

# Safety Review of Merck's Adenovirus Type-5 (Ad5) HIV Vaccines in Healthy Adults

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## Abstract

**Background:** The safety profile of the Merck Ad5-based HIV vaccines was reviewed using data from Phase I studies.

**Methods:** Healthy adults aged 18-50 at low-risk for HIV-infection were randomized to receive 1M injections of 3x10<sup>10</sup> - 1x10<sup>11</sup> viral particles (vp) of a monovalent (Ad5gag or MRKA5gag) or trivalent (MRKA5gag/pol/nef) vaccine. Data were reviewed from all subjects who received at least one dose of an Ad5 vaccine. Adverse experiences (AEs) were collected for 29 days after each injection using a vaccination report card with causal relationships to vaccine determined by the study investigator. Laboratory parameters were collected routinely 1 and 2 weeks following each injection, and in the trivalent study in all subjects 3 days following the first injection. The impact of baseline anti-Ad5 antibody titers on the safety profile of the vaccines was also evaluated.

**Results:** Preliminary safety and tolerability data from approximately 760 subjects enrolled in phase I studies have been reviewed. The vaccines were generally well tolerated. The AE profile of the monovalent and trivalent vaccines were similar. Injection site reactions (pain, swelling, erythema) were commonly observed at an overall rate of 55.1% and were similar among subjects with Ad5 titer ≤ 200 and > 200. The most common systemic AEs were fatigue (22.4%), fever (14.2%), headache (43.7%), myalgia (15.7%) and rigors (11.2%). No clinically significant laboratory abnormalities were observed. 27 vaccine-related serious AEs were reported in 4 subjects (transient lymphopenia [2], fatigue and chills [1], fever, cough, headache, and chest pain [1]). No discontinuations from study occurred due to vaccine-related AEs. The majority of AEs were reported within 3 days after injection. The occurrence of AEs did not increase with subsequent doses and the incidence of fever decreased.

**Conclusions:** In these studies, the Ad5gag, MRKA5gag, and MRKA5gag/pol/nef vaccines were generally well tolerated and had similar safety profiles. Systemic AEs occurred most commonly in subjects with low pre-existing immunity to Ad5 and occurred most frequently at the 1x10<sup>11</sup> vp dose.

## Methods

- Adverse experiences (AEs) collected for 29 days after each injection
  - Subject recorded daily temperatures and symptoms on a vaccination report card
  - Causal relationships to vaccine determined by the study investigator
  - Safety labs collected 1 and 2 weeks following each injection
- In addition, in Protocol 016 (study of trivalent vaccine) labs collected 3 days following the first injection
- Serious adverse experiences (SAEs) were collected throughout the studies

## Study Design

- Non-serious adverse experiences will be summarized from three randomized, double-blind, placebo-controlled, dose escalating Phase I studies
  - Protocol 007
    - Ad5 HIV-1 gag vaccine
    - Dose levels: 1x10<sup>10</sup>, 1x10<sup>11</sup>, 1x10<sup>10</sup>vp/dose
  - Protocol 012
    - MRKA5 HIV-1 gag vaccine
    - Dose levels: 1x10<sup>10</sup>, 1x10<sup>11</sup>, 1x10<sup>10</sup>vp/dose
  - Protocol 016
    - MRKA5 HIV-1 gag/pol/nef trivalent vaccine
    - Dose levels: 3x10<sup>10</sup>, 3x10<sup>11</sup>, 3x10<sup>10</sup>, 3x10<sup>10</sup>, 1x10<sup>11</sup>vp/dose
- Adverse experiences in the 3 lowest doses in Protocol 016 were similar to placebo, therefore, non-serious adverse experiences will only be summarized for doses of 3x10<sup>10</sup> or higher
- In addition, vaccine related serious adverse experiences will be summarized for any subject receiving at least one dose of an adenovirus type 5 HIV-1 vaccine or placebo in Merck's Phase I HIV vaccine studies. As of 01-Jan-2005 this represents a total of ~870 subjects (includes above studies as well as subjects in DNA prime/Ad5 boost studies and therapeutic vaccine studies in HIV-infected subjects).

