

The STEP Study: a test of concept trial

November 7, 2007

STEP: a test of concept trial

Test-Of-Concept study

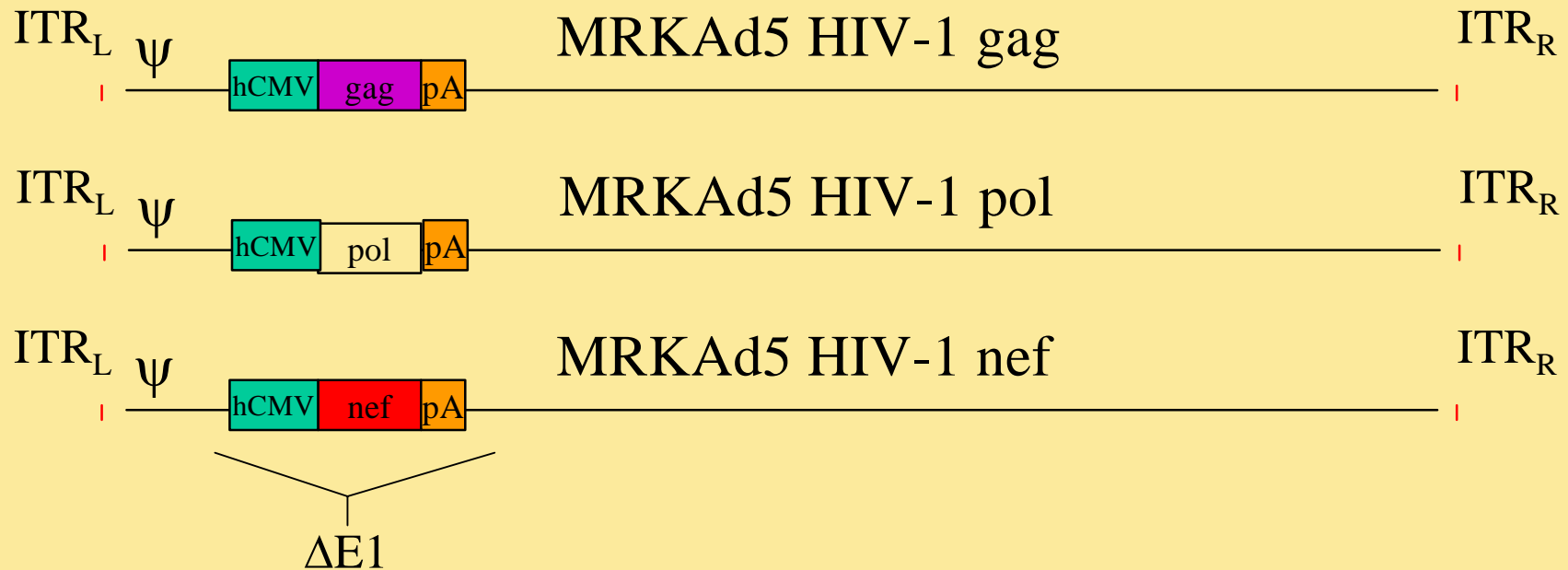
- Designed to guide later development
- May use surrogate endpoint
- May use prototype product
- Study population may be limited and focused
- Smaller, cheaper, faster (in general)

STEP

- Testing ability of MRK Ad5 trivalent HIV vaccine to
 - Decrease HIV acquisition and/or
 - Reduce viral load set-point
- Initiated in population thought to be most likely to benefit
 - participants in clade B regions
 - low prior immunity to Ad5

Efficacy testing of a clade B HIV vaccine

MRKAd5 trivalent vaccine



- Vaccine: 1:1:1 admixture of 3 Ad5 vectors
 - Encoded transgenes: codon-optimized, near-consensus clade B HIV-1 sequences
- Placebo: vaccine dilution buffer without Ad5

