HIV Vaccine Trials: Perspectives on Progress

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Understanding the past is useful for helping define the future
HIV Vaccine Development

- The last 10 years has seen progress.

- We have had our disappointments, but we have achieved a milestone with RV144.
  - RV144 results are equal to the CAPRISA 004 microbicide trial; overall rates of 31%, peak efficacy rates of 55%.

- Our follow up response to this success has however yet to be defined.
  - Protocol for follow up CAPRISA study to be submitted October 2010 - within 4 months of the announcement of the results.
  - First significant clinical trials follow up to RV144 is currently planned for 2013 - 3.5 years post announcement of the results.
Questions I Will Ask in this Talk

- Is the pace of HIV vaccine development appropriate to the science and resources?
  - I will make the case that I think not.

- Then why? Or more importantly...
  - What can we as a field do to improve?
The RV144 Follow Up

- There is considerable energy in a coordinated laboratory activity to define potential correlates of protection and how to best follow up the RV144 findings.

- Caprisa 004 is easy: the mechanism of action is an antiviral one.

- In contrast, we have no mechanism of action for the reduced acquisition rate in the RV144 trial.
The RV144 Follow Up

- Lack of an Immunological Mechanism leaves a large hole in the development of a consensus.
  - Correlates of some sort are a critical need for our field.

- Our prior failures have shaken our confidence and our resolve, and left doubts about the path forward.
  - The fear of failure syndrome.

- We are also burdened by a fear of success syndrome. We must be ready to vaccinate the world immediately if we achieve even a modicum of success.
  - This leads to long process development timelines for each product, slowing the pace of discovery and magnifying the cost of producing reagents, as well as affecting the “opportunity costs”.
A Quick Review of the Facts

- The VaxGen trials:
  - gp 120 vaccines had no effect in either MSM populations in the US or IDU populations in Thailand in reducing acquisition.

- The MRK Ad 5 gag/pol/nef vaccine, while highly immunogenic in Phase 1/2 clinical trials, neither prevented infection nor controlled viremia in MSM in the US or in heterosexual populations in South Africa.
  - The power to detect the effects on post acquisition viremia in heterosexual men and women was markedly impaired by the early stoppage of the trial.
  - In a subset of MSM, the MRK Ad 5 vaccine transiently increased the rate of acquisition of HIV in uncircumcised Ad 5 seropositive MSM; an unexpected and unanticipated effect that has introduced a level of caution to the HIV vaccine field.
Covariate-adjusted hazard ratios (V:P) for at-risk subgroups decrease over time

<table>
<thead>
<tr>
<th>Subgroup (N, MITT analysis)</th>
<th>1st 18 month Hazard Ratio 95% C.I.</th>
<th>Multiple comparison adjusted p-value*</th>
<th>All follow-up Hazard Ratio 95% C.I.</th>
<th>Multiple comparison adjusted p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncirc &amp; Ad5+ (N= 622)</td>
<td>4.18 (1.37, 12.71)</td>
<td>0.05</td>
<td>1.58 (0.86, 2.93)</td>
<td>0.57</td>
</tr>
<tr>
<td>Uncirc &amp; Ad5- (N=171)</td>
<td>2.66 (0.65, 10.86)</td>
<td>0.69</td>
<td>2.35 (0.86, 2.93)</td>
<td>0.38</td>
</tr>
<tr>
<td>Circ &amp; Ad5+ (N=419)</td>
<td>1.98 (0.84, 4.67)</td>
<td>0.47</td>
<td>1.61 (0.88, 2.94)</td>
<td>0.48</td>
</tr>
<tr>
<td>Circ &amp; Ad5- (N=578)</td>
<td>0.38 (0.16, 0.90)</td>
<td>0.11</td>
<td>0.97 (0.56, 1.65)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Instantaneous hazard ratio over time for at-risk groups (uncirc + circ/ad5+)

- Red line: Estimated HR (V:P)
- Dotted green line: 95% simultaneous CIs
- Dashed black line: HR = 1.0

Hazard ratio vs. Time since randomization (months)
A Quick Review of the Facts

- Alvac gag/pol/env plus gp 120 (identical to the gp 120 used in VaxGen IDU trial) reduced HIV acquisition in a low risk heterosexual population in Thailand.

