Current Approaches to HIV Vaccine Development – Do We Get a Boost?

Vaccines and Vaccination During and Post Covid Pandemics "Vac&Vac 2022"
December 7-9, 2022, Riga, Latvia

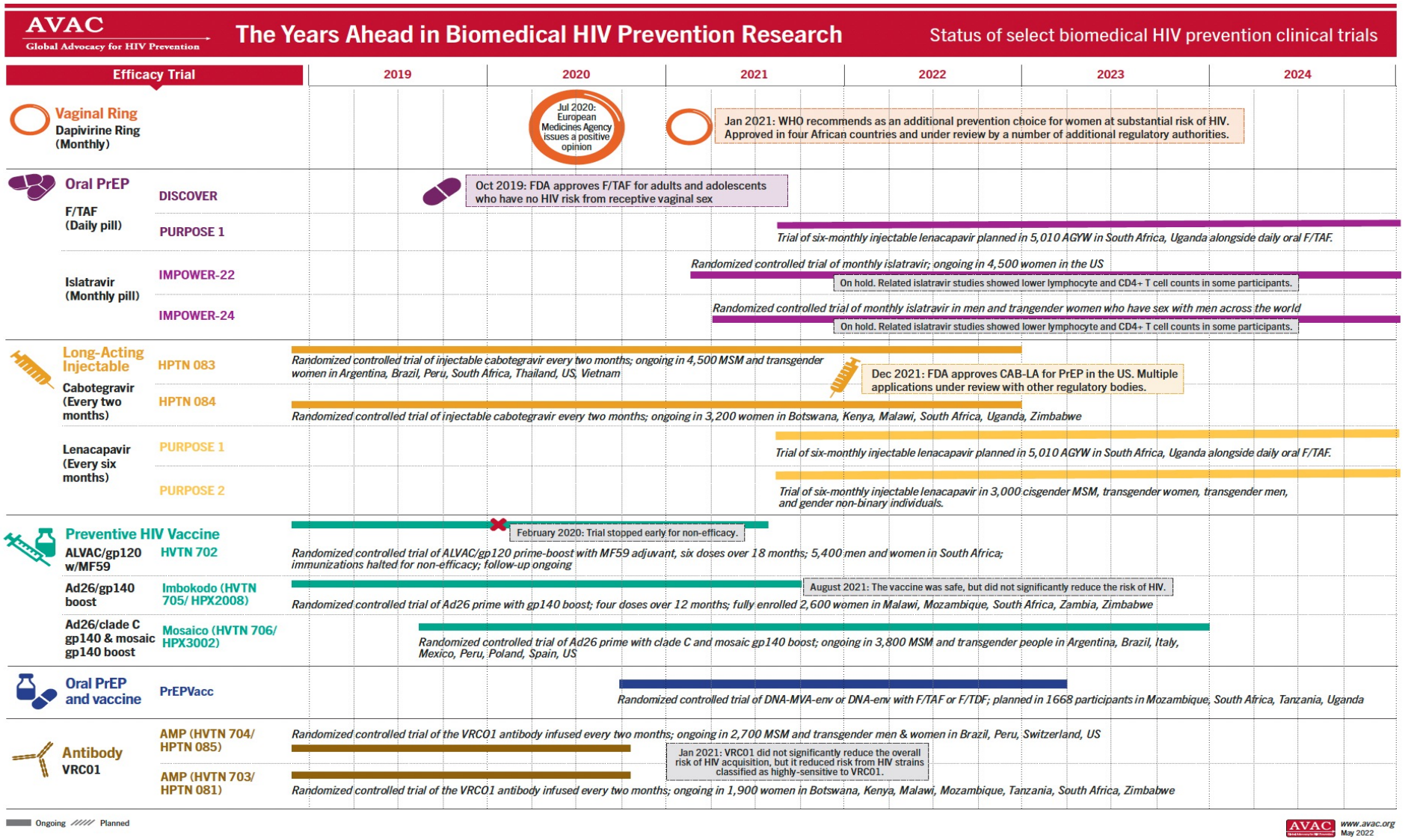
Jean-Louis Excler, MD
Program Director, New Initiatives

ACCELERATING VACCINES FOR GLOBAL HEALTH

SINCE 1997

International Vaccine Institute

Biomedical HIV Prevention Research Landscape (AVAC, May 2022)

