Developing a Commercial VISP Test: Selectest Experience

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March 2013
HIV Selectest: A Journey

EVERY JOURNEY BEGINS WITH A SINGLE STEP,
BUT YOU'LL NEVER FINISH IF YOU DON'T START.
Human Immunodeficiency Virus (HIV) Vaccine Trials: a Novel Assay for Differential Diagnosis of HIV Infections in the Face of Vaccine-Generated Antibodies


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Novel Approach for Differential Diagnosis of HIV Infections in the Face of Vaccine-Generated Antibodies:

Utility for Detection of Diverse HIV-1 Subtypes

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HIV Selectest: novel HIV immunoassay discriminates true HIV infection from VISP

- The HIV Selectest was initially developed by Khurana & Golding at CBER/FDA \(^1,2\)

- HIV Selectest peptide antigens were derived from HIV-1 env and gag regions that are not present in most vaccine candidates, or which are not immunogenic in uninfected vaccine recipients (original peptides comprised env gp41-1, gp41-2 and gag p6-1, p6-2). \(^1,2\)

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\(^1\) Novel approach for differential diagnosis of HIV infection, Khurana et al. J AIDS, 2006; 43: 304-312

HIV Selectest: NIH Contract

- RFP issued by Westat/NHLBI – October 2008

  “Refinement and Manufacture of HIV Blood Donor Screening Tests to Distinguish Between HIV-1 Antibodies from HIV-1 Infected Donors and Uninfected HIV-1 Vaccine Recipients”

  The objectives of this HIV Test Development/Evaluation Component of the REDS-II program are to refine, assemble, validate and obtain FDA approval for HIV-SELECTEST EIA kits for distribution to national and international laboratories conducting blood donor screening in developing countries where HIV vaccination is likely to become prevalent. These kits will be used for distinguishing true HIV-1 infections from vaccine-induced HIV-1 antibody responses in blood donors. Work will be conducted in two stages to include preclinical studies/test refinement, and clinical trials/test validation.

- Subcontract to Immunetics from NHLBI under Westat REDS-II prime contract, 2010 - 2013

- Technical expertise from NIDCR (Isaac Rodriguez-Chavez)

- Support from NIH/OAR
Challenges in Development of Assay

- Market - Is there a commercial market that justifies the investment?
- Vaccine design – a moving target
- Antigen discovery – Scylla vs. Charybdis
- Sample acquisition – a perpetual challenge
- Regulatory approval - no precedent
- Intellectual Property – multiple patents
- User acceptance - “The perfect is the enemy of the good”
Is there a commercial market?

Factors to consider

- No precedent for use in the clinical research market
- No precedent for use in the commercial testing market
- No regulatory requirement
- No reimbursement

Upside

- No commercial competition

Funding/Investment Rationale?

????
Vaccine design – a moving target

- > 30 different HIV vaccines developed to stage of human trials to date\(^1\)
- ≥ 7 different types of vaccines\(^2\)

<table>
<thead>
<tr>
<th>Vaccine Type and Product Description</th>
<th>HIV Insert(s)</th>
<th>HVN Protocol</th>
<th>N</th>
<th>Product Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA only</td>
<td>gag, pol, vpr, nef, rev, env</td>
<td>048, 064</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>EP-1233 (Pharmex-Epimmune)</td>
<td>gag, pol, vpr, nef, rev, env</td>
<td>067</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>pGA2/352 (GeoVax)</td>
<td>gag, pol, env, tat, vpu, rev</td>
<td>045</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>pGA2/357 (GeoVax)</td>
<td>gag, pol, env, tat, rev, vpu</td>
<td>065</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>VRC-HIVDNA009-00-VP (4 plasmid) (VRC)</td>
<td>gag, pol, nef, env</td>
<td>044, 052, 066, 069</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>VRC-HIVDNA-016-00-VP (6 plasmid) (VRC)</td>
<td>gag, pol, nef, env</td>
<td>204</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>VRC-HIVDNA04+00-VP (VRC) gag DNA (Wyeth)</td>
<td>gag</td>
<td>072, 10</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td>PENNAX-B (University of Pennsylvania)</td>
<td>env, gag</td>
<td>060, 063</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Peptide or protein only or as boost</td>
<td>gag, pol, nef, env</td>
<td>042</td>
<td>23</td>
<td>Used alone or with Chiron DNA/PLG (gag, env, tat, vpu, rev)</td>
</tr>
<tr>
<td>LIPO-5 (Aventis-Pasteur) Gp140 (Chiron)</td>
<td>pol, vpu, env, gag nef, tat + env</td>
<td>064</td>
<td>47</td>
<td>Used alone or with EP HIV-1090</td>
</tr>
<tr>
<td>EP-1043 (Epimmune)</td>
<td>pol, vpu, env, gag nef, tat + env</td>
<td>041</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>NeTat (GSK) only</td>
<td>env, gag, nef</td>
<td>056</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>NeTat (GSK) + gp120W6D6 (GSK)</td>
<td>env, gag, nef</td>
<td>026, 039, 305</td>
<td>203, 042</td>
<td>Products administered together</td>
</tr>
<tr>
<td>HIV CTL MEP (Wyeth)</td>
<td>env, gag, nef</td>
<td>026, 039, 305</td>
<td>203, 042</td>
<td></td>
</tr>
<tr>
<td>Poxvirus only or as boost</td>
<td>env, gag, pol, nef</td>
<td>026, 039, 305</td>
<td>203, 042</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)http://www.who.int/hiv/topics/vaccines/Vaccines/en/
\(^2\)Cooper C. et al., Vaccine-induced HIV seropositivity/reactivity in noninfected HIV vaccine recipients, JAMA 2010;304(3):275-283
Antigen discovery – Scylla vs Charybdis

