High Sensitivity HIV Testing and Translational Science around PrEP

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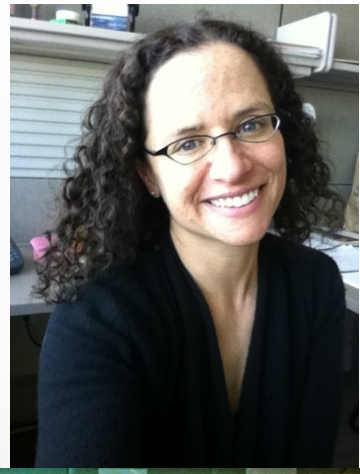
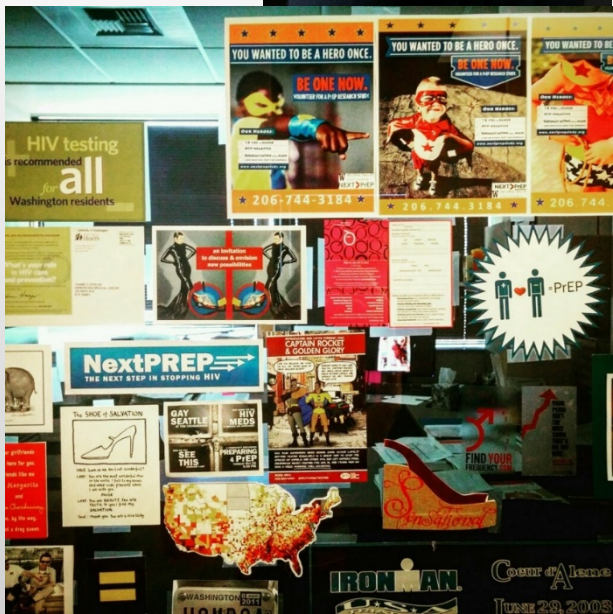


Inter-Center for AIDS Research
Antiretrovirals for Prevention Working Group

November 13, 2017



Disclaimers

Discussion of:

1) Commercial products

2) Off-label/investigational use of products

3) Alere (now Abbott) provided Determine Combo kits for my research prior to FDA approval.

4) I didn't know this was supposed to be a work-in-progress talk when I started putting together my slides.

Outline

- HIV testing technologies
- Screening for acute HIV infection (AHI)
- Impact of PrEP on HIV tests during seroconversion
- Sampling of implementation science questions around HIV testing and PrEP

- Not included: discussion of PrEP failures (3/12/18)

1989: State of the art technology

slide courtesy of Bernie Branson

Technology: next generations

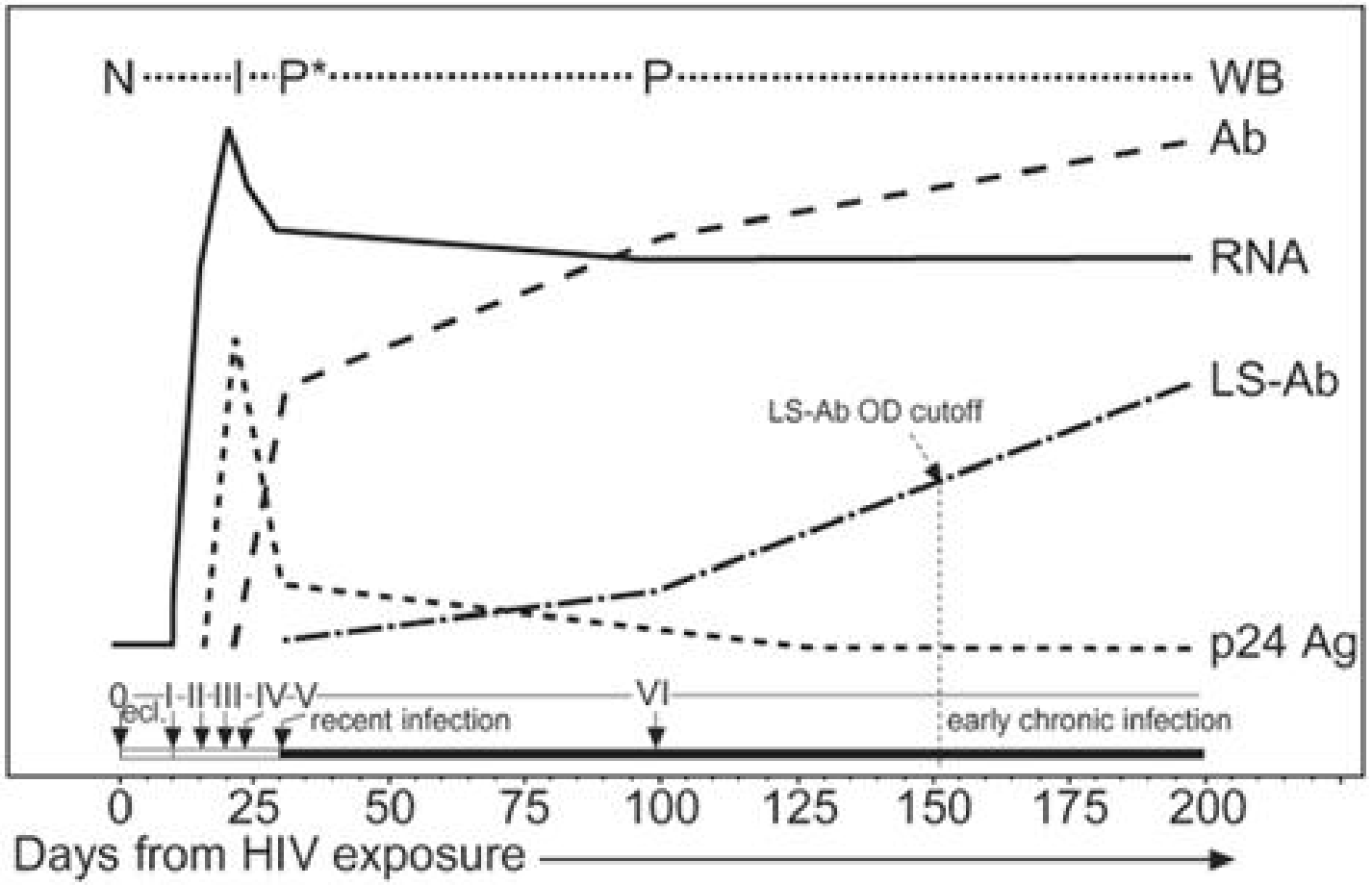
slide courtesy of Bernie Branson

HIV tests: next generations

HIV test	Method	Window
1st gen EIA (Ab)	viral lysate	~ 4-6 wks
2nd gen EIA (Ab)	purified HIV-1/2 Ag or recombinant	~ 3-4 wks
3rd gen EIA (Ab)	synthetic peptide, "antigen sandwich" detects IgM	~ 2-3 wks
4th gen assay (Ab plus p24 Ag)	detects either antibody or p24 Ag	~ 2 wks
Pooled HIV RNA (HIV NAAT)		<1-2 wks