### Demographics of Subjects

	Placebo (N=69)	1x10 <sup>10</sup> (m) (N=63)	3x10 <sup>10</sup> (t) (N=41)	1x10 <sup>10</sup> (m) (N=65)	3x10 <sup>10</sup> (t) (N=42)	1x10 <sup>11</sup> (m) (N=65)	1x10 <sup>11</sup> (t) (N=31)
<b>Gender</b>							
Male	27 (39%)	30 (48%)	20 (49%)	35 (54%)	29 (69%)	31 (48%)	17 (55%)
Female	42 (61%)	33 (52%)	21 (51%)	30 (47%)	13 (31%)	34 (53%)	14 (45%)
<b>Age</b>							
Mean	35.5	35.4	34.3	32.3	37.9	33.7	34.8
SD	9.6	9.9	10.4	8.8	9.0	9.5	9.6
Median	34.0	36.0	34.0	31.0	39.5	33.0	35.0
Range	18 TO 51	18 TO 50	18 TO 50	18 TO 49	19 TO 50	19 TO 49	19 TO 50
Male	21 TO 50	19 TO 50	18 TO 50	18 TO 48	18 TO 49	19 TO 49	23 TO 49
Female	18 TO 51	18 TO 50	18 TO 47	20 TO 49	19 TO 50	20 TO 47	19 TO 50
<b>Race/Ethnicity</b>							
Asian/Pacific	1 (2%)	0 (0%)	3 (7%)	1 (2%)	1 (2%)	2 (3%)	1 (3%)
Black	8 (12%)	8 (13%)	7 (17%)	5 (8%)	6 (14%)	4 (6%)	3 (10%)
Caucasian	60 (87%)	52 (83%)	27 (66%)	54 (84%)	32 (76%)	56 (86%)	27 (87%)
Hispanic	0 (0%)	3 (5%)	2 (5%)	5 (8%)	2 (5%)	1 (2%)	0 (0%)
Indian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Native American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Other	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)

### Patient Disposition of Subjects

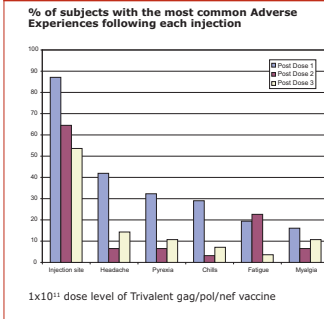
Status	Placebo (N=69)	1x10 <sup>10</sup> (m) (N=63)	3x10 <sup>10</sup> (t) (N=41)	1x10 <sup>10</sup> (m) (N=65)	3x10 <sup>10</sup> (t) (N=42)	1x10 <sup>11</sup> (m) (N=65)	1x10 <sup>11</sup> (t) (N=31)	Total
Randomized	69	63	41	65	42	65	31	376
Completed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Continuing	65 (94.2%)	60 (95.2%)	38 (92.7%)	62 (95.4%)	41 (97.6%)	59 (90.8%)	31 (100%)	356 (94.7%)
Discontinued	4 (5.8%)	3 (4.7%)	3 (7.3%)	3 (4.7%)	1 (2.4%)	6 (9.2%)	0 (0.0%)	20 (5.3%)
<b>Clinical AE</b>								
(brachial plexus neuritis, back pain, throat/chest tightness, depression)	0 (0.0%)	2 (3.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	4 (1.1%)
<b>laboratory AE</b>								
(urine RBCs)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
lost to follow-up	1 (1.4%)	1 (1.6%)	1 (2.4%)	2 (3.1%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	6 (1.6%)
withdrew consent	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.1%)	0 (0.0%)	3 (0.8%)
moved	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
protocol deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.3%)
other reasons	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (2.4%)	1 (1.5%)	0 (0.0%)	4 (1.1%)

### In general, Adverse Experiences were more common at higher doses and the majority of Adverse Experiences were reported within 3 days after injection

