HIV vaccine strategies: overview and perspective

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INTRODUCTION

A) VACCINE

B) VACCINE HESITANCY

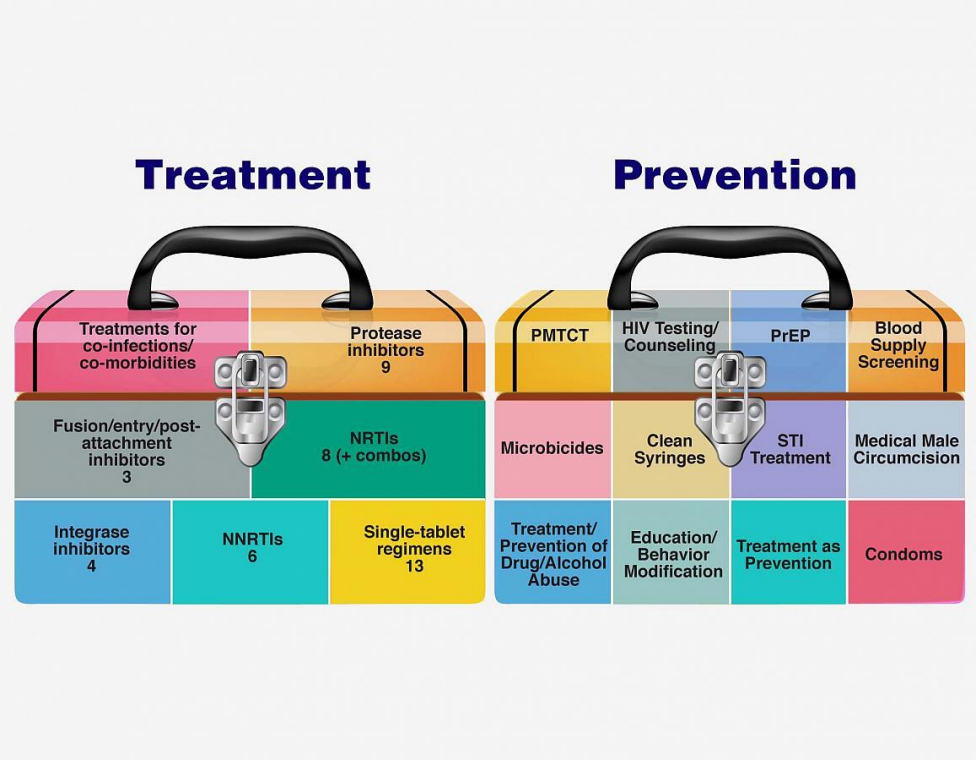
Vaccine = *lat.* VACCINUS, COW

"As we must account for every idle word, so must we account for every idle silence."

