Phase 1 evaluation of a 2nd second-generation N+S SARS-CoV-2 vaccine with human adenovirus 5 vector

Graeme Meintjes

Department of Medicine and IDM

University of Cape Town

Groote Schuur Hospital

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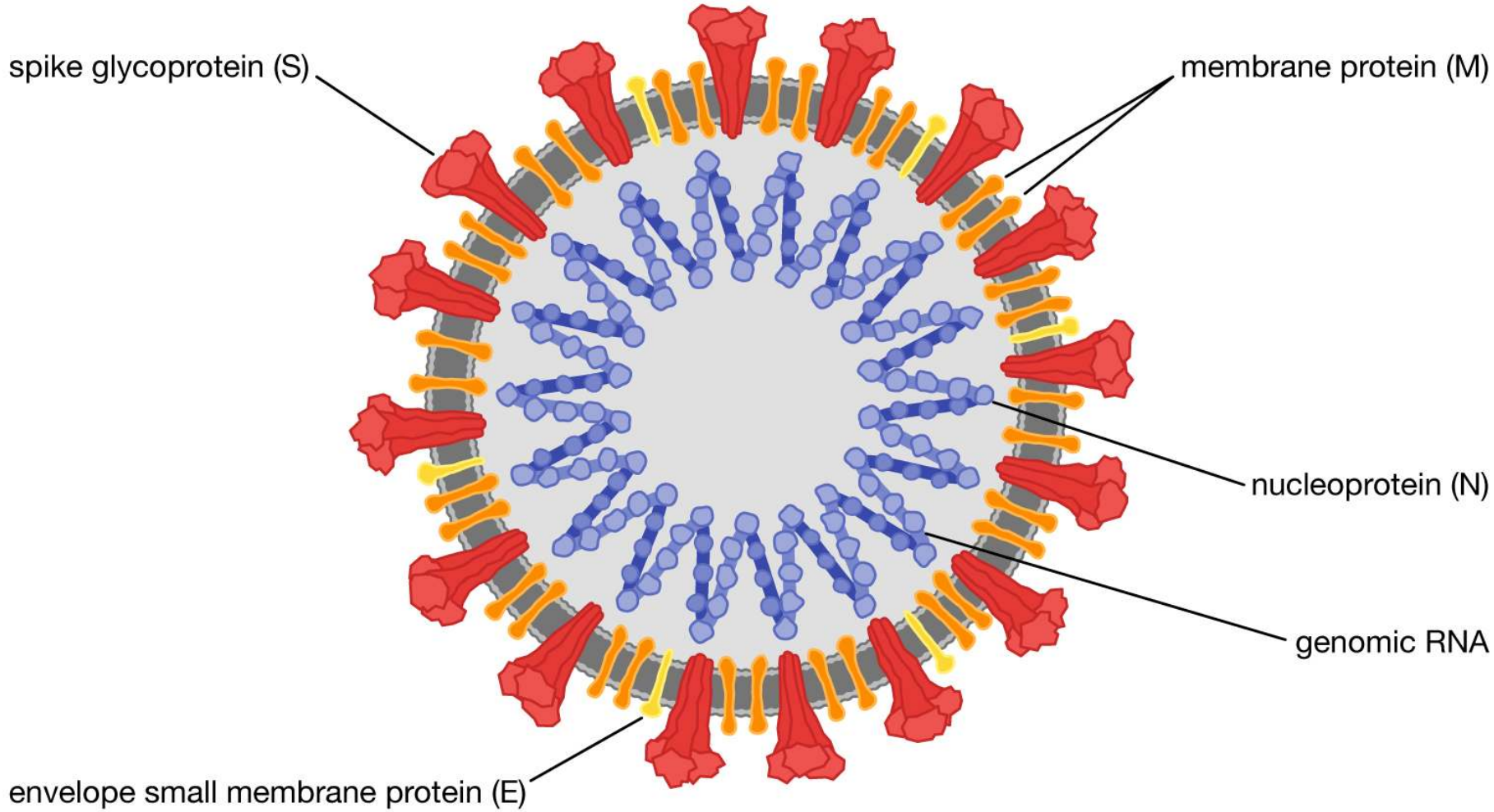
Potential deficiencies with current vaccines

