

# **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



# 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

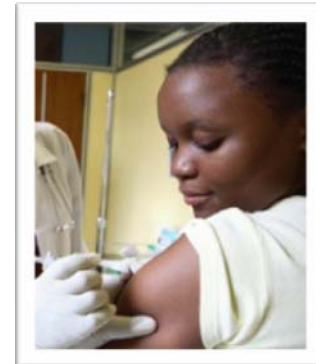
## STOC Design

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- ▶ 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  $\leq 30\%$
- ▶ Detects  $\geq 1.0 \log_{10}$  reduction in VL at set point (1-sided, 0.05 alpha level test, power  $\geq 80\%$ )
- ▶ Requires 30 per protocol infections to have adequate statistical power
- ▶ Consider advancing candidate if  $\geq 1.0 \log_{10}$  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



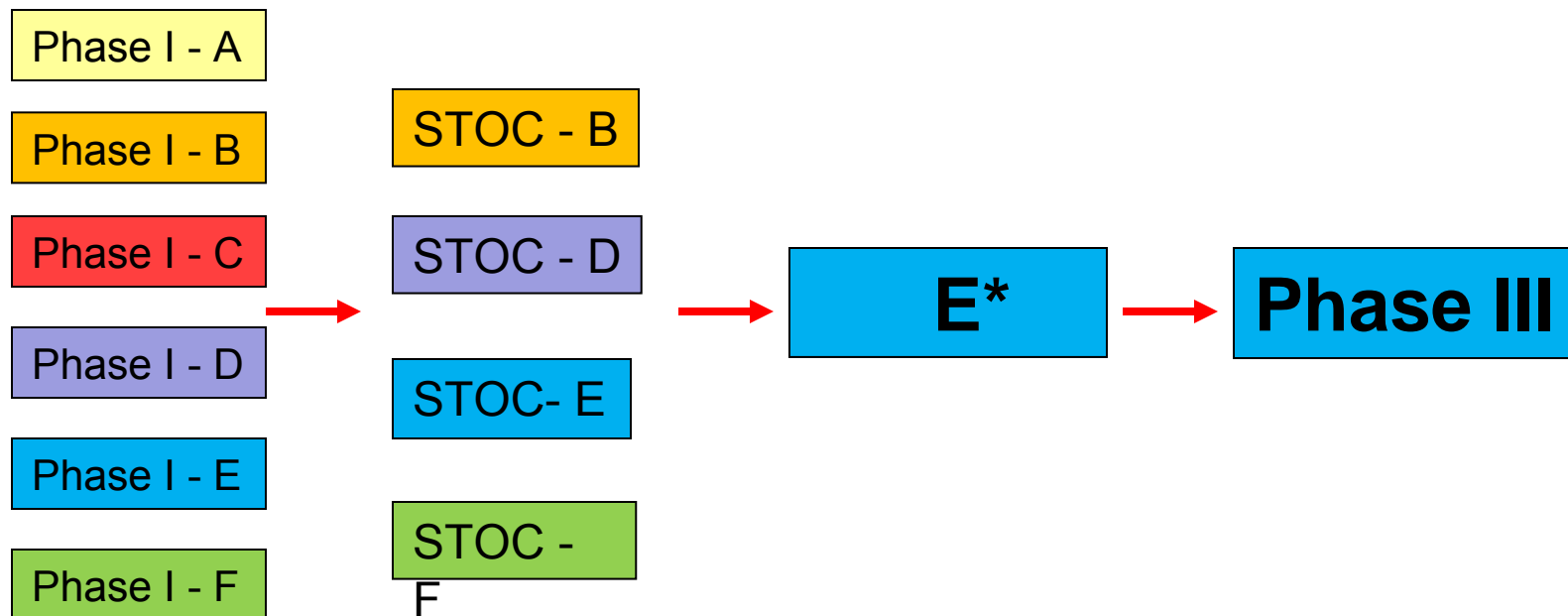
# Example of STOC Sample Size to Achieve 30 Endpoints

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:

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



## Monitoring for Harm – HIV Acquisition

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- ▶ STOC is designed to screen for efficacy, not to rule-out harm
- ▶ However, STOC can rule-out  $\geq 2.4$ -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 <sup>1</sup>
STOC (interim)	20-25 mITT	$\geq 3.6$	80%
STOC	40 mITT	$\geq 2.4$	80%
PAVE100A	60 wITT	$\geq 2.1$	80%
Large safety trial <sup>2</sup>	509	$\geq 1.33$	90%