Adapted from Stekler CID 2007

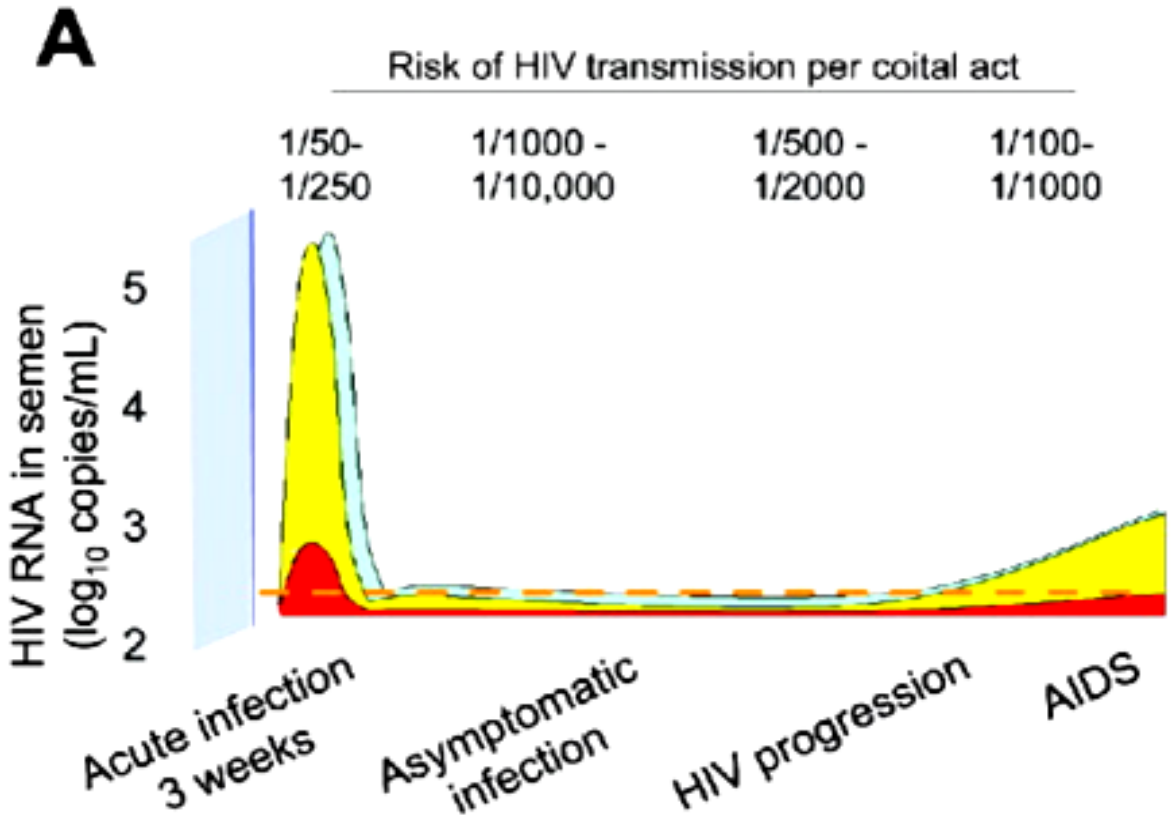
Events in primary HIV infection
Fiebig Staging



