

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

National Laboratory Training Network

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Acknowledgment

- **Dr. Merlin Robb (rapid testing/Uganda; vaccine)**
- **Dr. Jerome H. Kim (vaccine)**
- **Hassan Zahwa (rapid testing)**
- **Jennifer Malia (vaccine; rapid testing)**

*The Impact of HIV Vaccines on the
Laboratory Diagnosis of HIV*

Molecular diagnostics (NAT)

Challenges to the serodiagnostic algorithm

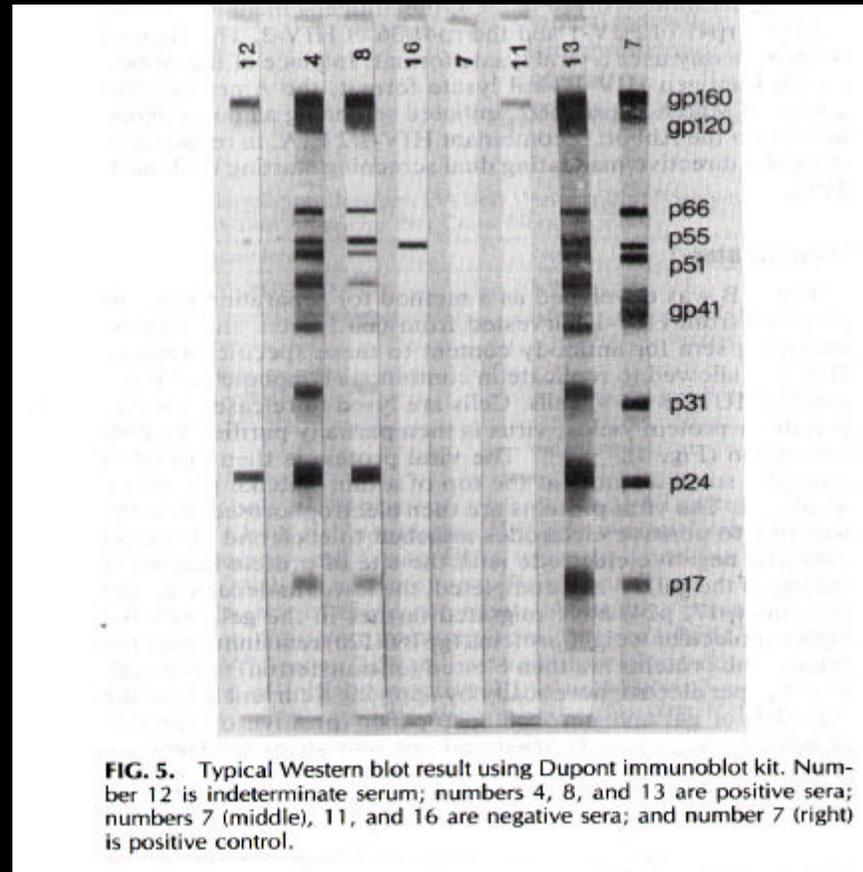
Impact of HIV Vaccine Development on HIV Diagnosis