Adverse Experiences	Placebo (N=69)			1x10 <sup>10</sup> (m) (N=63)			3x10 <sup>10</sup> (t) (N=41)			1x10 <sup>10</sup> (m) (N=65)			3x10 <sup>10</sup> (t) (N=42)			1x10 <sup>11</sup> (m) (N=65)			1x10 <sup>11</sup> (t) (N=31)		
	3 days	29 days	3 days	29 days	3 days	29 days	3 days	29 days	3 days	29 days	3 days	29 days	3 days	29 days	3 days	29 days	3 days	29 days	3 days	29 days	
Injection site	34.8	34.8	56.7	56.7	84.4	84.4	92.2	92.2	56.1	56.1	76.2	76.2	93.5	93.5							
Headache	24.6	49.3	21.7	46.7	35.9	64.1	46.9	56.3	17.1	29.3	33.3	45.2	41.9	45.2							
Fatigue	7.2	15.9	11.7	18.3	21.9	34.4	34.4	35.9	14.6	29.3	16.7	21.4	25.8	35.5							
Pyrexia	1.4	7.2	0	8.3	1.6	9.4	20.3	25	2.4	12.2	19	26.2	35.5	35.5							
Chills	0	4.3	1.7	6.7	10.9	12.5	35.9	37.5	4.9	7.3	14.3	19	29	29							
Diarrhoea	4.3	17.4	6.7	23.3	4.7	7.8	10.9	20.3	9.8	22	7.1	16.7	12.9	22.6							
Myalgia	2.9	11.6	5	13.3	12.5	17.2	29.7	35.9	7.3	7.3	14.3	16.7	19.4	22.6							
Nausea	7.2	11.6	8.3	13.3	9.4	12.5	21.9	29.7	4.9	7.3	4.8	14.3	9.7	12.9							
Pain	2.9	4.3	6.7	11.7	14.1	18.8	26.6	29.7	4.9	7.3	7.1	9.5	9.7	12.9							
Arthralgia	1.4	7.2	1.7	5	7.8	12.5	9.4	10.9	7.3	12.2	4.8	7.1	6.5	9.7							
Back pain	1.4	8.7	6.7	15	7.8	17.2	7.8	17.2	4.9	7.3	2.4	4.8	3.2	9.7							
Pharyngolaryngeal pain	7.2	21.7	5	18.3	14.1	28.1	12.5	31.3	9.8	24.4	9.5	21.4	3.2	9.7							
Body temperature increased	1.4	4.3	0	3.3	4.7	6.3	12.5	12.5	0	0	4.8	4.8	6.5	6.5							
Cough	5.8	15.9	5	11.7	4.7	12.5	4.7	14.1	2.4	12.2	0	2.4	0	6.5							
Lymphadenopathy	0	5.8	1.7	1.7	3.1	4.7	1.6	1.6	0	0	0	0	6.5	6.5							
Malaise	0	1.4	0	1.7	1.6	1.6	7.8	9.4	2.4	2.4	4.8	4.8	6.5	6.5							
Nasal congestion	5.8	10.1	3.3	8.3	1.6	9.4	7.8	20.3	2.4	2.4	4.8	9.5	3.2	6.5							
Nasopharyngitis	0	5.8	1.7	5	3.1	12.5	1.6	4.7	0	9.8	2.4	7.1	6.5	6.5							
Neck pain	1.4	5.8	3.3	8.3	1.6	1.6	6.3	7.8	0	4.9	2.4	2.4	6.5	6.5							
Upper resp. tract infection	1.4	7.2	0	5	0	4.7	1.6	10.9	2.4	9.8	2.4	9.5	6.5	6.5							
Abdominal pain upper	1.4	4.3	1.7	3.3	0	6.3	3.1	3.1	4.9	4.9	0	2.4	0	3.2							
Dizziness	0	1.4	0	1.6	0	1.6	7.8	10.9	2.4	2.4	0	2.4	3.2	3.2							
Dysmenorrhoea	0	4.3	0	5	0	6.3	3.1	3.1	0	0	0	2.4	3.2	3.2							
Pain in extremity	0	2.9	0	5	3.1	6.3	4.7	14.1	7.3	7.3	0	0	3.2	3.2							
Sinus congestion	0	2.9	3.3	15	1.6	12.5	6.3	7.8	2.4	9.8	0	2.4	3.2	3.2							
Vomiting	7.2	8.7	0	5	1.6	1.6	7.8	14.1	4.9	7.3	0	4.8	0	3.2							
Dyspepsia	1.4	2.9	1.7	5	3.1	6.3	1.6	3.1	2.4	2.4	0	0	0	0							
Insomnia	0	0	1.7	3.3	3.1	4.7	4.7	4.7	0	0	4.8	11.9	0	0							
Musculoskeletal stiffness	1.4	2.9	1.7	3.3	1.6	4.7	3.1	4.7	0	0	0	0	0	0							
Respiratory tract congestion	0	1.4	0	6.7	1.6	6.3	1.6	3.1	0	2.4	0	2.4	0	0							
Rhinorrhoea	2.9	7.2	3.3	10	6.3	9.4	3.1	7.8	2.4	2.4	4.8	4.8	0	0							
Sneezing	0	4.3	3.3	10	1.6	3.1	0	3.1	0	0	0	0	0	0							
Throat irritation	1.4	2.9	0	1.7	1.6	4.7	1.6	6.3	0	0	0	0	0	0							

(m) = monovalent (gag)  
(t) = trivalent (gag/pol/nef)

### Adverse events tended to be more frequent after the first injection



### Summary of common Adverse Experiences within 29 Days of first Vaccination by Dose Level

POST DOSE 1 Adverse Experiences	Placebo (N=69)	1x10 <sup>10</sup> (m) (N=63)	3x10 <sup>10</sup> (t) (N=41)	1x10 <sup>10</sup> (m) (N=65)	3x10 <sup>10</sup> (t) (N=42)	1x10 <sup>11</sup> (m) (N=65)	1x10 <sup>11</sup> (t) (N=31)
Injection site	23.2	35	26.8	<67.2>	<54.8>	<81.3>	<87.1>
Headache	31.9	35	22	37.5	31	43.8	<41.9
Pyrexia	2.9	3.3	4.9	1.6	<14.3>	<21.9>	<32.3>
Chills	1.4	1.7	4.9	<7.8>			