Merck-sponsored HIV vaccine clinical trials

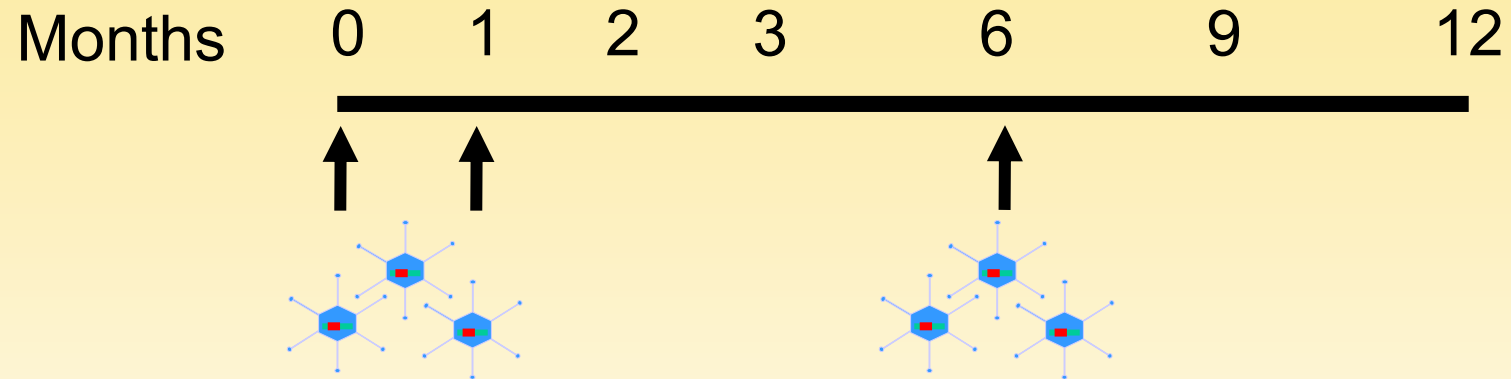
Several candidates selected for human trials

- DNA vaccine
- Replication defective adenovirus serotype 5
- Canarypox (in collaboration with Sanofi-Pasteur)
- "Prime-boost" strategies with each of above

First study began in Dec. 1999

- 12 Phase I trials involving >1300 volunteers
- Replication defective adenovirus serotype 5 selected as lead candidate to take into further development

STEP Study Design



3 Adeno vectors:

clade B gag

clade B pol

clade B nef

STEP Study: primary hypotheses

Efficacy

- Subjects who receive the vaccine will have a lower likelihood of acquiring HIV-1 infection than those who receive placebo,
 - AND/OR
- Among subjects who become HIV-1 infected, those who receive the vaccine will have a smaller average viral load set-point than those who receive placebo.

Safety

- Vaccine will be generally safe and well tolerated.

STEP Study design: Ad5 stratification

- Initial trial design: 1500 HIV-seronegative individuals with low (≤ 200) Ad5 titers
- Trial modified in July 2005 to add 1500 individuals with high (> 200) Ad5 titers
- Maintained original study hypotheses as primary:
 - Among study participants with low Ad5 titers, vaccinees will have a lower likelihood of acquiring HIV infection, and/or
 - Among study participants with low Ad5 titers who become HIV infected, vaccinees will have a smaller average viral load set point.
 - Among study participants with low Ad5 titers, vaccine will be safe and well tolerated.
- Secondary hypotheses were the same but in entire study population (≤ 200 and > 200)
- Enrollment stratified by Ad5 titer (< 18 , 18-200, 201-1000, > 1000)

The STEP Study inclusion criteria

- Between 18 and 45 years old
- Signed informed consent and the HIPAA authorization
- Within 45 days of randomization:
 - Negative serologic tests for HIV-1
 - ALT \leq 3x upper limit of normal
- Participants at risk for HIV infection. IDU are not excluded but must also have sexual risk factors.

The STEP Study inclusion criteria: men

During last 6 months

- Unprotected anal intercourse with another man
- Anal intercourse with ≥ 2 male sexual partners
- Heterosexual men (Caribbean): 1 or more risk
 - Diagnosed with syphilis or genital ulcer diseases
 - 2 or more sexual partners
 - Exchanged sex for money, drugs, services or gifts
 - Used crack cocaine at least 3 times