<sup>1</sup> Power is 80%, one-sided 0.025 level test when true RR is 1.0

<sup>2</sup> Fleming, *NEJM* 2008

## Monitoring for Harm – HIV Acquisition

### Significance of potential case-splits at STOC interim safety analysis

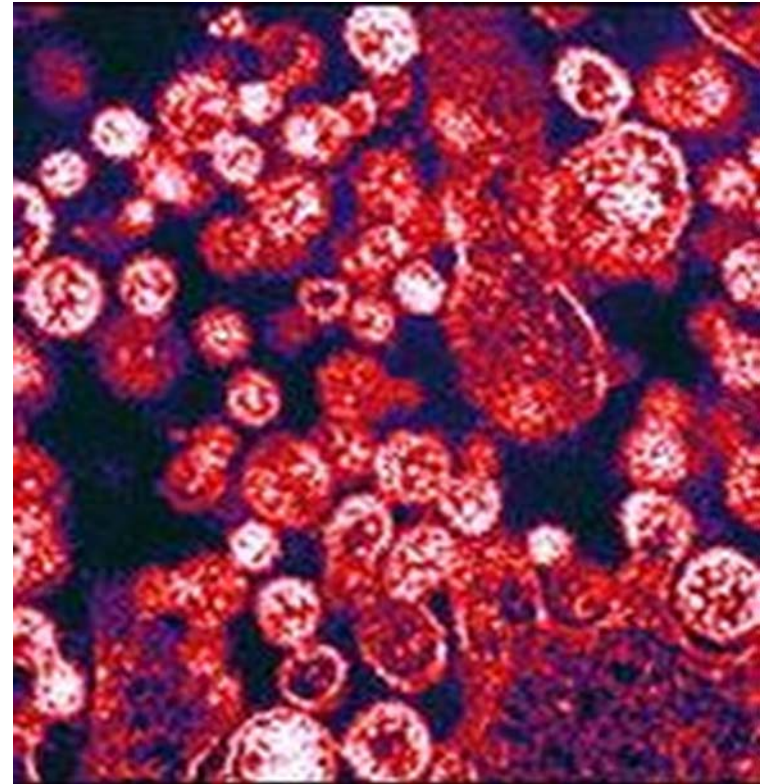
HIV infections		P value <sup>1</sup>
Vaccine	Placebo	
17	8	0.05
18	7	0.03
19	6	0.007
20	5	0.002

<sup>1</sup> One-sided, exact binomial test

# Correlates of Immunity

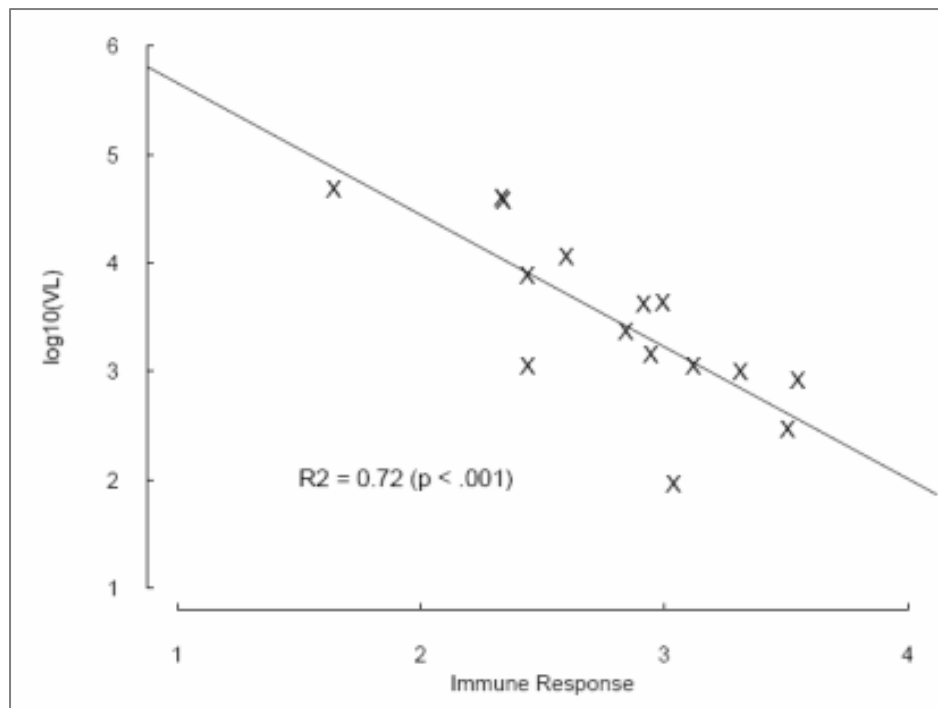
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- ▶ Correlates of immunity can be explored, but with limited power
- ▶ Correlates should be assessed in subsequent trials once some level of efficacy demonstrated in STOC



# Correlates of Immunity

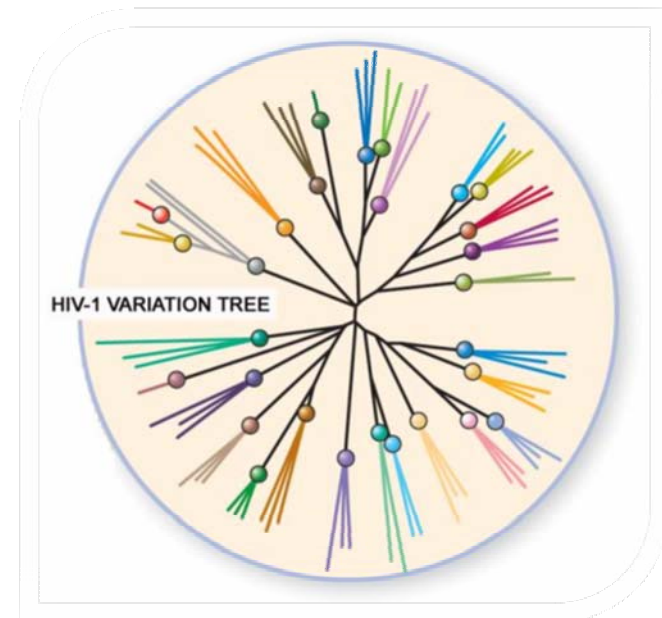
**Correlation between viral load set point and immune response variable (eg ELISPOT) in STOC trial with 15 infected vaccinees ( $r=-0.85$ )**



► The immune response explains 72% of the variation in log<sub>10</sub> VL

# Heterogeneity

- ▶ Heterogeneity can decrease ability to assess VEs and VE<sub>p</sub>
  - Known predictors of increased acquisition risk
    - ▶ Route of transmission
    - ▶ Gender
    - ▶ Circumcision status
    - ▶ HSV-2 infection
  - Vector serostatus
  - Circulating virus
  - Immune response



# Heterogeneity

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- ▶ 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

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- ▶ 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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# IMAGINE a World Without AIDS