- Activity against variants
- Durability
- Prevention of transmission

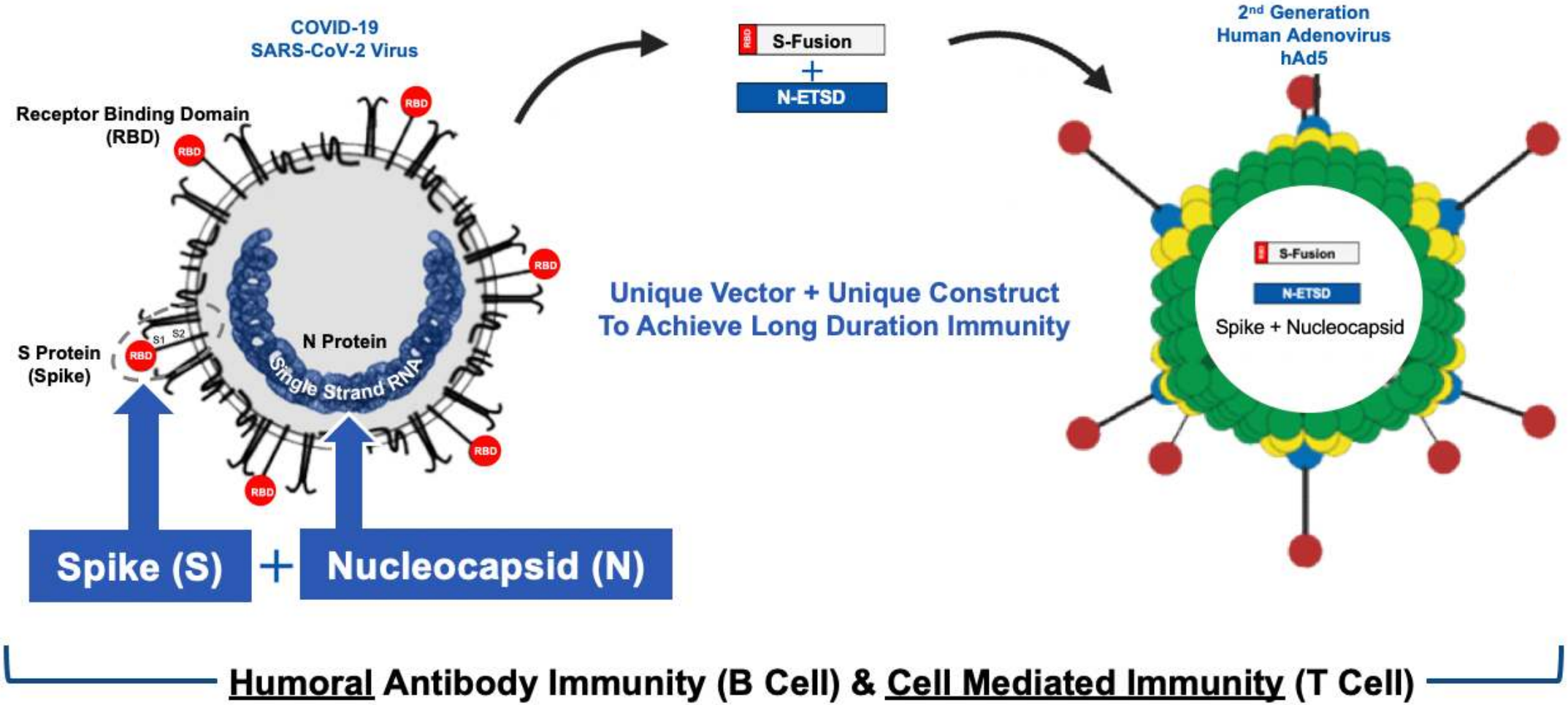
They all target one protein
= S-protein of the virus
which tends to develop more
mutations than other proteins

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)



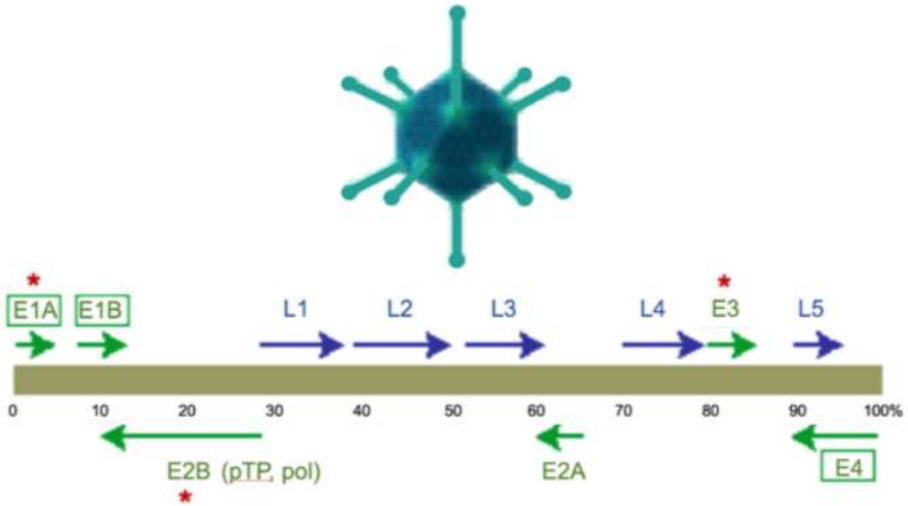
Novel hAd5 N+S SARS-CoV-2 vaccine

- Developed by ImmunityBio in USA
- Vector = attenuated human adenovirus 5 (hAd5) with additional genetic deletions to make it relatively immune “silent”
- This vector had been developed for cancer vaccines
- Inserts:
  - SARS CoV-2 spike protein (S)
  - SARS CoV-2 nucleocapsid protein (N)
- Nucleocapsid insert is linked to an Enhanced T-cell Signalling Domain

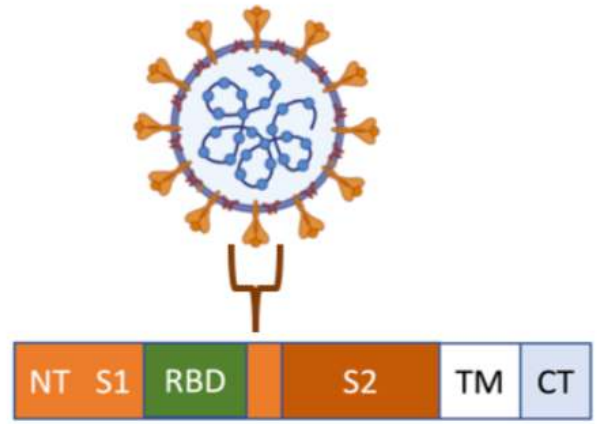


Humoral Antibody Immunity (B Cell) & Cell Mediated Immunity (T Cell)