- Antigenic epitopes which are highly immunogenic for circulating antibodies but non-protective/no CTL response

- To meet sensitivity and specificity objectives required
  - Antigen discovery
  - Redesign of peptide antigens
  - Elimination of peptides and incorporation of new peptides
  - Redevelopment of other assay reagents and assay chemistry
  - Redevelopment of cut-off algorithm
Sample acquisition—a treasure hunt

- Place in line – probably not first.....
- Timeline, legal agreements with multiple parties
- Commercial vs. non-commercial research?
- HIV-positive sera – different clades (beyond B), other requirements
- HIV vaccine recipient sera from vaccine trials
  - Retrospective – availability limited
  - Prospective – trials are planned years ahead
- HIV vaccine recipient/intercurrent infections – vanishingly available
- Numbers adequate for statistical validity of results?
Sample acquisition-a treasure hunt

Statistical validity

95% CI at 99% sensitivity
Sample acquisition-a treasure hunt

- **Timeline:**
  - Permissions
  - MTA
  - Sample and data retrieval
  - Shipment
Regulatory approval

- No precedent for FDA
  - Regulatory mechanism is being defined by the agency
  - Relevance of U.S. requirements to usage outside U.S.
- Approval for use in other countries – additional, varying requirements
Intellectual Property

- HIV antigens covered by patents require licensing
  - U.S. government patent portfolio
  - HIV-2 patents – owned commercially
  - HIV Group O patents – owned commercially
  - Others
“The perfect is the enemy of the good”

- Does the market have the appetite to support assay improvements over time and successive generations?
“The perfect is the enemy of the good”

- Will funding sources have the commitment to support assay development and clinical trials from start to finish?
- You have to walk before you can fly:

### HIV Selectest Evolution

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First generation</th>
<th>User wish list</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>&gt;97%</td>
<td>&gt; 99.9%</td>
</tr>
<tr>
<td>Specificity</td>
<td>&gt;99.5%</td>
<td>&gt; 99.9%</td>
</tr>
<tr>
<td>Early detection</td>
<td>No window period, limited seroconversion</td>
<td>Window period and seroconversion</td>
</tr>
<tr>
<td>Assay format</td>
<td>Manual microtiter</td>
<td>Automated or single use</td>
</tr>
</tbody>
</table>
HIV Selectest assay clearly distinguishes true HIV infections from non-infected vaccine recipients and normal donors.

Absorbance distribution in HIV Selectest

- **HIV-positive sera**
  - N=648
  - (red = false negative)

- **Normal donors**
  - N=400

- **Vaccine and placebo recipients, HIV-negative**
  - from HVTN204 & RV144 trials N=544
  - (red = false positive)
HIV Selectest Sensitivity for different HIV clades

<table>
<thead>
<tr>
<th>Serum panels from HIV infected individuals</th>
<th></th>
<th></th>
<th>Global panels (clades A, B, C, D, E, F, G, J, O, ut)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clade A</td>
<td>Clade B</td>
<td>Clade C</td>
<td></td>
</tr>
<tr>
<td>Sensitivity based on combined samples</td>
<td>100% N=100</td>
<td>94.5% N=200</td>
<td>99.3% N=267*</td>
<td>98.8% N=81</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>96.4 - 100%</td>
<td>91.3 - 97.7%</td>
<td>97.4 - 99.9%</td>
<td>93.4 - 100%</td>
</tr>
</tbody>
</table>

* Clade C samples included 32 from South Africa, 35 from Malawi and 200 from Zambia.

**Sensitivity is high for all clades, and > 99% for Clades A and C.**

The slightly lower sensitivity for Clade B (USA, Europe) sera could be due to a higher proportion of early/asymptomatic infections in this panel.
HIV Selectest performance vs. infection recency in clade C panel of early infections

- Sensitivity was high except in very early infections (63% detection).
- Improved detection of very early immune responses to HIV infection has the potential to increase overall assay sensitivity.
Sera from 6 HIV vaccine trials and from healthy normal donors as negative controls were assayed with the HIV Selectest.

Overall HIV Selectest sensitivity is high and specificity is excellent.

Assay performance was comparable in vaccinated and control groups, suggesting that the HIV vaccine immune response does not interfere with the HIV Selectest assay.

