



Global HIV Vaccine
Enterprise

Approaches to Expediting HIV Vaccine Efficacy Evaluation

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Promoting innovation and collaboration
to speed the search for an HIV vaccine

- + Meeting of clinical trials experts
- + Discuss different approaches to the design of clinical trials for the expeditious assessment of HIV vaccine efficacy
- + April 4-5, 2007; New York, NY
- + Hosted at IAVI
- + Organized by Ripley Ballou, Jerome Kim, Steve Self, Katherine Kripke, Pat Fast, & Nina Russell
- + Attended by 38 scientists from the U.S., Europe and Thailand

Goals

- + Create more coherence across the HIV vaccine field regarding the goals and potential interpretation of results from the different types of intermediate-sized trials that have been designed or proposed.
- + Propose a draft mapping, or matrix, in general terms, of the characteristics of different trial designs in order to provide a common framework to guide discussion and decision-making around the conduct of future trials.

- + AVEG/HIVNET Workshop
 - + April 1995 – Intermediate-Sized Trials
 - + JAIDS, Nov 1997 (Rida, Fast, et al)

- + DAIDS workshop
 - + 2004 – Endpoints & Regulatory issues in HIV Vaccine Trials
 - + Explored use of surrogate endpoints for licensure of an HIV vaccine
 - + JAIDS, Jan 2007 (Follmann, Duerr et al)

- + WHO/UNAIDS/IAVI Expert Group Consultation
 - + January 2006 – Phase 2B Test-Of-Concept trials as a novel strategy for evaluation of preventive HIV vaccines
 - + AIDS 2007, Vol. 21 No. 4 - Exec Summary & Recommendations

- + Robust pipeline of candidates in clinical development –
 - + **Phase 3** USMHRP/Sanofi canarypox + gp120
 - + interim analysis Q3'07, final results Q4'09
 - + **Phase 2B** Merck Adenovirus 5 (Ad5) trials
 - + STEP study – interim analysis Q4'07, final results Q1'09
 - + Phambili – interim analysis Q4'08, final results Q1 '10
 - + **Phase 2B** VRC DNA + Ad5 (PAVE 100)
 - + opens in '07
 - + final results in 2011
 - + **Phase 2** Eurovacc DNA & NYVAC
 - + **Phase 1** multiple DNA plasmids, MVA candidates; alternative adenovirus candidates (e.g. Ad6)

Plan for Future Trials

- + The multiple possible clinical trial outcome scenarios require planning for the potential impact of results from ongoing trials and their effect on the design of future vaccine trials.

- + Current HIV vaccines in advanced development are designed to elicit T cell-mediated immune responses and, in theory, will:
 - + Prevent acquisition of HIV infection
and/or
 - + Reduce HIV viral load (VL) in vaccinated individuals who become infected

- + **But, we really don't know what they will do....**

The Issues

- + The current Phase 2B trials are intended as an *initial* assessment of efficacy in the face of *substantial* uncertainties...
 - + Correlates of protection are not known
 - + 'Efficacy', as it relates to VL reduction as an endpoint, is yet to be defined
 - + Requirements for licensure are yet to be defined
 - + Manufacturing and delivery issues

- + If the current class of T-cell vaccine candidates has a moderate effect on viral load (VL) set point, how do we continue to optimize these approaches while we are waiting for the next major improvement with a better T-cell vaccine or an antibody-inducing vaccine?

- + How do we make decisions about the value of incremental improvements in vaccine candidates without exhausting major resources?

- + Agenda:
 - + Mapping of primary trial objectives for different trial designs
 - + Lessons learned from malaria vaccine trials
 - + Goals and objectives of test-of-concept Phase 2B trials in contrast to Phase 3, and the sequence of trials leading up to a Phase 2B
 - + Goals and objectives of IAVI's proposed comparative screening-test-of-concept trials, and the sequence of trials leading up to them
 - + Statistical considerations
 - + Adaptive trial designs: Bayesian approaches
 - + Role of efficacy trial designs in the broader context of vaccine development programs
 - + Efficiency and feasibility: Challenges to identifying appropriate cohorts and to planning, analysis and coordination of information
 - + Ethical challenges
 - + Regulatory considerations