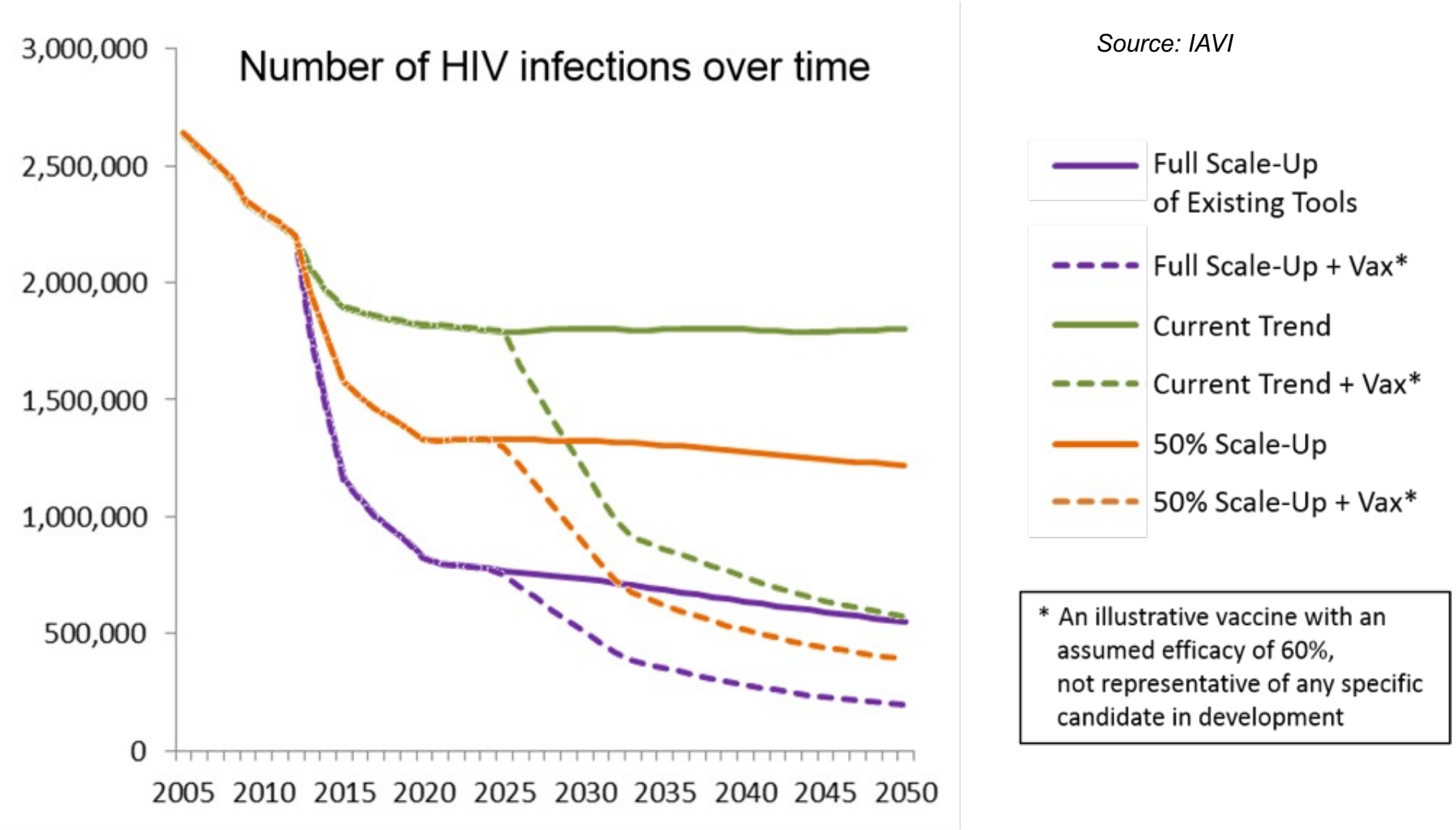


HIV Vaccine Challenges

- HIV-1 Genetic Diversity
- Conserved epitopes hard to reach
- Envelope with dense and poorly immunogenic glycan shield
- Integration of the virus into the host genome
- No natural recovery from infection
- Broadly neutralizing antibodies slowly and rarely develop
- No HIV animal models
- Trial execution challenges due to evolving prevention landscape
- Cost and length of efficacy trials

A. S. Fauci, An HIV vaccine is essential for ending the HIV/AIDS pandemic. JAMA 318, 1535–1536 (2017). doi: 10.1001/jama.2017.13505; pmid: 29052689

Potential for HIV Vaccine Impact



Source: IAVI

* An illustrative vaccine with an assumed efficacy of 60%, not representative of any specific candidate in development

The First Four HIV Vaccine Efficacy Trials

AIDS Vaccine Fails in Trials

Clinical trials suspended after dismal results for most promising vaccine

Jane Yager, Newser Staff
Sep 22, 2007 8:25 AM CDT

(Newser) – Heavy hopes riding on an HIV vaccine were dashed as the vaccine proved so ineffective in a clinical trial that manufacturer Merck has ended the trial early. The vaccine had shown promise in animal and small-scale human tests but neither prevented nor reduced the severity of infection in a large-scale trial, the *New York Times* reports.

Failed to show efficacy

VAX003 – Thailand

VAX004 – Americas

STEP – Americas

Phambili – South Africa
(halted early)

RV144: The Thai Efficacy Trial

- US Army collaboration with Thai MoPH
- Only HIV vaccine candidate to show modest effectiveness in preventing HIV in humans.
- A preventive vaccine IS possible
- Immune correlates identified (including IgG V1V2)
- Importance of non-neutralizing antibody functions

