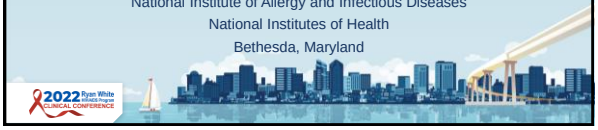
# mRNA Vaccine Development for HIV Vaccines

**Richard A. Koup, MD**
Acting Director, Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland



## Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Koup has no relevant financial relationships with ineligible companies to disclose. (Updated 09/23/22)

Slide 2

## Learning Objectives

After attending this presentation, learners will be able to:

- Describe the current status of HIV vaccine development
- Articulate how the application of mRNA technology may speed the testing of new and existing HIV vaccine concepts

Slide 3

## A Tale of Two Pandemic Vaccine Efforts

**HIV pandemic: >40 years**

- 79.3 million have been infected
- 36.3 million have died of AIDS
- No successful vaccine

**SARS-CoV-2 pandemic: 2½ years**

- 522 million have been infected
- 6.27 million have died of COVID-19
- Multiple successful vaccines

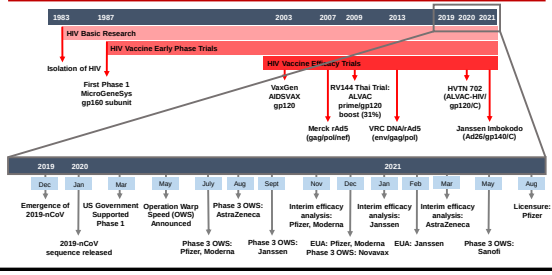
**Questions:**

- Why the difference?
- Is it all related to mRNA technology?
- Will mRNA vaccines revolutionize the HIV vaccine field?

## Answers

- **Why the difference between HIV and COVID vaccine development?**
  - HIV and SARS-CoV-2 are inherently different viruses with vastly different susceptibility to pre-existing or vaccine-induced immunity
  - Vaccines against SARS-CoV-2 protect against symptomatic disease and severe infection, but don't provide sterilizing immunity
  - Vaccines against HIV will almost certainly have to provide sterilizing immunity
- **Is the rapid development of COVID vaccines all related to mRNA technology?**
  - No, but mRNA helped because mRNA is inherently faster to develop, test, and deploy than protein vaccines
- **Will mRNA vaccines revolutionize the HIV vaccine field?**
  - Maybe not revolutionize, but they will certainly help speed the process

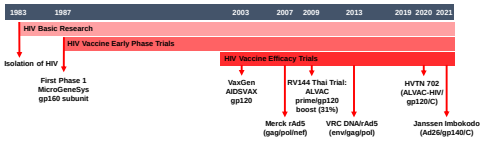
## HIV and COVID-19 Vaccine Clinical Development



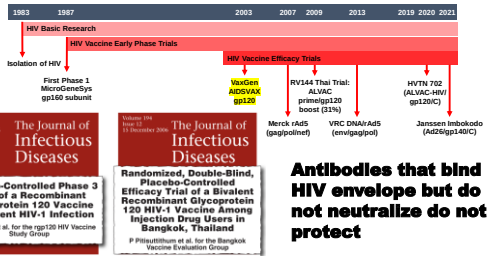
## SARS-CoV-2 and HIV Vaccine Development

- Lessons learned in HIV vaccine development
- Current approaches in HIV vaccine development
- SARS-CoV-2 vaccine development and the role of mRNA technology
- How will mRNA technology be applied to HIV vaccines?

## HIV Vaccine Clinical Development

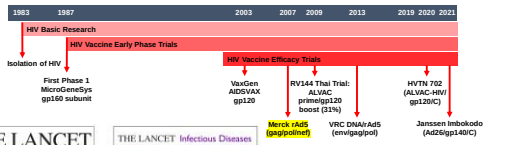



## HIV Vaccine Clinical Development




**Antibodies that bind HIV envelope but do not neutralize do not protect**

## HIV Vaccine Clinical Development




THE LANCET

Efficacy Assessment of a Cell-Mediated Immunity HIV-1 Vaccine (the Step Study): a Double-Blind, Randomised, Placebo-Controlled, Test-of-Concept Trial

SP Buchbinder, MN Robertson et al.