Fiebig et al. AIDS, 2003 Sep 5; 17(13): 1871-9

The Importance of Screening for Acute HIV Infection

Why screen for acute HIV infection? Greater risk of transmission…



Cohen, JID 2005

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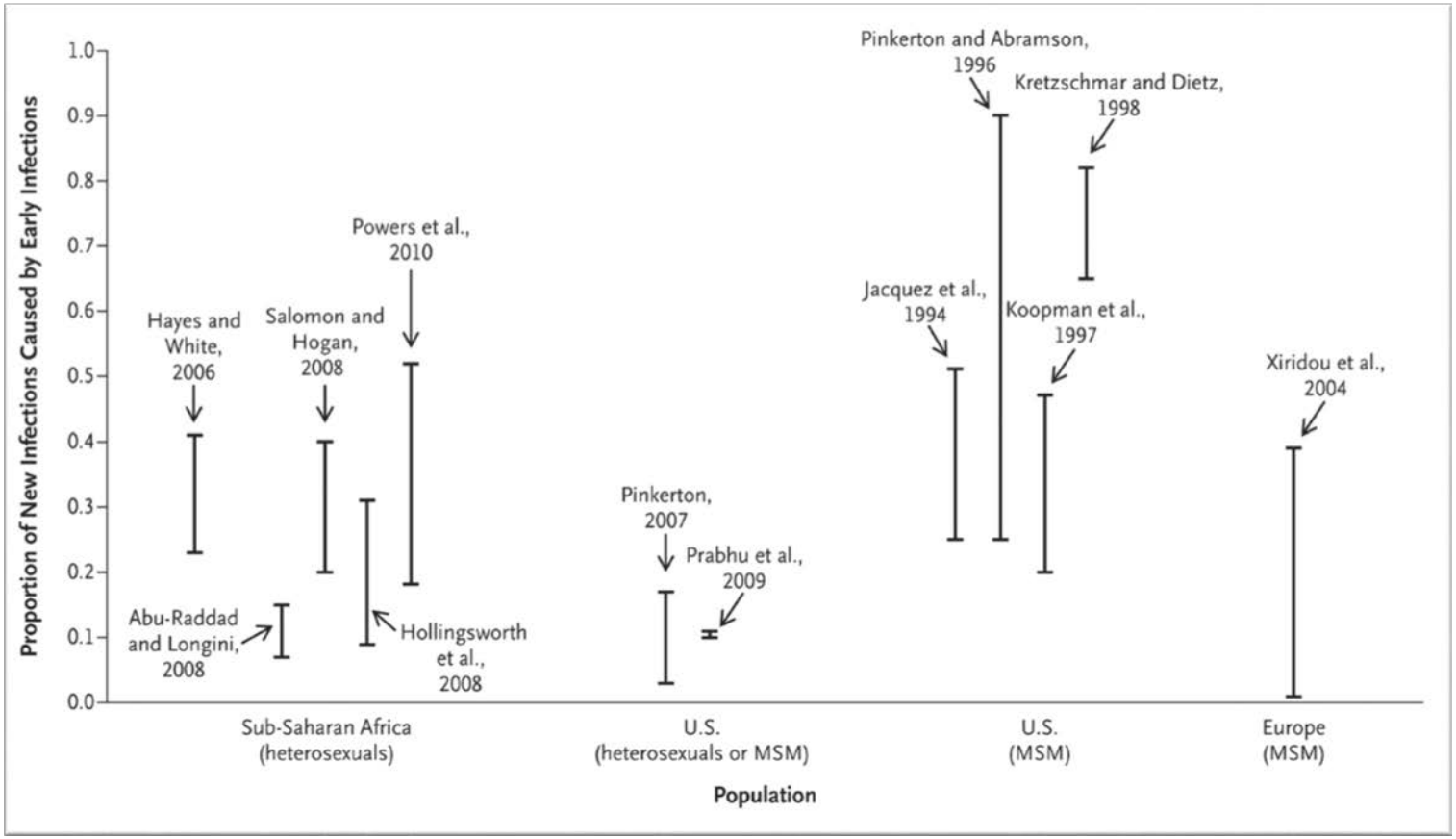
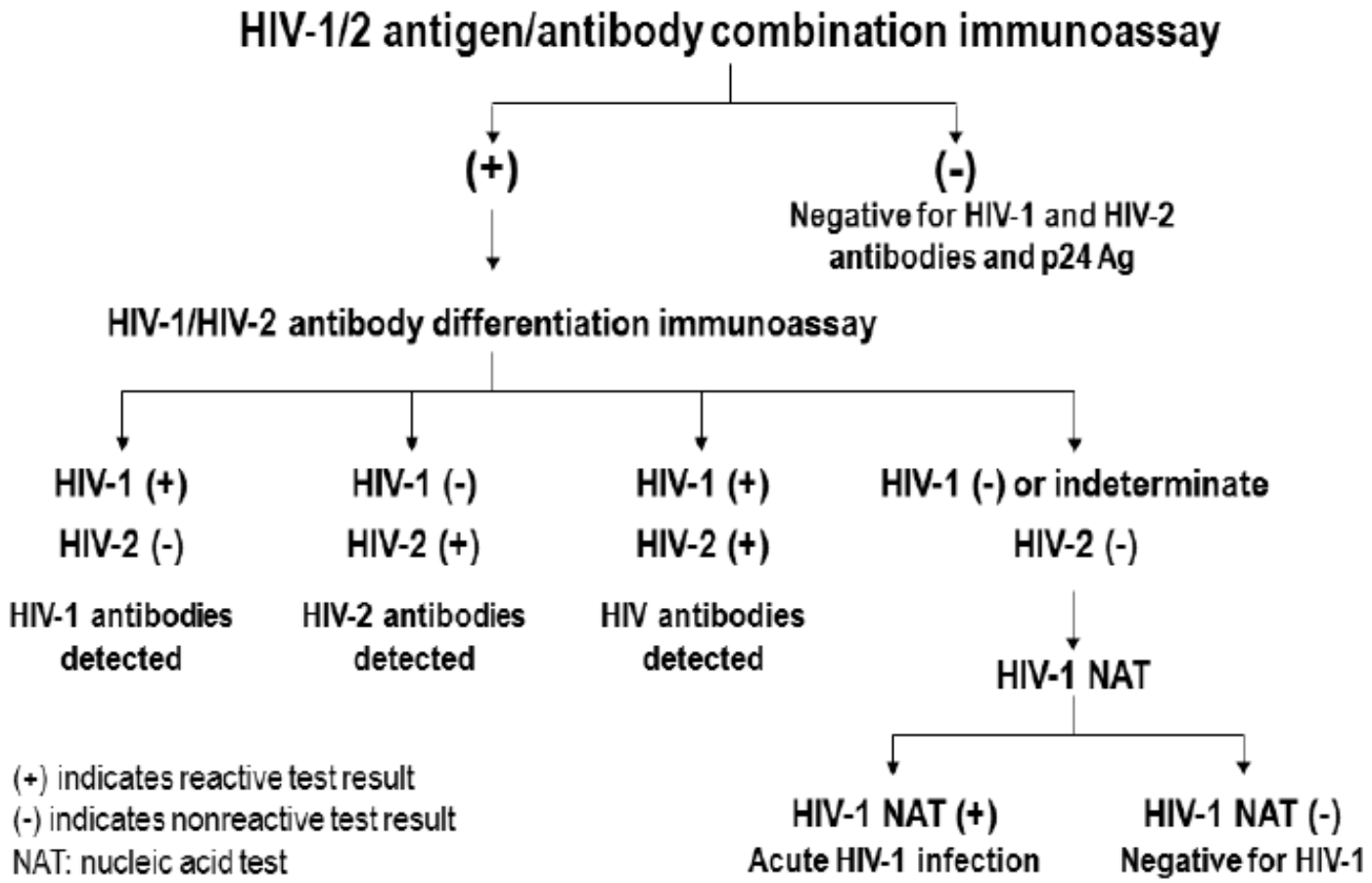


Cohen et al. NEJM, 2011; 364:1943-1954

Recommended laboratory HIV testing algorithm for serum/plasma specimens



Why screen for acute HIV infection in PrEP? Drug resistance

Number of HIV Seroconverters on Active PrEP Arms With HIV Resistance*

Trial	N mITT (oral drug)	HIV Infected After Enrollment, Resistant / Seroconverters (randomized to active drug)
iPrEx[1,2]	1224	0/36
Partners PrEP[3,4]*	3140	4/51
TDF2[5]	601	0/10
FEM-PrEP[6,7]*	1024	4/33
VOICE[8]	1978	1/113
TOTAL	7967	9/243 (3.7%)
Modified Total§	**7967**	**5/243 (2.0%)**

** For 454 sequencing, resistance levels >1% of variants*

§After exclusion of resistance likely to be transmitted

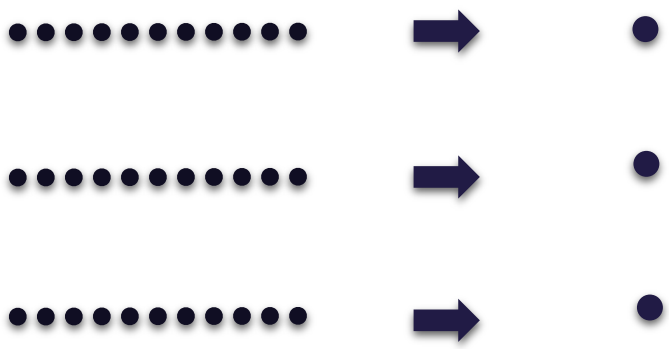
Resistance with oral PrEP in AHI: 8/29 (28%)

1. *Liegler T, et al. J Inf Dis. 2014.*
2. *Grant RM, et al. N Engl J Med. 2010.*
3. *Baeten JM, et al. N Engl J Med. 2012.*
4. *Lehman DA, et al. J Inf Dis. 2015.*
5. *Thigpen MC, et al. N Engl J Med. 2012.*
6. *Van Damme L, et al. N Engl J Med. 2012.*
7. *Grant RM, et al. AIDS. 2015.*
8. *Marrazzo JM, et al. NEJM. 2015*