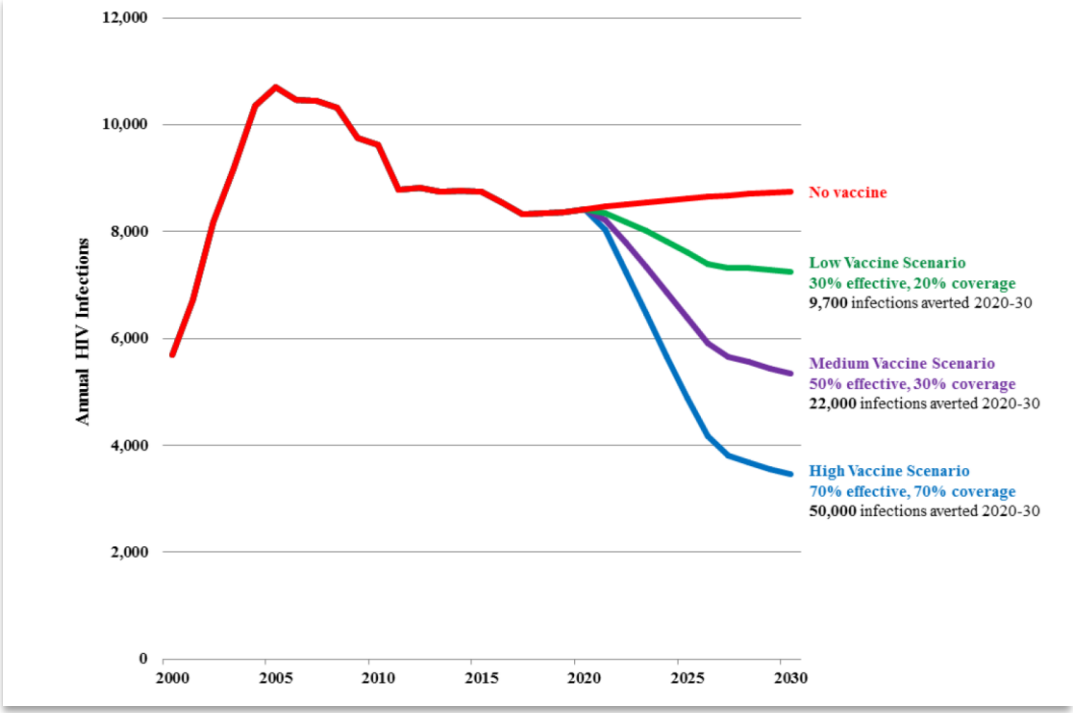
Benjamin Franklin

U.S. Diplomat

ENDING HIV WILL REQUIRE OPTIMIZING TREATMENT AND PREVENTING TOOLS

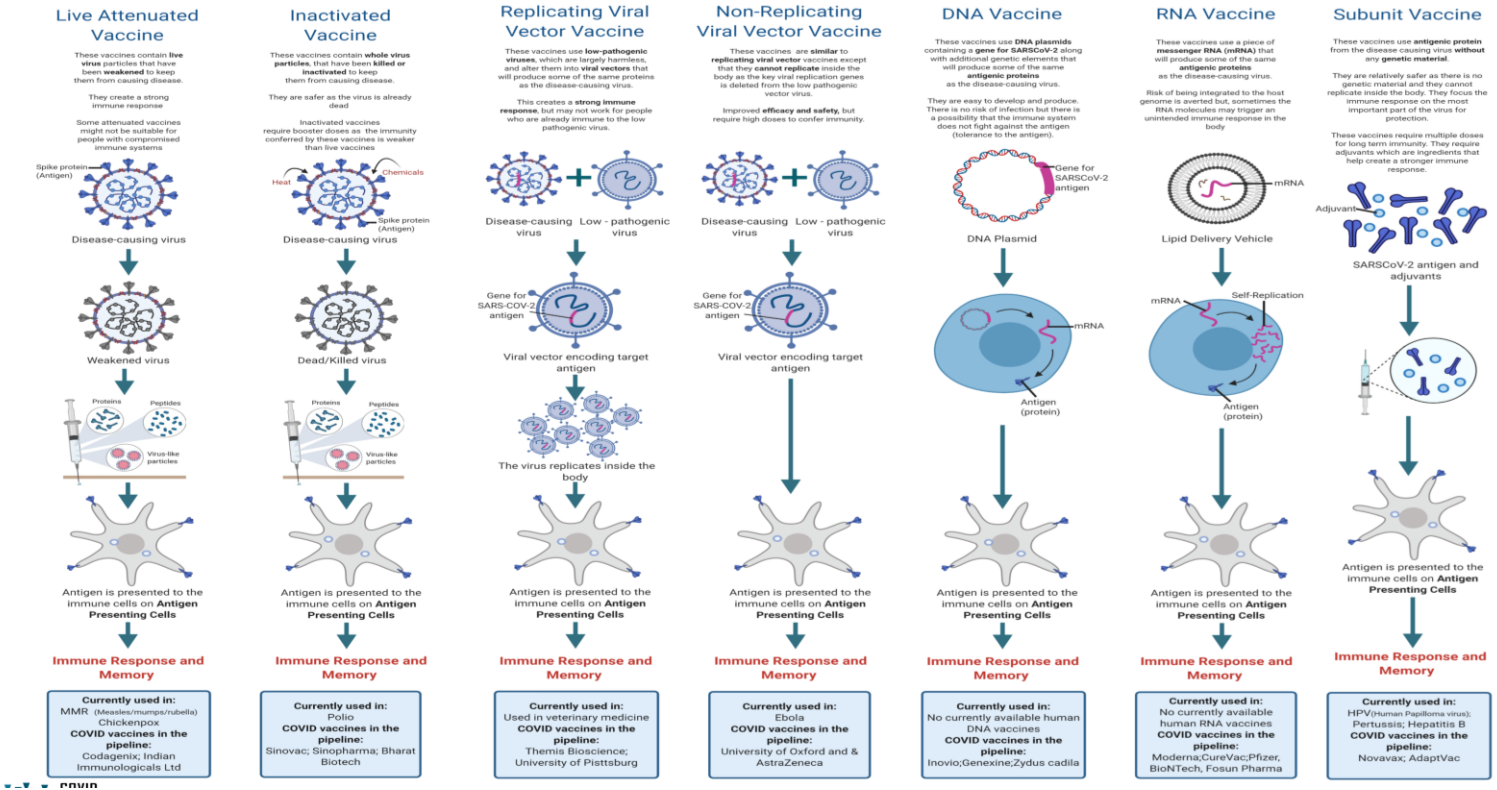


THE POTENTIAL IMPACT OF AN HIV VACINATION

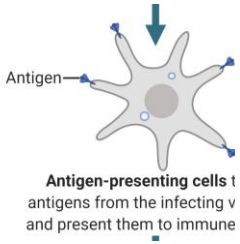


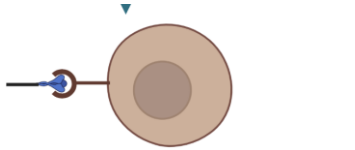
Harmon T, Schwartlander B, Vaccines, 2015

TYPES OF VACCINES

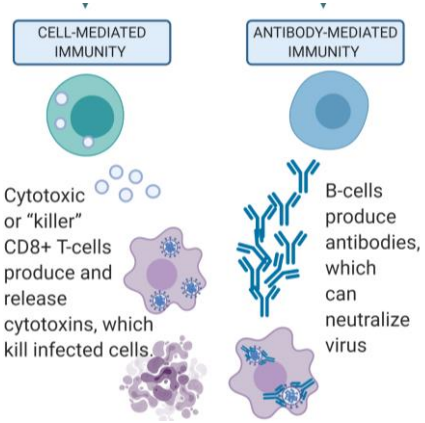


HOW VACCINES WORK?





This teaches “helper” CD4+ T-cells to recognize the antigen



T cell-mediated response: Stimulate branch of immune system (mainly T cells) that recognizes and destroys infected cells

Neutralizing antibody response: Induce antibodies that pathogens, preventing pathogens from infecting the body’s cells

Non-neutralizing antibody response: Induce antibodies that recognize pathogens and recruit other immune cells to help destroy the pathogens or the infected cells

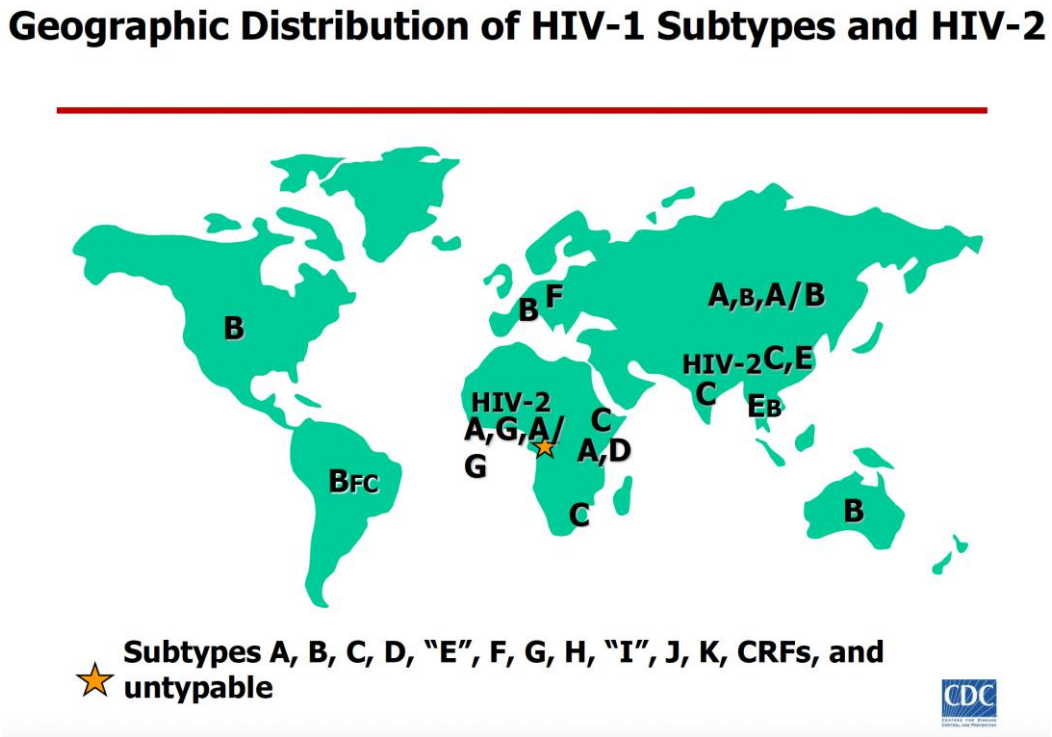
Combination responses: Stimulate multiple parts of the adaptive immune system to recognize and defend the body against pathogens