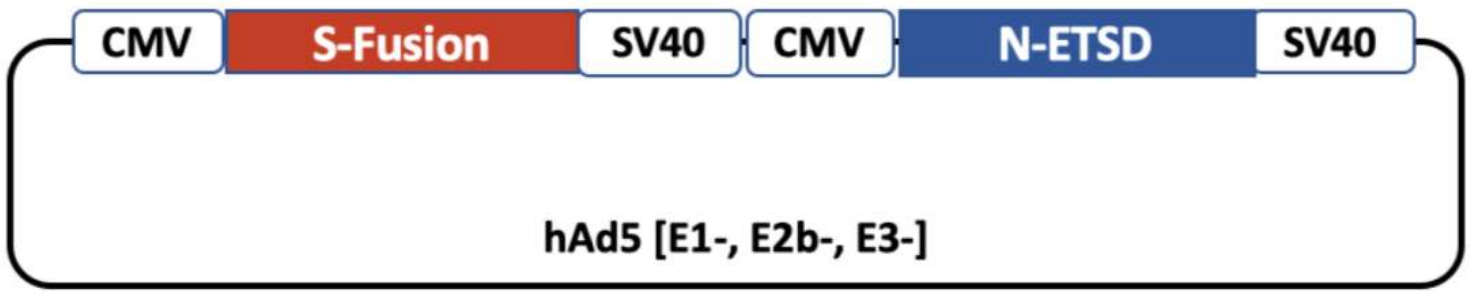
A hAd5 [E1-, E2b-, E3-]



B SARS-CoV-2

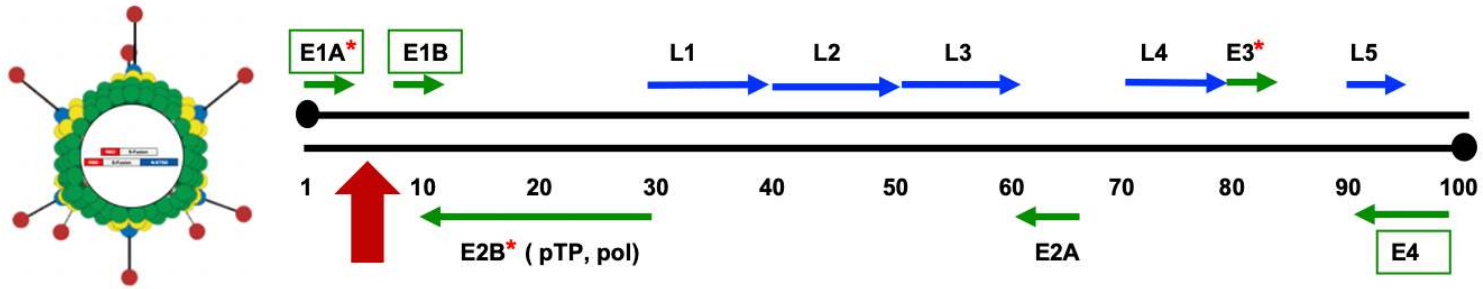


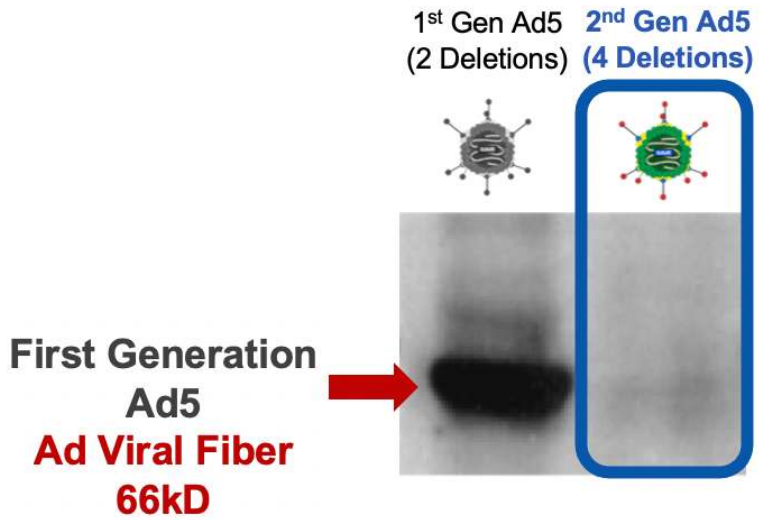
C hAd5 S-Fusion + N-ETSD



A Second Generation Human Adenovirus Serotype 5 (hAd5) with Four Deletions Enabling Multiple Reinjections Even in the Presence of Ad Immunity

hAd5 [E1-, E2b-, E3-]





Second Generation Human Ad5 (hAd5)
hAd5 [E1-, E2b-, E3- Deleted]

- "Immunogenically Stealth"
- Overcomes Pre-Existing Ad Immunity
- Demonstrated Safety and Immunogenicity in >150 Patients Across 14 Phase 1 / 2 Clinical Trials

Amalfitano, A., Hauser, M.A., Hu, H., Serra, D., Begy, C.R., and Chamberlain, J.S. (1998). Production and characterization of improved adenovirus vectors with the E1, E2b, and E3 genes deleted. J Virol 72, 926-933.

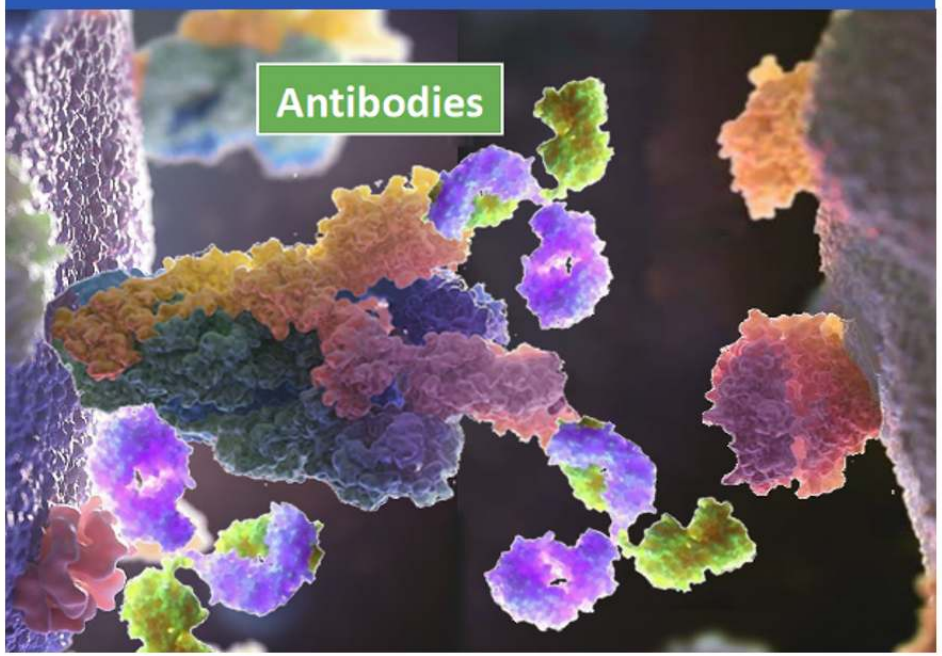
SARS-CoV-2 B Cell and T Cell Based Vaccine: **hAd5 S-Fusion + N-ETSD**