- 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.*

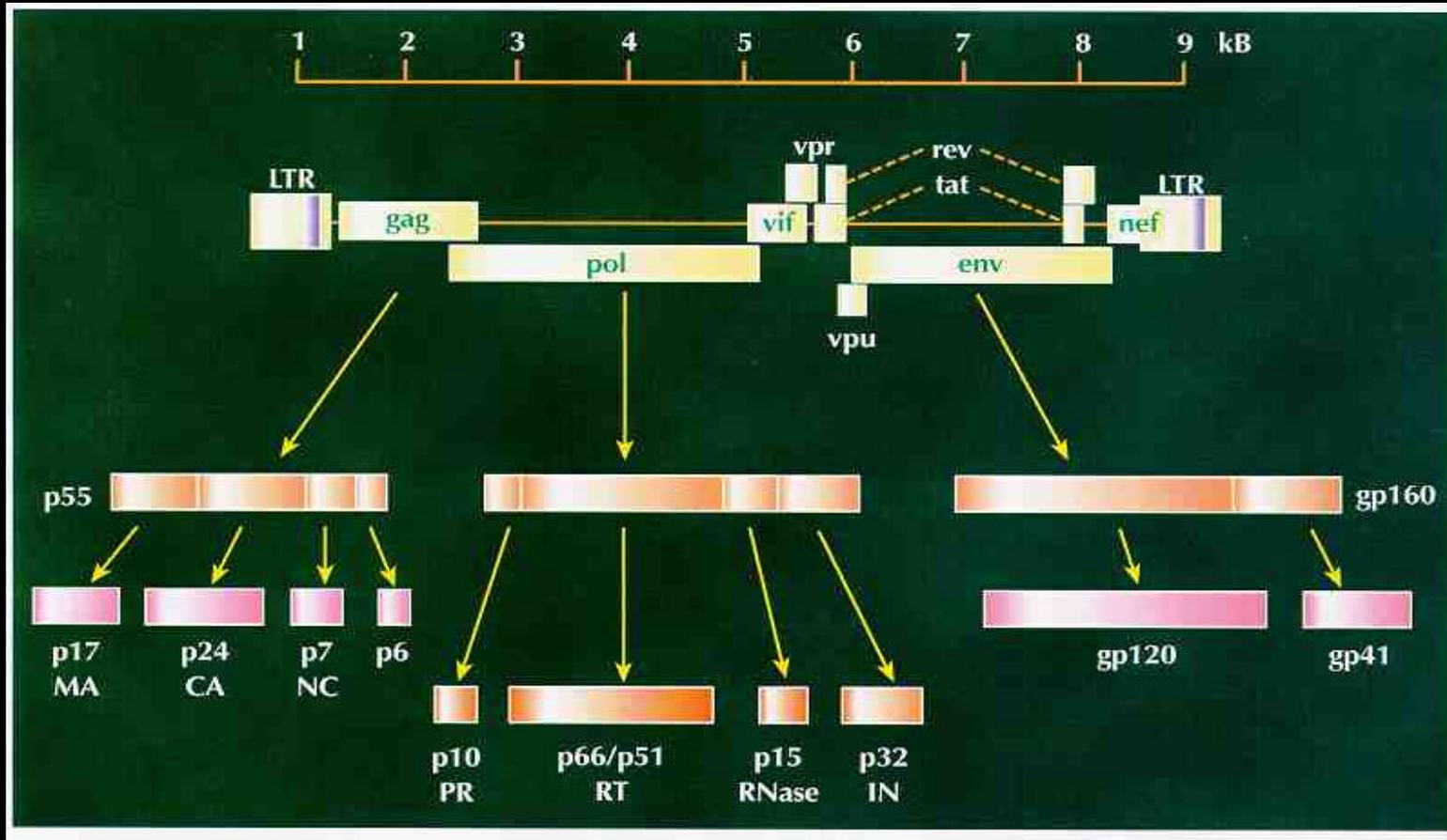
*Western blots from subjects with chronic HIV infection are “screaming hot”**



***RADM C. Schable**

**Mandell, 4th Ed, Churchill
Livingstone, NY1995**

HIV-1 genomic organization



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

Reservation of HIV epitopes for serodiagnosis is a faulty strategy

- **Natural immune response to infection is disease delaying.**
- **Vaccine development is hindered by imperfect understanding of the protective cellular and humoral immune response.**
- **Make the best vaccine possible.**
- **Let testers like us figure out how to diagnose in this setting.**

Hypothesis:

**Complexity (valence) of HIV-1 antigens
in experimental vaccines positively
correlates with the broadness of induced
Western blot reactivities**

