HIV diagnosis schemes in the context of PrEP

Katrien Fransen

BREACH Nov 2017

Outline

- Seroconversion and other diagnostic markers
- How can PrEP affect these markers (lit.)?
  - -Partner PrEP studies
  - -IPERGAY data
  - -FemPrEP study
  - -Case report Amsterdam
- Guidelines
- Conclusions, thoughts and recommendations

HIV seroconversion

- Definition old: Seroconversion is the period of time during which HIV antibodies develop and become detectable.

  New: Seroconversion is the period of time during which HIV become serological detectable.

- Other laboratory markers than serological ones can be used to diagnose early or acute infection.

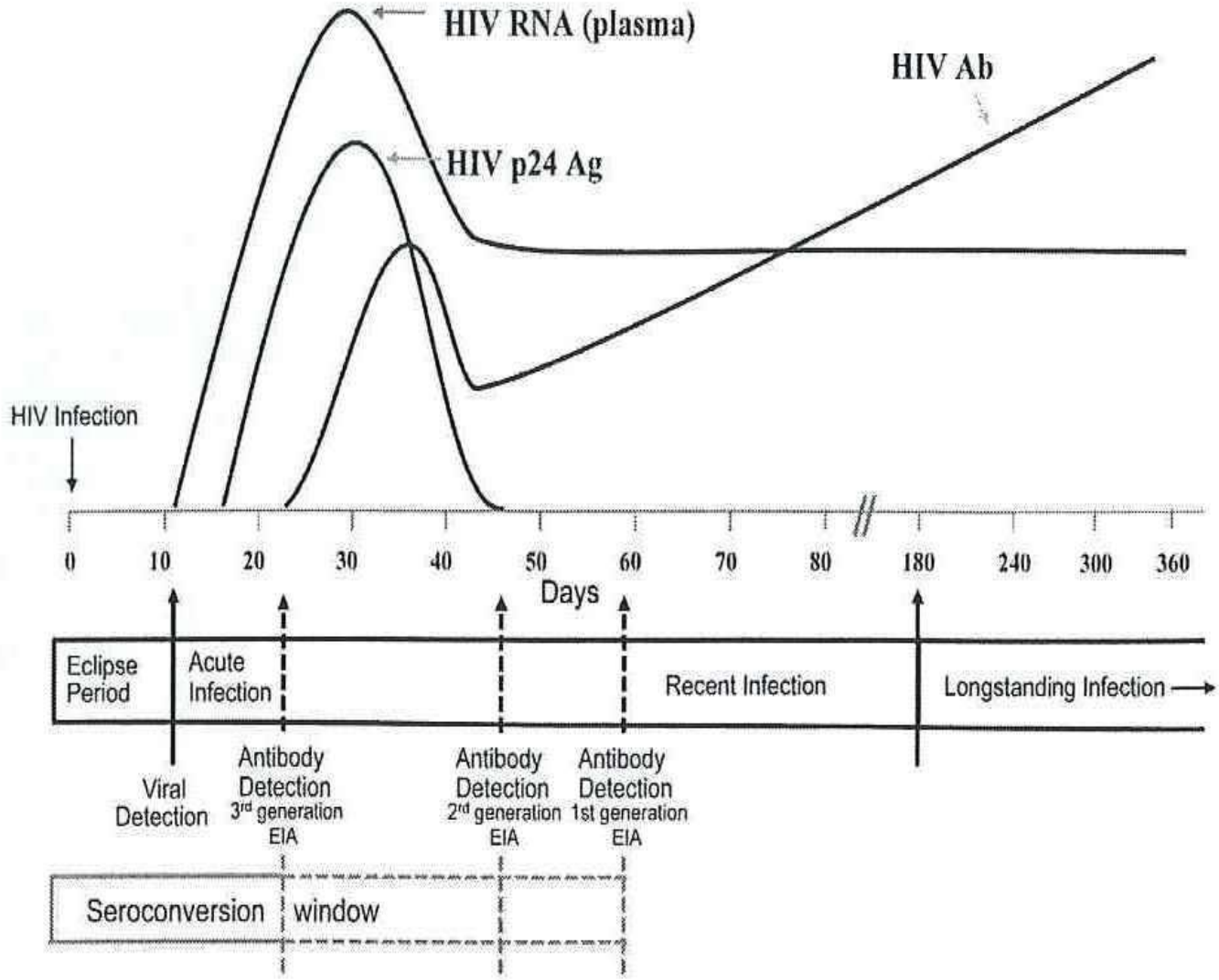
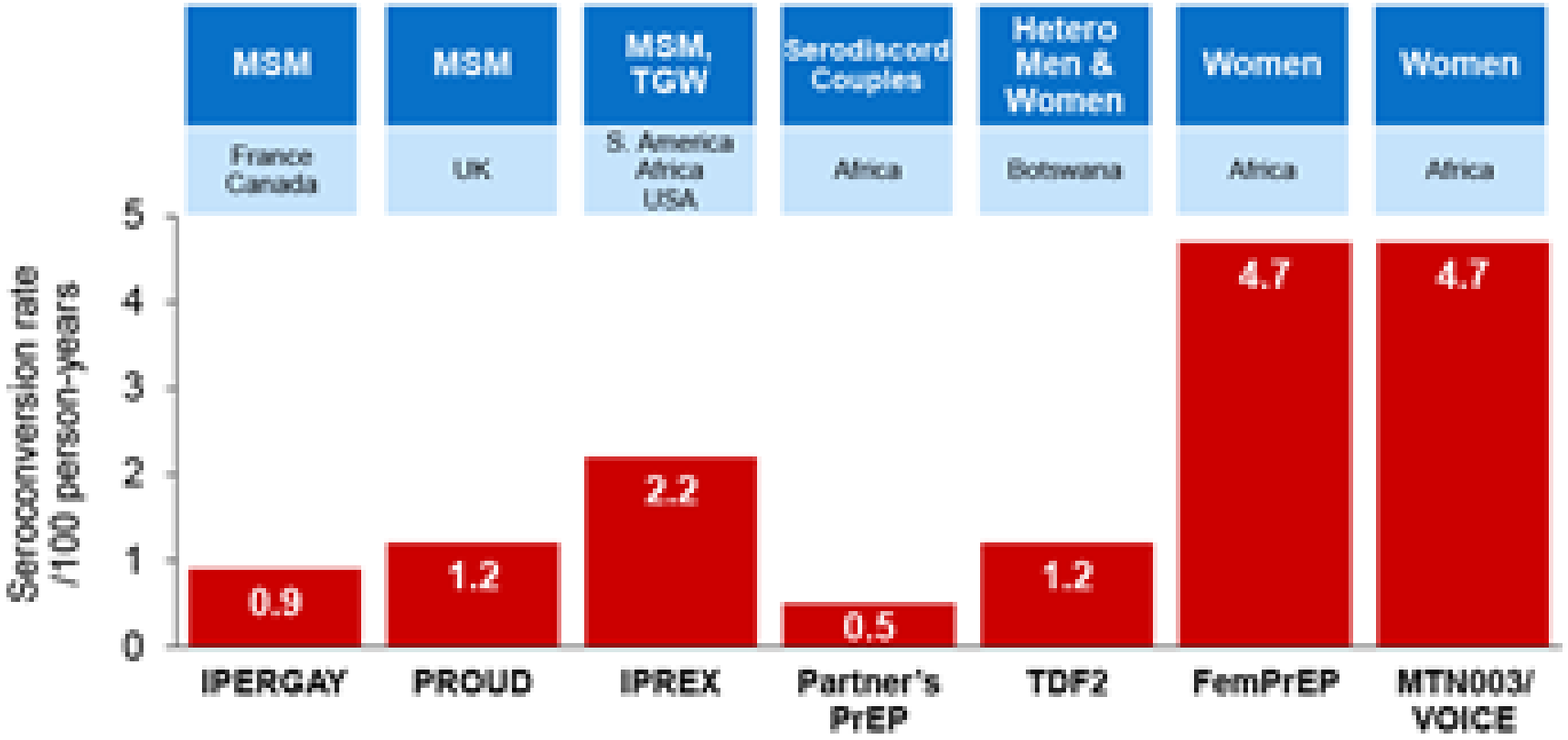