MOPH-TAVEG

GS ID GLOBAL SOLUTIONS FOR INFECTIOUS DISEASES

sanofi pasteur
The vaccines division of sanofi-aventis Group

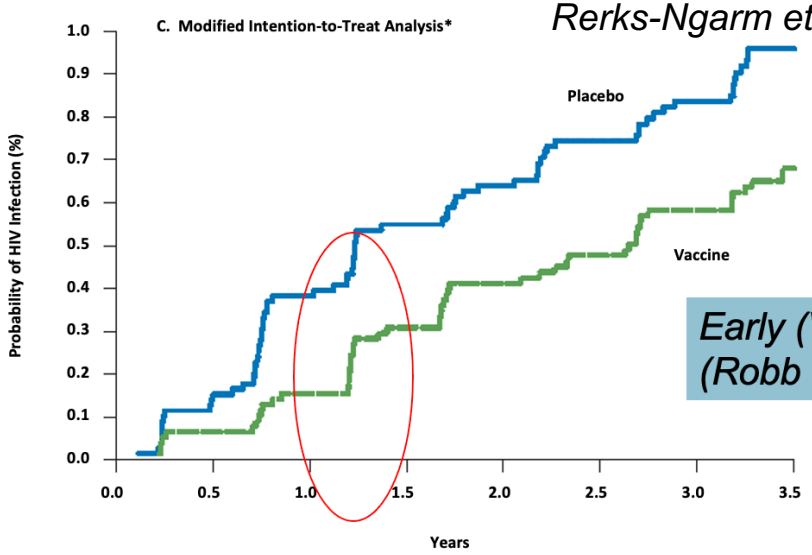
NIAID

MHRP
U.S. MILITARY HIV RESEARCH PROGRAM

AFRIMS
Research Excellence

WRAIR
Walter Reed Army Institute of Research
Soldier Health • World Health

RV144 Demonstrated Efficacy



Rerks-Ngarm et al. NEJM 2009

Early (VE = 60%) effect wanes (Robb et al, Lancet ID 2012)

Based on these promising results, the RV144 regimen was retooled with subtype C products and a new adjuvant for the HVTN 702 HIV vaccine efficacy trial enrolling very high risk populations in RSA

It took almost a decade after the RV144 results to initiate another efficacy trial with a similar prime-boost strategy.

Excler JL, Kim JH. ERV 2019. https://doi.org/10.1080/14760584.2019.1640117

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2012 VOL. 366 NO. 14

Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

Barton F. Haynes, M.D., Peter B. Gilbert, Ph.D., M. Juliana McElrath, M.D., Ph.D., Susan Zolla-Pazner, Ph.D., Georgia D. Tomaras, Ph.D., S. Munir Alam, Ph.D., David T. Evans, Ph.D., David C. Montefiori, Ph.D., Chitraporn Karnasuta, Ph.D., Ruengpueng Sutthent, M.D., Ph.D., Hua-Xin Liao, M.D., Ph.D., Anthony L. DeVico, Ph.D., George K. Lewis, Ph.D., Constance Williams, B.S., Abraham Pinter, Ph.D., Youyi Fong, Ph.D., Holly Janes, Ph.D., Allan DeCamp, M.S., Yunda Huang, Ph.D., Mangala Rao, Ph.D., Erik Billings, Ph.D., Nicos Karasavvas, Ph.D., Merlin L. Robb, M.D., Viseth Ngauy, M.D., Mark S. de Souza, Ph.D., Robert Paris, M.D., Guido Ferrari, M.D., Robert T. Bailer, Ph.D., Kelly A. Soderberg, Ph.D., Charla Andrews, Sc.M., Phillip W. Berman, Ph.D., Nicole Frahm, Ph.D., Stephen C. De Rosa, M.D., Michael D. Alpert, Ph.D., Nicole L. Yates, Ph.D., Xiaoying Shen, Ph.D., Richard A. Koup, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Jaranit Kaewkungwal, Ph.D., Sorachai Nitayaphan, M.D., Ph.D., Supachai Rerks-Ngarm, M.D., Nelson L. Michael, M.D., Ph.D., and Jerome H. Kim, M.D.

- **IgG antibodies against the V1V2 region of the HIV-1 envelope protein associated with reduced infection**
- **Non-neutralizing antibodies mediate ADCC activity**
- **IgA antibodies correlated with increased infection**

Kim, Excler, Michael.
Annu Rev Med 2015.
https://doi.org/10.1146/annurev-med-052912-123749

Sieve analysis: Genetic signatures of RV144 vaccination in V2 complement the finding of an association between high V1/V2 binding antibodies and reduced risk of HIV-1 acquisition and provide evidence that vaccine-induced V2 responses plausibly played a role in the partial protection conferred by the RV144 regimen.

Rolland M, et a;. Nature 2012
https://doi.org/10.1038/nature11519

HVTN 702 Showed No Efficacy

Combo of two HIV vaccines fails its big test

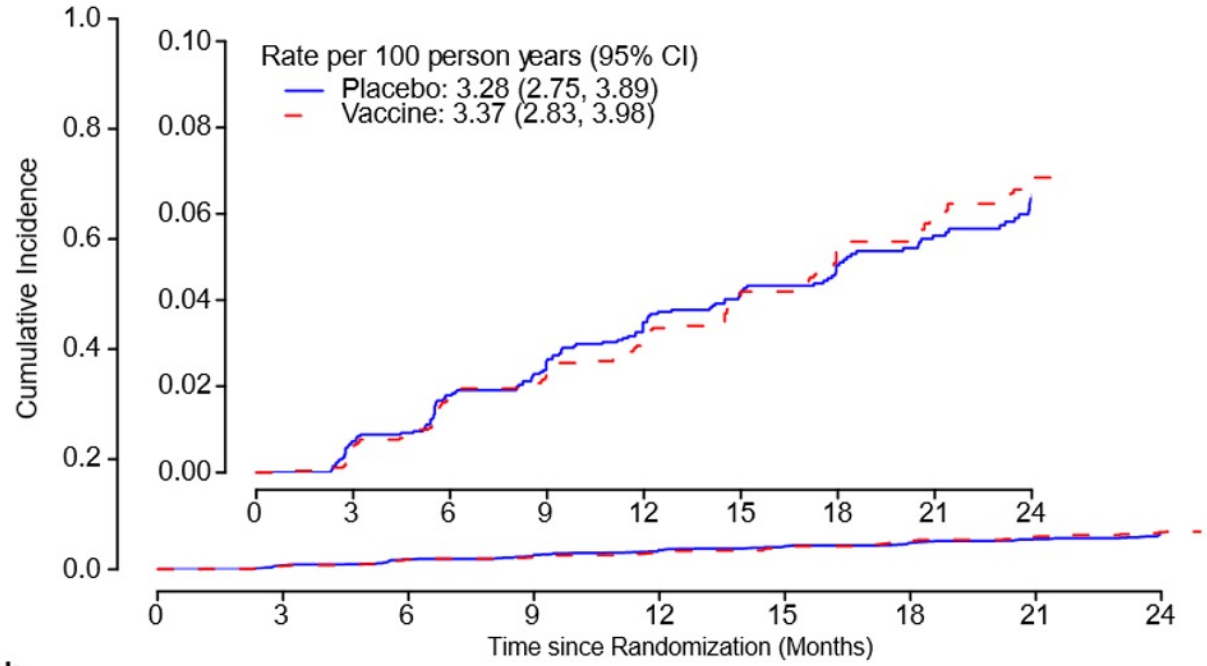
Jon Cohen
– Hide authors and affiliations