Vaccine constructs

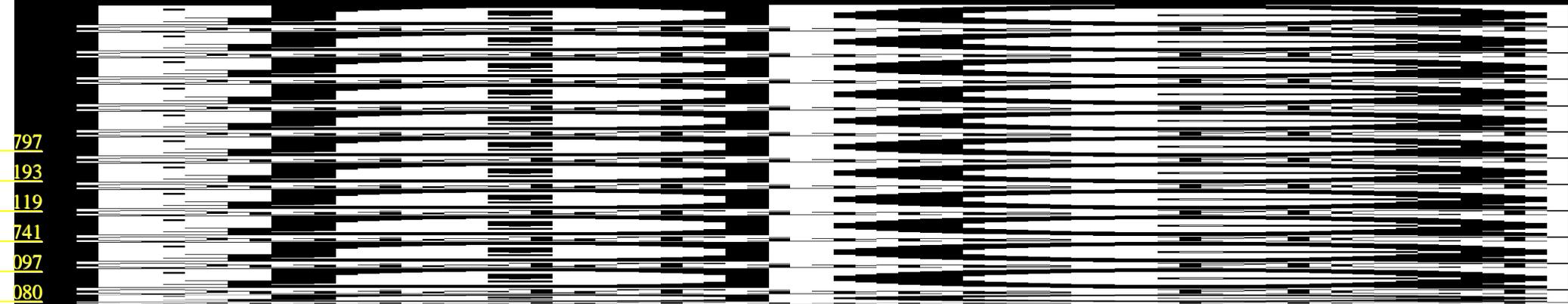
- **Subunit**
 - gp120 and gp160
- **ALVAC (canarypox vector)**
 - vCP65 (rabies placebo)
 - vCP125 (gp160)
 - vCP205 (gp120, gp41, gag, pol)
 - vCP300 (gp120, gp41, gag, pol, nef)

AVEG Western blot results

- **Blots performed on 41/42 EIA screened positives.**
- **3 (7%) were negative**
- **13 (32%) were indeterminate**
- **25 (61%) met ASTPHLD/CDC WB criteria for reactive test result**
- **23/25 (92%) of these false positive blots were from canarypox prime/gp120 boost study arms**

*Indeterminate Western blot profiles from Env subunit
vaccination (RV124)*

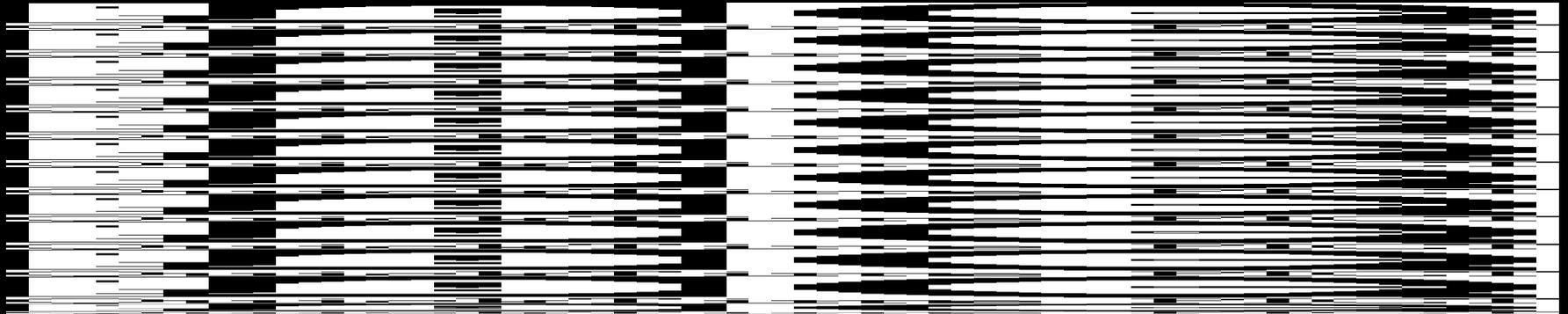
S/C



*Reactive Western blot profiles from multi-antigen
vaccinia vector vaccination (RV124)*