FIGURE 1. Sequence of appearance of laboratory markers in HIV infection.

BM Branson, Acquir Immune Defic Syndr 2010,vol 5

Seroconversion Rates in Clinical Studies of FTC/TDF for PrEP

- In the active treatment arms of clinical studies, seroconversion rates varied form 0.5 to 4.7/ per 100 person-years of FTC/TDF exposure



1. Molina, NEJM 2015;373:2237-46;2. McCormack , Lancet 2016;387:53-60;3. Grant, NEJM 2010;363:2587-99; 4. Baeten, NEJM 2012;367:399-410;5. Thigpen, NEJM 2012;367:423-34; 6. Peterson, PLoS Clin Trials 2007;2:e27. 7. Marrazzo, NEJM 2015;372:509-18.

Partner PrEP studies

The effect of oral preexposure prophylaxis on the progresion of HIV-1 seroconversion. **D. Donnell et all**. **AIDS** 2017, 31:2007-2016

Investigated whether oral PrEP alters timing and patterns of seroconversion when PrEP use continues after HIV-1 infection

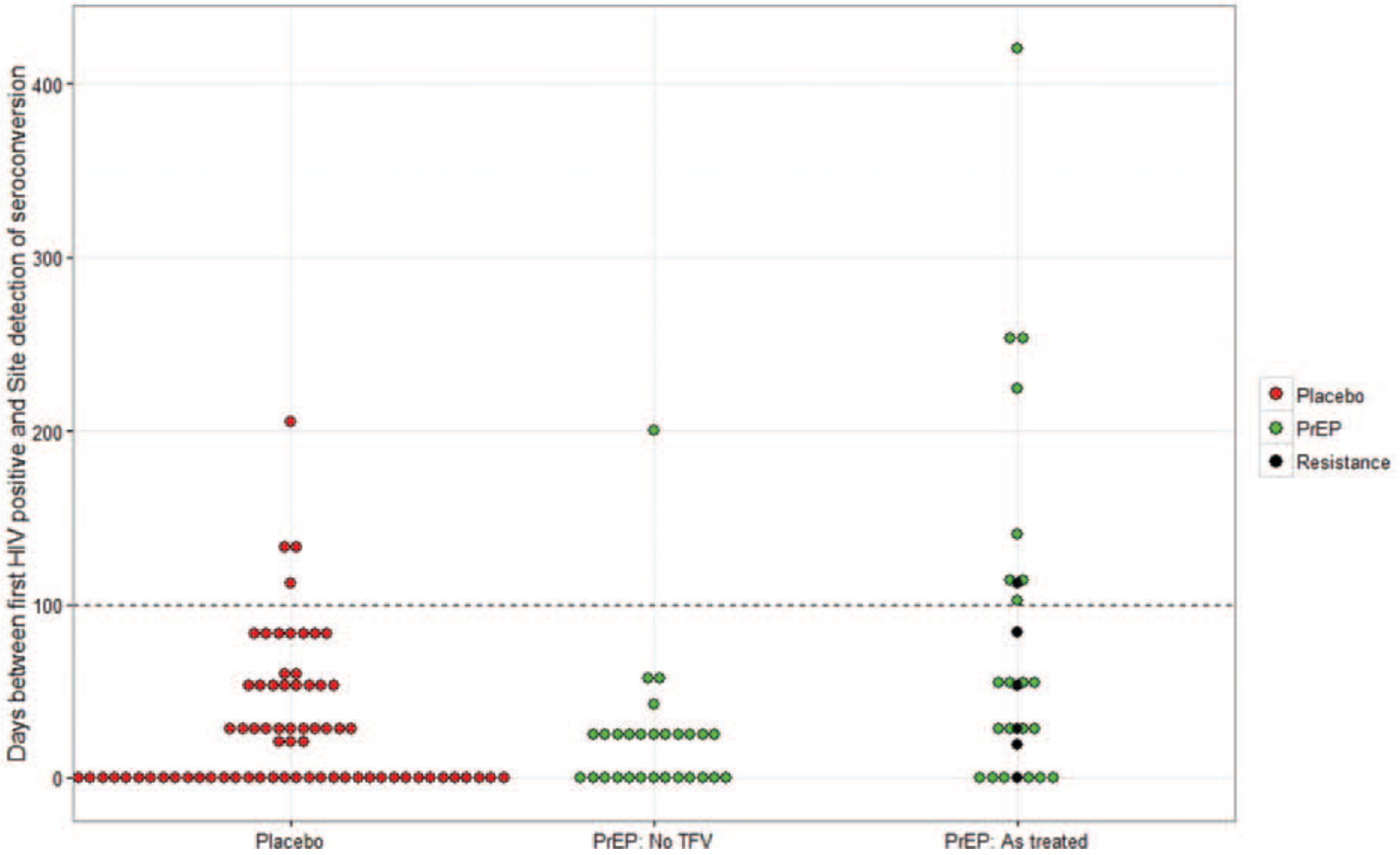
Kenya and Uganda

Data of 138 seroconverters: 67 on PrEP

71 Placebo

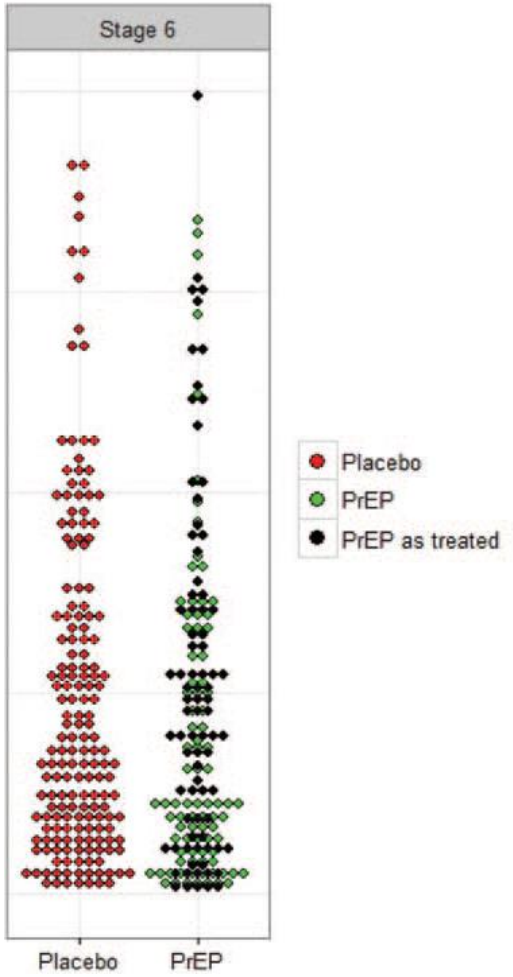
Time between first HIV-infected sample and site detection of seroconversion

D. Donnell et all. AIDS 2017. **31**:2007-2016



Architect signal to cut-off ratio is plotted for each sample by stage and arm

D. Donnell et all. AIDS 2017, **31**:2007-2016



Time to reach last stage (6) of seroconversion (WB positive).

	Estimated mean number of days to reach full confirmation			