- This vaccine regimen is clearly less immunogenic than the MRK Ad 5 vaccine in every T cell assay utilized pre-clinically; leaving us confused about the types of T cell assays we should be using to evaluate vaccines in pre-clinical and Phase 1/2 trials.
Cumulative Rates of Infection in RV144 – Modified Intent to Treat

No. at Risk
Placebo  8198  7775  7643  7441  7325
Vaccine  8197  7797  7665  7471  7347

Cumulative No. of Infections
Placebo  30   50   65   74
Vaccine   12   32   45   51

P=0.04
Time Line of HIV Vaccine Efficacy Trials

VaxGen USA

VaxGen Thai Trial

Step Trial

Thai Trial

HVTN 505

Trial start/end

Trial analysis/results

First correlates

The Pace of Conduct of HIV Efficacy Trials Has Been Slow By Any Standards

Ergo the major tool for the discovery of new concepts is too slow to lead the field forward
Two Observations of Relevance

- At the current pace, the rate at which the field generates critical immunological concepts is incompatible with an iterative mode of vaccine development.

- The approach we have used as a field has been very traditional; based upon the likelihood that pre-clinical assays or animal models are likely predictive models of outcome in human clinical trials.
Another Observation

- There are still structural barriers to the way the field needs to operate to achieve success.

- We need to develop the systems (rapidly producing GMP manufacturing of reagents for human trials and the governance of this resource) to perform iterative clinical trials.

  trial site capacity is no longer the issue.
Proposed Strategies for Altering this State of Affairs

☐ Back to basics

☐ Increased emphasis on NHP models

☐ More clinical trials research

All the above is the answer
Strategy for Changing the Landscape for Test of Concept Phase 2B Trials
Alterations in the Way We Work

- The landscape for the iterative process of conducting and evaluating test of concept efficacy trials needs to be restructured.

- The number and pace needs to be increased, but the trials must not be “me too” trials; the immunological hypotheses and underlying biological concepts of the trials need to be expanded.
Filling in the Immunological Space

- Innate Immune Responses
  - Mucosal Immune Responses
  - Cytokines/Chemokines Responses

- Optimization of Adaptive Immune Responses
  - CD4 Memory
  - Innate Immunity
  - CD8 Memory
  - Binding & neutralizing Antibodies
  - CD8 Effector Function
  - Intracellular Cytokine Induction

Innate Immune Responses
How Can we Accomplish these Goals?

- Use adaptive trial designs that will identify vaccines with no efficacy and reasonable efficacy quickly.

- Structure the laboratory/correlates work prospectively and concurrently.

- Run comparative arms to allow one to increase power of correlates and provide some ranking order of vaccines to prioritize.

- This approach also allows one to combine other prevention modalities more expeditiously.
Sequential Adaptive Design Phase 2B Trials

- Series of coordinated Phase 2B trials that are conducted in same population/geography over time.

- Start the process of identifying samples for correlate analyses at trial initiation and operationalize at the time of interim analyses.

  - Samples associated with correlates to be run real time; develop mechanisms to allow the lab to know what group subject was in, but to not make this accessible to trialists.
Adaptive Clinical Trial Design

Phase I

Phase II

Phase III

Time (years)

0

5

10

Early looks at data
Adaptive Clinical Trial Design

Phase I

Phase II

Phase III

Positive Signal

Early looks at data

Time (years)
Conceptually This Is Not A Radical Idea

- The trials are conducted as standard 2B trials with prevention of infection as the major endpoint.
  - All vaccine regimens should contain HIV-1 envelope components.

- One uses accelerated monitoring to identify a dog or a winner.