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- + **Merck Phase 2B & PAVE 100**
- + **HIV infection rate and VL setpoint as dual primary endpoints**
 - + 80% power to detect a 50% reduction in HIV acquisition **and/or** ≥ 0.5 log reduction in VL
- + **Smaller, faster**
 - + Traditional efficacy trial would require ~400 infection endpoints & ~12,000 participants
 - + TOC require ~ 30 infections to detect a 1 log reduction in VL setpoint & ~50 events to detect a 60% or greater reduction in HIV acquisition with 1500 participants per strata (3000 – 8500 total)
 - + ~4 years to conduct
 - + Formal interim analysis at 30 events could accelerate the go/no-go decision for a Phase 3 trial by as much as a year
- + Can evaluate short-to-medium term duration of a reduction in VL load or protection from acquisition, but not long-term persistence of these effects and detect direct evidence of clinical benefit (e.g., improved mortality, decreased rate of AIDS cases)

- + **IAVI proposal** ('06 Blueprint, AIDS Vaccine '06 – Pat Fast)

- + Smaller, faster, and cheaper
- + 'screen' T cell vaccines to select
- + ↑ efficiency of product development - answer specific questions on antigens, vectors, routes of delivery, etc

- + **Single primary endpoint – VL setpoint**, with HIV acquisition as secondary endpoint
 - + Requires 30 total infections to detect a 1 log reduction in VL setpoint with 80% power
 - + High incidence populations (>3%) for enrollment in order to maximize the efficiency and time-saving, e.g. sample size n=643 for a population with 3% annual incidence rate

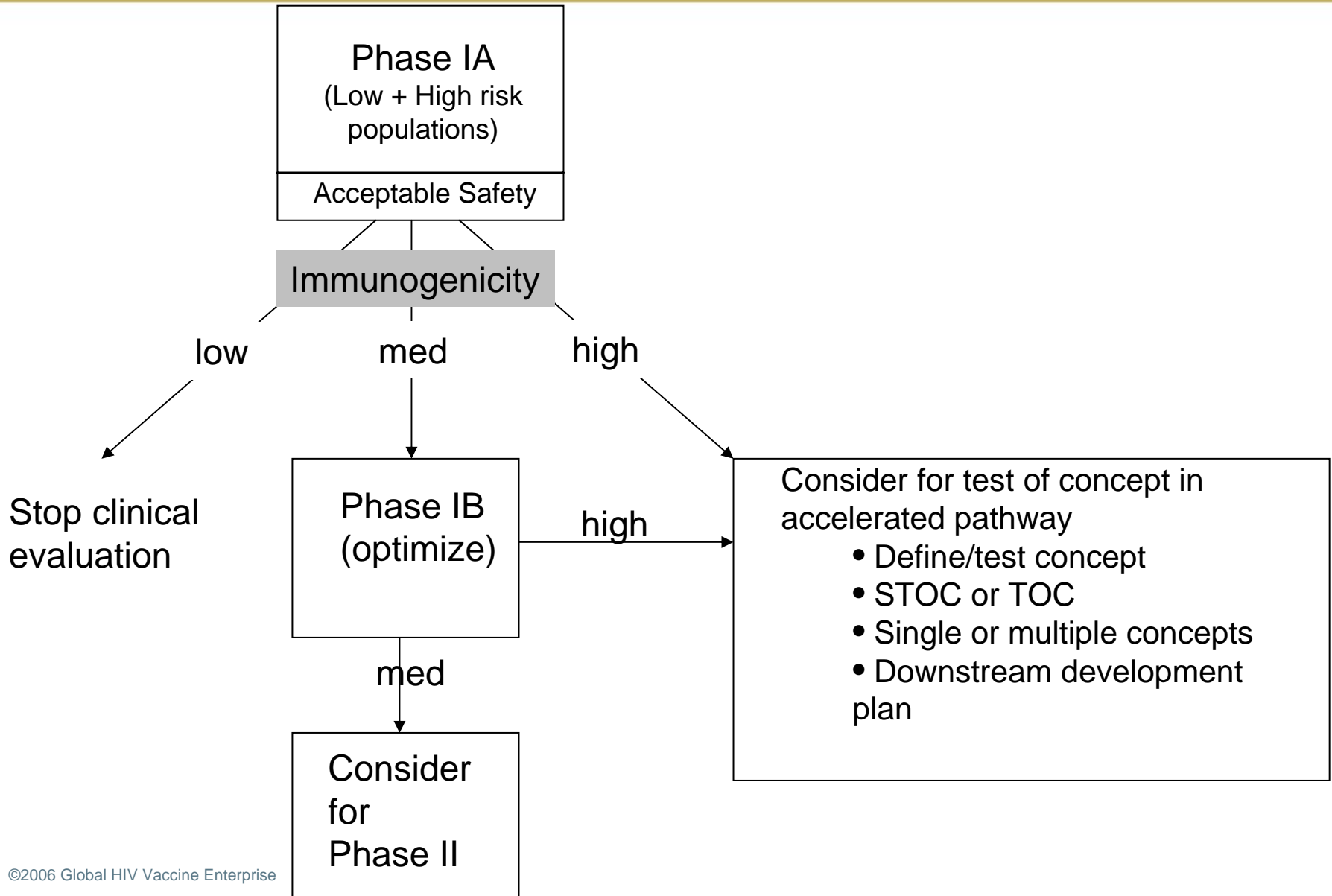
- + 18 months of follow-up, completion in 3 years
- + Provides ~ 50% of the statistical information of a Phase 2B TOC while testing more limited hypothesis that vaccine will have an effect on VL setpoint (biologic plausibility)