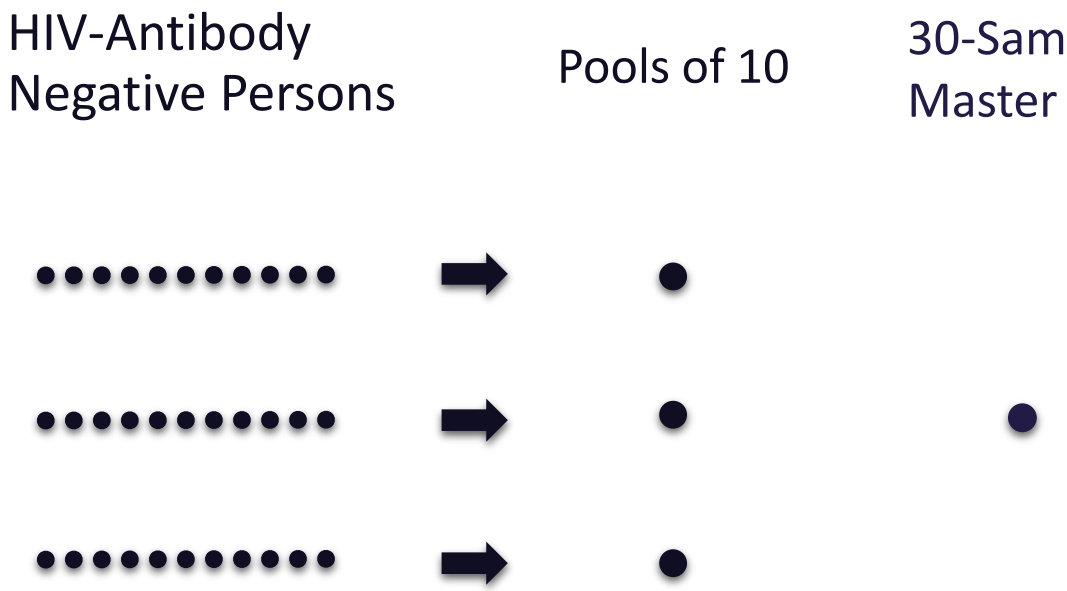
Detection of acute HIV infection by pooled HIV NAAT

HIV-Antibody Negative Persons

Pools of 10



Detection of acute HIV infection by pooled HIV NAAT



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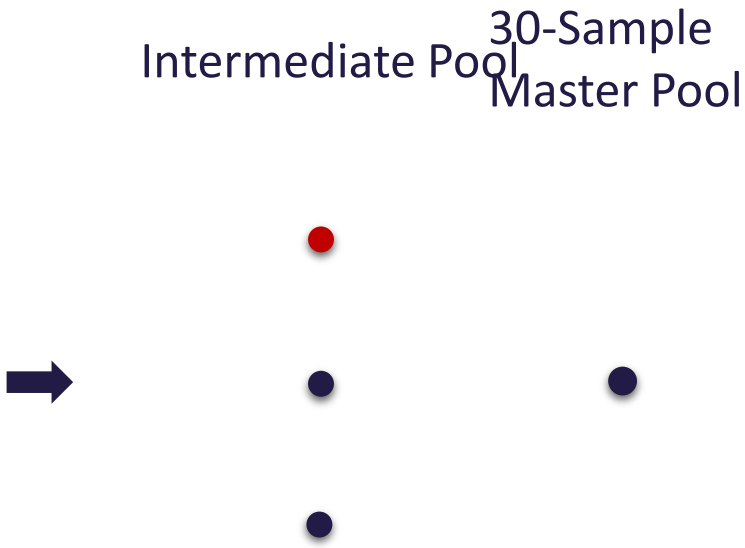

Detection of acute HIV infection by pooled HIV NAAT

Identification of Individual From Positive Pool

30-Sample Master Pool

Intermediate Pool

Individuals

Selection of U.S. Pooled HIV NAAT Programs

Location	Population	# Tested	# Ab pos	Pooling	# NAAT pos	Yield
North Carolina Pilcher JAMA 2002 Pilcher NEJM 2005	State funded sites	109,250	583	90:1	23 (0.02%)	3.9%
Seattle Stekler AIDS 2005 Stekler STI 2013	MSM at PH-funded sites	27,661	551	30:1, 3[3]	71 (0.25%)	EIA: 12.9% POC: 29.3%
San Francisco/LA Patel JAIDS 2006	SFCC, LA ST clinics	4787	119	SF 50:1 LA 90:1	12 (0.25%)	10.1%
Atlanta Priddy JAIDS 2007	HIV testing sites	2202	66	48:1	4 (0.18%)	6.0%
LA/NYC/FL Patel Arch Int Med 2010	STD and PH clinics	LA: 37,012 (1st) NYC: 6547 (2nd) FL: 54,948 (3rd)	427 29 663		35 (0.09%) 7 (0.1%) 7 (0.01%)	8.2% 24.1% 1.1%
Baltimore Temkin STD 2011	PH-funded sites	69,695	1766	65-70:1	7 (0.01%)	0.4%
Newark Martin J Clin Virol 2013	Hospital-based ER/outpatient	6845	115	3[3]	8 (0.12%)	7.0%
Dallas Emerson J Clin Virol 2013	Various	148,888	n/a	10:1 or 20:1	161 (0.11%)	n/a
NYC Borges PH Rep 2015	STD clinics	65,220	n/a	16:1	40 (0.06%)	n/a

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Advantages and disadvantages of 4th generation testing (compared to NAAT)

First 4th generation assay was approved in U.S. in 2010

Advantages

Cost
Time
Tech requirements

Disadvantages

Missed cases
- **Initial window of 3-5d**
- **2nd window period**

How do 4th generation laboratory assays compare to pooled HIV NAAT?

Retrospective studies

		N	% detected	Median (range) HIV RNA not detected
Stekler CID 2009	PHSKC	16	94%	16,300
Pandori J Clin Microbiol 2009	SF DPH	35	80%	6373 (1177 - 14,062)
Patel Arch Int Med 2010	STD clinics FL, LA, NY	27	85%	6961 (1827 - 21,548)

All studies used the Abbott ARCHITECT HIV Ag/Ab Combo Assay

How do 4th generation laboratory assays compare to pooled HIV NAAT?

