–2009. PLoS ONE 6(8): e17502., 2011

MAA: Multi-Assay Algorithm assay for subtype B



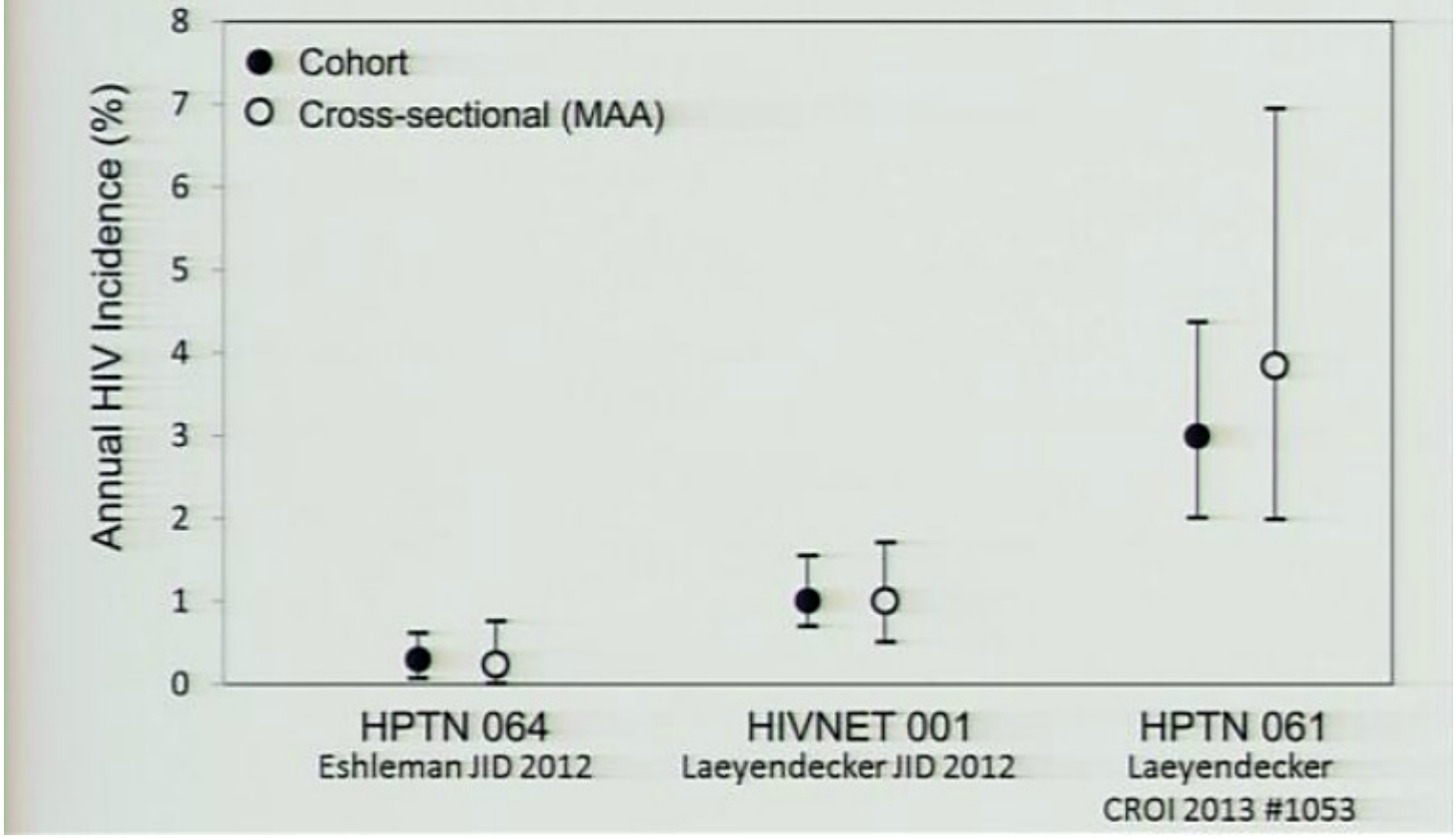
Laeyendecker O, et al. J Infect Dis. 207:232-9, 2013.

Comparative analysis of MAA with BED-CEIA for subtype B

		BED-CEIA		MAA	
Infection time (y)	No. Spec	No. Recent	% (95% CI)	No. Recent	% (95% CI)
0-0.49	142	80	56.3 (43.7-65.9)	68	47.9 (34.5-57.3)
0.5-0.99	166	61	36.7 (27.4-48.1)	15	9.0 (6.3-19.3)
1-1.99	263	65	24.7 (17.0-34.1)	2	0.8 (.0-2.4)
2-2.99	301	62	20.6 (14.0-28.3)	2	0.7 (.0-1.9)
3-3.99	440	64	14.5 (10.4-18.4)	2	0.5 (.0-1.5)
4-4.99	125	15	12.0 (7.5-20.2)	0	0.0 (.0-1.4)
≥5	345	47	13.6 (10.2-17.2)	0	0.0 (.0-1.1)
Total	1782	394	22.1	89	5.0

Laeyendecker O, et al. J Infect Dis. 207:232-9, 2013.