Conclusions

- + Common goal - rapid evaluation of T cell vaccines in high-risk populations
- + Agreement that accelerated efficacy trials should be designed in the context of a coherent product development plan
- + Clinical trial designs are on a continuum in which considerations of saving time and money need to be balanced against answering fewer questions with less certainty
- + STOC trials best to *eliminate* vaccines with no efficacy and for ranking similar products – with a caution about the possibility of discarding a vaccine that might have an impact on acquisition or discarding a product tested in a specific risk group (e.g., women) that might be efficacious in another risk group that has not been evaluated.
- + VL endpoint –
 - + not validated & level of VL reduction sufficient for licensure not yet known
- + Most accelerated efficacy trials (TOC or STOC) are not designed to definitively establish correlates of protection
- + If regulatory approval is sought through the accelerated approval pathway, e.g., based on a viral load endpoint, this will require the design and implementation of a confirmatory trial to demonstrate clinical benefit.

1. For expedited efficacy trials (TOC or STOC) to provide an effective alternative pathway, there must be a clearly defined roadmap to phase III trials or termination, with coordination between protocols, and a group to coordinate and expedite funding, execution, analyses and advancement of products in an industry-like manner. Additionally, conduct of accelerated trials should probably be limited to countries with experience in HIV vaccine trials.
2. A high-level decision tree, or algorithm, should be developed that describes the potential different accelerated product development pathways.

Algorithm for Accelerated Product Development Pathways



3. A modular approach to protocol design should be considered, with standardized Phase 2 TOC or STOC type trials and pre-established decision rules to support the rapid testing of products in high-risk volunteers.

4. Agreed that the *definition of efficacy endpoints* would be a topic of a different Enterprise-sponsored workshop in the near future, with a particular focus on defining a ‘significant’ reduction in VL set point.

- + In support of the Global HIV Vaccine Enterprise, the WHO and the Agence Nationale de Recherches sur le Sida (ANRS) are organizing a

“Global Consultation on Potential Endpoints of HIV Vaccine Efficacy”

- + 5 – 6 September, 2007; Paris, France
- + Organizing Committee: Saladin Osmanov, Yves Levy, Peggy Johnston, Jonathan Heeney, Joep Lange, Jose Esparza, Nina Russell & Karen Goldenthal
- + ~ 50 participants invited
- + Goals:
 - + To build consensus among key stakeholders regarding the interpretation of viral load as an endpoint in preventive HIV vaccine trials
 - + Publication of a guidance document(s) on what is known and not known about the significance of viral load reduction, and data to be considered in regulatory decision making.

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