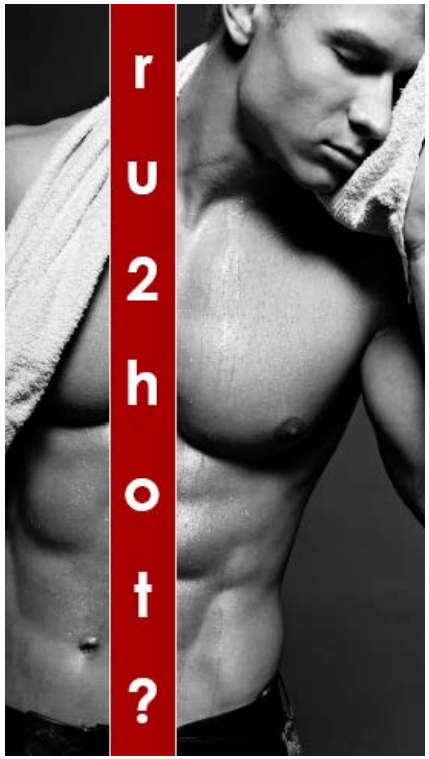
Prospective studies

	Location	N	#4th gen-pos	#NAAT-pos	Yield
DeSouza AIDS 2015	Thailand	74,334	10.9% = 8102? 81 "AHI"	30	~0.04%? 37%
Peters JAMA 2016	NC, NYC, SF	86,836	1158 POC+ 134 POC-	164 POC- (4 FN)	0.2% 22.4%

Peters: Median HIV RNA not detected 6019 (IQR 1225-25,866) copies/mL

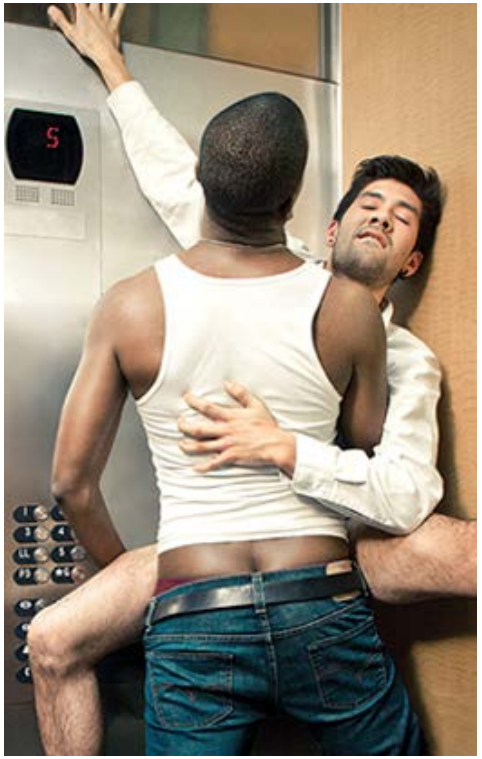
How to increase recognition of AHI symptoms

Approximately 50-90% of individuals have ≥1 symptoms ~2 weeks after infection



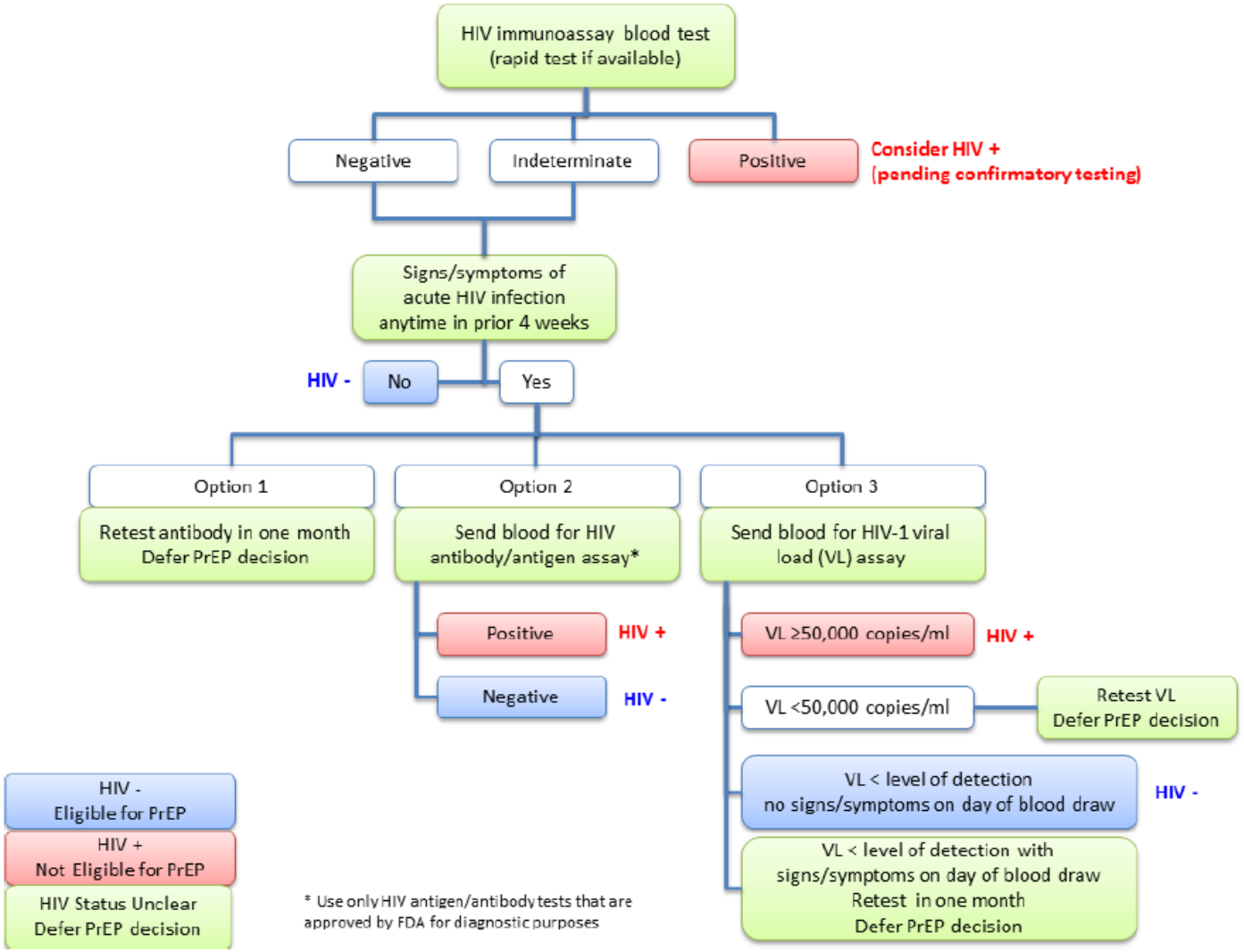
Stekler, STI 2013
ru2hot.org

- Fever
- Fatigue
- Sore throat
- Muscle/joint aches
- Night sweats
- Headaches
- Diarrhea
- Rash