Comparison of Observed Longitudinal Incidence to Incidence Estimated Using the MAA



Laeyendecker, CROI 2013, Abs#164

Summary of Clade B MAA for incident estimation

- AT a mean window period of 159 days
- MAA didn't identify any of the 970 samples from individuals infected >4 years
- Incidence estimates using MAA are nearly identical to observed incidence in 3 longitudinal cohorts

Laeyendecker, CROI 2013, Abs#164

Limited Antigen (LAg) Avidity Assay for HIV Incidence Estimation

Commercial kit was developed and now available by 2 different manufacturers

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PLoS one

Detection of Recent HIV-1 Infection Using a New Limiting-Antigen Avidity Assay: Potential for HIV-1 Incidence Estimates and Avidity Maturation Studies

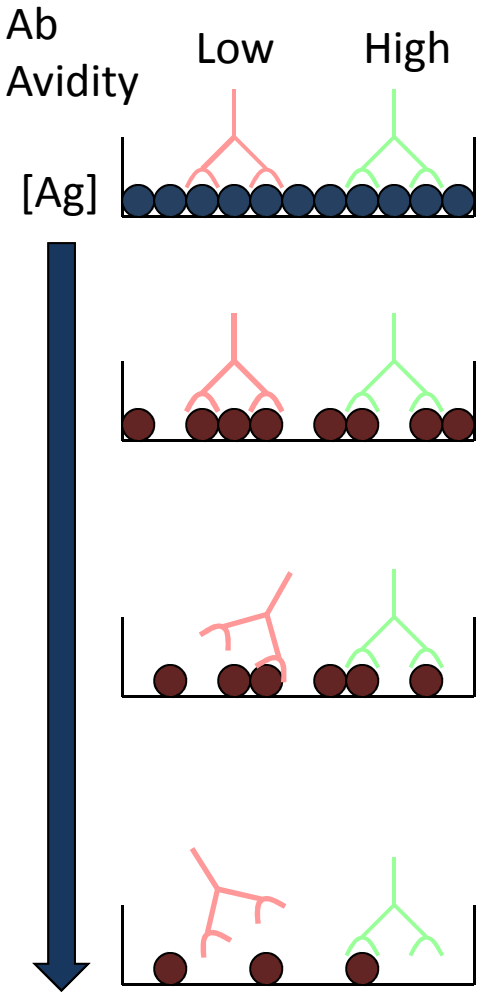
Yen T. Duong, Maofeng Qiu¤, Anindya K. De, Keisha Jackson, Trudy Dobbs, Andrea A. Kim, John N. Nkengasong, Bharat S. Parekh*

Division of Global HIV/AIDS, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

Aims of the development of LAg Avidity Assay

- **An assay to detect new HIV infections for incidence surveillance**
- **LAg-Avidity EIA was developed to address limitations of the BED assay (avidity = binding strength)**
  1. Similar mean window periods in all subtypes/populations
  2. Low misclassification rates among known long-term infections, people with AIDS, elite controllers and ARV-treated people
  3. Accurate incidence estimates in cross-sectional populations

What happens when you limit the antigen?



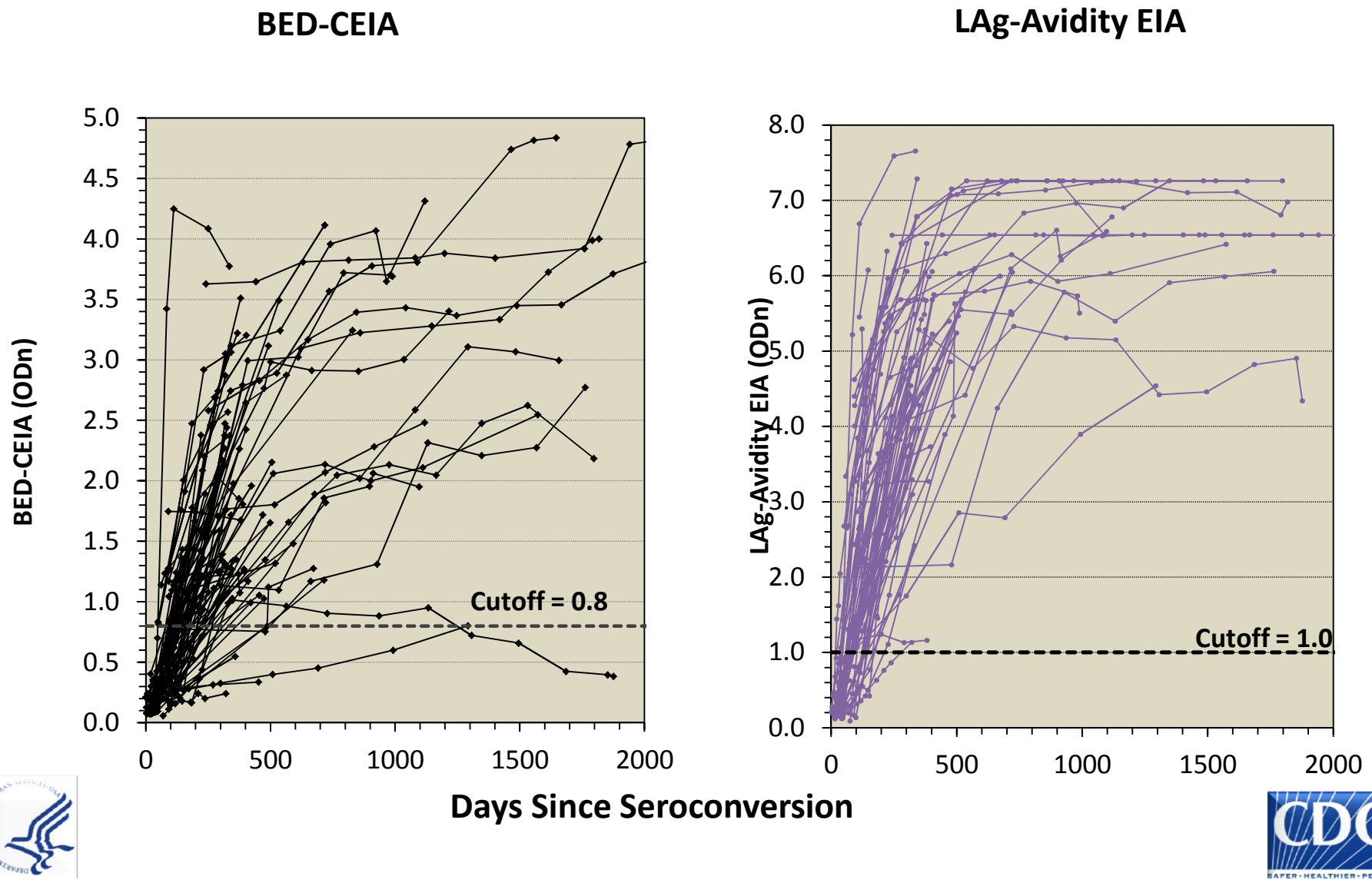
Excess Antigen:

- Bivalent binding of both low avidity and high avidity antibodies
- Takes more effort to dissociate low avidity antibodies

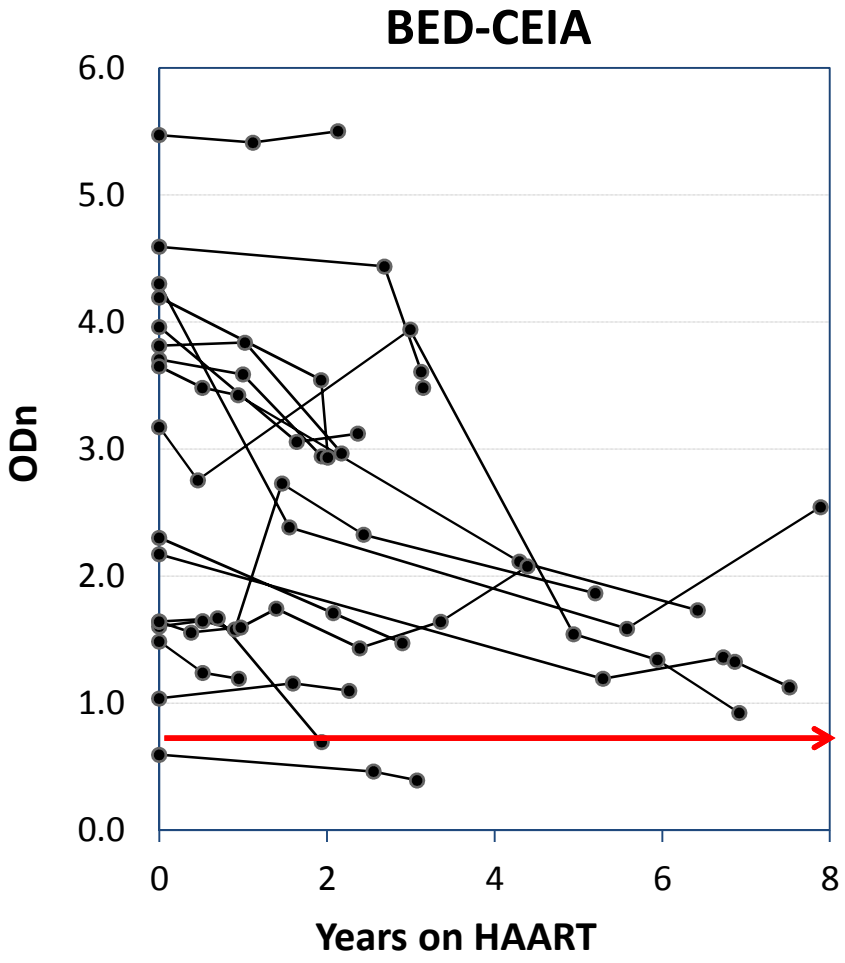
Limiting Antigen:

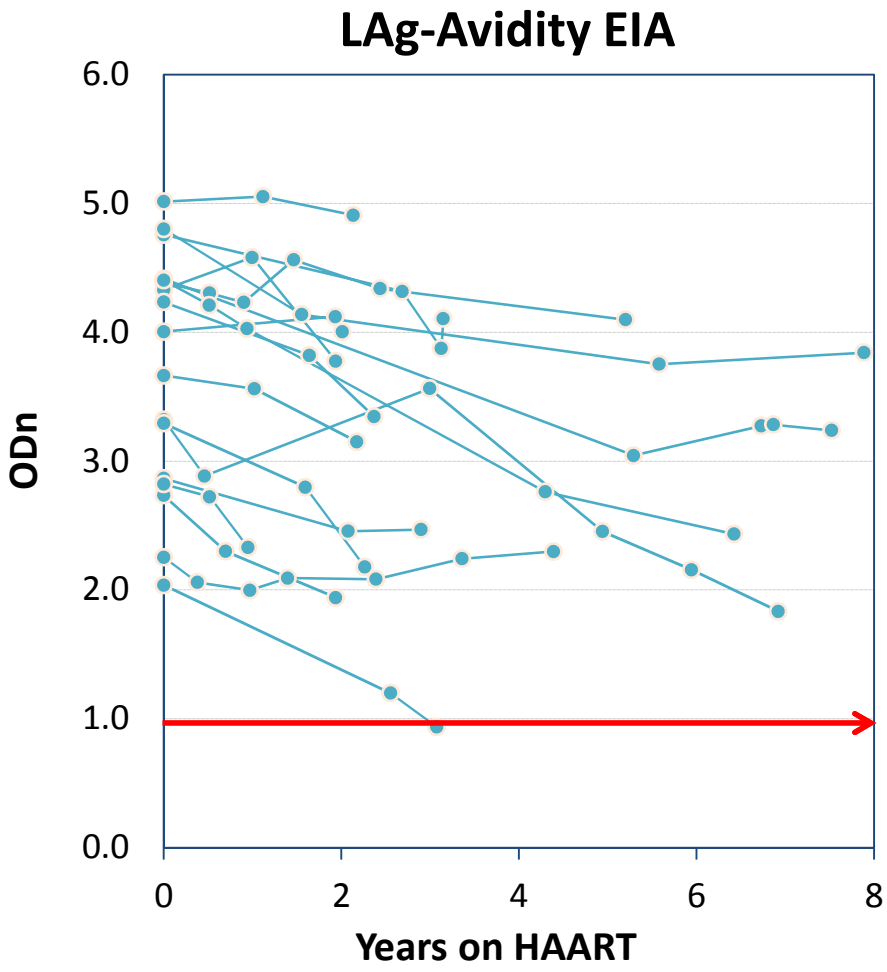
- Monovalent binding of antibodies
- Low avidity antibodies, if present, are easily dissociated