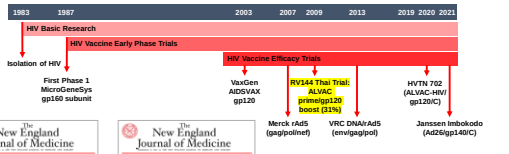
THE LANCET Infectious Diseases

Safety and Efficacy of the HVTN 503/Phambili Study of a Clade-B-Based HIV-1 Vaccine in South Africa: a Double-Blind, Randomised, Placebo-Controlled Test-of-Concept Phase 2b Study

GE Gray, JG Kublin et al

**Classical CD8+ T-cell responses in the absence of neutralizing antibodies do not protect**

## HIV Vaccine Clinical Development




The New England Journal of Medicine

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

S Rerks-Ngarm, JH Kim, NL Michael, et al. for the MOPH–TAVEG Investigators

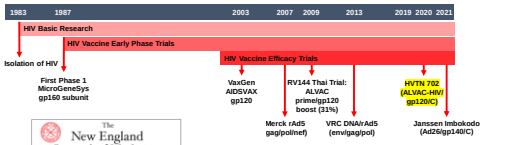
The New England Journal of Medicine

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

BF Haynes, PB Gilbert, MJ McElrath, et al.

**Maybe non-neutralizing antibodies can protect?**

## HIV Vaccine Clinical Development



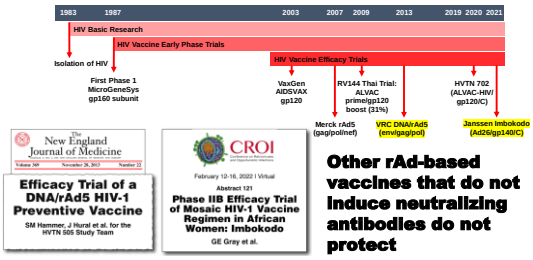

The New England Journal of Medicine

Vaccine Efficacy of ALVAC-HIV and Bivalent Subtype C gp120-MF59 in Adults

GE Gray, LCorey et al. for the HVTN 702 Study Team

**Thai Trial results not repeated in a population with higher HIV incidence/prevalence**

## HIV Vaccine Clinical Development





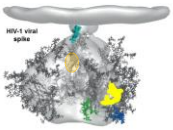





**Other rAd-based vaccines that do not induce neutralizing antibodies do not protect**

## Lessons Learned

- HIV vaccines so far have failed to induce neutralizing antibodies – and failed to protect
- Efforts should be directed towards developing immunogens that stimulate neutralizing antibodies
- It has been difficult to induce neutralizing antibodies to HIV
  - Variable loops
  - Envelope is heavily glycosylated
  - Shielding of neutralization domains
  - Multiple clades of HIV with only limited cross-neutralization



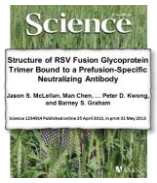

## SARS-CoV-2 and HIV Vaccine Development

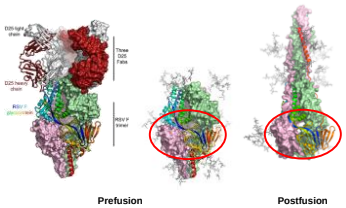
- Lessons learned in HIV vaccine development
- Current approaches in HIV vaccine development
- SARS-CoV-2 vaccine development and the role of mRNA technology
- How will mRNA technology be applied to HIV vaccines?

## Structure-Based Vaccine Design Leading to Stabilized Pre-Fusion Immunogen Structures are Critical to Eliciting the Correct Antibody Response

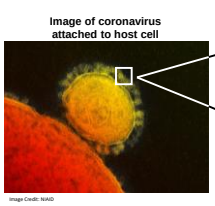
## RSV, SARS-CoV-2, HIV

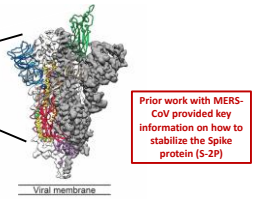
## Structure of Prefusion RSV F Glycoprotein




## SARS-CoV-2 Spike Protein (vaccine target)

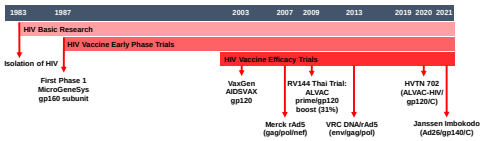



Prior work with MERS-CoV provided key information on how to stabilize the Spike protein (S-2P)

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, **Graham BS, McLellan JS.** Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eaabb2507. doi: 10.1126/science.abb2507.