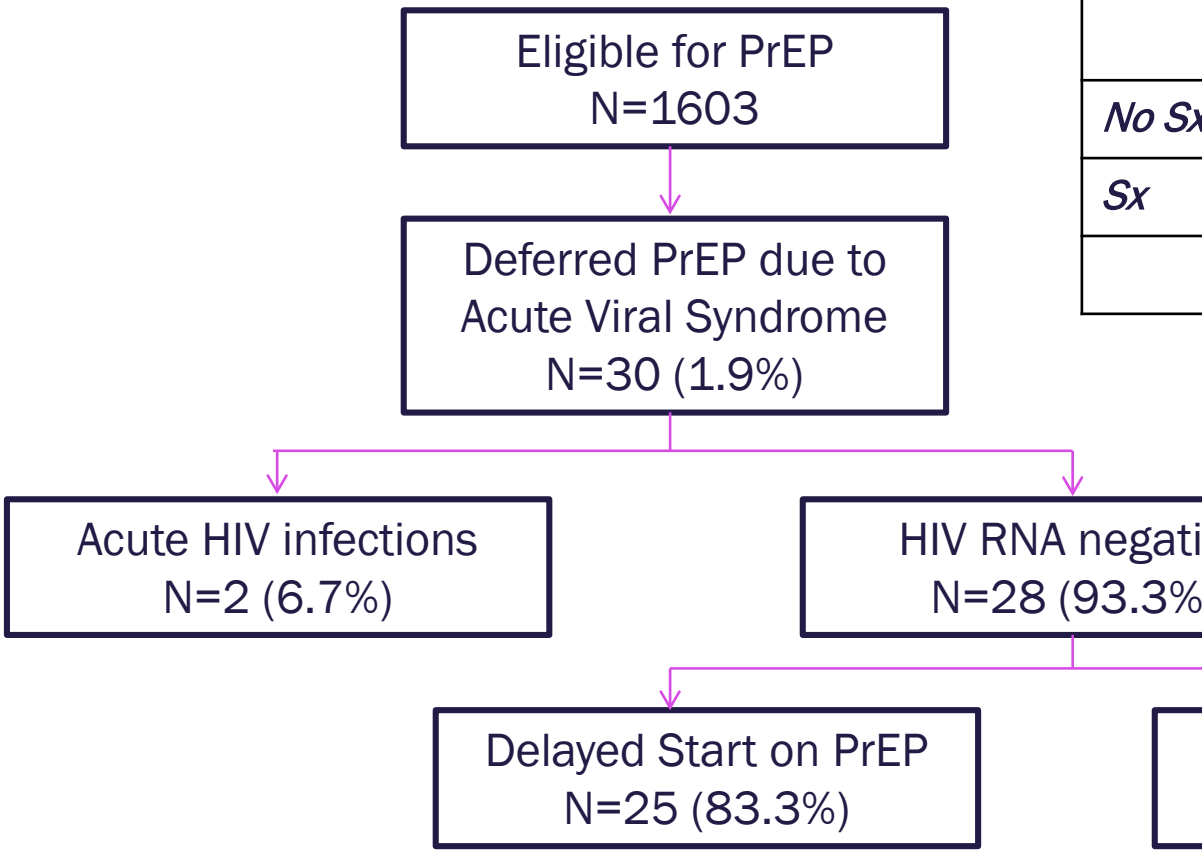
Gilbert, AIDS 2013
http://checkhimout.ca/hottest

HIV testing and AHI symptom screening in PrEP



US Public Health Service PrEP Clinical Practice Guideline, 2014

Clinical Screening for Acute Viral Syndromes and Acute HIV infection in iPrEx OLE



	No HIV	*Acute HIV*	
No Sx	1573	0	1573
Sx	28	2	30
	1601	2	1603

Sensitivity = 100%
Specificity = 98%
PPV = 6.7%
NPV = 100%

Grant et al, Lancet ID, 2014; Grant IAS 2016 (Durban)

Clinical Screening for Acute Viral Syndromes and Acute HIV infection in iPrEx OLE

Symptom screens in iPrEx OLE.

- Good sensitivity,
- Low PPV given the low prevalence of acute HIV infection,
- Require clinical training and judgment,
- Delayed PrEP initiation for 2% of the cohort.

FTC/TDF PrEP prevented at least 8 infections for every FTC resistant infection that occurred overall.

- Screening for acute infection would increase benefits relative to drug resistance risks, by more than 2 fold.
- Yet such screens are not feasible in all settings, and are not required to achieve a favorable risk/benefit for PrEP.

Grant et al, Lancet ID, 2014; Grant IAS 2016 (Durban)