Comparative performance of BED-CEIA and LAg-Avidity EIA in seroconverters infected with subtypes A, B, C & D (N=89)



Impact of ART (N=17)





Slower decline and less misclassification on LAg-Avidity compared to BED over >6 yrs

False Recent Rate (FRR) among people-infected with different HIV subtypes and long duration (N=3841)

Cohort	Type	Subtypes	Total Tested	BED FRR	LAg FRR
Ghana	Long-term	A	953	6.4%	0.7%
Vietnam	Long-term	AE	1845	3.6%	0.8%
US+Thai+ IVC	AIDS+/- TB	B, Thai B, AE, AG	488	2.9%	0.2%
China	Long-term	C	551	NA	0.2%
TOTAL	**Long-term + AIDS**	**A, B, Thai B, C, AE, AG**	**3841**	**4.3%**	**0.5%**

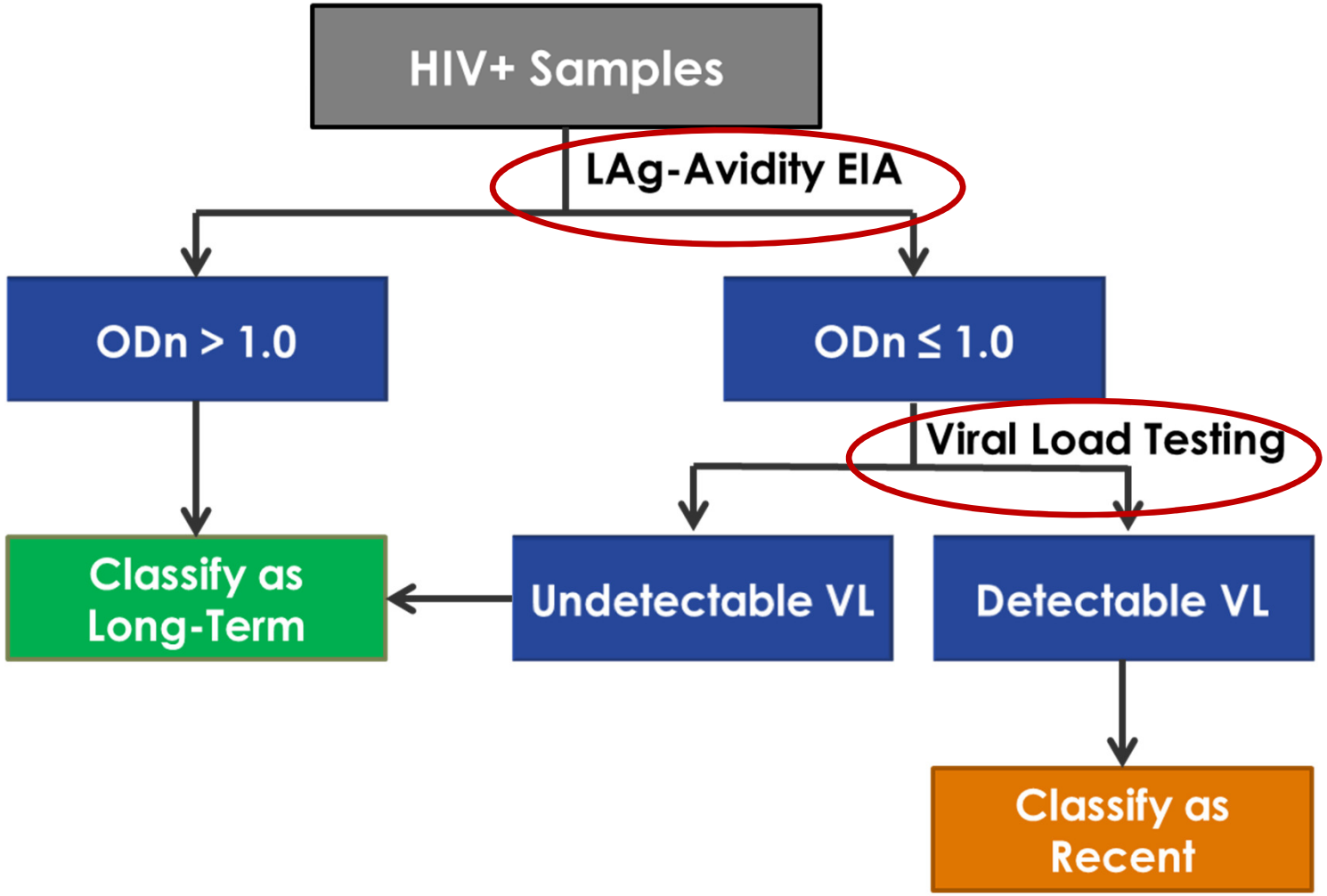
Overall LAg FRR is < 1% among different subtypes and populations.

Mean Window Period for LAg-Avidity EIA by Cohort/Subtypes (N=89)

Cohort	No. of Subjects (No. Spec)	HIV-1 Subtypes	Mean Recency Period in days (95% CI)*
Amsterdam & Trinidad	32 (170)	B	132 (104-157)
Ethiopia	23 (143)	C	139 (106-178)
Kenya	34 (80)	A, D	143 (103-188)
ALL	**89 (393)**	**A, B, C and D**	**141 (119-160)**

*Additional calculations to be performed on recalibration of mean window period in collaboration with Consortium for Evaluation and Performance of HIV Incidence Assay (CEPHIA).

