Preparing for Future Efficacy Trials: Revisiting the Screening Test of Concept (STOC) Design for AIDS Vaccines

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Background

- Multiple duplicative CMI vaccine candidates
- Correlate(s) of protection is not known
- Vaccines designed to elicit cellular immune response are not expected to prevent infection
- Vaccines that elicit effective humoral responses are years away
- High incidence cohorts are harder to identify

And…

- Trend towards harm seen in recent large trial of Ad5 vectored vaccines

Source: UNAIDS 2004

Screening Test of Concept (STOC) Origins

Problem: How to rapidly select the CMI-based vaccine approaches worthy of advancement?

- UNAIDS/IAVI/WHO Consensus Mtg - Phase IIB TOC, February 2006
  - → *AIDS* 2007
- AIDS Vaccine Amsterdam, September 2006
- Excler, *AIDS* 2007
- UNAIDS Vaccine Advisory Committee, May 2008
- NIAID Summit on HIV Vaccine R&D, March 2008
  - → Consider smaller trial design instead of PAVE100A
- Enterprise Consultation, New York, April 2008

A Spectrum of Efficacy Trials

- HIV infections required to evaluate efficacy

STOC	~ 30 per protocol, ~ 40 mITT
Ph2B TOC	~ 50 per protocol
PAVE 100A	~ 60 weighted ITT
USMHRP-RV 144	~ 129 mITT
VaxGen 004	~ 200 mITT (design), ~368 mITT(actual)

- Limitations of larger end of spectrum
  - Resources
    - Time, money, high incidence cohorts
  - Number of people at risk

STOC Design

- Screens CMI candidates for evidence of impact on disease progression or surrogates (VEp)
- Accepts greater uncertainty about vaccine effect on acquisition (VEs) to accelerate candidate selection; assumes VEs ≤ 30%
- Detects ≥ 1.0 log10 reduction in VL at set point (1-sided, 0.05 alpha level test, power ≥ 80%)
- Requires 30 per protocol infections to have adequate statistical power
- Consider advancing candidate if ≥ 1.0 log10 VL reduction observed

STOC Design

- Randomized 1:1, vaccine: placebo
  - Stratified by important predictors of HIV susceptibility
- Duration ~ 3 years
- HIV testing every 2 months
- Endpoint is ‘set point’ viral load
  - Geometric mean of VL at first 2 time points
- HIV infections followed in separate study

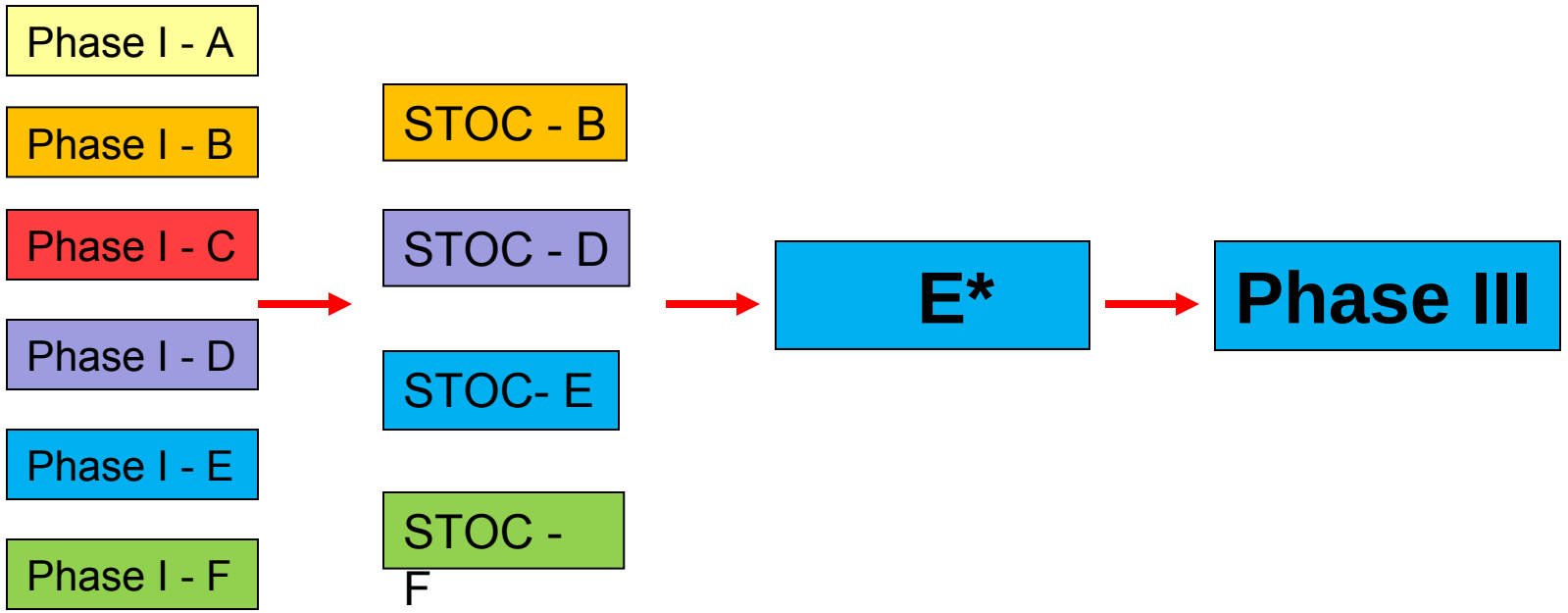
Example of STOC Sample Size to Achieve 30 Endpoints