Designed Based on Novel Mechanism of Antigen-Target Localization to Lysosomal Compartments

Driving Both B Cells (antibodies) and CD8+ Killer T Cells through Activation of CD4+ MHC-II Restricted T Helper Cells

hAd5 S-Fusion + N-ETSD SARS-CoV-2 Vaccine

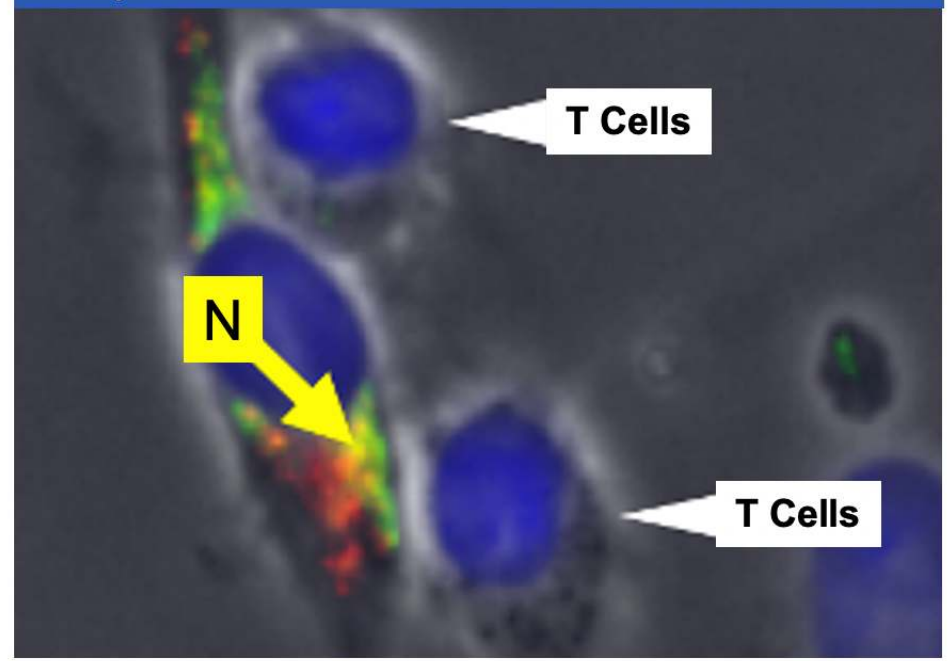
S-Fusion Driving Neutralizing Antibody Production



Block the Entry of the Virus

+

Nucleocapsid (N) Targeted to Endosomal/Lysosomal System to MHC-II CD4+ and CD8+ T Cell Generation