THE CHALLENGES OF ACHIEVING AN EFFECTIVE HIV VACCINE

- Wide viral genetic diversity and variability, particularly of the HIV envelope glycoprotein Env, a complex trimer with multiple antibody epitopes, which is a key target of neutralizing antibodies (Partly driven by errant reverse transcriptase)
- Immune escape: HIV that can evade immune responses (including neutralizing antibodies)
  - High mutation rates (estimated at 1-10 mutations per genome per replication cycle) and recombination
    - Broad conformational adaptability
    - Widespread glycan shielding of Env
- Dissimilar animal models (eg, nonhuman primate, humanized mouse) used in preclinical studies
- Certain vaccine platforms not viable for HIV because of risk of proviral DNA integration in host genome
- Multiple components of immunity (eg, humoral, cell mediated) that need stimulation in vaccine design rather than a singular approach or methodology
- Cost, feasibility, and investment, and TIME!
- Growing repertoire and availability of effective biomedical HIV prevention approaches that pose challenges for vaccine trial recruitment

1. Ng'uni T et al *Front Immunol*. 2020
2. Laher F. *Arch Virol*. 2020
3. Hannah S *J Int AIDS Soc*. 2022
4. Harris JE. *Health Policy Technol*. 2022
5. Morris L. mRNA vaccines offer hope for HIV. *Nat Med*. 2021

THE CHALLENGES OF ACHIEVING AN EFFECTIVE HIV VACCINE



Vaccine hesitancy

"There's something about human behavior that we're still not really understanding"

Dr. Nicole Lurie

U.S. director of the Coalition for Epidemic Preparedness Innovations

INFODEMICS

The **volume and velocity of information** in a digitalized, interconnected world presents new challenges.

- **Acceleration of mis- and disinformation**
- **Difficulty for individuals to assess truth from falsehoods**
  - Risk-taking health behaviors
  - Mistrust in health authorities
- **Difficulty for the scientific community to stay updated with rapid publication**

Source: Palayew A, Norgaard O, Safreed-Harmon K, Andersen TH, Rasmussen LN, Lazarus JV. Pandemic publishing poses a new COVID-19 challenge. Nat Hum Behav. 2020 Jul;4(7):666-669. doi: 10.1038/s41562-020-0911-0. PMID: 32576981.

THE ERAS HIV VACCINE TOUR

A) 40 YEARS OF AIDS VACCINE RESEARCH

B) PROTEIN BASED HIV VACCINES

C) ADENOVIRUS BASED HIV VACCINES

D) ALVAC BASED HIV VACCINES

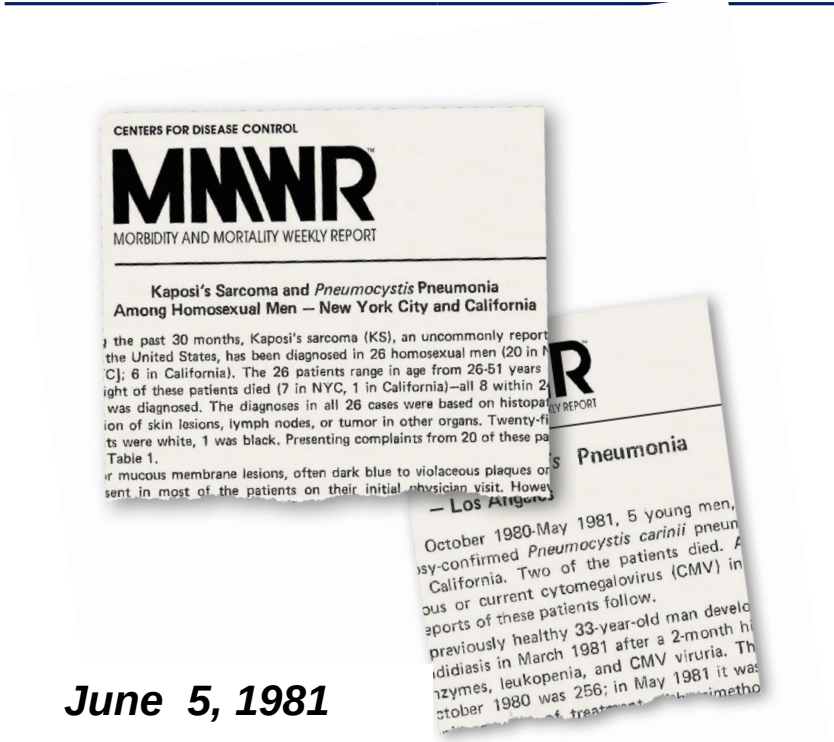
40 years of of AIDS vaccine research

"Believe and work hard, and all your dreams will come true."