Annual HIV incidence	Minimum post-vaccination follow-up		
	12 mo	18 mo	24 mo
2%	1312	956	757
3%	881	643	511
4%	665	487	388
5%	535	393	314
6%	449	331	265
7%	388	286	230

Assumptions:

- Enrollment period is 6 months
- 5% loss to follow-up rate during the 6 month vaccination period and a 5% annual loss to follow-up rate during the post vaccination follow-up
- Infections occurring during the vaccination period are excluded
- Protective vaccine effect on susceptibility is 0%

The Development Pathway



*Larger STOC, Phase IIB if needed to collect additional safety data and screen for efficacy in other populations

How well does STOC address:

- Harm
- Correlates of immunity
- Heterogeneity – host or viral

Monitoring for Harm – HIV Acquisition

- STOC is designed to screen for efficacy, not to rule-out harm

- However, STOC can rule-out ≥ 2.4-fold increase in relative risk of HIV acquisition

Monitoring for Harm – HIV Acquisition

Minimum increase in RR of HIV acquisition ruled out with various study designs

Design	Number of Events	RR	Power[1]
STOC (interim)	20-25 mITT	≥3.6	80%
STOC	40 mITT	≥2.4	80%
PAVE100A	60 wITT	≥2.1	80%
Large safety trial[2]	509	≥1.33	90%

[1] Power is 80%, one-sided 0.025 level test when true RR is 1.0

[2] Fleming, *NEJM* 2008

Monitoring for Harm – HIV Acquisition

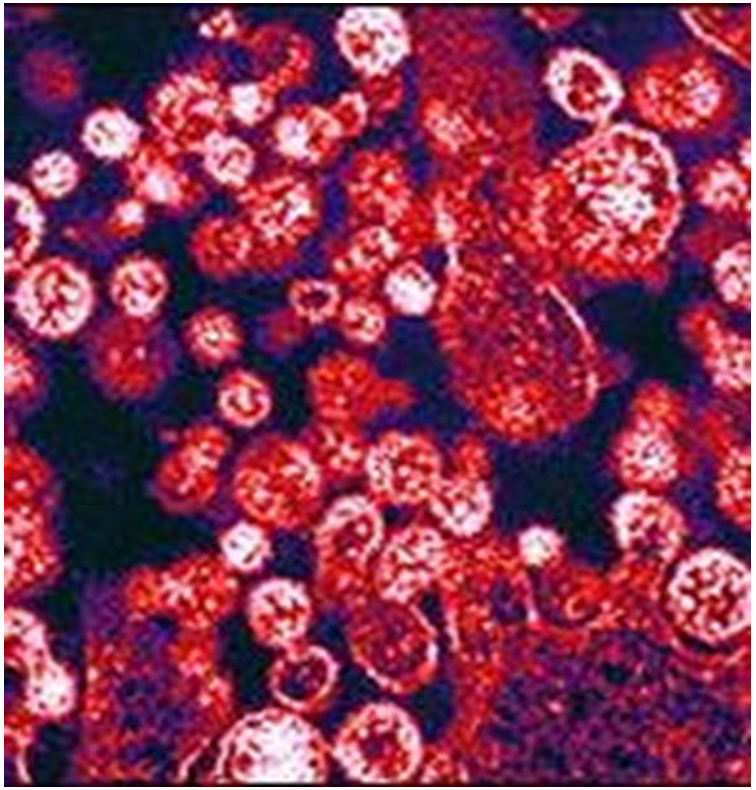
Significance of potential case-splits at STOC interim safety analysis

HIV infections		P value[1]
Vaccine	Placebo	
17	8	0.05
18	7	0.03
19	6	0.007
20	5	0.002