Science 07 Feb 2020:
Vol. 367, Issue 6478, pp. 611-612
DOI: 10.1126/science.367.6478.611

- Operational success
- High incidence – “force of infection”
- Underscored need for effective biomedical interventions for at risk women in RSA

MITT Cohort 0-24 Months

Gray et al, NEJM, 2021



No. at Risk									
Placebo	2689	2577	2421	2240	2040	1817	1494	1219	964
Vaccine	2695	2588	2443	2274	2088	1830	1515	1227	944
Cumulative Events									
Placebo	0	19	46	65	85	99	110	120	130
Vaccine	0	16	46	60	80	99	117	127	137

Janssen Ad26 Mosaic HIV Vaccine Efficacy Trials - failed

HVTN 705

2,600 female participants

Month 0	Month 3	Month 6	Month 12
Ad26Mos4	Ad26Mos4	Ad26Mos4	Ad26Mos4
		Clade C gp140 + aluminum phosphate	Clade C gp140 + aluminum phosphate

Enrollment and Vaccinations complete

Aug 2021: JnJ announced the study will not continue to due to lack of efficacy at 24 months

MOSAICO

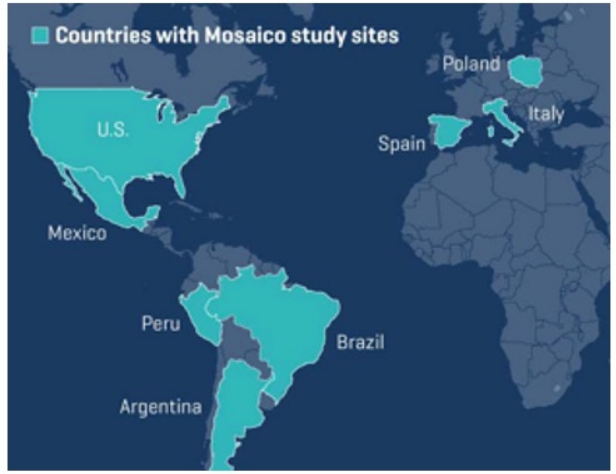
HPX3002/HVTN 706

Janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

3,800 MSM/TGW participants

Month 0	Month 3	Month 6	Month 12
Ad26Mos4	Ad26Mos4	Ad26Mos4	Ad26Mos4
		Clade C gp140 + Mosaic gp140 + aluminum phosphate	Clade C gp140 + Mosaic gp140 + aluminum phosphate



Enrollment complete

ICMM BRUSSELS 2021

Combination strategy – The example of PrEPVACC

- The concept of a synergy between vaccine and PrEP was published > 10 years ago
  - Excler JL, et al. https://doi.org/10.1089/aid.2010.0206 (VAXPREP !)
  - McNicholl JM. https://doi.org/10.1080/21645515.2016.1231258
- African-led, European-supported *HIV* prevention study running in 4 sites in 3 countries, Uganda, Tanzania and Southern Africa, from 2018 to 2024. https://www.prepvacc.org/ (NCT04066881)
  - Adaptive trial design - RCT of alternative oral PrEP and HIV vaccines
    - 1) DNA with protein based vaccine (DNA-HIV-PT123 + monomeric AIDSVAX®B/E) + PrEP
    - 2) DNA, MVA and protein based vaccine (DNA-HIV-PT123 + trimeric CN54gp140, followed by poxvirus-based MVA CMDR + trimeric CN54gp140) + PrEP
    - 3) New form of oral PrEP, TAF/FTC (Descovy) taken daily

The headache of inducing broadly protective neutralizing antibodies

Antibody-mediated prevention

- HVTN 704/HPTN 085 and HVTN 703/HPTN 081 trials evaluated two doses of VRC01 CD4 binding site targeting broadly neutralizing monoclonal antibody
- No overall prevention efficacy, however pooled analysis demonstrated efficacy of 75.4% against sensitive isolates
- Mixed implications for vaccines
  - ➢ PoC for bnAb prevention
  - ➢ Only 30% of placebo isolates sensitive to VRC01