<table>
<thead>
<tr>
<th>Sample group</th>
<th>Sensitivity in HIV infected vaccine trial participants (VAX 003/004)</th>
<th>Specificity in uninfected vaccine trial participants (RV144, HVTN 203, 204, 039, VAX 003/004)</th>
<th>Specificity in normal donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-immune and placebo</td>
<td>96.2% n=105</td>
<td>99.4% n=353</td>
<td>100% n=400</td>
</tr>
<tr>
<td>Vaccine recipients</td>
<td>97.5% n=160</td>
<td>99.6% N=667</td>
<td>N/A</td>
</tr>
<tr>
<td>Combined vaccine trial</td>
<td>97.0% (94.1-98.7%) n=265</td>
<td>99.5% (98.9-99.8%) n=1020</td>
<td>100% (99.3-100%) n=400</td>
</tr>
</tbody>
</table>
## PPV and NPV of HIV Selectest vs. FDA-approved assays that exhibit VISP

<table>
<thead>
<tr>
<th>Test</th>
<th>HIV % infected</th>
<th>Sensitivity in Vaccine Recipients</th>
<th>Specificity in Vaccine Recipients</th>
<th>Positive Predictive Value (PPV)</th>
<th>Negative Predictive Value (NPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average across different tests ¹</td>
<td>0.7%</td>
<td>99.9%</td>
<td>41.7%</td>
<td>1.19%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Abbot HIV 1/2 (rDNA) EIA</td>
<td>0.7%</td>
<td>99.9%</td>
<td>59.1%</td>
<td>1.69%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Bio-Rad rLAV EIA</td>
<td>0.7%</td>
<td>100.0%</td>
<td>78.6%</td>
<td>3.19%</td>
<td>100.00%</td>
</tr>
<tr>
<td>BioMerieux HIV-1 Plus O Microelisa</td>
<td>0.7%</td>
<td>100.0%</td>
<td>85.3%</td>
<td>4.58%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Bio-Rad HIV-1/2 peptide &amp; HIV-1/2 Plus O</td>
<td>0.7%</td>
<td>100.0%</td>
<td>91.2%</td>
<td>7.42%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Current HIV Selectest EIA</td>
<td>0.7%</td>
<td>98.3%</td>
<td>99.5%</td>
<td>58.09%</td>
<td>99.99%</td>
</tr>
</tbody>
</table>

*In a model based on HIV prevalence in USA high-risk populations (0.7%), PPV of the current prototype HIV Selectest assay is already much higher than for FDA-approved HIV assays.*

¹Vaccine-Induced HIV seropositivity/reactivity in noninfected HIV Vaccine Recipients, Cooper et al. JAMA, 2010; 304(3): 275-283
In practice, the HIV Selectest assay will likely be used as part of a multi-test algorithm to distinguish true HIV infection from VISP.

In this multi-test algorithm model, the use of the HIV Selectest with a confirmatory Western blot improves PPV from 1.6% to > 98.5%.
Public Health Impact

- Availability of a VISP-resolving assay for HIV vaccine trials will simplify procedure, avert a major risk to participants and dramatically reduce costs and resources for monitoring and post-trial follow-up.

- Post licensure of an HIV vaccine, a VISP-resolving assay will enable resolution of potentially thousands of false positive HIV test results in the U.S. high risk population and up to millions of false positives in endemic countries such as in southern Africa, at a cost far less than that of current protocols.
Questions/Action Items

- What organizations – public and private – will constitute the actual market and end users of the assay?
- Will vaccine trial organizations collaborate in retrospective and prospective evaluations of the assay?
- What would be the process to achieve a commitment for use of the assay in future trials? In the event of a licensed vaccine?
- Will organizations with clinical sample collections make them available for evaluation in the assay?
- What level of assay performance is expected to justify use of the assay?
- What regulatory hurdles will need to be dealt with to make the assay available commercially?
- What type of testing algorithm will the assay be incorporated into?
- How will cost-effectiveness of the assay be measured?
Acknowledgements

- Supported by a subcontract from Westat, Inc. under a REDS-II prime contract from NHLBI and NIH/OD/OAR.

- HIV Selectest was originally developed and published by Drs. H. Golding and S. Khurana at CBER/FDA.

- HIV Selectest Project Team: Simone Glynn, George Nemo, Lis Welniaak, Shimian Zou (NHLBI), Isaac Rodriguez-Chavez (NIDCR), Michael Busch (BSRI), Melissa King, Deborah Todd, Sunitha Mathew, Danielle Carrick, David Wright (Westat).

- Serum panels provided under MTA agreements by: RV144: Jerome Kim, Charla Andrews (WRAIR); Vax003/004: Faruk Sinangil, Carter Lee (GSID); HIVIS03: Said Aboud, MUHAS/Tanzania; HVTN203,204,039: HVTN; Rwanda, Zambia: Eric Hunter (Emory Univ./IAVI), S. Africa: Barton Haynes (Duke Univ./CHAVI), Michael Busch (BSRI), Biolincc (NHLBI).
HIV Selectest: The Journey Continues