Rapid HIV tests and point-of-care (POC) testing

Point-of-care HIV antibody tests

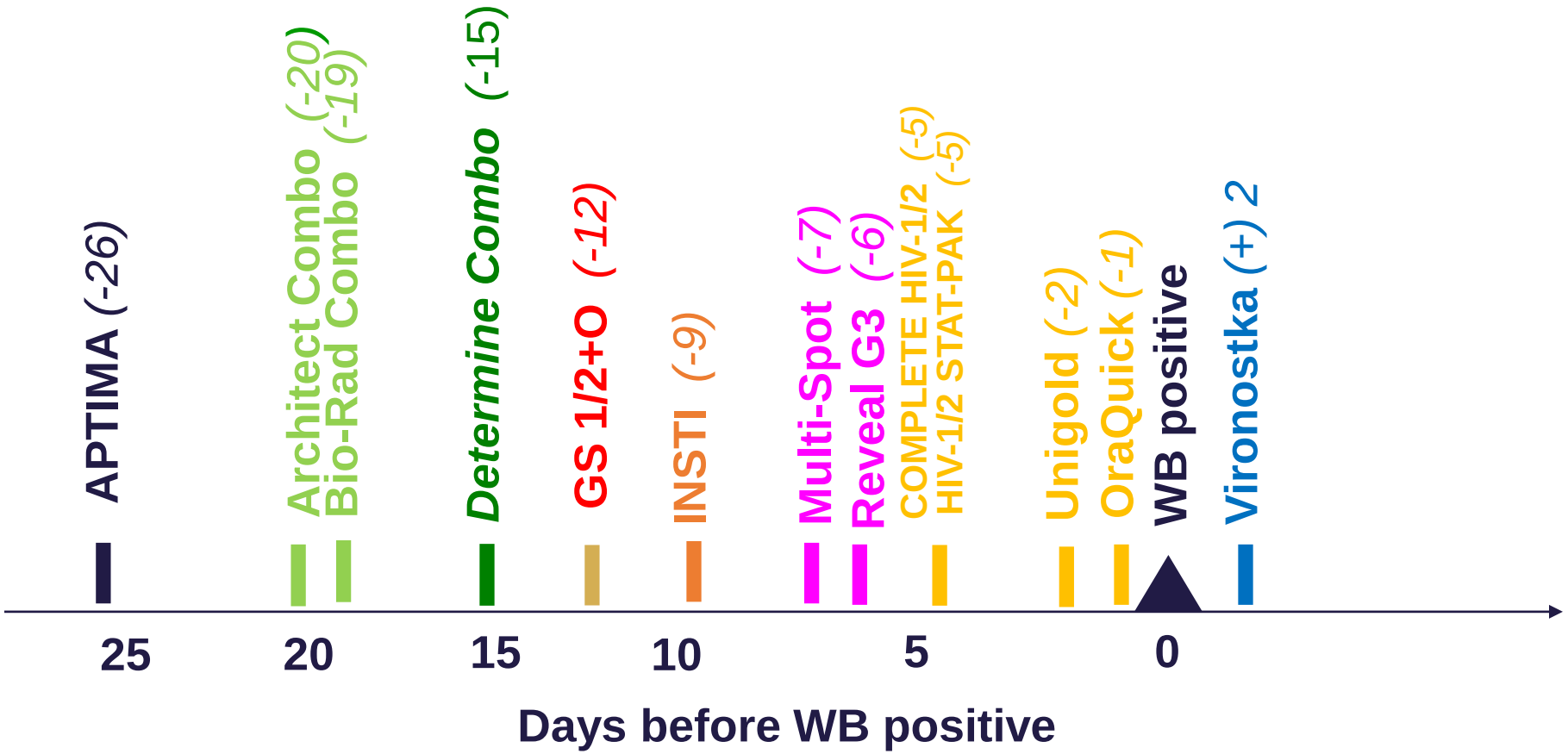
ADVANTAGES

- Patient Preference?
- Potential Avoidance of Blood Draw/ Biohazard
- More Persons Receive Results

DISADVANTAGES

- Potential for Preliminary False-Positive Results
- Longer window period

Sequence of test positivity relative to WB
166 plasma specimens, 17 seroconverters



Modified from *Masciotra et al, J Clin Virol 2011* and *Owen et al, J Clin Micro 2008*

slide courtesy of Bernie Branson

Rapid test comparison study (2/2010 - 8/2014)

	STD Clinic & Gay City n=3404
Concordant Positive POC Tests	82 (77%)
Discordant POC Antibody Tests	10 (9%)
All POC Negative/EIA Positive	6 (6%)
Acute (EIA Neg / NAAT Pos)	9 (8%)
Total HIV Positive	107 (3.1%)

Stekler J Clin Virol 2016; Stekler J Clin Virol 2013; O'Neal JAIDS 2012

Discordant rapid test results

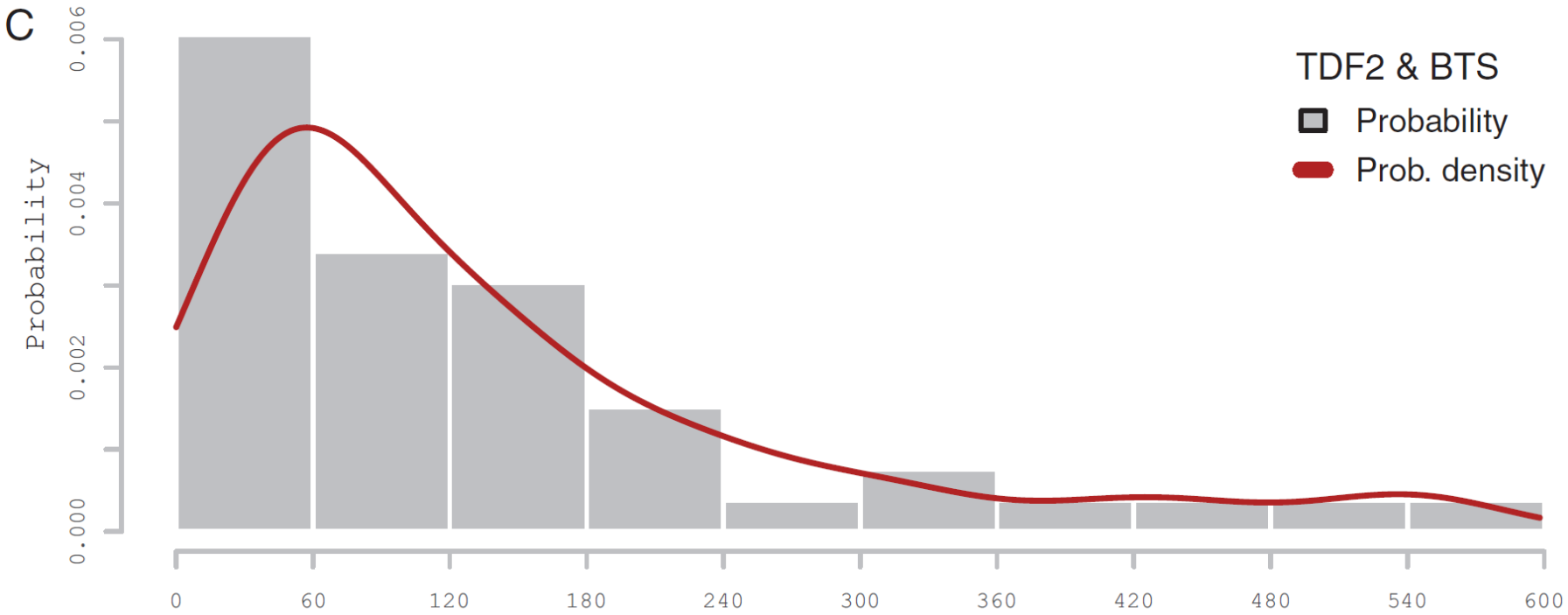
	Last neg HIV test	OraQuick OF	OraQuick FS	Uni-Gold	INSTI	Determine Ag/Ab	3rd or 4th gen EIA	WB results	HIV RNA (copies/mL)
1	2mo	—	—	—	ND	+/—	3rd —	negative	5.8 million
2	4yr	+	+	—	ND	ND	3rd +	24, 31, 40, 55, 120	141,000
3	2yr	—	+	+	ND	ND	3rd +	24, 31, 40, 55, 160	128,000
4	2yr	—	+	+	ND	ND	3rd +	18, 24, 31, 40, 51, 55, 120, 160	25,000
5	NA	—	—	+	ND	ND	3rd +	24, 51, 55, 160	12.8 million
6	NA	—	—	+	ND	—/+	3rd +	24, 40, 55, 160	21,000
7	1yr	—	+	—	ND	—/+	4th Ab+	24, 51, 55	719,000
8	1yr	—	+	+	ND	—/+	4th Ab+	24, 31, 55, 160	436,000
9	6mo	—	+	+	ND	—/+	4th Ab+	24, 55, 160	33,000
10	2mo	—	+	+	ND	—/+	4th Ab+	24, 55, 160	9000
11	3mo	—	+	+	ND	—/+	4th Ab+	18, 24, 55, 160	32,000
12	2mo	—	+	+	ND	—/+	4th Ab+	24, 160	94,000
13	2mo	—	—	+	ND	—/+	3rd +	18, 24, 31, 41, 51, 55, 65, 120, 160	ND
14	2yr	—	—	+	ND	—/+	3rd +	18, 24, 31, 40, 51, 55, 65, 120, 160	ND
15	4mo	—	—	ND	+	—/+	3rd +	24, 55, 160	ND
16	3mo	—	—	ND	+	—/+	3rd +	24, 51, 55, 160	347,000
17	7mo	—	—	ND	+	—/+	3rd +	18, 24, 65, 160	110,000
18	5mo	—	—	ND	+	—/+	3rd +	24, 51, 55, 160	62,000
19	4mo	—	+	ND	+	—/+	3rd +	18, 24, 31, 41, 51, 55, 65, 120, 160	7000
20	8mo	—	+	ND	+	—/+	4th Ab+	24, 51, 55, 65, 120, 160	70,000
21	NA	—	+	ND	+	—/+	4th Ab+	24, 55, 160	7000
22	2mo	—	+	ND	+	—/+	4th Ab+	negative	323,000
23	2mo	—	+	ND	+	—/+	4th Ab+	160	316,000
24	NA	—	—	ND	+	—/+	4th Ag+	24	4.4 million