Corey et al., NEJM 2021

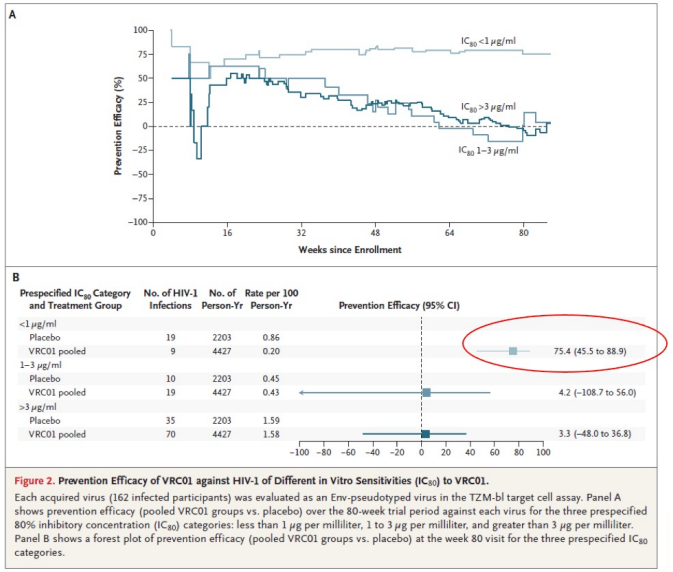


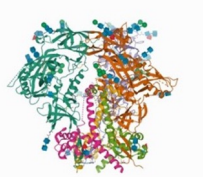
Figure 2. Prevention Efficacy of VRC01 against HIV-1 of Different in Vitro Sensitivities (IC_{80}) to VRC01.
Each acquired virus (162 infected participants) was evaluated as an Env-pseudotyped virus in the TZM-bl target cell assay. Panel A shows prevention efficacy (pooled VRC01 groups vs. placebo) over the 80-week trial period against each virus for the three prespecified 80% inhibitory concentration (IC_{80}) categories: less than 1 μg per milliliter, 1 to 3 μg per milliliter, and greater than 3 μg per milliliter. Panel B shows a forest plot of prevention efficacy (pooled VRC01 groups vs. placebo) at the week 80 visit for the three prespecified IC_{80} categories.

Novel Adjuvants

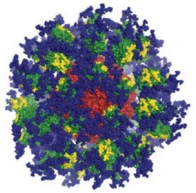
3M-052 TLR 7/8 agonist
CpG with alum
GLA-LSQ
Alum
SNMP (e.g., Matrix M from Novavax)
Adjuplex
Cationic liposomes with TLR or non-TLR agonist ligands (Cationic Adjuvant Formulation or CAF from SSI)
Army Liposomal Formulations with monophosphoryl lipid A: ALF, ALFA, ALFQ, ALFQA

Vaccines

- Conformation based
  - E.g., Native-like envelope trimers
- Antibody epitope based design
  - E.g., Fusion Peptide
- Germline targeting (lineage based)
  - E.g., Peptide liposomes targeting MPER gp41
  - E.g., eOD-GT8 60mer
- Multiple founder virus-like cocktails



BG505 SOSIP.664 Trimer: RCSB PDB (A Ward)



eOD-GT8 nanoparticle: iavi.org

Haynes BF, et al. Nature Reviews Immunology 2022
https://doi.org/10.1038/s41577-022-00753-w

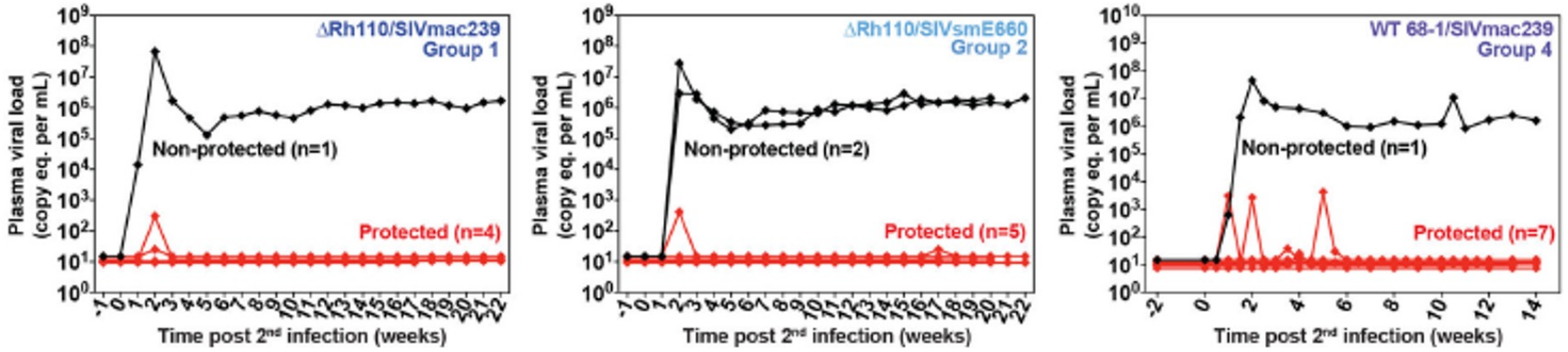
Saunders KO, (Bart Haynes) et al. Sci Transl Med 2022.
https://doi.org/10.1126/scitranslmed.abo5598

Lewitus E, (Morgane Rolland) et al. PloS Pathog 2022
https://doi.org/10.1371/journal.ppat.1010369

Leggat DJ, (Bill Schief) et al. Science 2022
https://doi.org/10.1126/science.add6502

Viral vectors

- Attenuated CMV vector-based vaccine
- Mechanism: **Durable** MHC-E mediated protection elucidated in NHP
- VIR-1111 clinical trial in CMV seropositive individuals is ongoing NCT04725877
- Potential for combination with nAb-eliciting antigens



In SIV model, 80% protection from a second infection approx. 3y following initial challenge

Hansen, et al, 2019

DNA and mRNA HIV Vaccines – the 'Boost', the 'Accelerator', and the Hope?