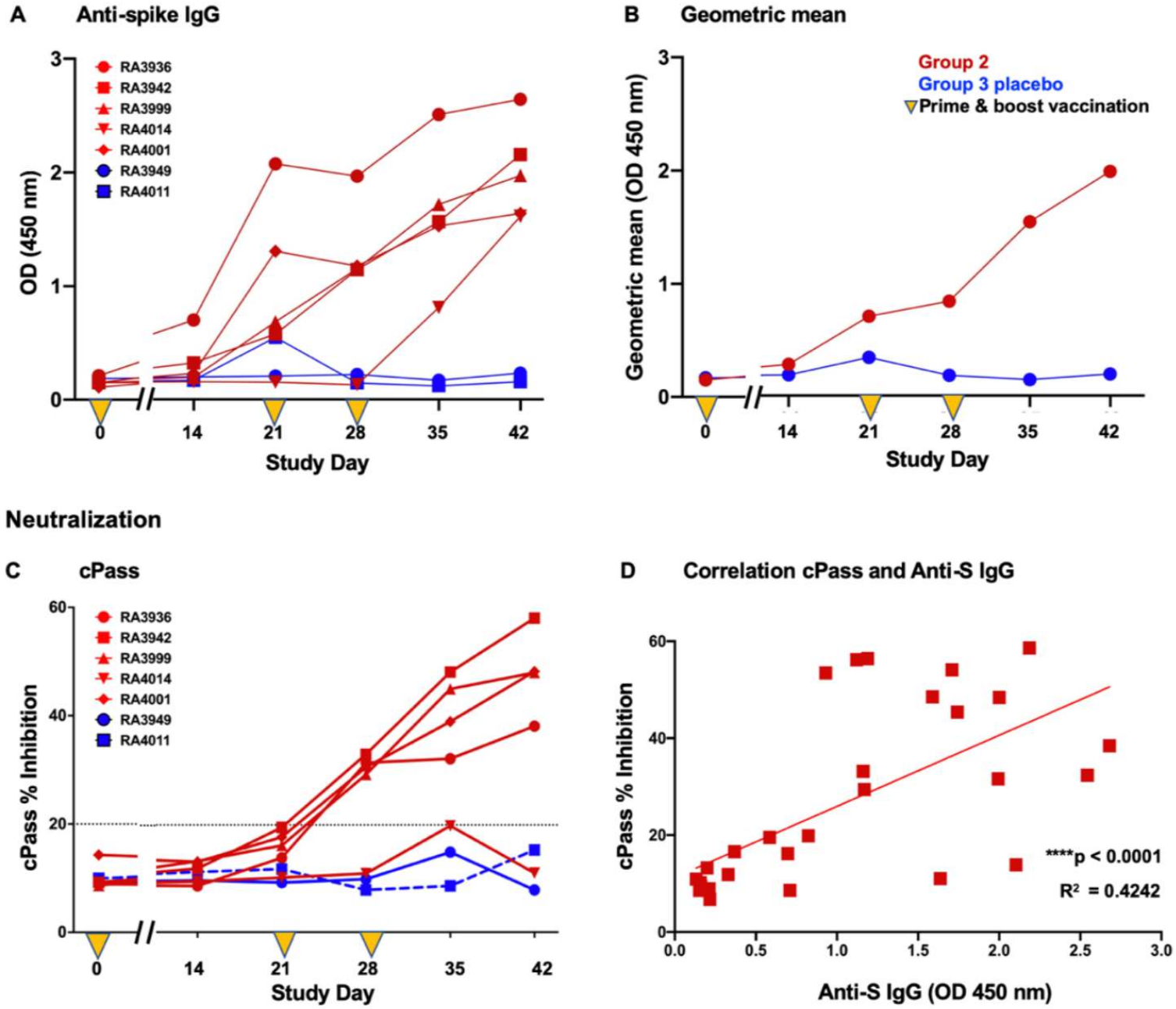
T Cell Killing of Virus Infected Cells

Prevent Lateral Transmission
Durable Long-Term Protection

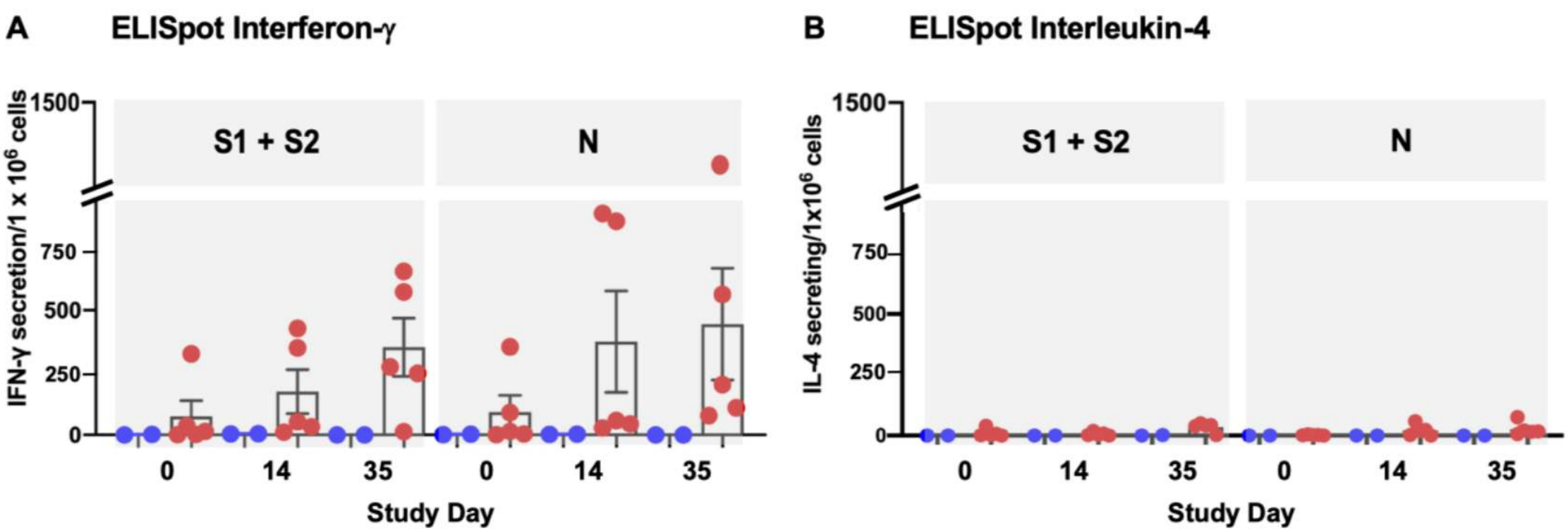
Complete Protection of Nasal and Lung Airways Against SARS-CoV-2 Challenge by Antibody Plus Th1 Dominant N- and S-Specific T-Cell Responses to Subcutaneous Prime and Thermally-Stable Oral Boost Bivalent hAd5 Vaccination in an NHP Study

Elizabeth Gabitzsch[1], Jeffrey T. Safrit[2], Mohit Verma[1], Adrian Rice[1], Peter Sieling[1], Lise Zakin[1], Annie Shin[1], Brett Morimoto[1], Helty Adisetiyo[1], Raymond Wong[1], Ashish Bezawada[2], Kyle Dinkins[1], Joseph Balint[1], Victor Peykov[1], Hermes Garban[1], Philip Liu[1], Andrew Bacon[3], Jeff Drew[3], Patricia Spilman[1], Lennie Sender[2], Shahrooz Rabizadeh[1], Kayvan Niazi[1], and Patrick Soon-Shiong[1*]

Group 2: Anti-Spike Antibodies



Group 2 T-Cell Responses



Complete Inhibition of Viral Replication in Nasal Passages Following SC+Oral Vaccination

Nasal Viral Load (RT qPCR)