S/C

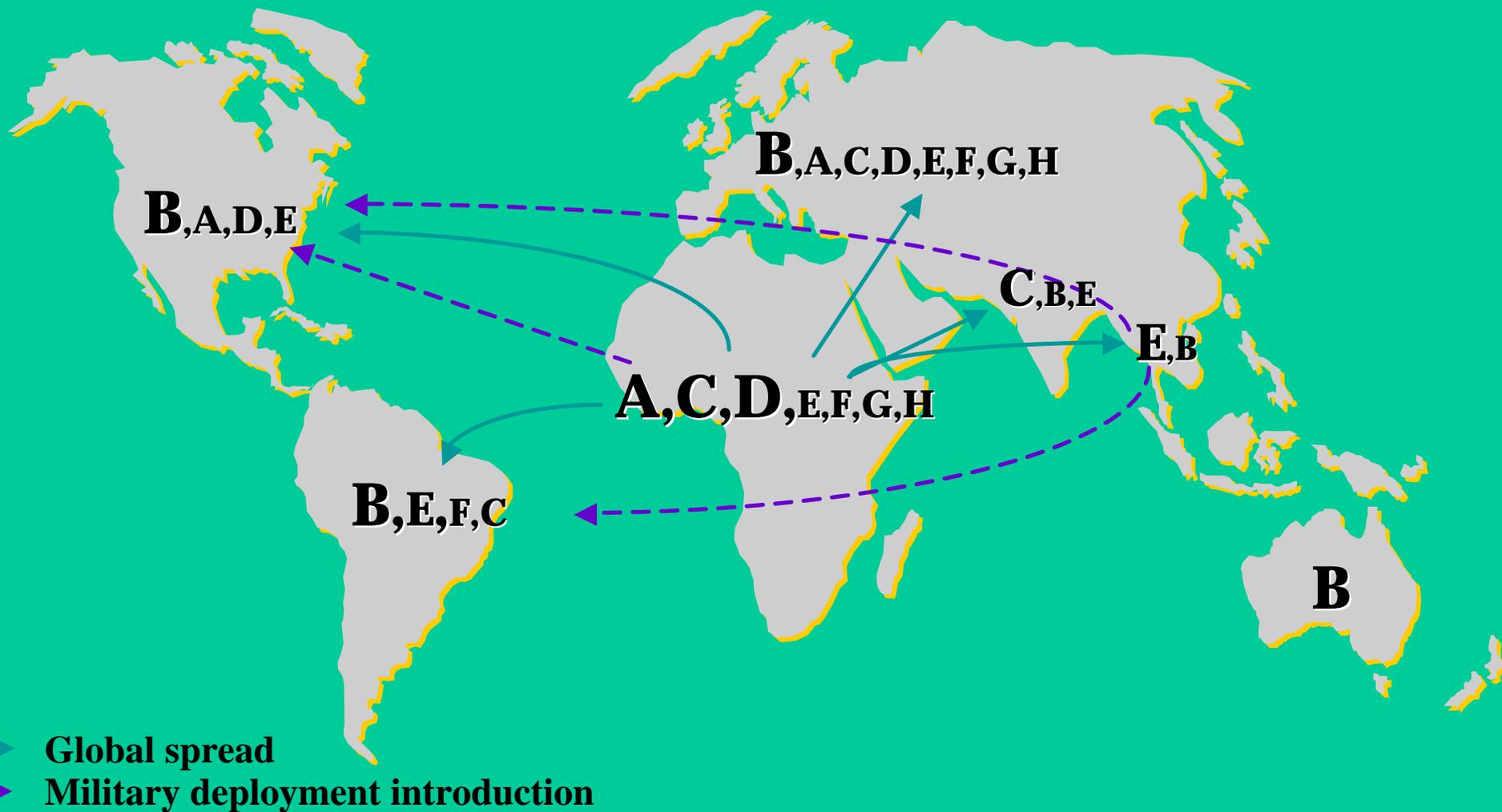
1.335
4.065
3.314
3.422
0.990
0.302



Challenge: Molecular diagnostic tests must be capable of uniformly detecting prevalent HIV-1 subtypes