DNA ZyCoV-D (India): Modest efficacy (66.6%), intradermal needle-free administration, storage 2-8C, more affordable, and perhaps more easily transferable.
Khobragade A, et al. Lancet. 2022, doi: 10.1016/S0140-6736(22)00151-9

mRNA

- Long history of delivery and formulation work pre-COVID-19 across HIV and other pathogens
- Striking vaccine efficacy of Moderna and Pfizer vaccines against SARS-CoV-2
- In lipid nanoparticles, induces important T cell as well as antibody responses
- The antigen design issue remains the same as for any other platform
- Durability?
  - Protection and long-lasting humoral responses demonstrated in preclinical testing of single dose of Zika mRNA candidate (Pardi (Weissman) et al, Nature 2017 http://www.ncbi.nlm.nih.gov/pmc/articles/pmc5344708/)
  - COVID-19 experience raises important questions - Safety
  - Boosting with homologous vs. heterologous platforms relevant in HIV space as well

NIAID/Scripps/BMGF/Moderna

NIAID launches Phase 1 clinical trials for three mRNA HIV vaccines: HVTN 302 (NCT05217641)

- BG505 MD39.3 mRNA
- BG505 MD39.3 gp151 mRNA
- BG505 MD39.3 gp151 CD4KO mRNA

Moderna and IAVI/Scripps announced the first-in-Africa mRNA HIV vaccine clinical trial (Rwanda, RSA). IAVI G003

- mRNA-1644: eOD-GT8 60mer (previously Phase I with soluble protein)

"100% of the winners have gambled"

Access

So, the vaccine is efficacious to a level acceptable for large scale use

What do you do now?

What saves people is not vaccine

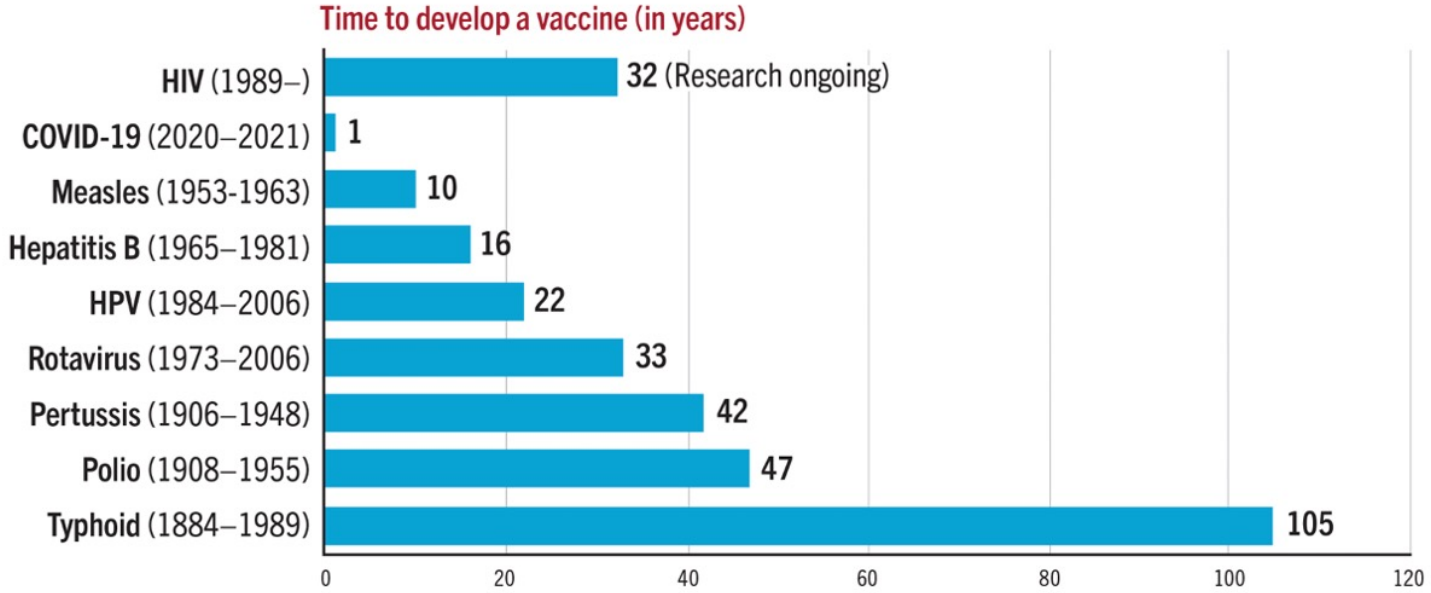
but vaccination!!

Work on Access and Equity at Inception

Boost, Yes - Hope? Yes

Vaccine Development in History

Time to Develop a Vaccine: Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine



Emile Roux 1902

"Science appears calm and triumphant when it is completed; but science in the process of being done is only contradiction and torment, hope and disappointment."