Proposed LAg Testing Algorithm



Current WHO recommended method for TDR population selections

- Sentinel sites based on epidemiologic data:
  - Age <25; preferably <22 years, if feasible
  - No previous pregnancies (females)
  - First HIV-risk defining event within past three years, if available
  - CD4 >500 cells/µl, if available

Table 1 Frequency of WHO surveys reporting moderate prevalence of transmitted HIV drug resistance, by period (before or after 2007)[a]

		Number (%) of surveys with moderate (5–15%) prevalence			
Year	Total surveys	Any drug class	NNRTI	NRTI	PI
2004-2006	22	4 (18%)	1 (5%)	3 (14%)	0 (0%)
2007-2010	50	16 (32%)	11 (22%)	7 (14%)	2 (4%)

a Mid-point period.

WHO HIV Drug Resistance Report 2012

Bioinformatics Algorithm in detecting recent HIV infection using WHO TDR data

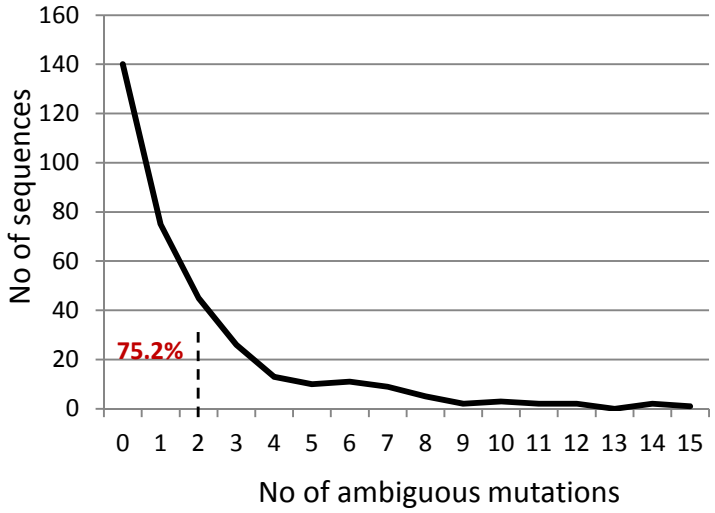
Anderson E et al. CROI 2011, Abs# 1056

- Ambiguity threshold (AT) at 0.47% to differentiate recent (<1 year) from chronic infection (>1 year)
- 8 WHO TDR surveys data from 6 countries were analyzed by ambiguity threshold
- **71% of the patients were defined as infected within 1 year**

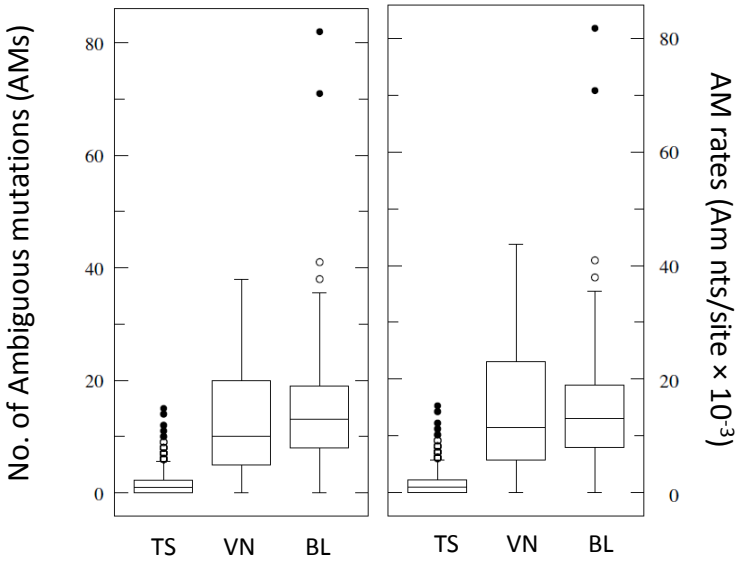
Zheng D et al. Int wkshop on HIV & Hep Virus DR and Curative Strategies, 2012, Abs#135

- 8 TDR surveys from 7 countries
- 2 surveys from patients eligible for ART from one country
- **Based on ambiguous mutation rate (AMR) at 2.0×10^{-3}/yr, 75.2% of the TDR patients were infected within 1 year**

