mRNA Vaccine Technology and the Prospects for an HIV Vaccine

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

Dr Goepfert served as a consultant for Janssen in 2021. (Updated 03/13/23)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe how mRNA vaccines induce immune responses
- List the benefits of mRNA technology for rapid vaccine development
- Describe the rapid but safe development of COVID-19 vaccines
- Contrast the rapidity of COVID-19 vaccine development with the inability to develop an HIV vaccine

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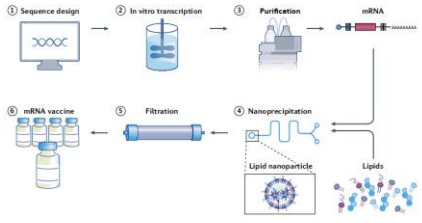
How are mRNA vaccines made?



Chaudhary et al. *Nature Reviews Drug Discovery* 2021 Slide 4

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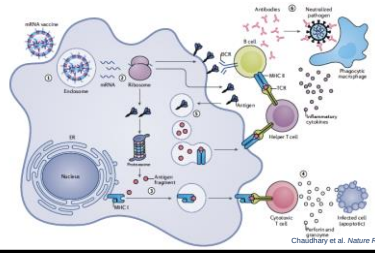
How do mRNA vaccines work?



Chaudhary et al. *Nature Reviews Drug Discovery* 2021 Slide 5

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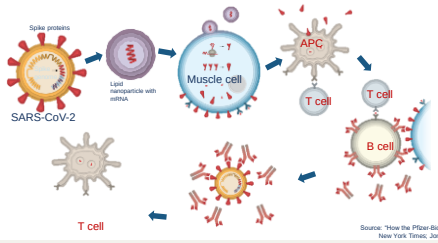

Source: "How the Pfizer-BioNTech Vaccine Works"; The New York Times; Jonathan Corum & Carl Zimmer Slide 6

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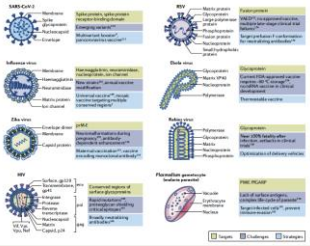
mRNA to be used for other vaccines



Chaudhary et al. *Nature Reviews Drug Discovery* 2021

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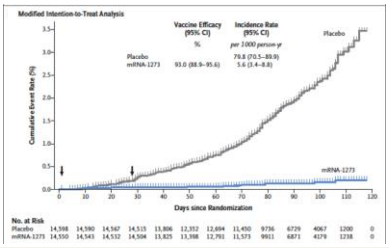
mRNA-1273 Vaccine Efficacy



Baden et al. NEJM 2020

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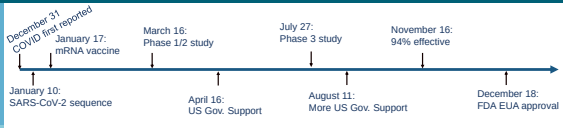
mRNA-1273 COVID-19 Vaccine Timeline



How so fast?

1. Targeting the Spike protein (2003)
2. Rapid identification and sequencing
3. Rapid mRNA vaccine development
4. Combined phases 1&2
5. Rapid enrollment (>30,000)
6. Large numbers of infections

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COVID-19 Vaccines in U.S. Government Development Portfolio

Platform	Immunogen		Developer	Status
Nucleic Acid (mRNA)	S2P		Moderna	BLA (Age 18+); EUA (Age 6 mo-17)
	S2P		BioNTech SE/Pfizer Inc.	BLA (Age 16+); EUA (Age 6 mo-15)
Adenovirus Vector	S2P		Johnson & Johnson	EUA (Age 18+)
	Wild-type spike		AstraZeneca	EUA/BLA TBD
Recombinant Protein and Adjuvant	S2P		GSK/Sanofi S.A.	EUA request 2/2022
	S2P		Novavax, Inc.	EUA (Age 12+)

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Real world effectiveness

Emergency Department or Urgent Care Visits

Vaccine	Vaccine Effectiveness (95% CI)	No. of Patients	% Positive for SARS-CoV-2 Unvaccinated/fully vaccinated
BNT162b2	89% (83–93)	11,812/3,589	24.1/2.9
mRNA-1273	92% (89–94)	11,812/2,476	24.1/2.0
Ad26.COV2.S	75% (59–85)	8,461/456	26.0/6.4

Hospitalization

Vaccine	Vaccine Effectiveness (95% CI)	No. of Patients	% Positive for SARS-CoV-2 Unvaccinated/fully vaccinated
BNT162b2	87% (83–90)	20,406/8,500	18.1/1.9
mRNA-1273	91% (88–93)	20,406/6,374	18.1/1.5
Ad26.COV2.S	68% (50–79)	10,761/707	18.6/4.2

Thompson et al. NEJM 2021

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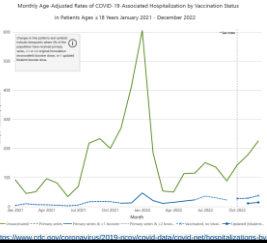
COVID-19 vaccines still work (including the bivalent boost)!