AVAC
25 Years and Counting

Acknowledgements

- Riga Stradins University, Riga, Latvia
- International Society for Vaccines
- Instituto Nationale Tumori, IRCCS – Fondazione Pascale, Napoli, Italy

- Jerome Kim, International Vaccine Institute (IVI)
- Julie Ake, Sandhya Vasan, Merlin Robb, and colleagues, US Military HIV Research Program (MHRP)
- International AIDS Vaccine Initiative (IAVI)
- The numerous colleagues and friends from the HIV / AIDS galaxy

AND

- All trial participants and communities for their dedication and constant support over more than three decades, who despite the failures remain engaged and standing.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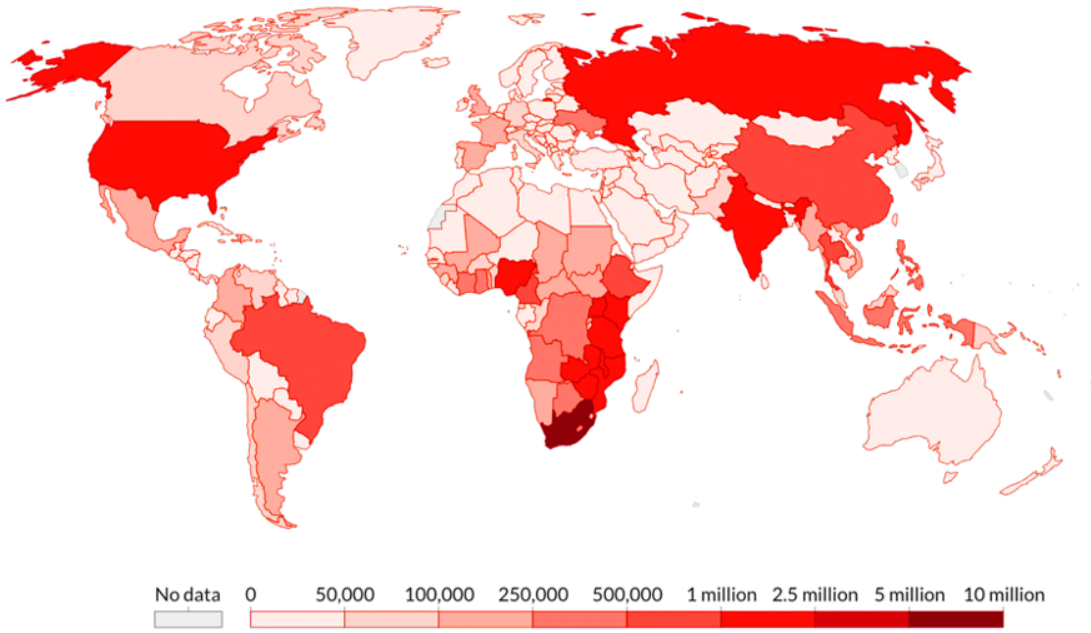
Geographic Burden of HIV and COVID-19 Cases

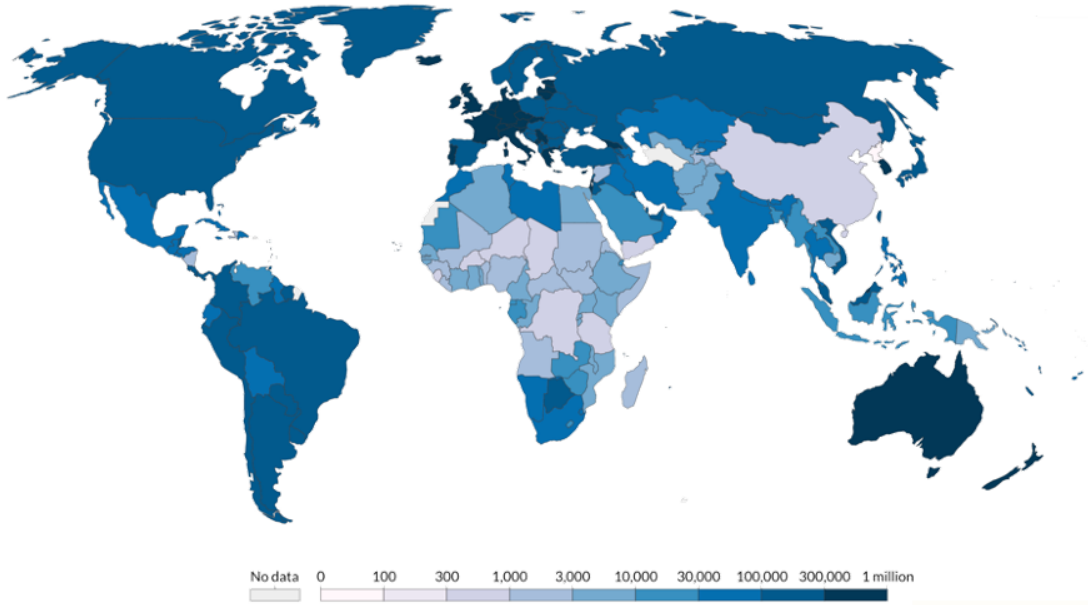
HIV

Number of people living with HIV, 2019



COVID-19

Cumulative confirmed COVID-19 cases per million people (Aug. 22, 2022)



Source: Johns Hopkins University CSSE COVID-19 Data

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HIV Vaccine Approaches in COVID-19 Vaccine Development

HIV Vaccine Approaches in COVID-19 Vaccine Development

Vaccine approaches orginally developed for HIV vaccine design are at the forefront of COVID-19 vaccine development. There are over 100 vaccine candidates in development against COVID-19, many of the vaccines and approaches in human trials have roots in HIV research. Below are some of the approaches moving forward in human trials.

Antibodies

The AMP trials, with results due in October, are now testing infusions of an HIV-neutralizing antibody every two months as a prevention method. Antibody approaches like this, including convalescent plasma, and neutralizing antibody infusions and injections, are being developed for both prevention and treatment of COVID-19.

Chimp adenovirus vector

A vaccine developed at Oxford University from a virus that infects chimpanzees is being developed for therapeutic and preventive clinical trials against HIV and a number of other diseases. That chimpanzee virus platform has been adapted as a COVID-19 vaccine candidate and is now in clinical trials.