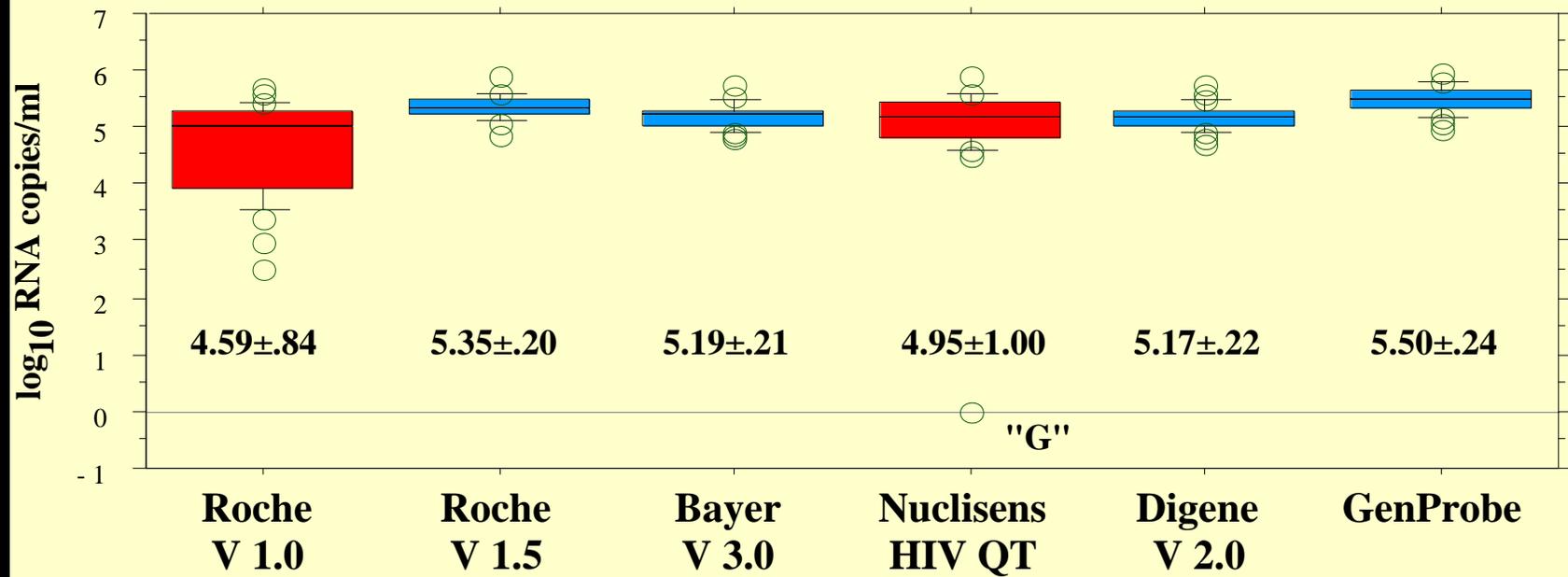
Global Threat—Evolving Risk

Geographic Distribution of HIV-1 Subtypes – 1990's



Evaluation of HIV-1 subtype on viral load assays

**Comparison of six quantitative HIV-1
RNA tests on HIV-1 subtypes A through G**

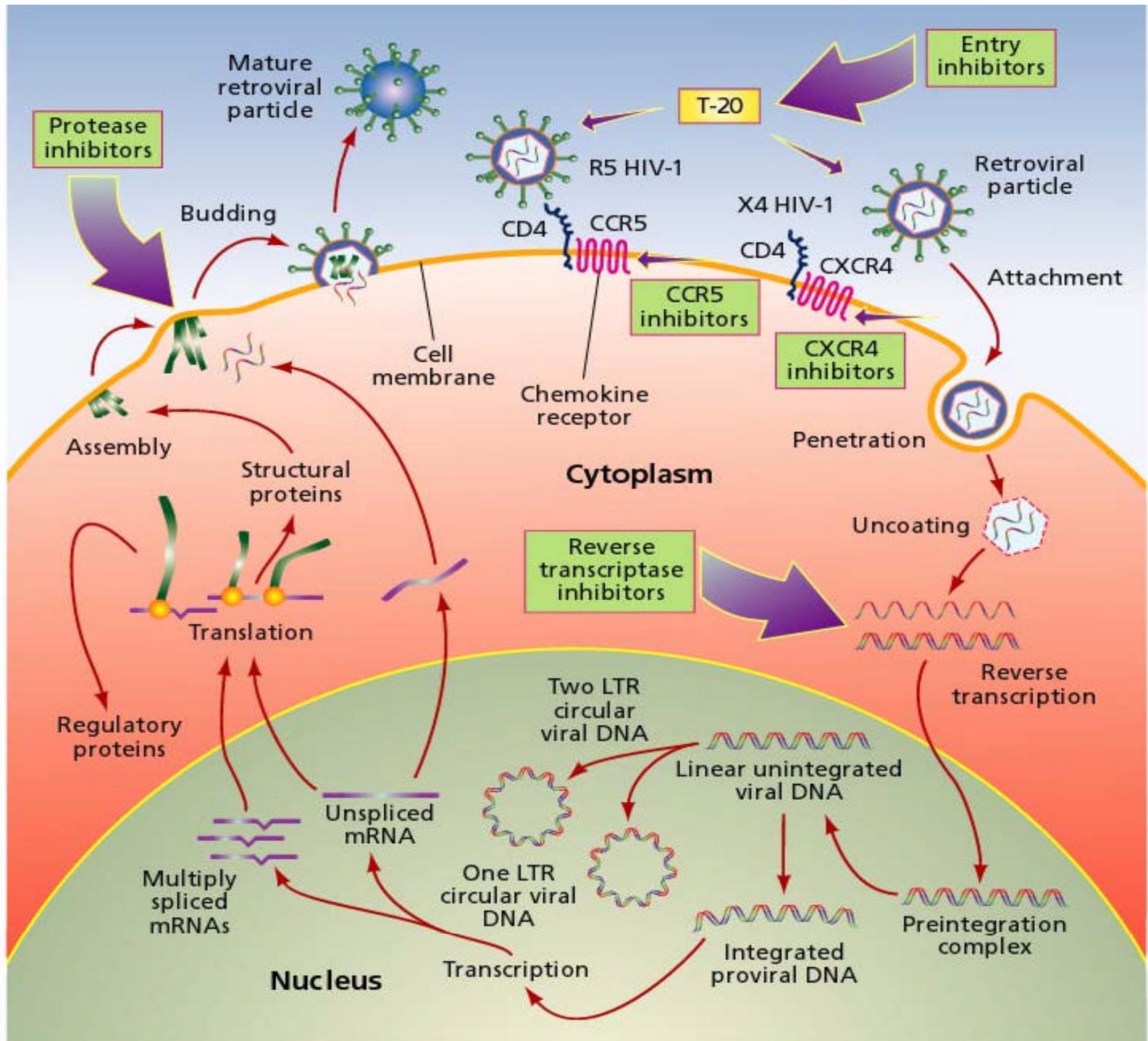


NAT for the blood supply ® clinical use

- **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.**

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

	n	TP	FN	TN	FP	Sens	Spec
Hemastrip	10,290	511	1	9,779	1	99.8	100.0
UniGold	10,261	122	0	10,139	217	100.0	97.9
Determine (1)	10,317	756	20	9,561	20	97.4	99.8
Determine (2)	168	112	0	56	0	100.0	100.0
Multispot (1)	982	380	0	602	4	100.0	99.3
Multispot (2)	11,000						
SUDS	921	357	2	564	125	99.4	81.9
InstantScreen	591	40	0	551	0	100.0	100.0
MedMira	852	91	17	743	1	84.3	99.9
OraQuick	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.***