Lady Gaga

American singer-songwriter and actress

40 YEARS OF AIDS VACCINE RESEARCH


CENTERS FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men -- New York City and California

the past 30 months, Kaposi's sarcoma (KS), an uncommonly report
the United States, has been diagnosed in 26 homosexual men (20 in N
C]; 6 in California). The 26 patients range in age from 26-51 years
ight of these patients died (7 in NYC, 1 in California)--all 8 within 2
was diagnosed. The diagnoses in all 26 cases were based on histopat
ion of skin lesions, lymph nodes, or tumor in other organs. Twenty-fi
ts were white, 1 was black. Presenting complaints from 20 of these pa
Table 1.
r mucous membrane lesions, often dark blue to violaceous plaques or
sent in most of the patients on their initial physician visit. Howev

R

Pneumonia

October 1980-May 1981, 5 young men,
sy-confirmed *Pneumocystis carinii* pneun
California. Two of the patients died. A
ous or current cytomegalovirus (CMV) in
eports of these patients follow.
previously healthy 33-year-old man develo
idiasis in March 1981 after a 2-month h
nzymes, leukopenia, and CMV viruria. Th
ctober 1980 was 256; in May 1981 it was

June 5, 1981

There have been more than 250 HIV vaccine trials, most of them early-stage, looking at whether the vaccine is safe and whether we mount an immune response following vaccination. There have been very few vaccine trials—10 or so—that have advanced to the point of looking at efficacy.

40 YEARS OF AIDS VACCINE RESEARCH

The New York Times

GORBACHEV URGES REAGAN TO FOCUS ON ARMS CONTROL

Deaver Inquiry Suggests Others Were Involved

ADVICE REAGAN GOT WAS INADEQUATE, CHIEF ADVISER SAYS

AIDS IMMUNIZATION TESTED ON HUMANS

Reagan Asks Senate Panel to Give Limited Immunity to 2 Ex-Aides

Florida Moving to Preserve Vast Area Along Gulf Coast

Cuomo and Key Legislators Agree On Subsidizing Drugs for Elderly

Rival Observances in a Divided South Africa

December 17, 1986

The Washington Post

March 18, 1987

French Doctor Testing AIDS Vaccine On Self

A French researcher has injected himself and several other volunteers with a potential AIDS vaccine, the first time such a test has been carried out on humans, according to a letter to be published today in the British scientific journal Nature. In the experiment, which other researchers have called "daring" and "exciting work," the French doctor, Daniel Zagury of the Pierre and Marie Curie University in Paris, reported feeling no ill effects from the injection. More importantly, he reported that his body raised immune defenses against two widely differing strains of the AIDS virus. This may be

March 18, 1987

Protein-based HIV vaccines

PROTEIN STRATEGY TO INDUCE ANTIBODIES RESPONSES

	VAX004 Study	VAX003 Study
HIV transmission	Sexual	Blood borne
Volunteers	5,400 5,100 MSM (men who have sex with men) and 300 women	2,500 2,500 men and women IDUs (IV drug users)
Location	North America and the Netherlands	Thailand
Expected annual infection rate	1.5%	4.0%
Expected retention rate	80%	
Duration of follow-up	36 months	
Follow-up after infection	24 months	
Clinical trial sites	61	17
Start date	June 1998	March 1999
Fully enrolled	October 1999	August 2000
Analysis completed	Q1 2003	Q4 2003

	VAX004 Study	VAX003 Study
Vaccine	AIDSVAX® B/B′	AIDSVAX® B/E
Vaccine design	Bivalent rgp120 with alum	
Vaccine antigens	MNrgp120/HIV-1 plus GNE8 rgp120/HIV-1 (subtype B and B′)	MNrgp120/HIV-1 plus A244 rgp120/HIV-1 (subtype B and E)
rgp120 dose	300 µg (MN)/ 300 µg (GNE8)	300 µg (MN)/ 300 µg (A244)
Placebo	alum	
Randomization: Vaccine to Placebo	2:1	1 :1
Vaccine administration	Intramuscular (deltoid)	

Adenovirus-based vaccines

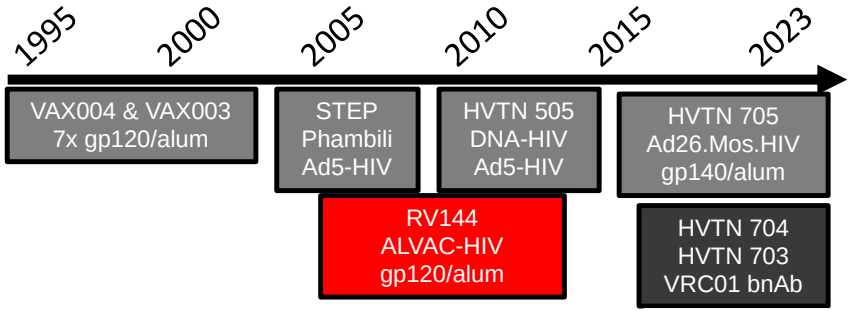
ADENOVIRUS STRATEGY TO INDUCE T-CELLS RESPONSES

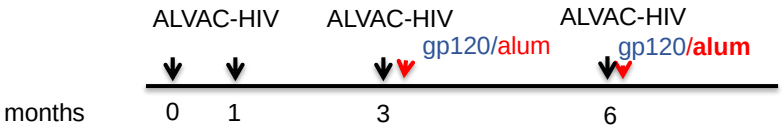
Trial Name	Phase	Design and Participants	Vaccine Platform	Outcome and Key Findings	NUMBER OF PARTICIPANTS
HVTN 502 (STEP)	Phase 2	Adenovirus serotype 5 (rAd) vectored vaccine, tested on MSM and sex workers in the Americas and Australia	Merck rAd5-gag/pol/nef	Induced strong HIV-specific CD8+ T cells but did not prevent HIV infection or reduce viral replication. Elevated risk of HIV acquisition noted, especially in uncircumcised men with pre-existing Ad5 immunity. Trial halted due to safety concerns.	3000 North America, the Caribbean, South America and Australia
HVTN 503 (Phambili)	Phase 2b	Used the same Merck Ad5 platform as STEP, in South Africa	Merck Ad5	Initially halted and unblinded during enrollment; follow-up showed no increased risk of HIV infection overall, but suggested a higher risk among vaccinated men in extended follow-up.	801, South Africa
HVTN 505	Phase 2b	DNA prime/rAd5 boost vaccine targeting Gag, Pol, Nef, and **Env**, involving 2504 high-risk participants including men and transgender females engaged in sex with men	DNA/rAd5 - Gag, Pol, Nef, and **Env**	Halted prematurely due to lack of efficacy; showed no decrease in HIV-1 acquisition or viral load set point. Inverse correlations between DNA/rAd5 vaccine-induced CD8+ T-cell responses to Env protein and HIV-1 infection risk.	2504, United States
HVTN 705 (IMBOKODO)	Phase 2b	Tested the Ad26.Mos4.HIV vector and aluminum-phosphate adjuvanted Clade C gp140 on young women in sub-Saharan Africa	Ad26.Mos4.HIV	Did not prevent HIV infection; vaccine efficacy was 25%. Trial demonstrated safety but lacked efficacy in preventing HIV.	2600, sub-Saharan Africa
HVTN 706 (MOSAICO)	Phase 3	Ad26.Mos4.HIV administered in four vaccinations over one year, targeting MSM and transgender people across various regions	Ad26.Mos4.HIV and Clade C/Mosaic gp140	Ineffective and discontinued in January 2023.	3900, Europe, North America and South America