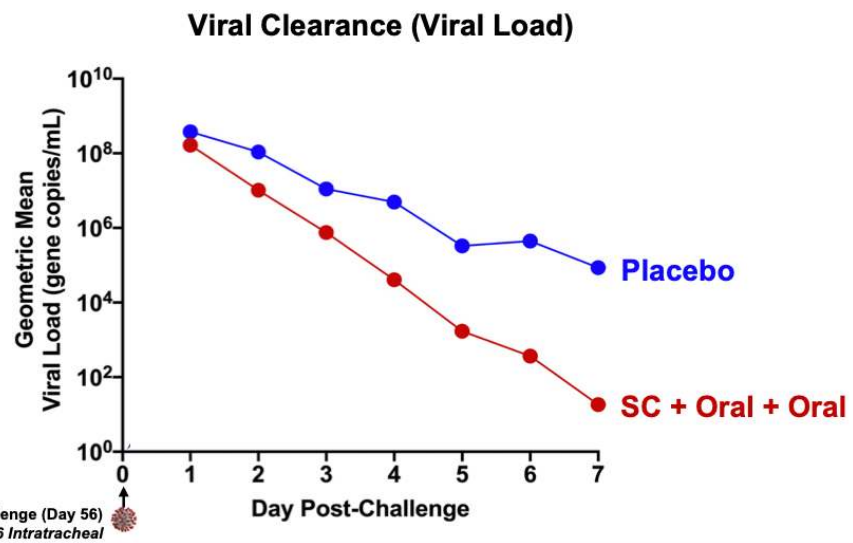
Viral Challenge (Day 56) TCID*50 1E6 Intratracheal*

Viral Clearance (Viral Load)

Days Post Challenge

NHP ID	Group	Gender	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
RA3936	2	Male	1.13E+08	5.06E+06	2.53E+06	5.02E+05	2.04E+03	1.50E+03	1.00E+00
RA3942	2	Male	3.13E+08	3.59E+06	8.15E+05	5.62E+03	3.32E+02	1.00E+00	1.01E+02
RA3999	2	Female	1.80E+08	2.65E+07	1.14E+06	3.31E+04	2.39E+03	1.41E+03	1.76E+02
RA4014	2	Female	1.18E+09	4.64E+07	2.69E+05	3.09E+04	1.59E+03	1.68E+03	1.18E+02
RA4001	2	Female	1.67E+07	4.87E+06	3.89E+05	3.95E+04	5.48E+03	1.90E+03	1.00E+00
Geometric Mean			**1.66E+08**	**1.02E+07**	**7.55E+05**	**4.09E+04**	**1.70E+03**	**3.68E+02**	**1.84E+01**

NHP ID	Group	Gender	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
RA3949	3	Male	2.06E+09	4.95E+08	4.12E+06	7.14E+07	7.02E+05	2.73E+05	1.62E+04
RA4011	3	Female	6.95E+07	2.38E+07	3.00E+07	3.44E+05	1.56E+05	7.19E+05	4.61E+05
Geometric Mean			3.79E+08	1.08E+08	1.11E+07	4.96E+06	3.31E+05	4.43E+05	8.65E+04



Nasal Viral Replication (sgRNA)

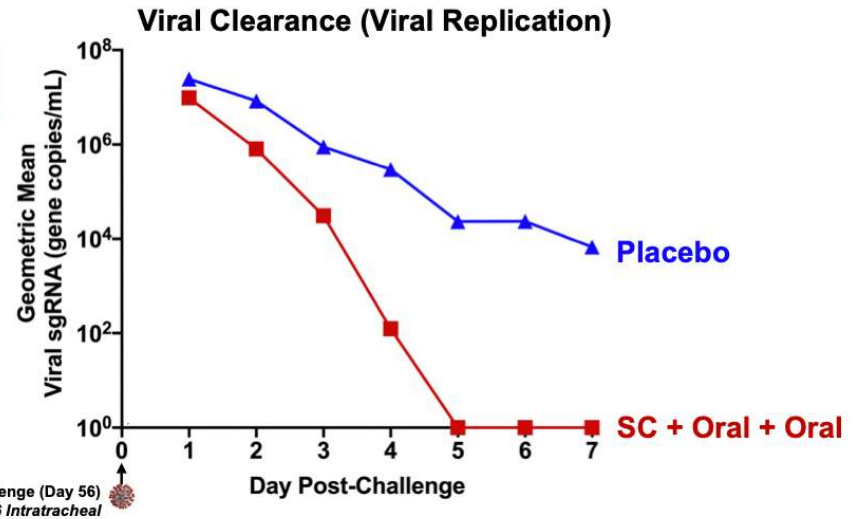
Viral Challenge (Day 56) TCID*50 1E6 Intratracheal*

Viral Clearance (Viral Replication)

Days Post Challenge

NHP ID	Group	Sex	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
RA3936	2	Male	6.57E+06	4.43E+05	1.71E+05	2.52E+04	1.00E+00	1.00E+00	1.00E+00
RA3942	2	Male	1.58E+07	3.43E+05	1.12E+03	1.00E+00	1.00E+00	1.00E+00	1.00E+00
RA3999	2	Female	1.81E+07	1.99E+06	1.16E+05	1.90E+03	1.00E+00	1.00E+00	1.00E+00
RA4014	2	Female	3.33E+07	2.32E+06	3.26E+04	1.00E+00	1.00E+00	1.00E+00	1.00E+00
RA4001	2	Female	1.42E+06	4.97E+05	3.84E+04	5.98E+02	1.00E+00	1.00E+00	1.00E+00
Geometric Mean			9.77E+06	8.10E+05	3.08E+04	1.23E+02	1.00E+00	1.00E+00	1.00E+00

NHP ID	Group	Sex	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
RA3949	3	Male	1.33E+08	1.84E+07	3.21E+05	1.49E+06	1.23E+04	2.73E+03	2.86E+02
RA4011	3	Female	4.47E+06	3.81E+06	2.48E+06	5.88E+04	4.40E+04	2.04E+05	1.56E+05
Geometric Mean			2.44E+07	8.38E+06	8.92E+05	2.95E+05	2.33E+04	2.36E+04	6.68E+03