	PrEP	Placebo	Relative rate to reach final stage for PrEP versus Placebo	*P*-value
PrEP as randomized	N=48	N=65		
Stage 6	**60**	**49**	0.820	0.490
PrEP as treated	N=21	N=65		
Stage 6	**80**	**49**	0.612	0.197

RNA (VL)

D. Donnell et all. **AIDS** 2017, **31**:2007-2016

Undetectable VL (Abbott, Roche)

	Prep	Placebo
Stage 6	11%	1%
Overall	11%	3%

Conclusions

-The majority of the HIV infections are detected within 3 months after infection

-People on PrEP who get infected may have a delay in detection of HIV infection (if under continued PrEP exposure). *What with 'event driven' application of PrEP ?*

-The cause of the delay is not related to infection with resistant strains.

-Highly sensitive rapid tests are needed to be able to detect the infection early.

-PrEP suppresses viral load during seroconversion

Assessment of HIV screening tests for Prep Programs

Constance Delaugerre et all. IPERGAY study group, Infectious disease Society of America, 2017

ELISA Ag/Ab

	Architect		Bioplex			
WB incomplete	reactive		Ag+/Ab-	Ag+/Ab+	Ag-/Ab+	Final
N=7	7		0	0	7	7
WB complete						
N=8	8		0	2	6	8
WB negative						
N=13	11		7	1	0	8
Total						
N=28	**26**		7	3	13	**23**

Simple rapid tests

	Vikia	Autotest	Alere
WB complete			
N=7	7	7	6
WB incomplete			
N=8	6	7	8
WB negative			
N=13	2	0	7
Total			
N=28	**15**	**14**	**21**