COVID-19 Hospitalizations:

16X higher in unvaccinated

2.6X higher in vaccinated without booster

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/hospitalizations-by-vaccination-status-report.pdf (accessed 02/MAR/2023

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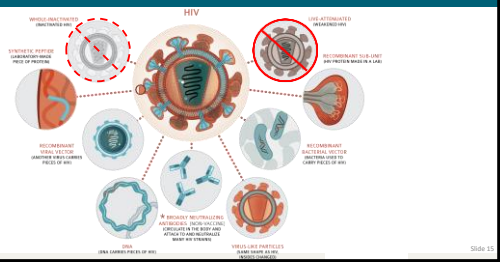
HIV Vaccine and Related* Designs



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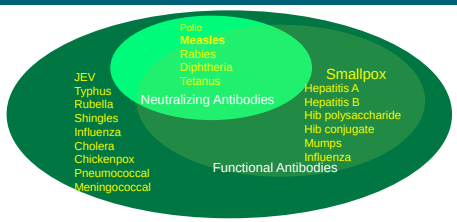
Antibodies are the Primary Correlates of Vaccine Protection



Adapted from Plotkin et al. Vaccine 2009

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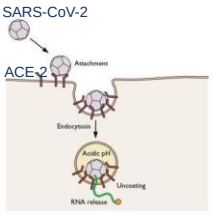
What are neutralizing antibodies?



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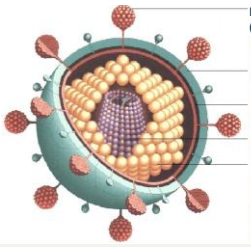
HIV Viral Structure



Proteins on the viral envelope (e.g. gp120)

Membrane or envelope (env)

Matrix proteins

Nucleus (genes) (e.g., Gag, Pol, Nef, Tat)

Core proteins (e.g. p24, p17)

HVTN Vaccine Slides

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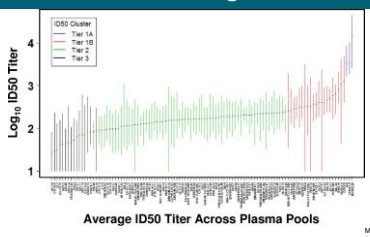
Current HIV Current Vaccines Poorly Induce Neutralizing Antibodies



Michael S. Seaman et al. J. Virol. 2010;84:1439-1452

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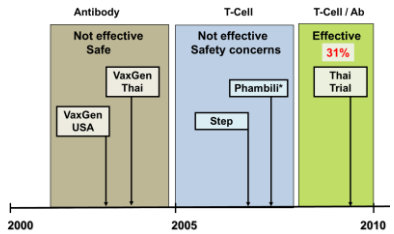
HIV Vaccine Efficacy Trials



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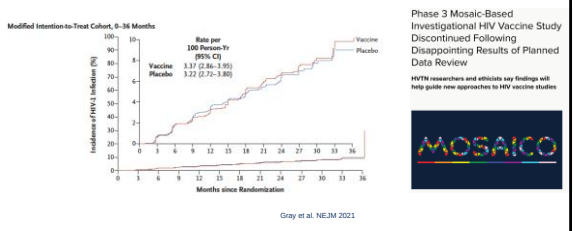
The Long Road to an HIV Vaccine



Phase 3 Mosaic-Based Investigational HIV Vaccine Study Discontinued Following Disappointing Results of Planned Data Review

HVTN researchers and ethicists say findings will help guide new approaches to HIV vaccine studies

MOSAICO

Gray et al. NEJM 2021

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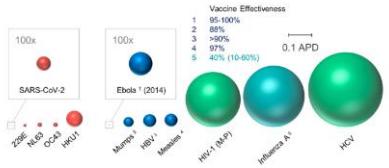
Why has it been so difficult to develop an HIV vaccine?