ALVAC-based vaccines

"If you haven't found it yet, keep looking."
Steve Jobs
Businessman, inventor, and investor

THE RV144 TRIAL

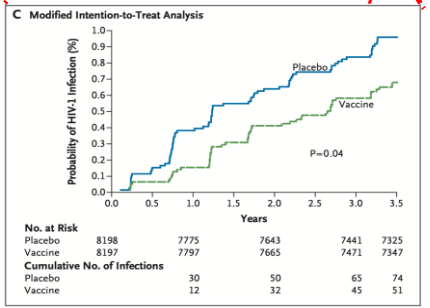




ALVAC (Avian Poxvirus)
Gag /pro / gp120-TM/
Clade AE/B

120 & alum
(bivalent)
Clades B,AE

31.2% vaccine efficacy



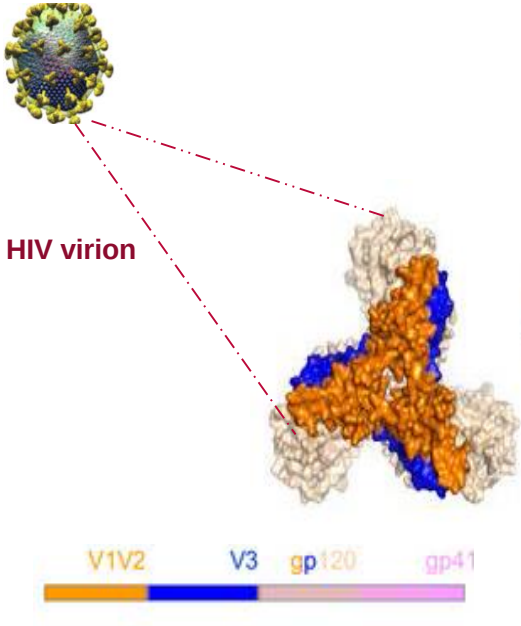
Rerks-Ngarm et al. 2009.

- 16,402 participants
- ALVAC canarypox vector
- Bivalent gp120 in alum
- 0.4% incidence in women

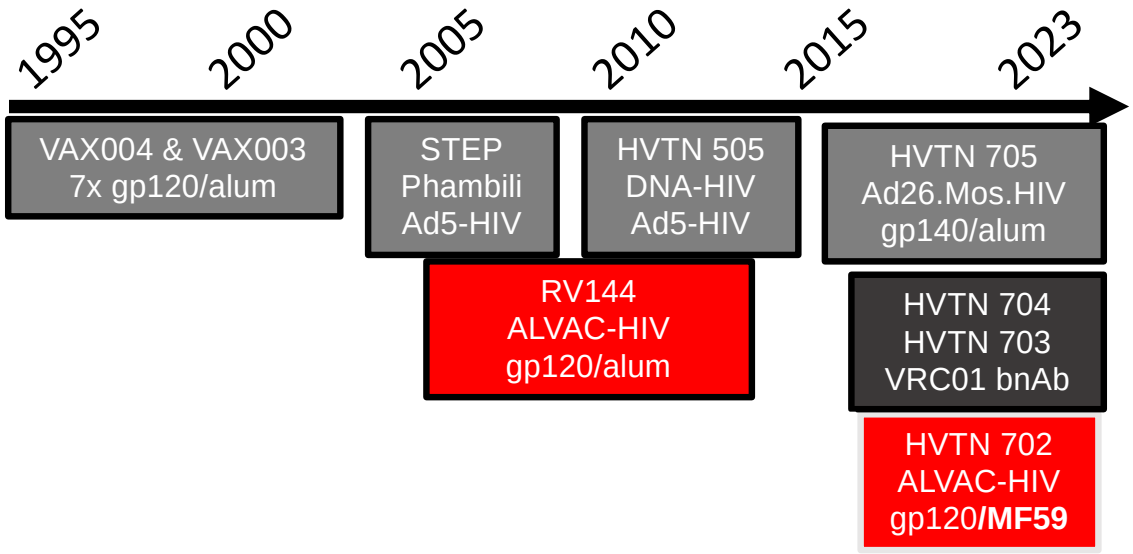
Flynn et al. *J Infect Dis.* 2005.
Pitisuttithum et al. *J Infect Dis.* 2006.
Buchbinder et al. *Lancet.* 2008.
Hammer et al. *NEJM.* 2013.
Gray et al. *NEJM.* 2021.
Corey et al. *NEJM.* 2021.
Rerks-Ngarm et al. *NEJM.* 2009.

RV144 immune correlates of reduced risk

- Binding, non-neutralizing anti-V1/V2 IgG
- ADCC in vaccinees with low Env IgA
- Polyfunctional V2-specific T-cells
  - V2 contains binding sites for $\alpha_4\beta7$ (*Artos J. Nature Immunology 2008*)
  - V2 differ in its conformation (*Kwon et al., Nat. Struct. Mol. Biol., 2015*)
  - The helical conformation of V2 co-stimulates T –cells (*Goes et al. PNAS , 2020*)



THE HVTN702 TRIAL: IS THAT THE PERFECT RV144 FOLLOW UP STUDY?