A. Threshold subset (n=346)



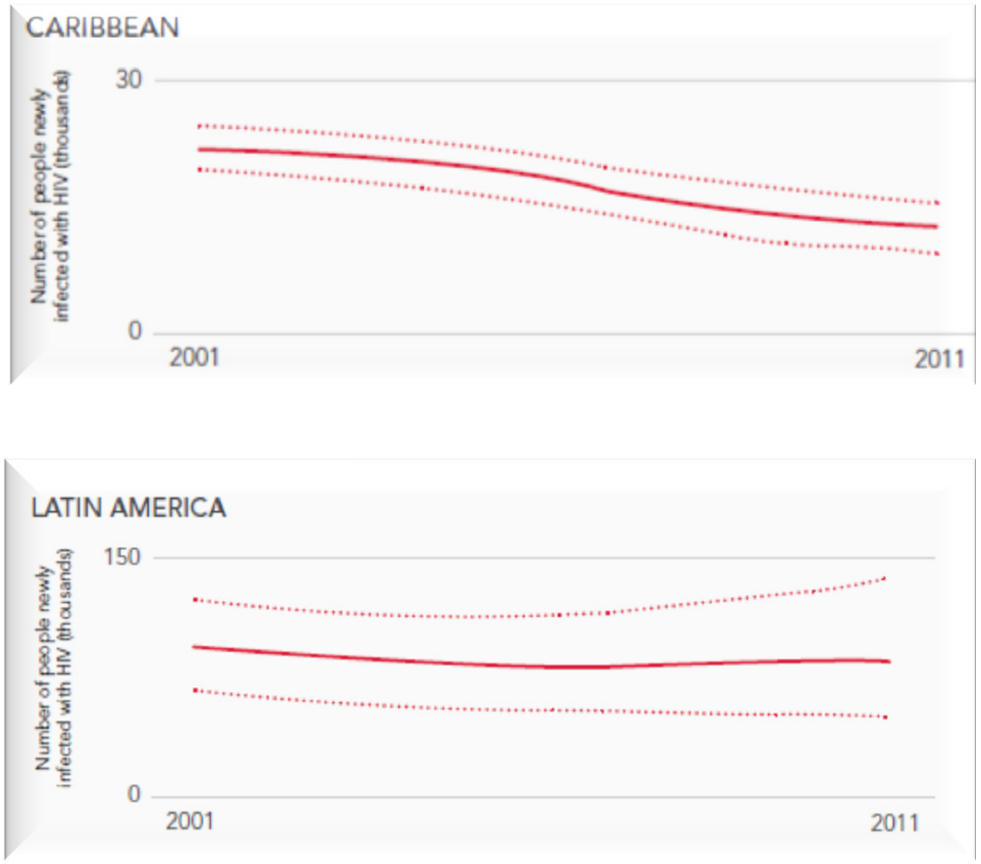
D. AM profile of 3 data subsets (*p <0.001)



***TS vs VN or BL**

CDC Unpublised data

New HIV infection in Caribbean and Latin America, 2001-2011



UNAIDS report on the global AIDS epidemic, 2012

HIV Prevalence among MSM vs general populations in LAC countries

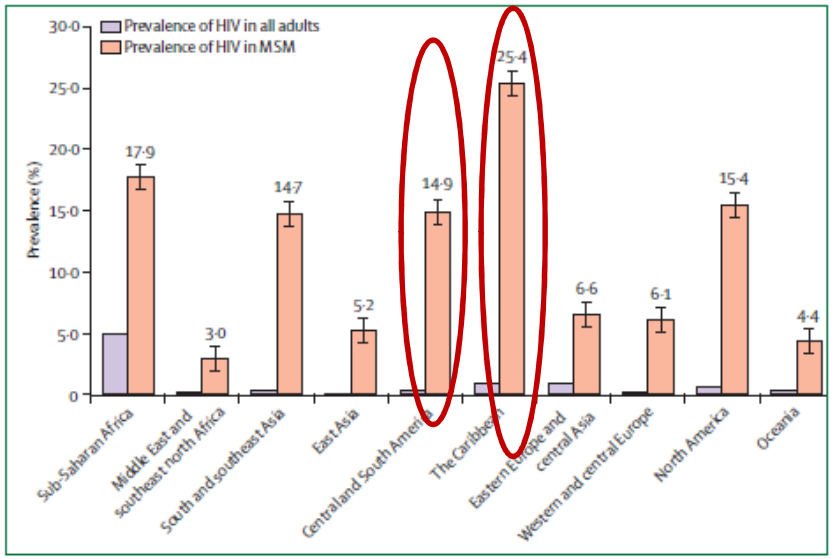
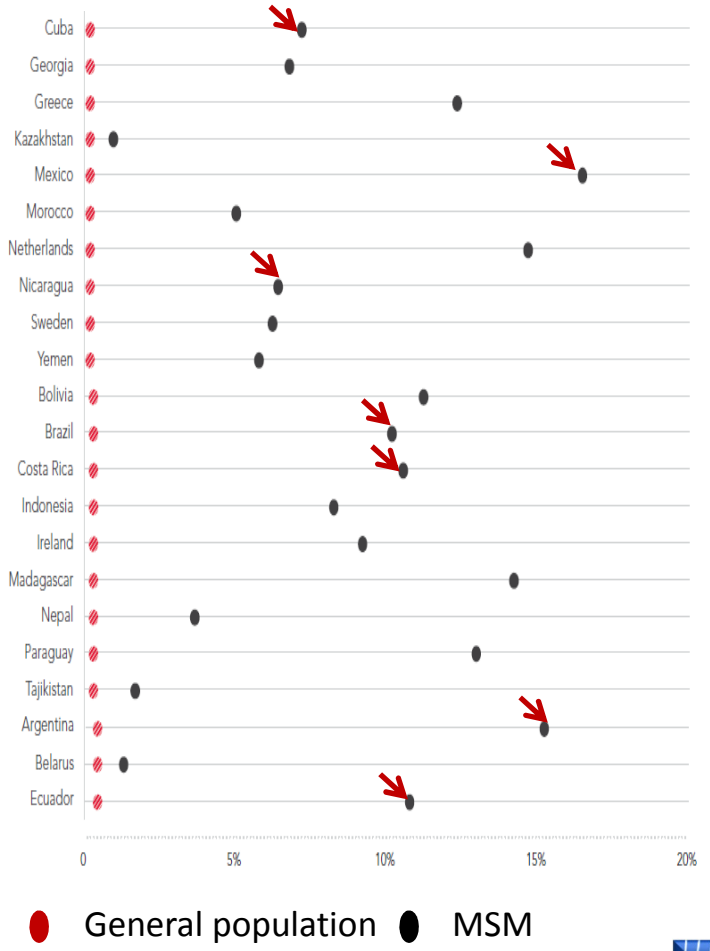
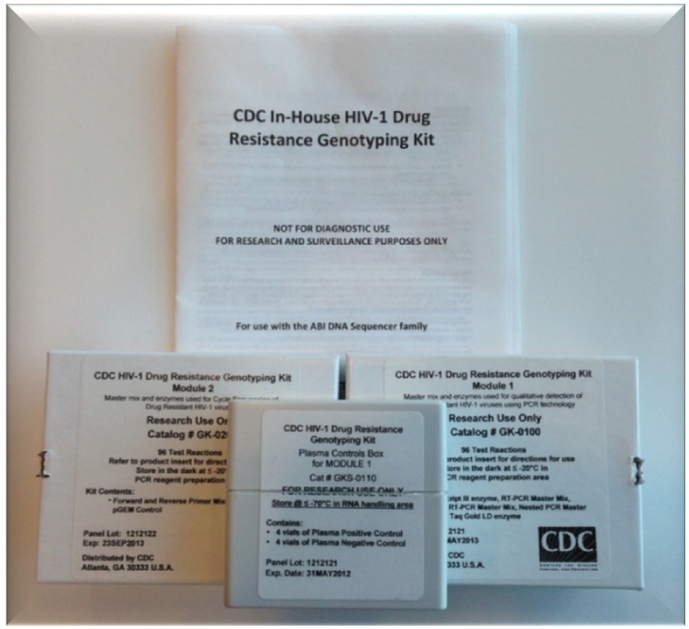