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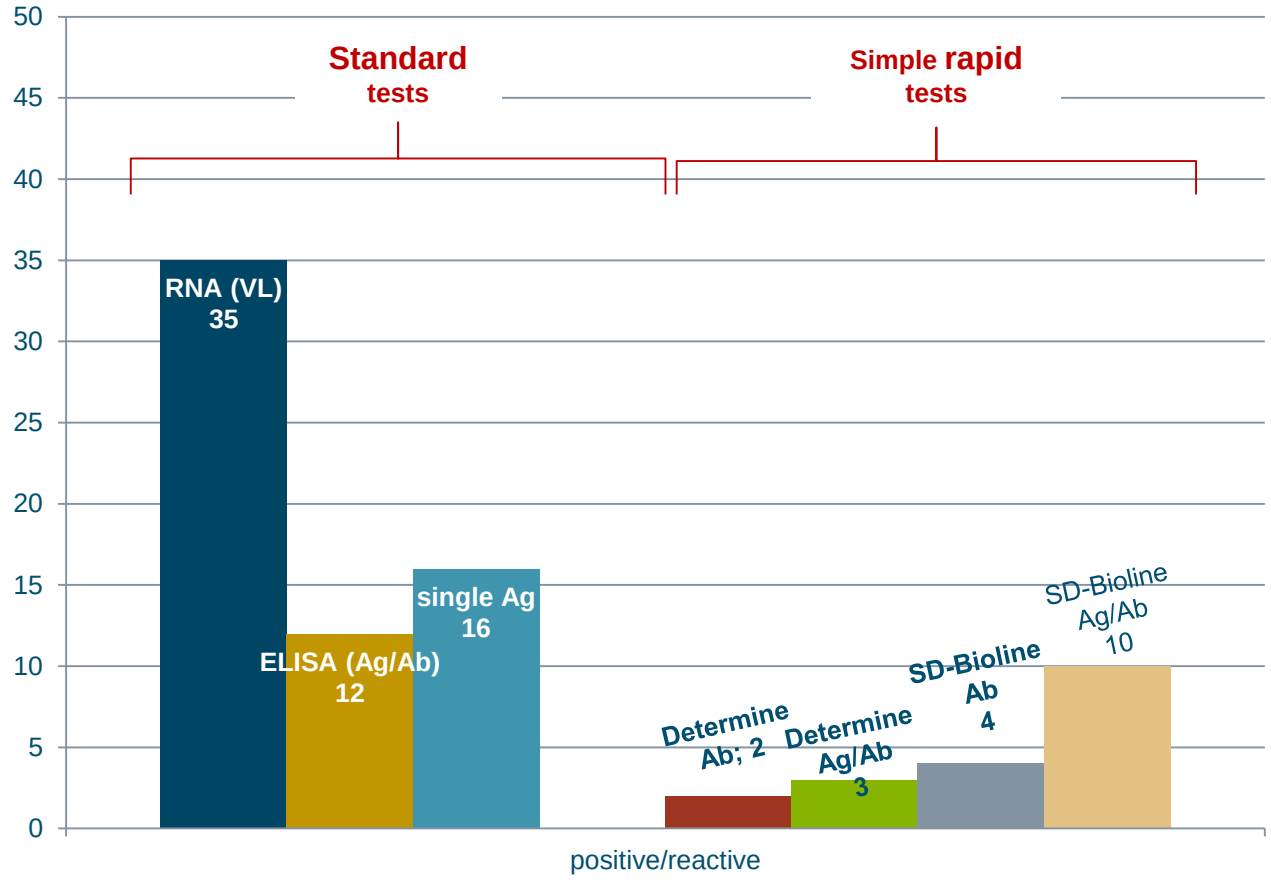
FemPrep Trial

Performance of serological and molecular tests within acute HIV infection. **K Fransen et all**. Journal of Clinical Virology 93 (2017)81-84



How does PrEP affect these markers?

Case report of the Amsterdam PrEP project (H-TEAM).

Acquisition of wild –type HIV-1 infection in a patient on pre-exposure prophylaxis with high intracellular concentrations of tenofovir diphosphate: a case report. **Elske Hoornenborg et all**. www.thelancet.com/hiv

Sep, 2017

	Sept 23, 2015	Oct 19, 2015	Dec 7, 2015	March 7, 2016	May 18, 2016	May 24, 2016	May 30, 2016	June 6, 2016	June 14, 2016	June 23, 2016	July 18, 2016
PrEP use	Start	Yes	Yes	Yes	Yes	Stop	..	..	..	..	..
Sexually transmitted infection diagnosed*	..	..	Anal chlamydia and gonorrhoea	Anal chlamydia and gonorrhoea	Anal lymphogranuloma venereum	..	..	..	..	..	..
Fourth-generation antibody and antigen test	Non-reactive	Non-reactive	Non-reactive	Non-reactive	Reactive†	Reactive†	..	..	..	..	..
Tenofovir diphosphate in dried blood spot (fmol per punch)	..	..	..	2234	..	2258	..	..	..	..	..
HIV RNA qualitative	Negative‡	..	..	..	ND	Negative§	..	..	..	..	..
HIV RNA quantitative¶	..	..	..	..	ND	<40 copies per mL	<40 copies per mL	..	12 882 copies per mL‖	101 156 copies per mL	..
Western blot	..	..	..	..	ND	gp120/160 positive	..	..	..	gp120/160 positive; p24 weak positive	gp120/160 positive; p24 positive; p17 positive
HIV cDNA in PBMCs	..	..	..	..	..	..	Negative	..	..	..	..
HIV cDNA in sigmoid biopsies	..	..	..	..	..	..	..	Negative	..	..	..
ART use	..	..	..	..	..	..	..	..	..	Start	Yes

PrEP=pre-exposure prophylaxis. ND=not done. PBMCs=peripheral blood mononuclear cells. ART=combination antiretroviral therapy. *Anal chlamydia and gonorrhoea were also diagnosed and treated in November, 2015. †Antibody positive and antigen negative. ‡Pooled HIV RNA using COBAS Taqscreen MPX version 2.0. §Analysed with the Xpert HIV-1 Qual test. ¶Analysed with the Abbott RealTime HIV-1 Viral Load Assay. ‖No resistance mutations detected.