- This identification results in some “adaptation” of the trial.
  - The most common adaptation is likely to be start another trial or start another arm.
Conceptually This Is Not A Radical Idea

- This approach is amenable to concurrent arms or sequential arms; the primary goal is to identify what is potentially good versus bad, but the design also allows some ranking of the vaccines.

- Approach is particularly useful for a correlates of protection program because vaccines with different immunological hypotheses with similar efficacy help define what potential correlates may be; similarly, differences in vaccines that do and do not work.
Important Characteristics of The Adaptive Design Trials

- The trial is a randomized blinded trial. It is designed as a standard comparative arm efficacy trial in which each arm is compared to placebo.

- Samples for correlates analyses are critical (cells and plasma at baseline, peak, and memory immunogenicity time points).

- Multiple arms are nice in that it provides stronger scientific base for correlates analysis.

- Need to think through potential adaptation scenarios prospectively.

- Very helpful to enroll trial quickly so endpoints come off expeditiously.
Real Life Issues

□ DSMB looks at data frequently using pre specified boundaries.

□ One starts seeing trends early, but the decision making regarding “adaptation” is more conservative both by pre-specified, as well as that an oversight board of the stakeholders which are the ultimate decision making group.
Here is a Real Life Proposal

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Number participants</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>2000</td>
<td>ALVAC</td>
<td>ALVAC</td>
<td>ALVAC + gp120</td>
<td>ALVAC + gp120</td>
</tr>
<tr>
<td>Group 2</td>
<td>2000</td>
<td>NYVAC</td>
<td>NYVAC</td>
<td>NYVAC + gp120</td>
<td>NYVAC + gp120</td>
</tr>
<tr>
<td>Group 3</td>
<td>2000</td>
<td>DNA</td>
<td>DNA</td>
<td>NYVAC + gp120</td>
<td>NYVAC + gp120</td>
</tr>
<tr>
<td>Group 4</td>
<td>2000</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>8000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each participant followed for up to 36 months and monitored for HIV infection at frequent intervals.
Here is another Real Life Proposal

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Number participants</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>2000</td>
<td>NYVAC</td>
<td>NYVAC</td>
<td>NYVAC + gp120</td>
<td>NYVAC + gp120</td>
</tr>
<tr>
<td>Group 2</td>
<td>2000</td>
<td>DNA</td>
<td>DNA</td>
<td>NYVAC + gp120</td>
<td>NYVAC + gp120</td>
</tr>
<tr>
<td>Group 3</td>
<td>2000</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>6000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each participant followed for up to 36 months and monitored for HIV infection at frequent intervals
How to efficiently weed out vaccines with low efficacy at best?

- **Group Sequential Monitoring Approach:**
  - Frequently monitor VE at spaced numbers of infections
  - Interim Analyses for Non-Efficacy
  - At each analysis examine evidence for VE(0-18) < 40%
**Non-Efficacy Boundary (P = 0.6)**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number MITT infections</th>
<th>Observed estimate of HR that defines the boundary*</th>
<th>Vaccine:Placebo infection split that just reaches boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>Est. HR $\geq$ 2.28</td>
<td>11:4</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>Est. HR $\geq$ 1.42</td>
<td>19:12</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>Est. HR $\geq$ 1.19</td>
<td>25:21</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Est. HR $\geq$ 1.07</td>
<td>32:29</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>Est. HR $\geq$ 0.99</td>
<td>38:38</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>Est. HR $\geq$ 0.94</td>
<td>45:47</td>
</tr>
<tr>
<td>7</td>
<td>107</td>
<td>Est. HR $\geq$ 0.90</td>
<td>51:56</td>
</tr>
<tr>
<td>8</td>
<td>122</td>
<td>Est. HR $\geq$ 0.88</td>
<td>58:64</td>
</tr>
<tr>
<td>9</td>
<td>138</td>
<td>Est. HR $\geq$ 0.85</td>
<td>64:74</td>
</tr>
</tbody>
</table>

*Reject H1: VE(0-18) $\geq$ 40% vs H0: VE(0-18) < 40% (1-sided alpha = 0.05) 86% chance to reject H1 when VE(0-18) = 0%
MITT versus Per Protocol Analyses

- While MITT is the statisticians gold standard for trials...