Figure 1: Global prevalence of HIV in MSM compared with regional adult prevalence reported by UNAIDS, 2010



Beyrer et al. Lancet, 2012; UNAIDS report on the global AIDS epidemic, 2012

CDC In-House HIV-1 Drug Resistance Genotyping Kit



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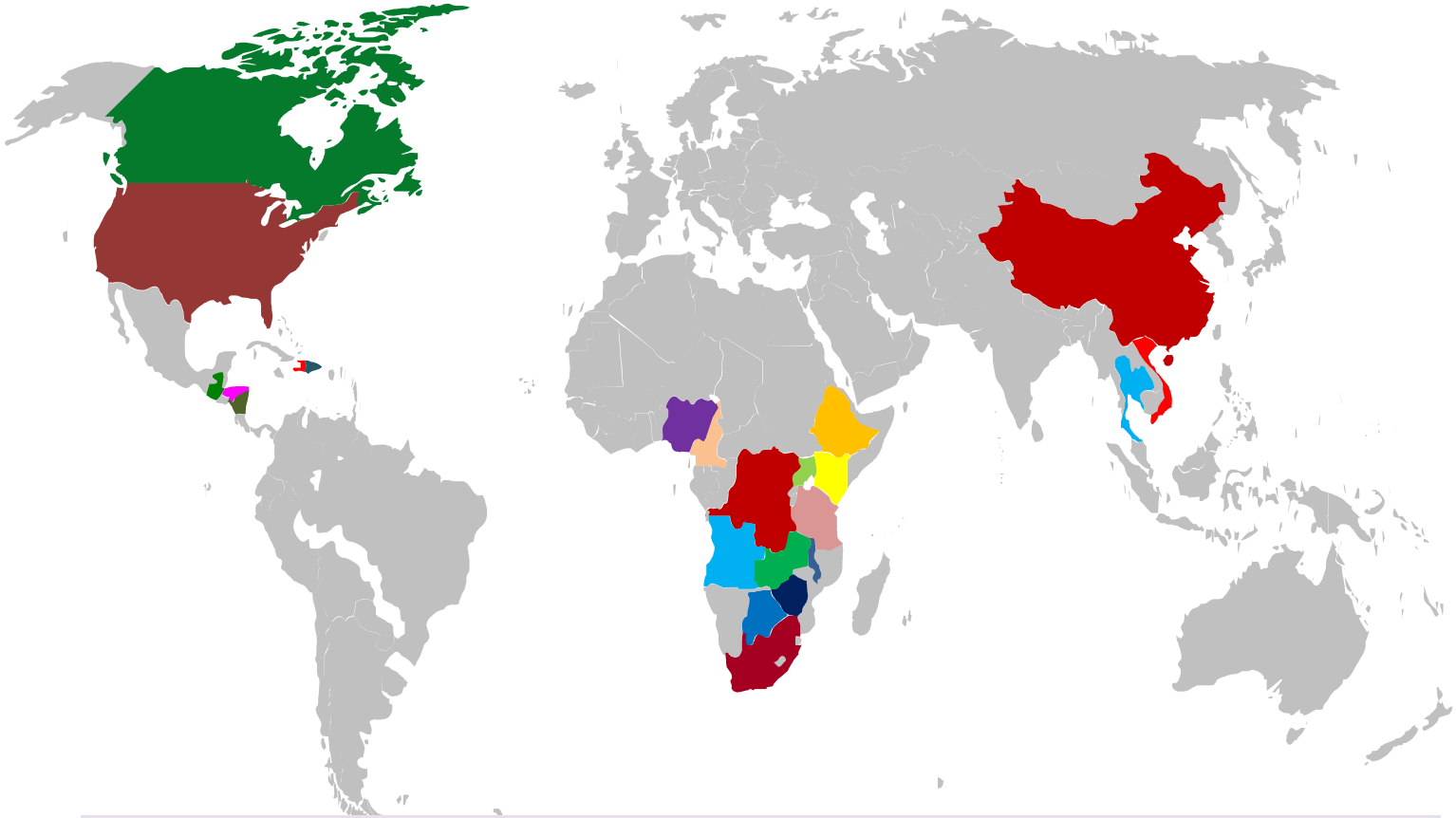
Optimization of a Low Cost and Broadly Sensitive Genotyping Assay for HIV-1 Drug Resistance Surveillance and Monitoring in Resource-Limited Settings

Zhiyong Zhou[1], Nick Wagar[1], Joshua R. DeVos[1], Erin Rottinghaus[1], Karidia Diallo[1], Duc B. Nguyen[2], Orji Bassey[3], Richard Ugbena[3], Nellie Wadonda-Kabondo[4], Michelle S. McConnell[1,5], Isaac Zulu[6], Benson Chilima[4], John Nkengasong[1], Chunfu Yang[1]*