FRANCHINI'S LAB VISION

A) THE IMPORTANCE OF A GOOD SIVmac251 MODEL

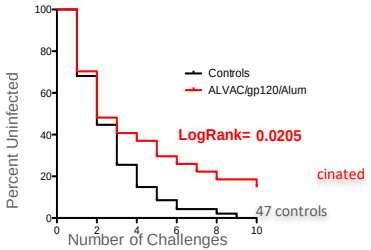
B) ADCC as A NEW CORRELATE OF PROTECTION

C) BREAKING THE DOGMA: EFFEROCYTOSIS

D) V1 DELETED IMMUNOGENS AND THE FIRST IN HUMAN NCI HIV VACCINE HUMAN TRIAL

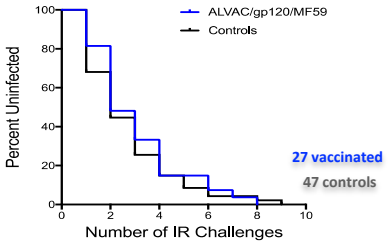
OUR SIVmac251 MODEL PREDICTED ALL HUMAN TRIALS

- Recapitulated results of RV144



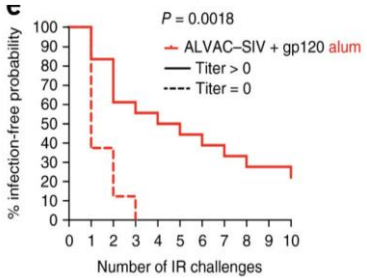
Decreased risk of SIV_{mac251}

- Predicted futility of HVTN-702



No decreased risk of SIV_{mac251}

- Confirmed Abs to V2 correlate

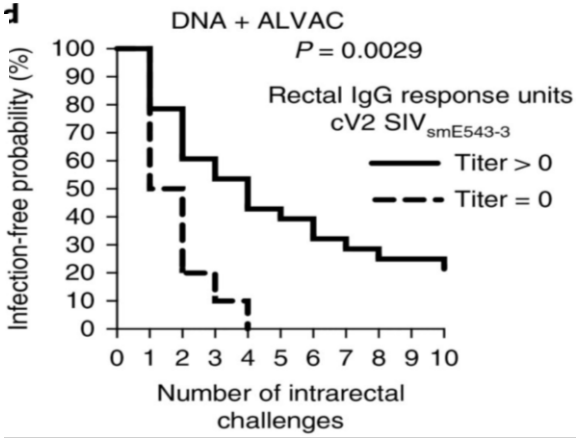


mucosal Abs to V2

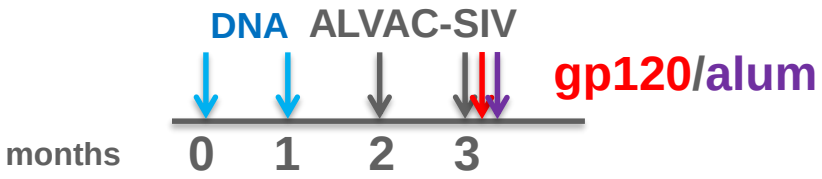
*Vaccari et al. *Nat. Med, 2016*

OUR SIVmac251 MODEL CAN ADD VALUE TO HIV VACCINE DESIGN

- Compared priming (DNA/ALVAC/Ad26)
- Compared viral vectors (NYVAC/ALVAC)
- Compared Adjuvants (alum/MF59)
- Compared genetically modified gp120s



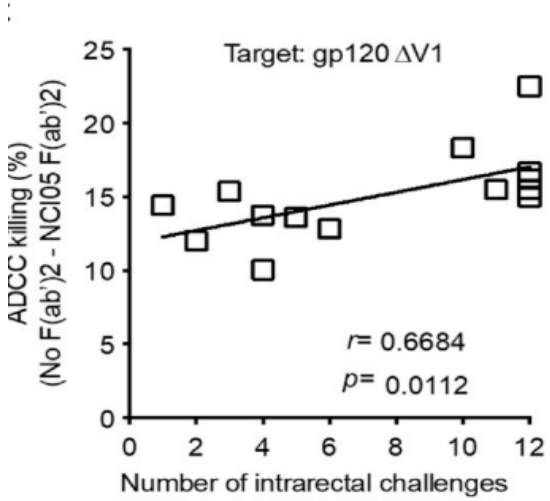
- **Streamlined regimen with DNA/ALVAC/gp120/alum**



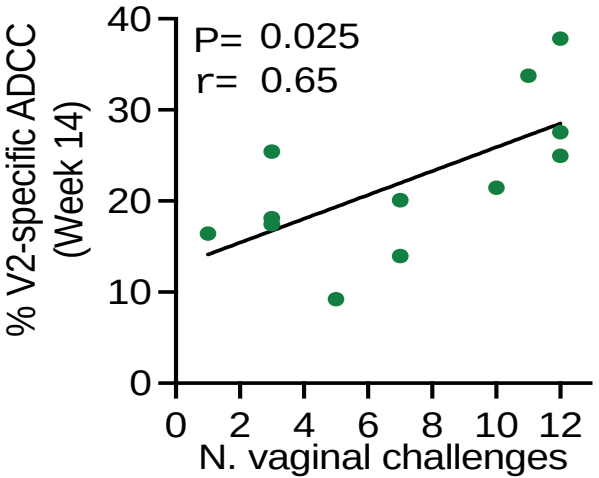
Pegu et al. *J.Virol, 2014*
Fouts et al. *PNAS, 2015*
Gordon et al. *J.Immunol, 2016*
Vaccari et al. *Nature Med., 2016*
Vaccari et al. *Nature Med., 2018*
Vaccari et al. *Frontiers in Immunology 2019*
Schifanella et al. *Plos Pathogens 2019*
Gorini et a .*Plos Pathogens 2021*
Silva de Castro et al. *J.Virol ,2020*

ADCC mediated by V2 antibodies correlates with reduced risk of SIVmac251 infection