USA Phase 1 COVID-19 Vaccine Trial

Started October 2020

PHASE 1B OPEN-LABEL STUDY OF THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF PROPHYLACTIC VACCINATION WITH 2ND GENERATION E1/E2B/E3-DELETED ADENOVIRAL-COVID-19 IN NORMAL HEALTHY VOLUNTEERS

Study Number:	QUILT-COVID-19-hAd5-Vaccine
IND Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	Sandeep Bobby Reddy, MD Chief Medical Officer ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Cell Phone: +1-562-631-4945 Email: Bobby.Reddy@ImmunityBio.com

Phase I: NCT04591717

Phase 1

Day 1 (Prime) & Day 22 (Boost)

Up to 35 healthy subjects will be divided into 3 dosing cohorts:

- Cohort 1 (n = 10): hAd5-S-Fusion+N-ETSD at 5 × 10^{10} VP per dose,
- Cohort 2 (n = 10): hAd5-S-Fusion+N-ETSD at 1 × 10^{11} VP per dose.
- Cohort 3 (n = 15): hAd5-S-Fusion+N-ETSD at 1 × 10^{11} VP per dose (or 5 × 10^{10} VP per dose if safety concerns identified at higher dose)

Hoag Hospital Newport Beach
1 Hoag Drive, Newport Beach, CA 92663
clinicalresearch@hoag.org
949-764-4430 / NCT04591717

hoag

Investigator:
Philip A. Robinson MD
Infectious Disease

Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial

Susan P. Buchbinder, MD[1], Devan V. Mehrotra, PhD[2], Ann Duerr, MD, PhD, MPH[3], Daniel W. Fitzgerald, MD[4], Robin Mogg, MS[2], David Li, PhD[2], Peter B. Gilbert, PhD[3], Javier R. Lama, MD, MPH[5], Michael Marmor, PhD[6], Carlos del Rio, MD[7], M. Juliana McElrath, MD, PhD[3], Danilo R. Casimiro, PhD[2], Keith M. Gottesdiener, MD[2], Jeffrey A. Chodakewitz, MD[2], Lawrence Corey, MD[3], and Michael N. Robertson, MD[2] the Step Study Protocol Team

STEP trial
Merck Ad5 HIV-1 vaccine

Participants Ad5 seronegative at baseline:
24 / 741 vaccinees became HIV infected
versus 21 / 762 placebo recipients

In exploratory multivariate analyses:
HIV incidence was higher in vaccinees versus placebo recipients:

- among Ad5 seropositive men (5.1% versus 2.2% per year)
- uncircumcised men (5.2% versus 1.4% per year)

HIV incidence similar in vaccinees versus placebo recipients among Ad5 seronegative men & circumcised men

Buchbinder, Lancet 2008

Table 4

Hazard Ratios of HIV Infection for Male Subgroups Defined by Demographic and Baseline Behavioral Risk Factors (Univariate Cox Model Analyses)

MITT Population	N	Number of HIV infections		HIV infection rate (% per year)		Hazard Ratio(Vaccine/ Placebo) (95% CI)	Interaction p-value[a]
		Vaccine	Placebo	Vaccine	Placebo		
Demographic factors							
Ad5– (titer ≤ 18)	776	20	20	4.1	4.0	1.0 (0.5 to 1.9)	0.08
Ad5+ (titer > 18)	1060	29	13	5.1	2.2	2.3 (1.2 to 4.3)	
Circumcised	999[b]	26	26	4.1	4.2	1.0 (0.6 to 1.7)	0.01
Uncircumcised	788[b]	22	6	5.2	1.4	3.8(1.5 to 9.3)	
Whites	907	24	18	4.4	3.2	1.4 (0.8 to 2.6)	0.71
Non-Whites	929	25	15	4.8	2.9	1.6 (0.9 to 3.1)	
Age≤ 30 yrs	970	28	19	5.0	3.5	1.4 (0.8 to 2.6)	0.81
Age > 30 yrs	866	21	14	4.1	2.6	1.6 (0.8 to 3.1)	
North America	1171	37	29	5.2	4.0	1.3 (0.8 to 2.1)	0.18
Others	665	12	4	3.4	1.1	3.0 (1.0 to 9.4)	
Behavioral risk factors							
UIAS: yes	1097	36	25	5.6	3.9	1.4 (0.9 to 2.4)	0.75
UIAS: no	739	13	8	3.1	1.8	1.7 (0.7 to 4.1)	
URAS: yes	916	37	25	7.2	4.7	1.5 (0.9 to 2.5)	0.99
URAS: no	920	12	8	2.2	1.5	1.5 (0.6 to 3.7)	
Any drug use: yes	792	29	19	6.2	4.3	1.5 (0.8 to 2.6)	0.96
Any drug use: no	1044	20	14	3.3	2.2	1.5 (0.8 to 3.0)	

RESEARCH ARTICLE

Continued Follow-Up of Phambili Phase 2b Randomized HIV-1 Vaccine Trial Participants Supports Increased HIV-1 Acquisition among Vaccinated Men

Zoe Moodie[1]*, Barbara Metch[1], Linda-Gail Bekker[2], Gavin Churchyard[3,4,5], Maphoshane Nchabeleng[6], Koleka Mlisana[8], Fatima Laher[9], Surita Roux[2], Kathryn Mngadi[7,8], Craig Innes[10], Matsontso Mathebula[6], Mary Allen[11], Carter Bentley[1], Peter B. Gilbert[1], Michael Robertson[12], James Kublin[1], Lawrence Corey[1], Glenda E. Gray[9,13]

Phambili trial follow-up
Merck Ad5 HIV-1 vaccine

465 enrolled for continued follow-up with 230 from vaccine and 235 from placebo groups

Estimated HR was 1.52 (95% CI 1.08–2.15, p = 0.02, 82 vaccine/54 placebo infections)

HR was significant for men (HR = 2.75, 95% CI 1.49, 5.06, p = 0.001)

But not for women (HR = 1.12, 95% CI 0.73, 1.72, p = 0.62)

Moodie, PLoSONE 2015

Table 2. Incident HIV-1 infections detected during Phambili and Phambili + HVTN 503-S follow-up periods.