- The per protocol analysis is what the vaccinologists and immunologists like - so one makes the major decisions on the per protocol analysis, especially for a correlates program.
### Number of endpoints for defining Non-Efficacy Boundary (P = 0.6)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number MITT infections</th>
<th>Observed estimate of VE that defines the boundary*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>Est. VE &lt; 15%</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>Est. VE &lt; 17%</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
<td>Est. VE &lt; 19%</td>
</tr>
<tr>
<td>4</td>
<td>108</td>
<td>Est. VE &lt; 20%</td>
</tr>
<tr>
<td>5</td>
<td>116</td>
<td>Est. VE &lt; 22%</td>
</tr>
<tr>
<td>6</td>
<td>123</td>
<td>Est. VE &lt; 23%</td>
</tr>
<tr>
<td>7</td>
<td>131</td>
<td>Est. VE &lt; 24%</td>
</tr>
<tr>
<td>8</td>
<td>138</td>
<td>Est. VE &lt; 25%</td>
</tr>
<tr>
<td>9</td>
<td>146</td>
<td>Est. VE &lt; 26%</td>
</tr>
</tbody>
</table>

*Reject H1: VE(0-18) ≥ 50% vs H0: VE(0-18) < 50% (1-sided α = 0.025)
97.5% chance to reject H1 when VE(0-18) = 0%
Time to Weed-Out a Useless Vaccine

Assumptions:

• N = 2,000 / group

• Annual sero-incidence in placebo group = 4%

• Annual rate of loss to follow-up = 5%

• 12-month accrual period

• Avg enrollment = 51 / group / week, halved during first 6 mo

• Vaccination regimen completed at 6 mo

• VE halved during first 6 mo

• Follow-up visits q3mo for 36 mo post entry

• Maximum of 146 HIV infections
What would have happened if this had been used for Monitoring of Vax004?

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Analysis at n MITT [0-18] month infections</th>
<th>Observed estimate of HR that defines the boundary*</th>
<th>Probability of reaching boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>Est. HR ≥ 2.28</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>Est. HR ≥ 1.42</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>Est. HR ≥ 1.19</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Est. HR ≥ 1.07</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>Est. HR ≥ 0.99</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>Est. HR ≥ 0.94</td>
<td>2.3</td>
</tr>
<tr>
<td>7</td>
<td>107</td>
<td>Est. HR ≥ 0.90</td>
<td>20.4</td>
</tr>
<tr>
<td>8</td>
<td>122</td>
<td>Est. HR ≥ 0.88</td>
<td>90.3</td>
</tr>
<tr>
<td>9</td>
<td>138</td>
<td>Est. HR ≥ 0.85</td>
<td>100</td>
</tr>
</tbody>
</table>

Final estimate from real trial: Est. HR = 0.93

Duration of trial: 90% chance completed in 2–2.5 years, >99% by 2.8 years 4.5 years for real trial
# Application of Non-Efficacy Monitoring to Vax003 (Bangkok IVDUs)

<table>
<thead>
<tr>
<th>Analysis</th>
<th># MITT infections [0-18] Mo</th>
<th>Non-Efficacy Stopping Boundary</th>
<th>Observed Results in Vax003</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td># Enrolled</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>Est. HR ≥ 2.28</td>
<td>1488</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>Est. HR ≥ 1.42</td>
<td>1985</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>Est. HR ≥ 1.19</td>
<td>2295</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Est. HR ≥ 1.07</td>
<td>2527</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>Est. HR ≥ 0.99</td>
<td>2527</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>Est. HR ≥ 0.94</td>
<td>2527</td>
</tr>
<tr>
<td>7</td>
<td>107</td>
<td>Est. HR ≥ 0.90</td>
<td>2527</td>
</tr>
<tr>
<td>8</td>
<td>122</td>
<td>Est. HR ≥ 0.88</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>138</td>
<td>Est. HR ≥ 0.85</td>
<td></td>
</tr>
</tbody>
</table>