Males



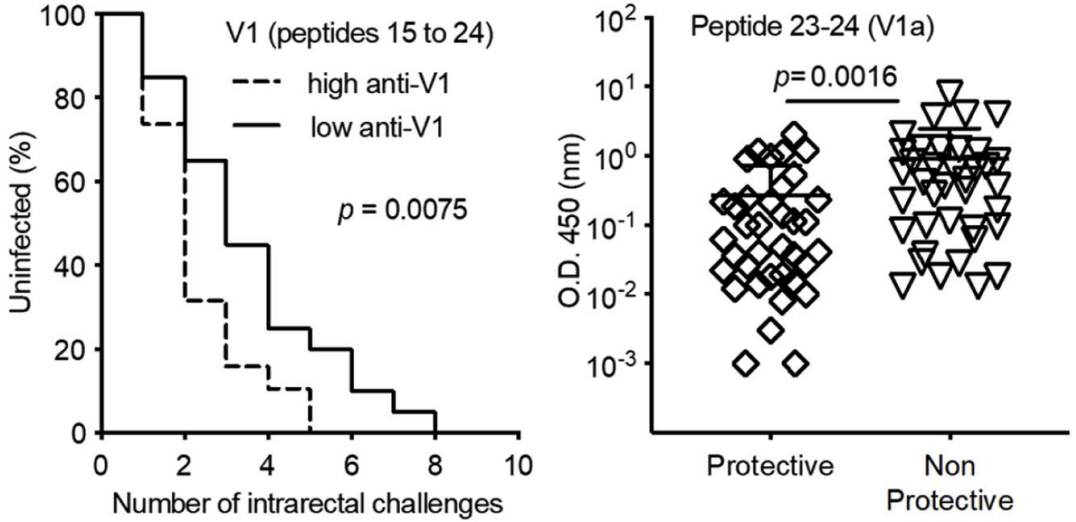
Females



Bissa M. et al *Nat Communication 2023*;
Stamos et al. *J.Virol ,2023*

THE V1 ANTIBODY RESPONSES ARE ASSOCIATED WITH INCREASED RISK

Vaccinated animals with higher Abs to V1 acquire SIV_{mac251} early

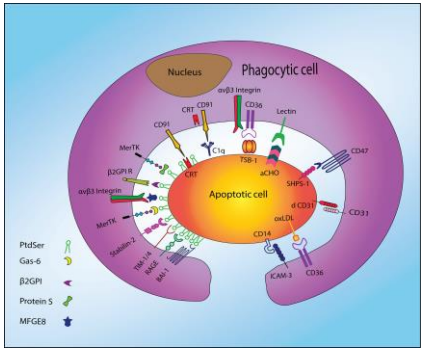


Silva de Castro et al. iScience, 2021

CD14+ cells efferocytosis

(latin: bring to the grave): **ability of CD14+ cells to engulf and destroy apoptotic cells**

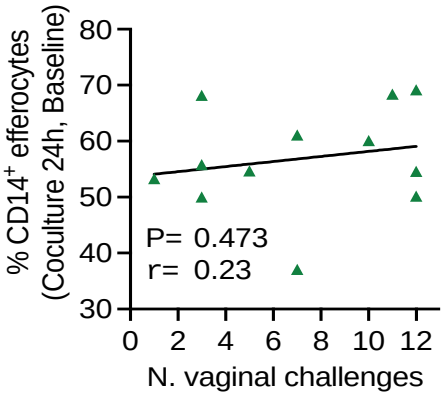
Efferocytes are induced by IL-10



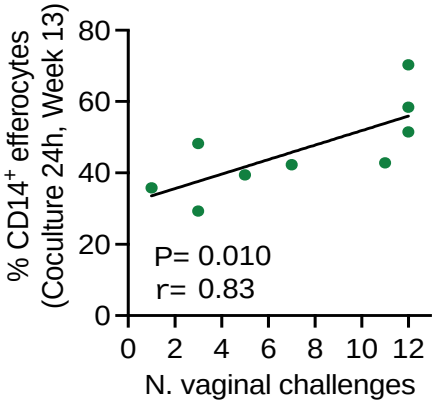
Every day, approximately 0.4% of the estimated 37.2 trillion cells in an adult human die . However, even in tissues where cell turnover is high, apoptotic cells (ACs) are scarce, indicating very high efficiency of and capacity for AC clearance.

Defective efferocytosis= inflammation

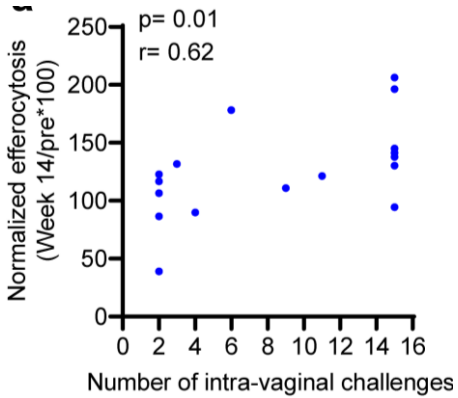
Pre-vaccination



Post-vaccination

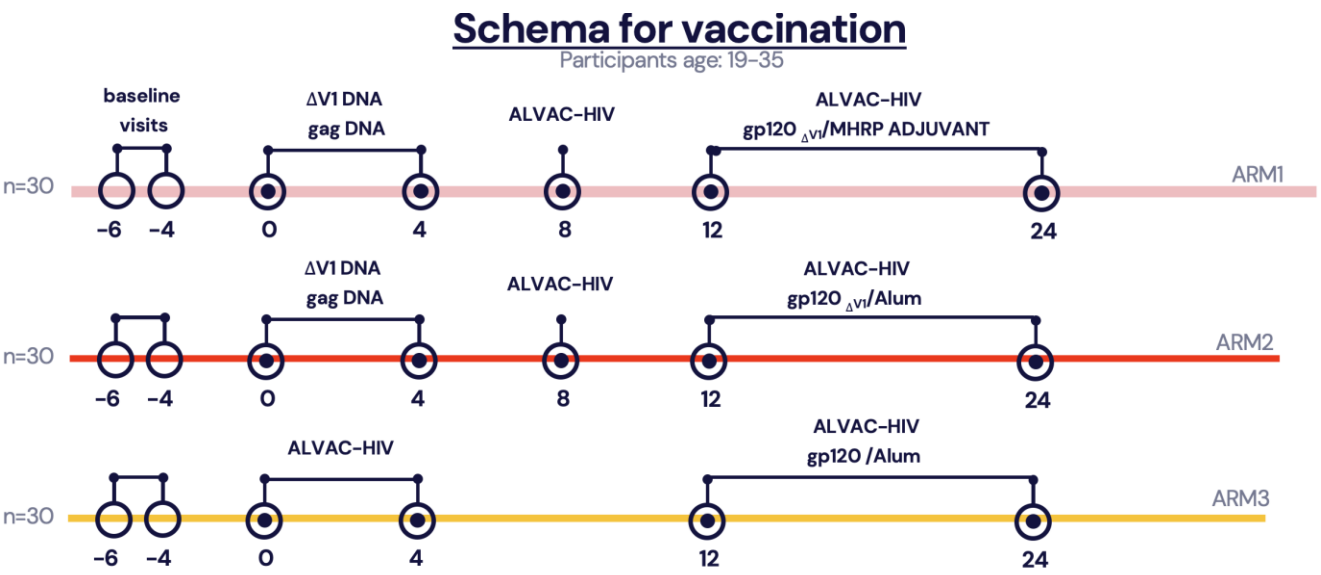


Post-vaccination



Bissa M. et al *Nat Communication 2023*;

