The Impact of HIV Vaccines and Rapid Tests on the Laboratory Diagnosis of HIV

National Laboratory Training Network

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The Impact of HIV Vaccines on the Laboratory Diagnosis of HIV

Molecular diagnostics (NAT)

Challenges to the serodiagnostic algorithm

Impact of HIV Vaccine Development on HIV Diagnosis

- **Preventive HIV vaccines development is a public health imperative.**
- **Number of uninfected volunteers exposed to experimental HIV vaccines is ↑.**
- **Complexity of HIV immunogens is ↑.**
- **"Reservation" of HIV epitopes for serodiagnosis confounds vaccine development and is the wrong approach.**

Impact of HIV Vaccine Development on HIV Diagnosis, cont..

- **HIV diagnostic laboratories will be increasingly asked to distinguish HIV infection from serologic response to HIV vaccines = molecular diagnostics/nucleic acid testing (NAT).**
- ***We need to be ready.***

Western blots from subjects with chronic HIV infection are "screaming hot"*

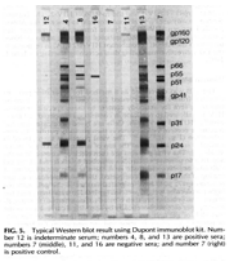
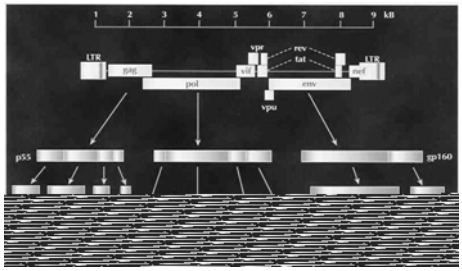


FIG. 1. Typical Western blot result using Dupont immunoblot kit. Number 12 is indeterminate serum; numbers 4, 8, and 13 are positive sera; numbers 7 (middle), 11, and 16 are negative sera; and number 7 (right) is positive control.

***RADM C. Schable**

Mandell, 4th Ed, Churchill Livingstone, NY1995

HIV-1 genomic organization
Vaccine antigen complexity ↑



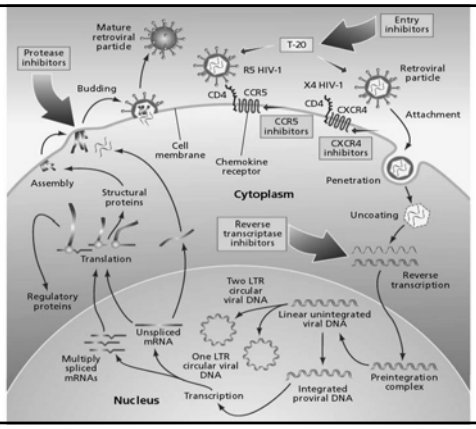
Why not delete portions of HIV genes incorporated into HIV vaccines to "reserve" epitopes that would only be seen in natural HIV infection?

NAT for the blood supply → clinical use

- **Chiron/GenProbe Procleix™ HIV-1/HCV assay FDA approved on 28 Feb 2002.**
- **FDA approval for blood banks will allow "off-label" clinical use of NAT for confirmatory testing.**

Blood banks using minipooling--can clinical labs?

- **Blood banks pool 8 to 16 samples prior to submitting to Procleix.**
- **Procleix has a 95% sensitivity at 50 RNA copies/ml and 100% sensitivity at 100 copies/ml.**
- **Isn't this sensitive enough?**



Blood banks using minipooling--can clinical labs?

- **Minipooling can miss samples with VL of 1-2 logs by dilution.**
- **Patients in early second window period can have low RNA and no HIV-specific antibodies.**
- **US Army blood banks do not minipool--nor will my clinical laboratory.**

The Impact of HIV Rapid Tests on the Laboratory Diagnosis of HIV

Outline

- **Rationale for rapid HIV diagnostics**
- **Retrospective evaluation of rapid serum tests**
- **Algorithm development & "corporate will"**

Rationale for rapid HIV diagnostics

National importance of rapid diagnostics

- **Impact on high prevalent/low return rate settings:**
  - **↑ true negative, ↑ true positive**
  - **↑ false positive?**
- **Occupational post-exposure prophylaxis (PEP) decisions.**
- **Perinatal antiretroviral drug Rx decisions.**