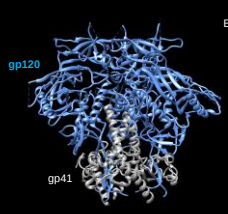
## HIV Vaccine Clinical Development




**None of the HIV vaccine efficacy trials used HIV envelope in a stabilized trimeric (pre-fusion) form.**

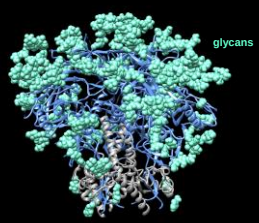
**However, these types of immunogens are now far along in clinical development.**

## Atomic Level Structure of HIV Env (2013 – present)
### [X-ray crystallography and Cryo-EM]




Sanders, Moore PlosPath (2013)
Lyumkis/Ward Science (2013)
Julien, Wilson Science (2013)
Pancera/Kwong Nature (2014)

BG505 SOSIP



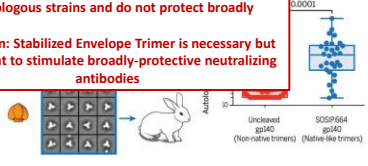

Lee, Ward et al., 2014;
Stewart Jones, Kwong et al, 2016
Lee, Ward et al., 2016

## Native trimer structure is important

**Only stabilized native trimers structures will stimulate neutralizing antibodies**

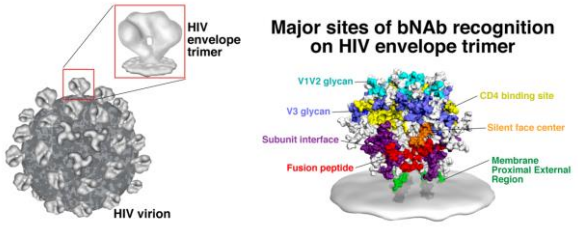
**But these neutralizing antibodies do not neutralize heterologous strains and do not protect broadly**

**Conclusion: Stabilized Envelope Trimer is necessary but insufficient to stimulate broadly-protective neutralizing antibodies**

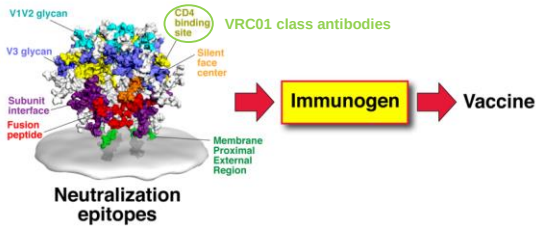



Sanders et al, *Science* 10 Jul 2015: Vol. 349, Issue 6244, pp. DOI: 10.1126/science.aac4223

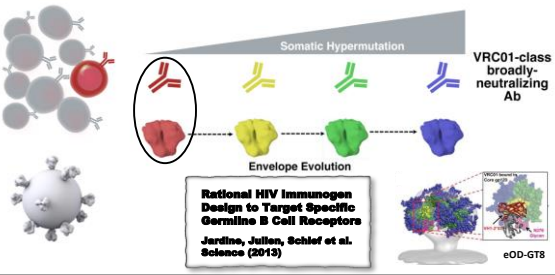
## Trimer Structure has Allowed Identification of Broadly Neutralizing Antibody Targets



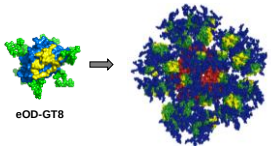

## Challenge: Designing Immunogens to Induce Antibodies to Neutralization Epitopes




## Co-Evolution of HIV and VRC01-class NAbs



## eOD-GT8 Immunogen is in Human Clinical Trials



eOD-GT8

60-mer
(Nano-particle)

- Multivalent expression
- Larger particle
- Improved immunogenicity

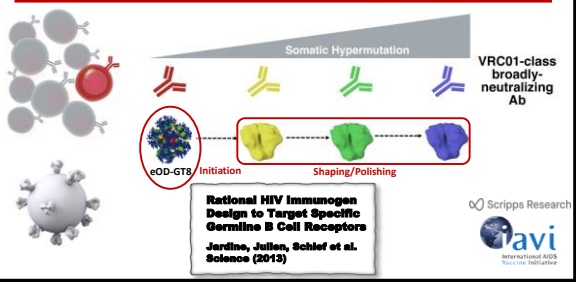
**Phase I human clinical trial completed**