1 Division of Global HIV/AIDS, Center for Global Health, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America, 2 Department of Health and Human Services/US CDC, Hanoi, Vietnam, 3 CDC/GAP, Abuja, Nigeria, 4 Community Health Sciences Unit, Malawi Ministry of Health, Lilongwe, Malawi, 5 Thailand Ministry of Public Health/US CDC Collaboration, Nonthaburi, Thailand, 6 Global AIDS Program CDC-Zambia, Lusaka, Zambia

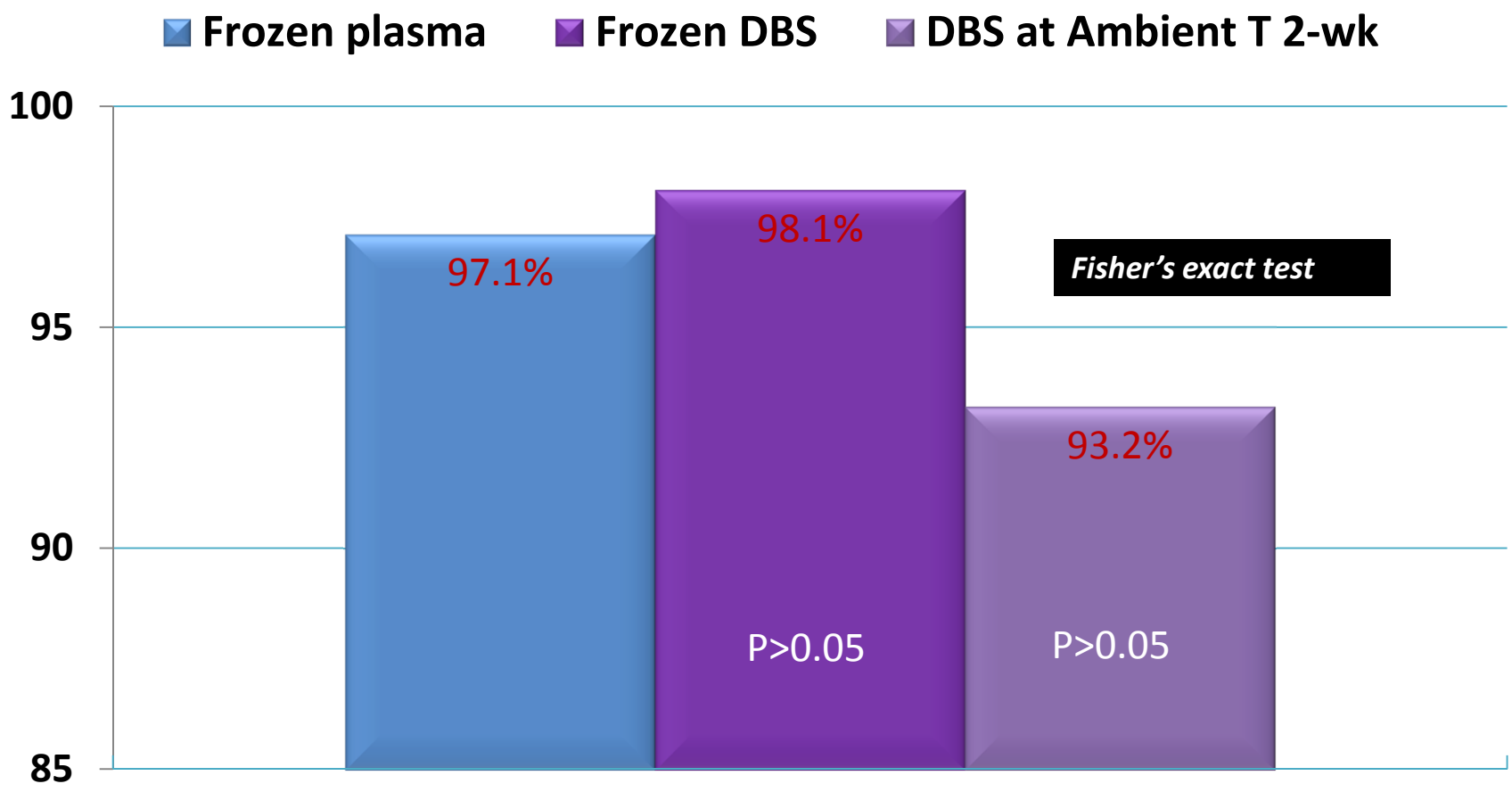
CDC
SAFER · HEALTHIER · PEOPLE

Implementation of CDC in-house assay for HIVDR genotyping worldwide



24 countries:
14 Africa, 5 Latin America, 3 Asia and 2 North America

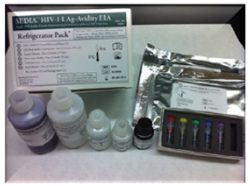
Sensitivity: CDC in-house assay for plasma and dried blood spots (DBS) collected from ART patients



N=103, median VL=4.76, range 3.03-6.47 log10

Neil et al. Int wkshop on HIV & Hep Virus DR and Curative Strategies, 2012, Abs#107

Summary




With more accurate incident detection assays at a misclassification rate of <1%, LAg Avidity EIA or MAA combining with CDC low cost HIVDR assay we would be able to:

- Identify recently HIV-infected populations to conduct TDR surveys in regions/countries with concentrated/generalized HIV epidemics using samples collected from sentinel surveys, ANC, AIS, DHS, IBBS, etc
- Provide more efficatious treatment regimens to those populations with high level of TDR and mitigate the emergency and transmission of HIVDR
- Improve care and treatment effectiveness and reduce the cost for program implementation

Know Our Epidemic and Virus!

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Chris Parry