DNA

HIV vaccine approaches using a DNA platform are now being explored for COVID-19. Inovio has begun testing its DNA vaccine platform, originally developed for HIV vaccines, for use as a COVID-19 vaccine.

Human adenovirus vectors

Multiple adenovirus subtypes have been developed as HIV vaccine candidates, most notably, Janssen's Ad26 candidate, which is now in two large HIV vaccine efficacy trials. Janssen is now adapting its Ad26 as a COVID-19 vaccine. There are also several other adeno-based COVID-19 vaccines in development, such as the Ad5 adenovirus being tested by the Chinese military.

mRNA

Messenger RNA (mRNA) vaccines, potentially more potent than DNA platforms, have been developed as HIV vaccine candidates. Now, several mRNA vaccine candidates against COVID-19 are in clinical trials sponsored by Moderna, CureVac and Pfizer/BioNTech.

AVAC, May 18, 2020

Vaccine strategies to elicit bnAbs

The HIV vaccine field is now pursuing at least three strategies to elicit bnAbs, each of which involves sequential vaccination with different antigens to guide the immune response through several stages of maturation. These strategies include:

- **B cell lineage vaccine design**, in which the series of immunogens derives from the series of Env variants isolated from longitudinal analysis of bnAb development in a person with natural HIV-1 infection, and the first (priming) immunogen is selected to have affinity for the unmutated common ancestor for the bnAb lineage, and is usually the transmitted-founder Env in that case study
- **germline-targeting vaccine design**, in which the priming immunogen is engineered to bind diverse precursors within a bnAb class (spanning many lineages), and boost immunogens are successively more like native Env trimers
- **epitope-focused vaccine design**, in which the series of immunogens aims to focus responses to one or more particular structural epitopes on the trimer

HIV vaccine trials using mRNA platform

Experimental mRNA-based Preventive HIV Vaccine Phase 1 Trials HIV Vaccine Awareness Day • May 2022

SNAPSHOT: Phase 1 HIV Vaccine Trials Using the mRNA Platform

Trials	IAVI G002	IAVI G003	HVTN 302
Name	A Phase 1 Study to Evaluate the Safety and Immunogenicity of eOD-GT8 60mer mRNA Vaccine (mRNA-1644) and Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core	A Phase I Trial to Evaluate the Safety and Immunogenicity of eOD-GT8 60mer delivered by an mRNA platform in HIV negative adults	A Clinical Trial to Evaluate the Safety and Immunogenicity of BG505 MD39.3, BG505 MD39.3 gp151, and BG505 MD39.3 gp151 CD4KO HIV Trimer mRNA Vaccines in Healthy, HIV-uninfected Adult Participants
Clinicaltrials.gov	NCT05001373		NCT05217641
Phase	1	1	1
Hypothesis	Sequential vaccination by a germline-targeting prime followed by directional boost immunogens can induce specific classes of B-cell responses and guide their early maturation toward broadly neutralizing antibody (bnAb) development through an mRNA platform	eOD-GT8 60mer delivered by an mRNA platform in HIV negative adults will induce immune responses in African populations as was seen in IAVI G001, which demonstrated this recombinant protein (eOD-GT8 60mer) safely induced immune responses in 97% of recipients, who were healthy U.S. adults	The BG505 MD39.3 soluble and membrane-bound trimer mRNA vaccines will be safe and well-tolerated among HIV-uninfected individuals and will elicit autologous neutralizing antibodies
Planned Dates	November 2021 – April 2023	May 2022 – 2023	February 2022 – October 2023
Sponsor	IAVI	IAVI	NIAID/NIH
Funder	Bill & Melinda Gates Foundation	PEPFAR via USAID and the Bill & Melinda Gates Foundation	NIAID/NIH
Participants	56 adults ages 18 to 50 years	18 healthy, HIV-negative adults	108 adults ages 18 to 55 years
Trial Sites	4 sites in the US (Atlanta; San Antonio; Seattle; Washington, DC)	2 sites: Kigali, Rwanda, and Tembisa, South Africa	11 sites in the US (Birmingham; Boston; Los Angeles; New York City; Philadelphia; Pittsburgh; Rochester; Seattle)
Vaccine Candidates	Two experimental HIV vaccines based on messenger RNA (mRNA) platform: 1. eOD-GT8 60mer mRNA Vaccine (mRNA-1644) 2. Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core)	One experimental HIV vaccine based on messenger RNA (mRNA) platform: 1. eOD-GT8 60mer delivered by an mRNA Vaccine platform (mRNA-1644)	Three experimental HIV vaccines based on messenger RNA (mRNA) platform: 1. BG505 MD39.3 mRNA 2. BG505 MD39.3 gp151 mRNA 3. BG505 MD39.3 gp151 CD4KO mRNA
Vaccine Manufacturer	Moderna	Moderna	Moderna
Immunogen Design	IAVI Neutralizing Antibody Center (NAC) at Scripps Research	IAVI Neutralizing Antibody Center (NAC) at Scripps Research	Scripps Consortium for HIV/AIDS Vaccine Development (CHAVD) and IAVI Neutralizing Antibody Center (NAC) at Scripps Research
Press Release	IAVI and Moderna launch trial of HIV vaccine antigens delivered through mRNA technology, January 27, 2022	IAVI and Moderna launch first-in-Africa clinical trial of mRNA HIV vaccine development program, May 18, 2022	NIH Launches Clinical Trial of Three mRNA HIV Vaccines, March 14, 2022