Reach stopping boundary at 7th analysis, 13 months before Vax003 was completed
Poor Efficacy and High Efficacy are identified quickly

Assumptions:
- N = 1,500 / group
- Annual sero-incidence in control group = 4%
- Annual rate of loss to follow-up = 5%
- Average enrollment = 100 / week
- Vaccination regimen completed at 6 months
- VE halved during first 6 mo
- Follow-up visits q3mo for 30 mo post vaccination
- Maximum of 176 HIV infections
## Application of Efficacy Monitoring to RV144

<table>
<thead>
<tr>
<th>Analysis</th>
<th># MITT Infections</th>
<th>Efficacy Stopping Boundary</th>
<th>Observed Results in RV144</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Enrolled</td>
<td>Months of Trial</td>
<td>Est. VE(0-18)</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>Est. VE(0-18) ≥ 94%</td>
<td>11,931</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>Est. VE(0-18) ≥ 75%</td>
<td>14,896</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>Est. VE(0-18) ≥ 60%</td>
<td>16,339</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Est. VE(0-18) ≥ 50%</td>
<td>16,402</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>Est. VE(0-18) ≥ 42%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>Est. VE(0-18) ≥ 37%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>107</td>
<td>Est. VE(0-18) ≥ 32%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>122</td>
<td>Est. VE(0-18) ≥ 29%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>138</td>
<td>Est. VE(0-18) ≥ 26%</td>
<td></td>
</tr>
</tbody>
</table>

Reach stopping boundary at 4th analysis, 2.8 years before the actual RV144 trial was completed.
With the prototype design would have initiated immune correlates assessment much sooner.
Immune Correlates Analyses

☐ **Goal:** Expeditiously evaluate priority immunological parameters as:
  - Correlates of HIV infection rate in the vaccine group.
  - Surrogates of protection that reliably predict VE.

☐ **As soon as warranted (at time efficacy is defined):**
  - Validate priority immunological measurements for reproducibility and biological variability post vaccination (much of this can be done in Phase1/2).
  - Begin measurements on vaccine arm cases to date and matched uninfected vaccinees.
  - Plan for selecting a random sample (10%) of placebo subjects to the vaccine arm, and measure priority immunological parameters.
  - Enables assessment of surrogates of protection.
Immune Correlates Concepts

- Similar efficacy in multiple arms provides an opportunity to define correlates from assays in which the vaccines give similar responses.

- Conversely, differences in vaccine arms allows one to priority select assays in which there are differences in the immunization arms.

- The power to define a correlate is increased with more arms.
Power to Determine a Correlate is higher with 4 versus 2 arm trial
Conclusions

- One can design activity trials that will weed effective and ineffective vaccine regimens at the 40% level quite expeditiously if one changes the mind set of how we do trials.

- Screening trial design followed by modification of the design once there is a readout with a reasonable probability of success or failure.

- We should initiate at least 1-2 such trials each year for the next 4 years.

  - This type of pace will desensitize communities and investigators so that the success or failure of clinical activity of a candidate immunogen is not central to the field (i.e. a mortal blow) and actually operationalize what we all know is true.

  - Provide the change agent we need to make the vaccine field competitive with other prevention modalities.
Do What We Preach

- HIV vaccine development will be an iterative march:
  - At the moment we say the above phrase, but we do not conduct our research programs that way.
  - The timeline for Phase 2B or 3 trials illustrated above proves the point.
Additional Questions/Issues

☐ Can the pipeline support this? Yes.

☐ Do we have the resources to do this? Yes and no.

- We have much of the infrastructure to enact the trials.

- We do not have the money to manufacture the potential products that could be useful in filling in the immunological grid/space to optimize the correlates analyses.
Acknowledgements

- **HVTN**
  - Peter Gilbert, Doug Grove and Steve Self
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