**Can the eOD-GT8 immunogen stimulate the expansion and initial maturation of naïve B cell precursors of VRC01-like CD4bs antibodies?**

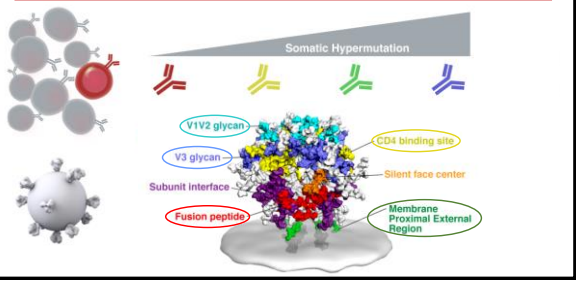
**Quantify, sort and sequence the Ig genes of B cells that bind eOD-GT8 before and after immunization**

- **Are the IgGs of the VRC01 class?**
- **Have they expanded after vaccination?**

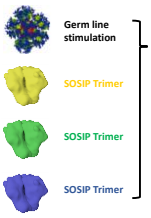
## Next Steps




## Similar Efforts Against Other Targets



## Next Steps




Each protein requires 1-2 years of manufacturing process development before phase 1 testing

This development pathway will be extremely long (years – decades)

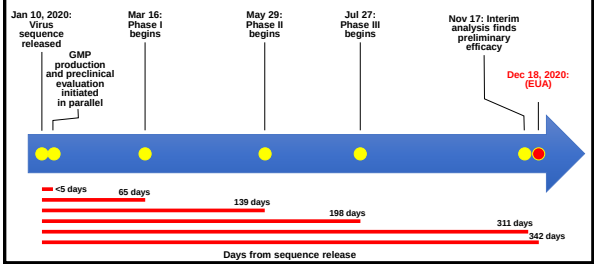
## Lessons Learned (2)

- Knowing the structural details of the HIV envelope has been crucial for designing the next generation of immunogens that can stimulate neutralizing antibodies to HIV
- Native envelope trimers as immunogens are unlikely to stimulate more than very limited autologous neutralizing antibodies
- A complex series of immunogens will be needed to direct the immune system to make broadly neutralizing antibodies
- Unless we can quicken the process of developing new immunogen platforms, the development of an effective HIV vaccine is still years (decades) away

## SARS-CoV-2 and HIV Vaccine Development

- Lessons learned in HIV vaccine development
- Current approaches in HIV vaccine development
- SARS-CoV-2 vaccine development and the role of mRNA technology
- How will mRNA technology be applied to HIV vaccines?

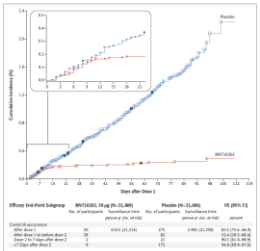
## Rapid SARS-CoV-2 Vaccine Development: Moderna mRNA-1273



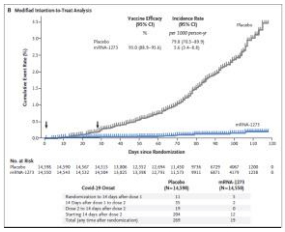

## USG Supported Six Vaccine Products

| | | | | |
|---|---|---|---|---|
| Moderna | mRNA | S2P | ➡ | FDA EUA Dec 18, 2020<br>FDA approval Jan 31, 2022 |
| BioNTech/Pfizer | mRNA +LNP | S2P | ➡ | FDA EUA Dec 11, 2020<br>FDA approval Aug 23, 2021 |
| AstraZeneca | Adenovirus vector | WT spike | ➡ | MHRA Dec 30, 2020<br>EMA Jan 29, 2021 |
| Janssen | Adenovirus vector | S2P | ➡ | FDA EUA Feb 27, 2021 |
| Novavax | Recombinant protein + adjuvant | S2P | ➡ | FDA EUA July 13, 2022 |
| Sanofi | Recombinant protein + adjuvant | S2P | ➡ | Efficacy Results Feb 23, 2022 |