The STEP Study inclusion criteria: women

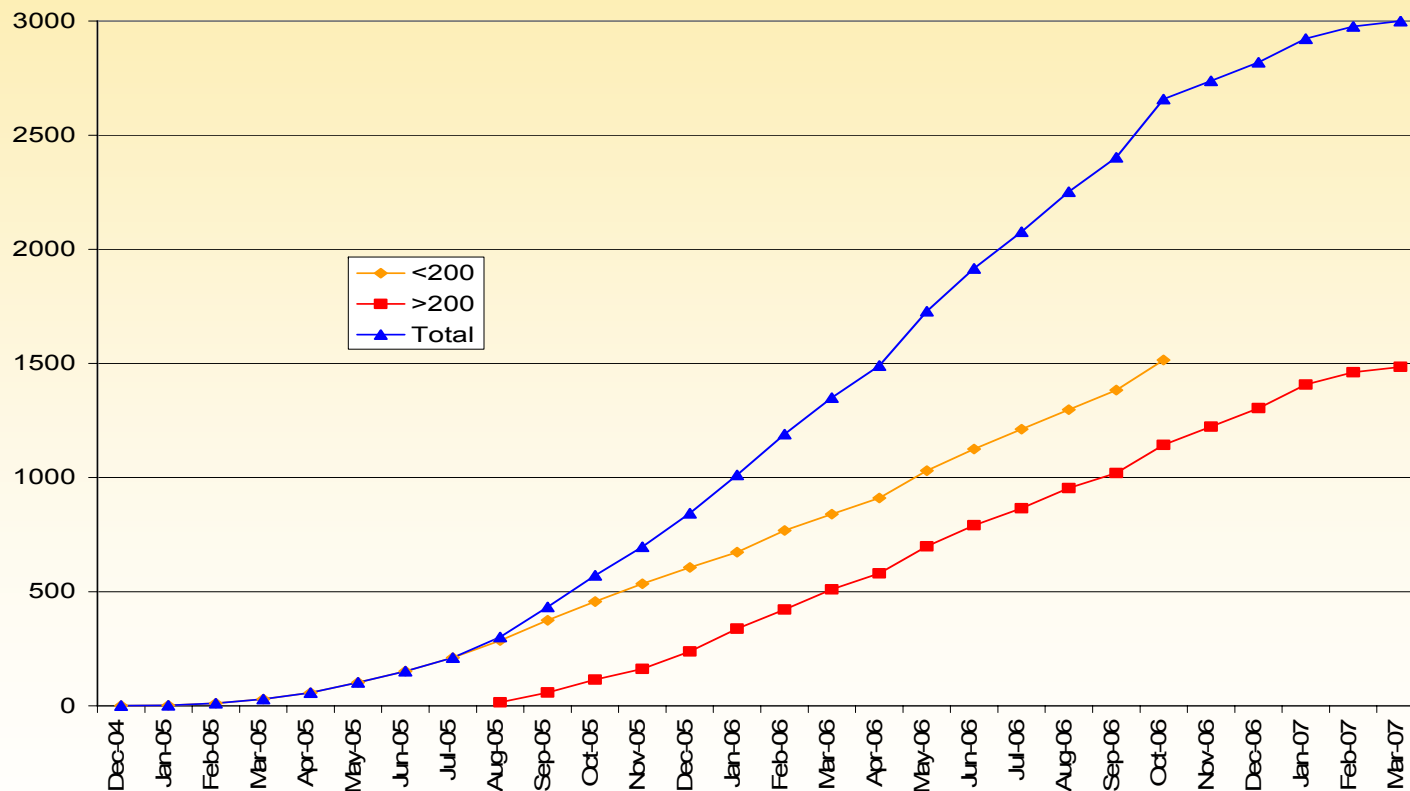
During last 6 months

- Unprotected vaginal or anal intercourse with a man known to be HIV-1 infected
- Unprotected vaginal or anal intercourse with a man who uses injection drugs
- Exchanged sex for money, drugs, services, or gifts
- Used crack cocaine at least 3 times
- Women in Caribbean or Latin America
 - Diagnosed with syphilis or pelvic inflammatory disease

STEP Study sites



Enrollment in high Ad5 stratum lagged behind low Ad5 stratum



STEP Study Data and Safety Monitoring Board (DSMB)

Members & their institutions not directly involved in STEP

- Vaccine specialist/physicians
- Statisticians
- Ethicist

Meets 3 times per year

- Reviews unblinded data on safety
- Reviews study operations

Two planned interim analyses for efficacy

- 30 infections in the Ad5 titer \leq 200 group (primary analysis)
- 30 infections in the Ad5 titer $>$ 200 group and at least 30 in the Ad5 \leq 200 group