Combined Long-term Efferocytosis and ADCC Responses (CLEAR) Phase-I HIV vaccine trial



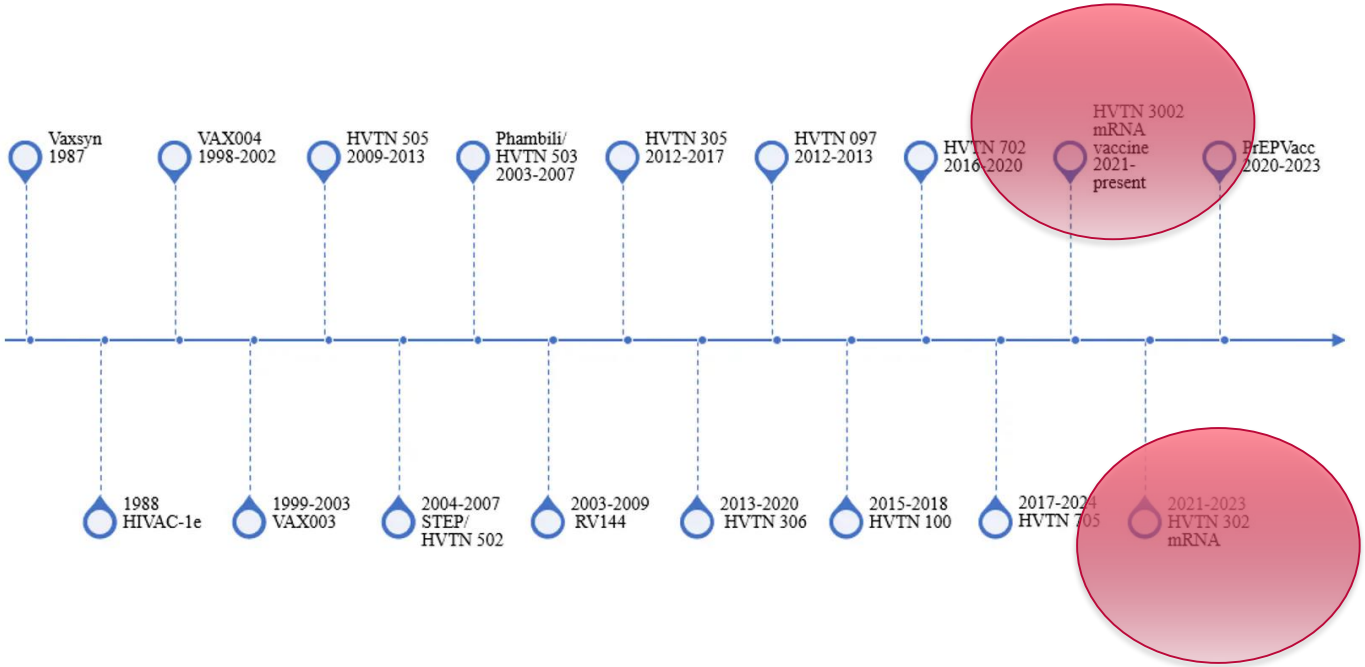
PRINCIPAL INVESTIGATORS

Genoveffa Franchini,
Frank Maldarelli, Julie Ake,
Merlin Robb, Mangala Rao
NCI, MHRP, WRAIR

ΔV1 gp160 HIV_{AE} DNA & p55Gag HIV_B DNA	ALVAC-HIV + diluent	ΔV1 $gp120_{AE}$	alum	MHRP ADJUVANT	$gp120_{AE}$
(NCI)	(Sanofi)	(NCI)	NIAID	WRAIR	NIAID/Duke

HIV mRNA VACCINES?

FIGURE. Timeline of Key HIV Vaccine Trials[1]



Adapted from Ng'uni T, Chasara C, Ndhlovu ZM. Front Immunol. 2020;11:590780. doi:10.3389/fimmu.2020.590780.

A PHASE I mRNA VACCINE TRIAL

The HVTN 302 study will examine whether the following three experimental HIV mRNA vaccines are safe and can induce an immune response: 1) BG505 MD39.3 mRNA, 2) BG505 MD39.3 gp151 mRNA, and 3) BG505 MD39.3 gp151 CD4KO mRNA

Start Date February 11, 2022
End Date October 13, 2023
Enrollment:108
Age range:18 Years ↔ 55 Years
Population: Cisgender Individuals

Alabama Vaccine CRS
UCLA Vine Street Clinic
Beth Israel Deaconess Medical Center, ACTG CRS
Brigham and Women's Hospital CRS
New York Blood Center
Columbia P&S CRS
University of Rochester HVTN CRS
Penn Prevention CRS
Pittsburg Clinical Research Site
Seattle Vaccine and Prevention CRS

CONCLUSION

HIV VACCINE: WHEN?

Development of Licensed Vaccines

Vaccine	Discovery of etiologic agent	Vaccine developed or licensed in U.S.	Years elapsed
Typhoid	1884	1896	12 years
Pertussis	1906	1926	20 years
Polio	1908	1955	47 years
Measles	1953	1983	30 years
Hepatitis B	1965	1981	16 years
Rotavirus	1970	1998	28 years
Hepatitis A	1973	1995	22 years
Lyme Disease	1982	1998	16 years
HIV	1983	???	> 20 years

From Susan Buchbinder and Johathan Fuchs, S.F. Dept of Health

Vaccine Advocacy

- HIV Vaccine Research: Building on Lessons from COVID

1. Sufficient and diversified research funding
2. Enhanced global coordination and collaboration
3. Support for research innovation and novel trial designs
4. Strengthened political commitment and urgency
5. Placing communities at the center of vaccine research
6. Planning early for success and equitable access

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