Table 2: HIV test results and tenofovir diphosphate concentrations in dried blood spot samples of a PrEP user who seroconverted for HIV with high tenofovir diphosphate concentrations

Resume

- Atypical seroconversion pattern

-*ELISA combotest (LIAISON XL Ag/Ab Murex):* reactive

-*Western blot (MP Biomedicals):* only gp 160 present

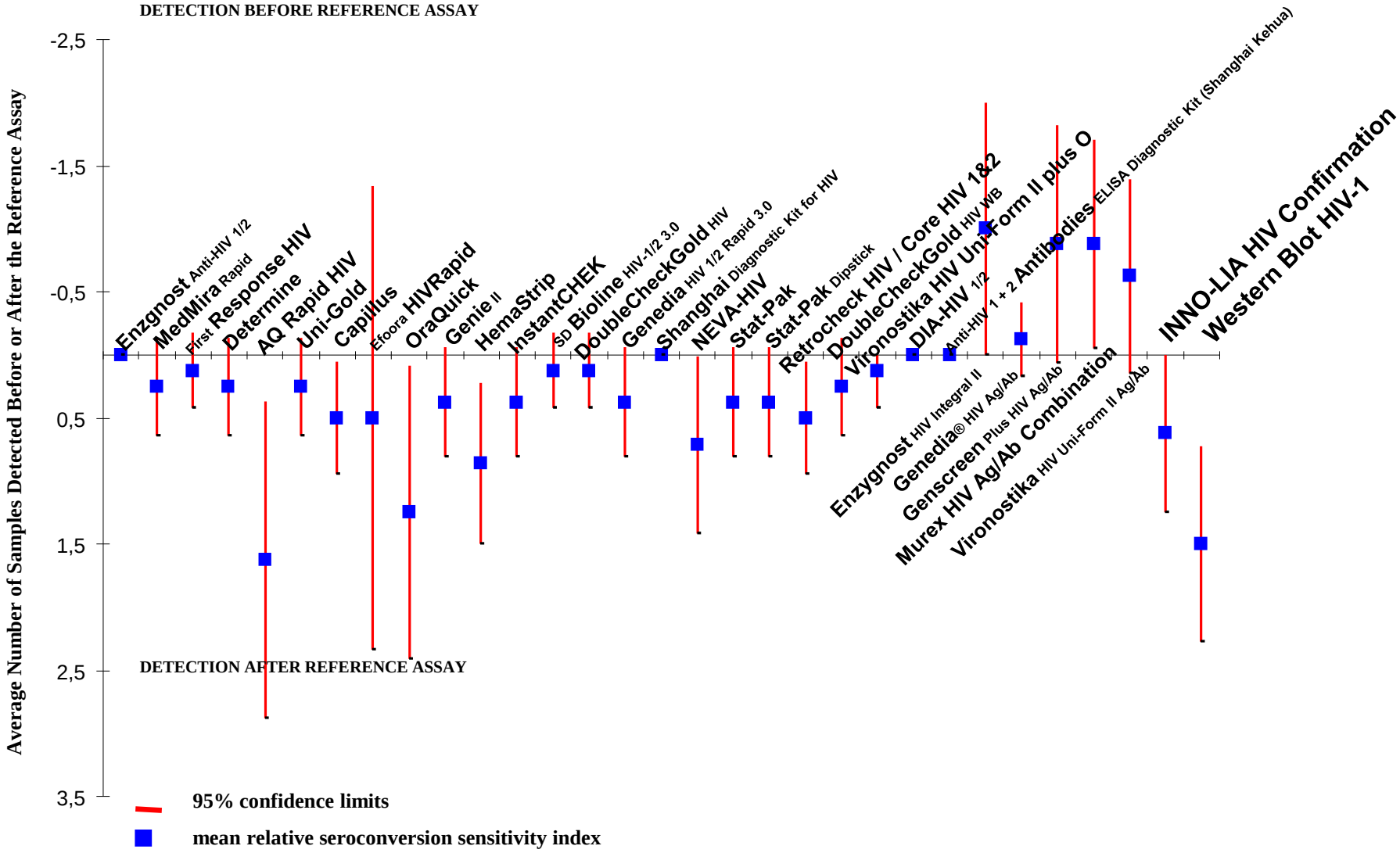
-*RNA (VL-ABBOTT):* not detectable (<40c/ml)