[1] One-sided, exact binomial test

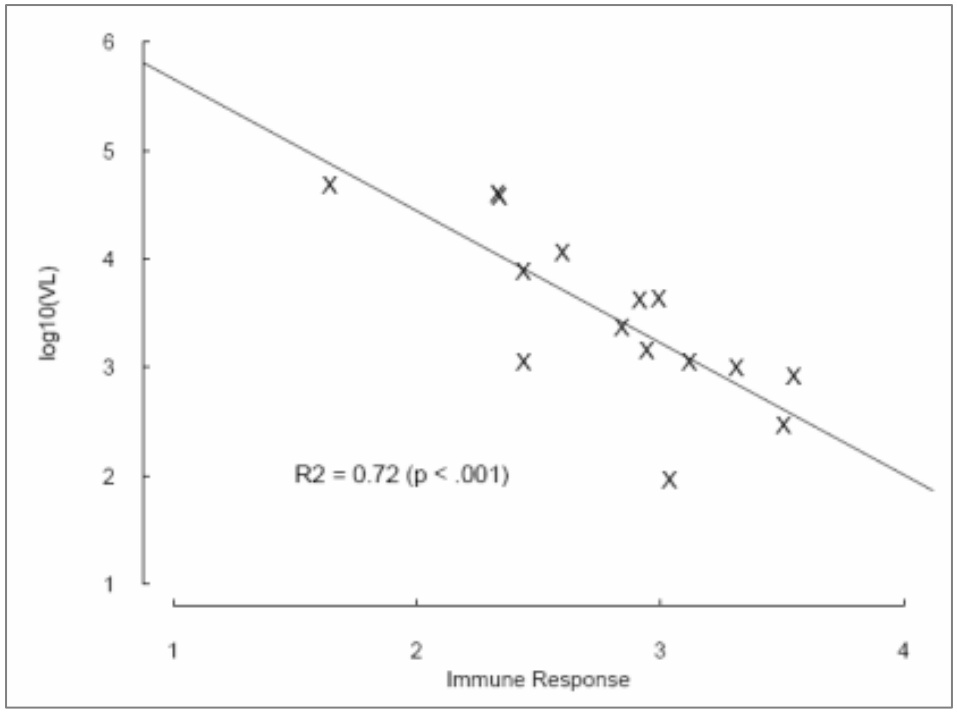
Correlates of Immunity

- Correlates of immunity can be explored, but with limited power
- Correlates should be assessed in subsequent trials once some level of efficacy demonstrated in STOC



Correlates of Immunity

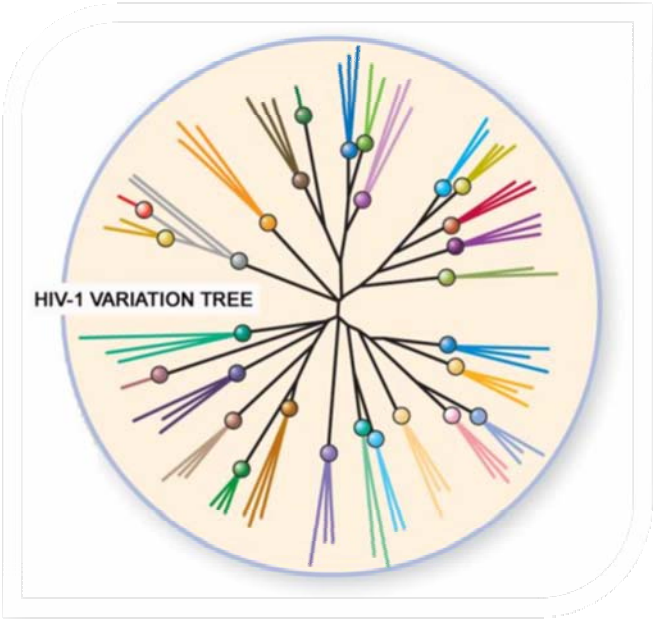
Correlation between viral load set point and immune response variable (eg ELISPOT) in STOC trial with 15 infected vaccinees (r=-0.85)



- The immune response explains 72% of the variation in log10 VL

Heterogeneity

- Heterogeneity can decrease ability to assess VEs and VEp
  - Known predictors of increased acquisition risk
    - Route of transmission
    - Gender
    - Circumcision status
    - HSV-2 infection
  - Vector serostatus
  - Circulating virus
  - Immune response



Heterogeneity

- STOC could select more homogeneous populations
  - single mode of transmission
  - same region or dominant subtype
  - same vector serostatus
  - same male circumcision status
- Smaller mechanism to test concepts
- Limited conclusions but fewer expectations

Conclusions

- Most candidates will fail → STOC is a means to minimize harm and maximize resources
- Screening for efficacy should be our initial goal
- STOC can assess harm and explore correlates of immunity
- Several STOC trials may be better than one larger heterogeneous trial

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Study volunteers

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