## Pfizer and Moderna Efficacy

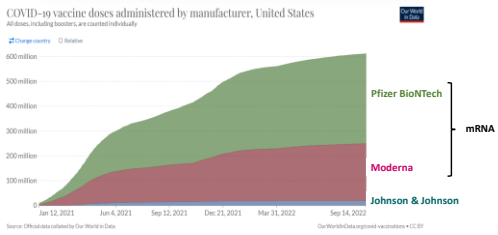


Polack et al, NEJM
Dec 10, 2020

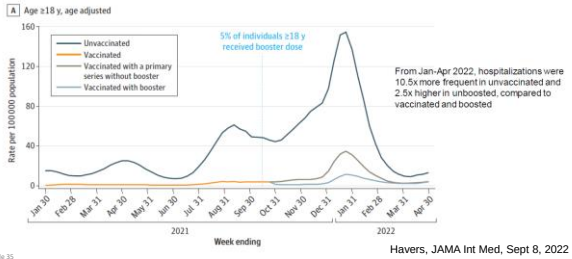


Baden & Sahly et al, NEJM
Dec 30, 2020

## COVID Vaccines Administered in the US Through September 2022




## COVID Vaccines Primarily Prevent Disease, Not Infection




Havers, JAMA Int Med, Sept 8, 2022

Slide 35

## USG Immunogenicity and Correlates Analysis

*SCIENCE* • 23 Nov 2021 • Vol 375, Issue 6576 • pp. 43-50 • DOI: 10.1126/science.abm3425

RESEARCH ARTICLE

CORONAVIRUS

**Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial**

Peter B. Gilbert[1,2,3]†, David C. Montefiori[4]†, Adrian B. McDermott[5]†, Youyi Fong[1,2], David Benkeser[6], Weiping Deng[7], Honghong Zhou[7], Christopher R. Houchens[8], Karen Martins[8], Lakshmi Jayashankar[8], Flora Castellino[8], Britta Flach[5], Bob C. Lin[5], Sarah O'Connell[5], Charlene McDanal[5], Amanda Eaton[5], Marcella Sarzotti-Kelsoe[4], Yiwen Lu[4], Chenchen Yu[4], Bhavesh Borate[3], Lars W. P. van der Laan[3], Nima S. Hejazi[1,9], Chuong Huynh[5], Jacqueline Miller[7], Hana M. El Sahly[10], Lindsey R. Baden[11], Mira Baron[12], Luis De La Cruz[13], Cynthia Gay[14], Spyros Kalams[15], Colleen F. Kelley[16], Michele P. Andrasik[1], James G. Kublin[1], Lawrence Corey[2,17], Kathleen M. Neuzil[18], Lindsay N. Carpp[1], Rolando Pajon[7], Dean Follmann[19], Ruben O. Donis[4]‡, Richard A. Koup[5]‡, on behalf of the Immune Assays Team§, Moderna, Inc. Team§, Coronavirus Vaccine Prevention Network (CoVPN)/ Coronavirus Efficacy (COVE) Team§, and United States Government (USG)/ CoVPN Biostatistics Team§

Acknowledgements: Matt Hepburn, Robert Johnson, John Mascola, Mary Marovich, Merlin Robb

## Summary of Correlates of Protection

**Vaccine efficacy against COVID-19 increases with vaccine-induced neutralizing antibody titer**

| VE Against COVID-19 Through 4 Months Post Dose 2 | |
|---|---|
| Day 57 cID50 Titer | Point Estimate (95% CI) |
| Undetectable (< 2.4) | 51% (−51, 83%) |
| 5 | 71% (30, 87%) |
| 10 | 78% (54, 89%) |
| 100 | 91% (87, 94%) |
| 1000 | 96% (94, 98%) |

~5-fold increase in VE from titer 5 to 1000

## Lessons Learned (3)

- Aspects of SARS-CoV-2 that led to rapid vaccine development include:
  - Prior work (knowledge) on SARS coronavirus Spike structure
    - Ease of Spike protein stabilization
  - Use of mRNA and viral vectors to express the Spike immunogen
  - Rapid mobilization of USG support of pharma/biotech
- High efficacy against symptomatic COVID was achieved by multiple different vaccine platforms
- Induction of neutralizing antibodies by the vaccines correlate with protection against COVID
- But vaccine protection was incomplete and waned in the face of the emergence of new variants of concern

## SARS-CoV-2 and HIV Vaccine Development

- Lessons learned in HIV vaccine development
- Current approaches in HIV vaccine development
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## Moderna (and others) are getting involved in HIV Vaccine Development