-*DNA/RNA (qualitative) in PBMC's*: negative

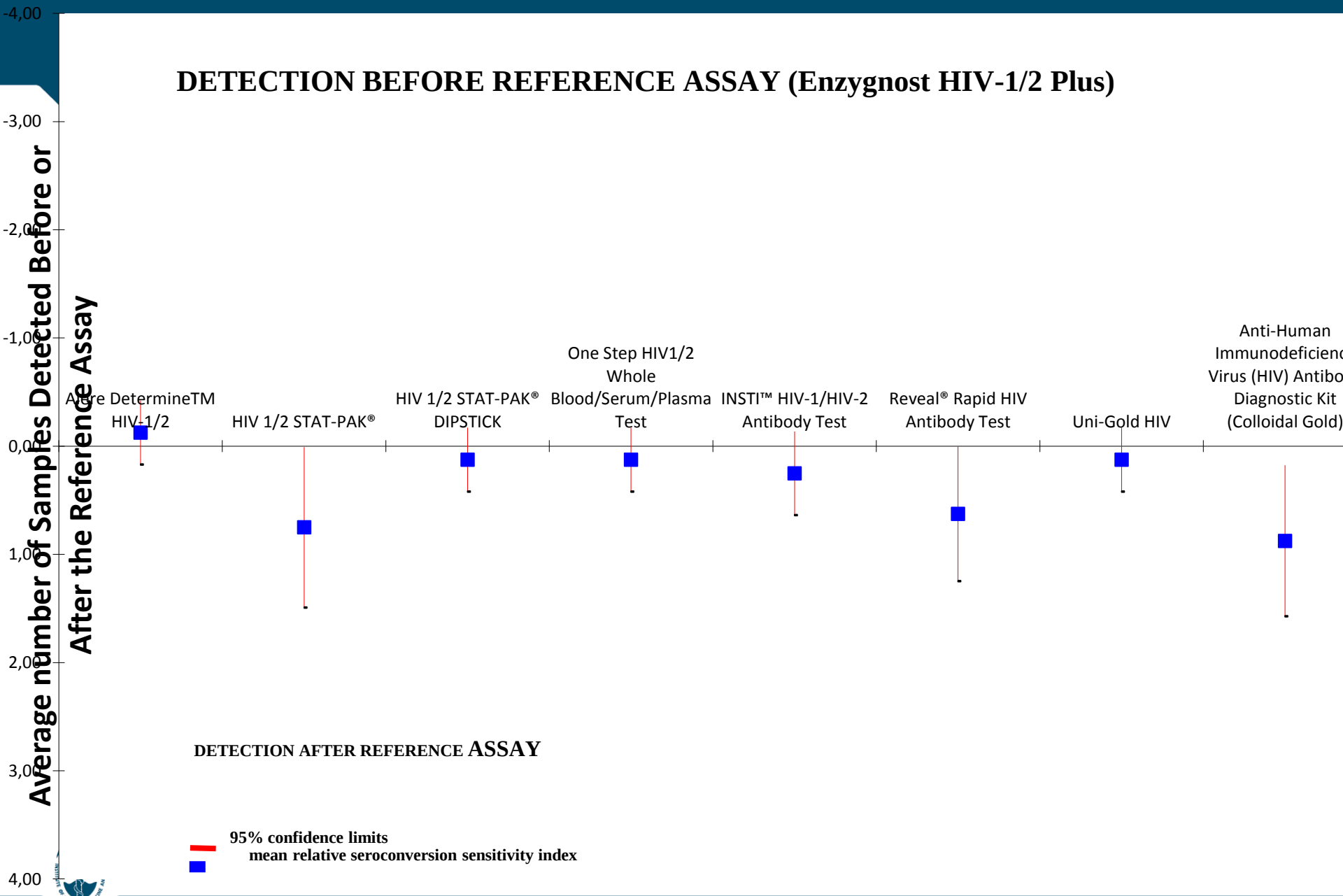
in biopsies: negative

Conclusion: Regular HIV testing and awareness of atypical patterns of seroconversion is needed.

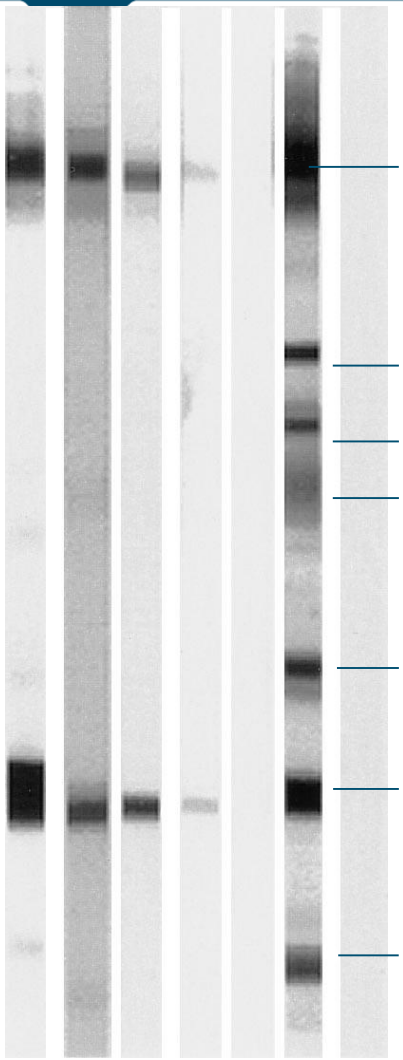
Relative performance on seroconversion panels as compared to the reference assay (Enzygnost Anti-HIV 1/2)