Screening for acute HIV infection
Alere Determine HIV-1/2 Ag/Ab Combo v NAAT

		# tested	# AHI detected
Taegtmeyer PLoSOne 2011	UK	953	none
Rosenberg JID 2012	Malawi	838	0/8
Kilembe PLoSOne 2012	Rwanda, Zambia		1/52
Conway PLoSOne 2014	Australia	3190	0/9
Duong J Clin Microbiol 2014	Swaziland	18,172	0/13
Stekler J Clin Virol 2016	US	3438	1/11
		>26,591	2/93

Impact of PrEP on HIV tests during seroconversion

Impact of PrEP on HIV tests during seroconversion



TDF2 and Bangkok Tenofovir Study
235 false negative OraQuick OF results in 80/287 seroconverters
Median delay 98.5 days (Range 14.5 – 547.5)

Partners PrEP
False negative FS antibody tests in 72/129 seroconverters
14 had delayed detection for > 100 days
>100 day delay in POC detection associated with PrEP (10 v 4, OR 3.49)
Estimated Fiebig stages were prolonged in seroconverters

Curlin CID 2017, Donnell AIDS 2017

Summary

PrEP and HIV tests?
Guiding principles…

- When starting PrEP, use the test with shortest window period available. Do not use oral fluid tests.
  Starting PrEP during AHI → resistance
- If you use individual HIV NAAT in the U.S., please be aware and counsel patients that negative results may be reported and lead to a public health case investigation.
- Do not ask people to remain abstinent/use condoms while waiting out the window period.
- Screen for symptoms of AHI
  If symptoms and recent exposure → delay PrEP start
  Almost all symptomatic AHI will test pos on lab 4th gen
  But…. There is a 2nd window period….
- PrEP may lead to delayed seroconversion and false-negative tests, particularly with oral fluid tests.

Implementation Question #1: Same day PrEP start

Rationale:
- Rapid HAART start associated with better outcomes in PLWH
- Many PrEP clients fail to return for visits or go to pharmacies to pick up prescribed medication

Challenges:
- POC HIV tests are not as sensitive as laboratory-based tests.
- Delays due to insurance/medication program coverage
- Some people sent with PrEP may not take it, or may take it months later without re-initiating care.

Correlate:
- How strongly do we pursue people who would otherwise not follow-up?

Implementation Question #2
PEP to PrEP transition

Question: Should someone who completes a 28 day course of PEP be started on PrEP on day 29 or wait for results of follow-up testing?

"Because there is no evidence that prophylactic antiretroviral use delays seroconversion, and PEP is highly effective if taken as prescribed, there is no need for a gap between ending PEP and beginning PrEP to evaluate HIV infection status. Such gaps create opportunities for HIV infection to occur, disrupt daily adherence habits, and create an opportunity for disengagement from care. It is rare for HIV infection to be present and undetected when starting PEP, and such infections would usually be detected by HIV testing performed after 4 weeks of PEP."

Bob Grant and Dawn Smith, OFID, 2015

Implementation Question #3
What is the role of telehealth in PrEP?

Gay City experience

- Seattle community-based clinic started in 2013

- Currently: safety net clinic, run by HIV counselors
  goal: transition to primary care by 3-6 months
  new patients seen Tuesdays 3-530

- WA requires "valid doctor-patient relationship"
  defined as one face-to-face visit, in person or videoconference
  designed to address unlawful internet prescribing

- Telemedicine appointments started August 2015
  Zoom videoconferencing (HIPAA-compliant)
  client physically at CBO with counselor
  prescriber in office, at home, etc.
  all other activities similar to standard visits

Implementation Question #3
What is the role of telehealth in PrEP?

Adherence and follow-up measures of Gay City participants, 7/2016-3/2017

	Telehealth (n=10)	All other (n=38)
Prescribed PrEP	70%	84%
Month 1: attendance	71%	71%
Month 1: median doses missed/last mo	2	1
Month 3: attendance*	40%	91%
Month 3: median doses missed/last mo	12	2

*p=.04

Implementation Question #3
What is the role of telehealth in PrEP?

Telehealth models, other examples:

- Direct to consumer
  - Nurx, PlushCare (for-profit)
  - Aaron Siegler (Emory University): PrEP@Home
  - TelePrEP (University of Iowa): pharmacist-based service
- Remote physician with local nurse or HIV counselor/tester
  - Medical Advocacy and Outreach of Alabama
- Specialist consultants
  - Project ECHO

Challenges:

- Direct to consumer models – how does HIV testing occur?
- Legality? Quality of care?
- Reimbursement

Implementation Question #3
What is the role of telehealth in PrEP?

Gay City experience, future projects
- Provision of additional support to telehealth participants
- Expansion into bathhouses
- Potential expansion across WA state
- Exploration of self-testing technologies

Implementation Question #4
What is the role of self-testing in PrEP?

Rationale:

- People at high risk for HIV may need/want to test frequently.
- Self-testing could minimize clinic burden.
- May be useful in conjunction with (not FDA approved) purchase of generic PrEP by people who can/do not access clinic services.

Challenges:

- Self-tests are not as sensitive as clinic-based tests. More frequent HIV tests may not be useful if window period is long.
- Self-tests for STIs are not yet FDA-approved.

Opportunities:

- POC NAAT opened the door to the possibility of home NAAT.
  - PAR-17-471: Detection of HIV for Self-Testing (R61/R33)
  - FY 2018: NIAID/NIMH commitment ~$3 million

Technology: next generations

Questions?