MMWR 47:211-215 (1998)

Military importance of rapid diagnostics

- **All issues for civilian community**
  - **TriCare**
  - **Humanitarian assistance**
- **Blood supply emergency screening.**
  - **Somalia, Bosnia, Kenya/Tanzania embassy bombings, *USS Cole***
- **Combat casualties testing.**

Civil-military importance of rapid diagnostics

- **Local blood supply demand high (trauma)**
- **Transportation interrupted (blood, test kits, ARVs)**
- **Increased occupational exposure (rescue & recovery)**
- **Smallpox attack response**
  - **Live attenuated vaccine...**
  - **…highly dangerous to HIV+ and...**
  - **….HIV+ vaccine-induced smallpox cases enhance epidemic**

Civil-military importance of rapid diagnostics

- **Need to pre-position rapid HIV tests devices and ARVs for civil-military emergencies?**
- **Need FDA approved devices**
- **Need recognized testing algorithm (APHL, WR AIR, CDC, etc.)**
- **Need training and awareness and engagement of state, local and federal public health laboratories prior to implementation.**

WRAIR/CDC collaboration on HIV rapid diagnostics: approach

- **CDC: Prospective testing in areas of high HIV prevalence (intended use).**
- **WRAIR: Retrospective testing of pedigreed serum archive.**
- **FDA: WRAIR retrospective testing as substitute for low risk HIV population testing (e.g., blood banks)?**

Retrospective evaluation of rapid serum tests

Retrospective testing at WRAIR

- **Serum panels are archived by EIA reactivity**
  - **All new panels are re-tested by EIA/WB**
- **WRAIR is blinded to clinical data**
- **Test devices were generally tested on unique panels**
- **Retrospective testing is not “intended use”**

Results

	10,290	511	1	9,779	1	99.8	100.0
	10,261	122	0	10,139	217	100.0	97.9
	10,317	756	20	9,561	20	97.4	99.8
	168	112	0	56	0	100.0	100.0
	982	380	0	602	4	100.0	99.3
	11,000						
	921	357	2	564	125	99.4	81.9
	591	40	0	551	0	100.0	100.0
	852	91	17	743	1	84.3	99.9
	871	137	2	732	0	98.6	100.0

Performance Modifiers

- **Determine testing in Rakai, Uganda.**
- **Use of single gp41 ID domain peptide for OraQuick.**

Rakai, Uganda (Determine)

- **Total specimens tested = 321**
- **Tests censored = 120**
- **EIA+/no WB f/u = 118 (data censored)**
- **EIA-/QNS for Determine =2 (data censored)**
- **Tests evaluated = 201**
- **True pos = 21**
- **False neg = 0**
- **False pos = 17**
- **True neg = 163**
- **Sensitivity= 100%**
- **Specificity = 90.6%**
- **PPV+ = 63.4% (14% PP)**
- **PPV- = 100%**

Algorithm development & "corporate will"

Algorithm development

- **Several rapid tests look technically promising**
- **Corporate sponsors are moving toward FDA approval**
- **WRAIR moving to algorithm testing on pedigreed serum panels**
- **Retrospective testing is not "intended use"**

"Strawman"

- **Posit: Multiple rapid tests will yield equivalent performance compared with EIA/WB algorithms.**
- **Sensitive screening & specific confirmatory test(s).**
- **Algorithms will differ based on HIV prevalence, performance modifiers, and cost-benefit analysis.**

Challenge to Industry

- **Rapid HIV testing technology is robust.**
- **Cost barriers to FDA approval reduce corporate will to pursue U.S. licensure of HIV rapid tests.**
- **Non-FDA approved HIV rapid tests will have no market value in the U.S. or where federal dollars support overseas health care delivery.**

Serial algorithm panel

- **N = 400 pedigreed sera (23 R, 377 NR)**
- **Two different rapid tests screen**
  - **Concordant NR = NR, final**
  - **Concordant R & discordant pair third rapid test.**
- **100% accurate**
- **Moving to N = 3,000**

Summary

- **HIV vaccines will confound the screening EIA and Western blot.**
- **Nucleic acid testing can dissect infection from vaccine response with careful interpretation.**
- **HIV rapid tests are a public health priority.**
- **HIV rapid tests are needed for civil defense.**
- ***HIV rapid tests implementation must be coordinated at ALL levels of government.***