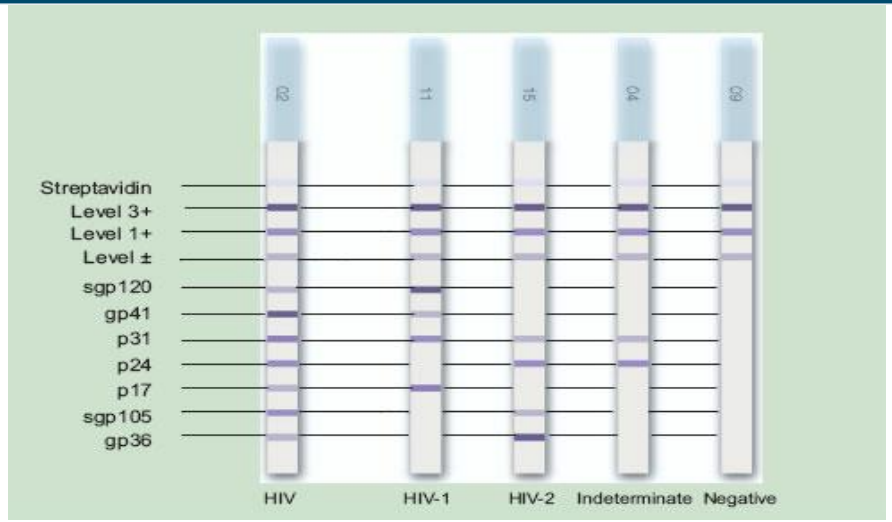


DETECTION BEFORE REFERENCE ASSAY (Enzygnost HIV-1/2 Plus)



Western Blot INNO-LIA GEENIUS





Seroconversion sensitivity of the different confirmation tests

F. Minard et all. Abstract XXXII[nd] International Congress of the ISBT, Cancun Mexico, July 7-12,2012

Results for 32 Serocoversion Panels (154 samples)				
	GS HIV-1 Western Blot	NEW LAV BLOT I	InnoLIA HIV 1/2 Score	Geenius
Negative	40.9%	36.4%	47.4%	47.4%
Indeterminate	27.3%	51.3%	13.0%	10.4%
Positive	**31.8%**	**12.3%**	**39.6%**	**42.2%**

Guidelines

- WHO guidelines (2012): guidelines for demonstration projects (feasibility studies). No details on which test to use, when.
- Eacs guidelines (2016) **http://www.eacsociety.org**

  1 page on testing

  ECDC: Although the risk for resistance is high if starting therapy in the acute phase, there is no recommendation in doing the RNA test before starting therapy
- 'Prep richtlijn Nederland' (2016) most detailed.

  In their demonstration project AmPrEP they also use an RNA test before the start of PrEP, but no extra HIV infection has been found.

HIV testing scheme for PrEP users

- Every 3 months: 4th generation ELISA
- No arguments to perform RNA
- At start of PrEP, RNA testing can be considered in case of symptoms suggestive for an acute infection

test	Before start PrEP	At start	1 month	3 months	
HIV 4° gen	X	X	X	X	

What in Belgium?

- Different 4th generation screening tests used.
  CE label: one criterium(< 2 IU P24 Ag)
- Confirmation in ARL is no longer the WB but LIA or Geenius
- ARL/ARC are adequate and unique structures not present in other countries: Additional tests can be done without delay or extra costs for the patient.
- ARL/ARC are used to deal with difficult diagnosis and atypical pictures: Treatment during seroconversion, elite controllers, children diagnosis…
- Close link with research (BREACH): new and more sensitive tests, techniques are followed up and evaluated.

Thoughts, recommendations

The current PrEP guidelines are apropriate, but …

- Improvement and structural involvement of the ARL is needed in the different ARC PrEP sites

….and in the PrEP Task Force (no lab representative present at this time) in order to:

- Standardise care in all ARC/ARL
- Collect specimen and data on tests.
- Negotiation of reïmbursement of some STI
- Perform research on testing optimalisation

- Information on PrEP use should be available to the ARL in order to be vigilant in a correct diagnosis