Rausch et al. PNAS 2020

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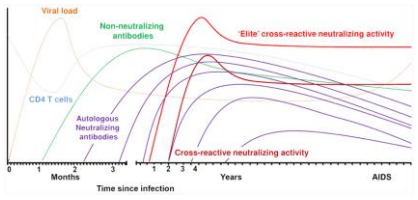
Sequentially elicited antibodies to HIV-1 envelope over the course of the infection



Front. Immunol., 20 July 2012

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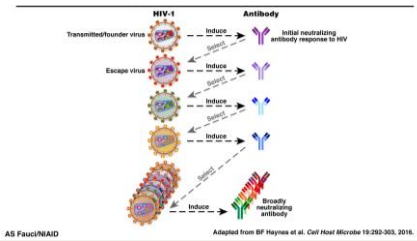
Co-Evolution of HIV and Evolving Neutralizing Antibodies



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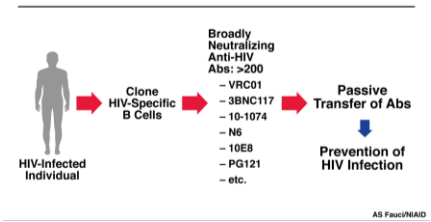
Derivation of broadly neutralizing antibodies from PWH



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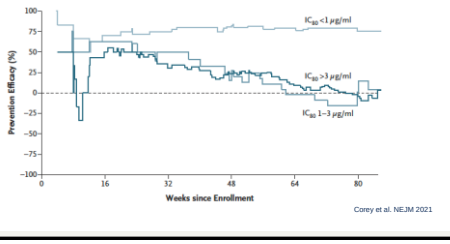
A correlate of protection: the AMP Study?



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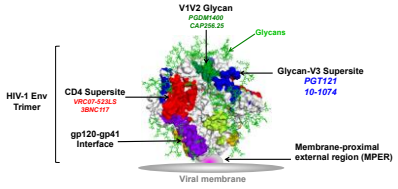
Lots more HIV bNAbs to come!



Key words to watch for: bnAb combinations, "Tri-specific antibody"

HVTN Vaccine Slides

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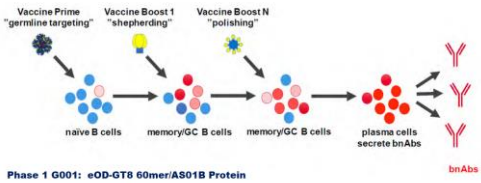
Sequential HIV vaccination to induce neutralizing antibodies



Phase 1 G001: eOD-GT8 60mer/AS01B Protein

"germline targeting proof-of-concept"

Deiffenbach HVTN Sub-Sarahan African Regional Meeting 2023; Leggat et a,; Science 2022

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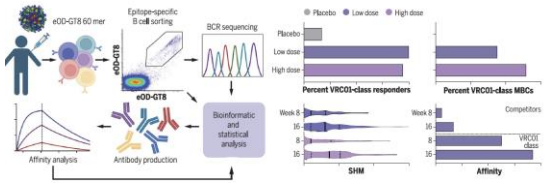
Induction of HIV Broadly Neutralizing Antibody Precursors in Humans



Leggat et a,. Science 2022

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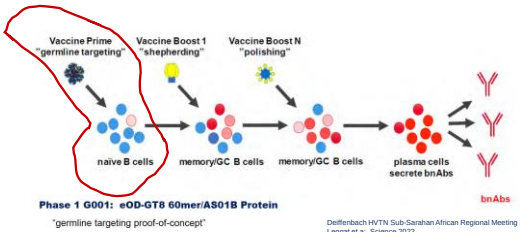
HIV bNAbs: It's a Start!



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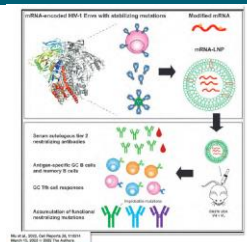
mRNA Vaccines Can Deliver Complex Multipart Immunogens



Deiffenbach HVTN Sub-Sarahan African Regional Meeting 2023

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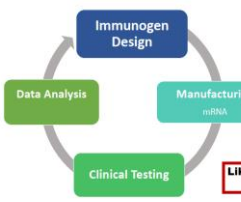
mRNA Allows Rapid Iterative Vaccine Design



Multiple Vaccine Targets

- CD4bs
- V1V2 glycan
- V3-glycan
- MPER
- Fusion Peptide

Likely to need multi-component vaccine that targets multiple epitopes

Deiffenbach HVTN Sub-Sarahan African Regional Meeting 2023

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Conclusions

- mRNA vaccine technology allows the rapid production of pathogen immunogens
- mRNA was essential in producing effective COVID-19 vaccines in record time
- HIV presents a much more formidable pathogen due to its broad genetic diversity
- An HIV vaccine must induce broadly neutralizing antibodies
- mRNA technology will assist with rapid HIV vaccine evaluation of promising immunogens

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Q and A Session

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