	Overall	Vaccine				Placebo			
	Person-years	N	# infections	Annualized HIV-1 incidence rate	(95% CI)	N	# infections	Annualized HIV-1 incidence rate	(95% CI)
Phambili follow-up									
All	2269	400	63	5.6%	(4.3, 7.2)	400	37	3.2%	(2.3, 4.5)
Men	1269	222	28	4.4%	(2.9, 6.4)	219	11	1.7%	(0.9, 3.1)
Women	1000	178	35	7.2%	(5.0, 10.0)	181	26	5.1%	(3.3, 7.4)
Phambili + 503-S follow-up									
All	3555	400	82	4.7%	(3.7, 5.8)	400	54	3.0%	(2.3, 3.9)
Men	1998	222	39	3.9%	(2.8, 5.3)	219	14	1.4%	(0.8, 2.3)
Women	1557	178	43	5.6%	(4.1, 7.6)	181	40	5.0%	(3.6, 6.9)
Completed Phambili FU	2968	312	75	5.1%	(4.0, 6.4)	299	50	3.4%	(2.5, 4.4)
Discontinued Phambili FU	586	88	7	2.5%	(1.0, 5.1)	101	4	1.3%	(0.4, 3.4)
Men completed Phambili FU	1605	167	33	4.0%	(2.8, 5.7)	150	14	1.8%	(1.0, 3.0)
Women completed Phambili FU	1363	145	42	6.4%	(4.6, 8.6)	149	36	5.1%	(3.6, 7.1)
Men discontinued Phambili FU	393	55	6	3.4%	(1.2, 7.3)	69	0	0.0%	0.0, 1.7)
Women discontinued Phambili FU	193	33	1	1.0%	(0.0, 5.4)	32	4	4.5%	(1.2,11.4)

Mechanism?

- Explored in immunology studies and animal studies
- Thought to be related to adenovirus immune responses increasing activated target cells in genital mucosa

Use of adenovirus type-5 vectored vaccines: a cautionary tale

We are writing to express concern about the use of a recombinant adenovirus type-5 (Ad5) vector for a COVID-19 phase 1 vaccine study,[1] and subsequent advanced trials. Over a decade ago, we completed the Step and Phambili phase 2b studies that evaluated an Ad5 vectored HIV-1 vaccine administered in three immunisations for efficacy against HIV-1 acquisition.[2,3] Both international studies found an increased risk of HIV-1 acquisition among vaccinated men.[2,4] The Step trial found that men who were Ad5 seropositive and uncircumcised on entry into the trial were at elevated risk of HIV-1 acquisition during the first 18 months of follow-up.[5] The hazard ratios were particularly high among men who were uncircumcised and Ad5 seropositive, and who reported unprotected insertive anal sex with a partner who was HIV-1 seropositive or had unknown serostatus at

immune responses in mitigating the effects of the Ad5 vector on HIV-1 acquisition.[7] The conclusion of this consensus conference warned that non-HIV vaccine trials that used similar vectors in areas of high HIV prevalence could lead to an increased risk of HIV-1 acquisition in the vaccinated population. The increased risk of HIV-1 acquisition appeared to be limited to men; a similar increase in risk was not seen in women in the Phambili trial.[4]

Several follow-up studies suggested the potential mechanism for this increased susceptibility to HIV infection among men. The vaccine was highly immunogenic in the induction of HIV-specific CD4 and CD8 T cells; however, there was no difference in the frequency of T-cell responses after vaccination in men who did and did not later become infected with HIV in the Step Study.[8] These findings suggest that immune responses induced by the HIV-specific vaccine were not the mechanism of increased acquisition. Participants with high frequencies of preimmunisation Ad5-specific T cells were associated with a decreased magnitude of HIV-

of CCR5-positive CD4 T cells could contribute to high rates of sexually transmitted infections, including HIV, in uncircumcised men.[13] On the basis of these findings, we are concerned that use of an Ad5 vector for immunisation against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could similarly increase the risk of HIV-1 acquisition among men who receive the vaccine. Both the HIV and COVID-19 pandemics disproportionately affect vulnerable populations globally. Roll-out of an effective SARS-CoV-2 vaccine globally could be given to populations at risk of HIV infection, which could potentially increase their risk of HIV-1 acquisition. This important safety consideration should be thoroughly evaluated before further development of Ad5 vaccines for SARS-CoV-2, and informed consent documents of these potential risks should reflect the considerable literature on HIV-1 acquisition with Ad5 vectors.

We declare no competing interests.

*Susan P Buchbinder, M Juliana McElrath, Carl Dieffenbach, Lawrence Corey

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How is this issue being addressed?

- Adenovirus 5 vector being used has further genetic deletions (E2b)
  - Less immunogenic
  - Evidence of this = can get vaccine take in Ad5+ individuals and can revaccinate

- Addressed in trial design and informed consent

Summary

- Novel vaccine by incorporating N+S and targeting T-cells could potentially provide immunity against variants, immunity of longer duration and more effectively prevent transmission

- hAd5 vectors previously associated with increased HIV risk in men
  - Vector in this vaccine is further modified to reduce Ad5 immune responses
  - Nonetheless this is addressed is trial design and informed consent

- This is a Phase 1 trial – plan to move rapidly to Phase 2/3 including oral or sublingual boost. Company committed to partnerships in SA.