**The same week that J&J announced that it's Ad26-based HIV vaccine was stopped for lack of efficacy:**

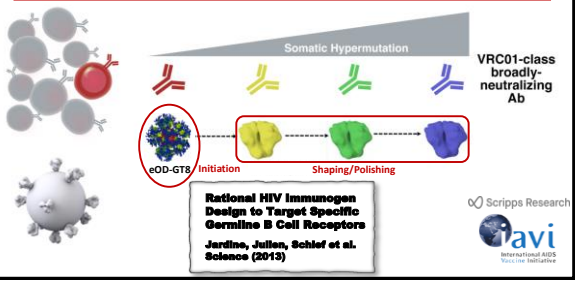

SMART NEWS

Moderna to Begin Human Trials for Two Experimental HIV Vaccines

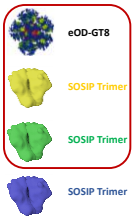
The vaccines are mRNA based, like the biotech company's Covid-19 vaccine

Elizabeth Gamillo
Daily Correspondent
August 26, 2021

## Which Vaccines?




## Which HIV Vaccines?




Each protein requires 1-2 years of manufacturing process development before phase 1 testing

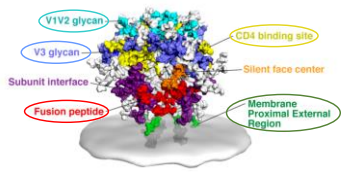
Changing to mRNA for each vaccine component shortens this timeline to a few months

Scripps Research
avi
International AIDS Vaccine Initiative

## In Addition to Moderna and Pfizer/BioNTech:

- **Other companies and non-profits are developing mRNA technology and/or lipid delivery for mRNA vaccines**
  - Greenlight Biosciences
  - Akagera
  - Afrigens
- **Government and Academic Centers are developing the technology for their own vaccine efforts**
  - Duke Vaccine Institute
  - Vaccine Research Center/NIAID

## Government, Academia, and Industry are Collaborating to Use mRNA Technology on the Other Vaccine Targets




**But funding is still expected to come from government and other sources – not direct investment by Pharma**

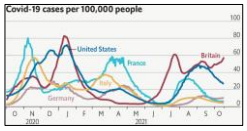
## What can mRNA Technology do for HIV Vaccine Development?

- Shorten timelines from production to clinical testing of vaccine concepts
- Eliminate time consuming and costly steps associated with protein vaccine manufacturing
- Decrease cost of production

**This will shorten the overall "design cycle time" which is the time from a vaccine concept to clinical testing of an actual product**

## What <u>can't</u> mRNA Technology do for HIV Vaccine Development?

- Induce some sort of magical sterilizing immunity
  - SARS-CoV-2 mRNA vaccines protect against symptomatic and severe infections
  - They do not provide sterilizing immunity
  - Progressive waves of infections within vaccinated populations clearly demonstrate that the current mRNA vaccines do not provide robust protection against infection – something that will be needed for an HIV vaccine




## Answers

- **Why the difference between HIV and COVID vaccine development?**
  - HIV and SARS-CoV-2 are inherently different viruses with vastly different susceptibility to pre-existing or vaccine-induced immunity
  - Vaccines against SARS-CoV-2 protect against symptomatic disease and severe infection, but don't provide sterilizing immunity
  - Vaccines against HIV will almost certainly have to provide sterilizing immunity
- **Is the rapid development of COVID vaccines all related to mRNA technology?**
  - No, but mRNA helped because mRNA is inherently faster to develop, test, and deploy than protein vaccines
- **Will mRNA vaccines revolutionize the HIV vaccine field?**
  - Maybe not revolutionize, but they will certainly help speed the process

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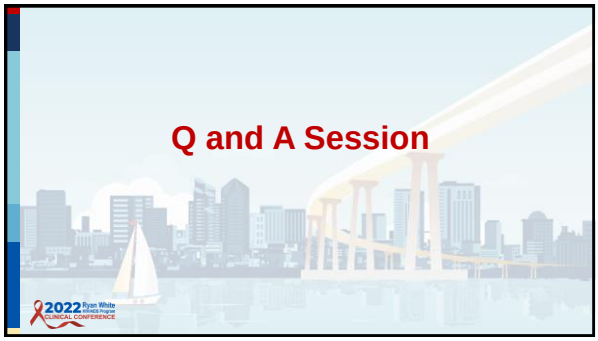
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