Discovery Medicine Trials of bnAb-inducing HIV Vaccines – Background and Recent Examples

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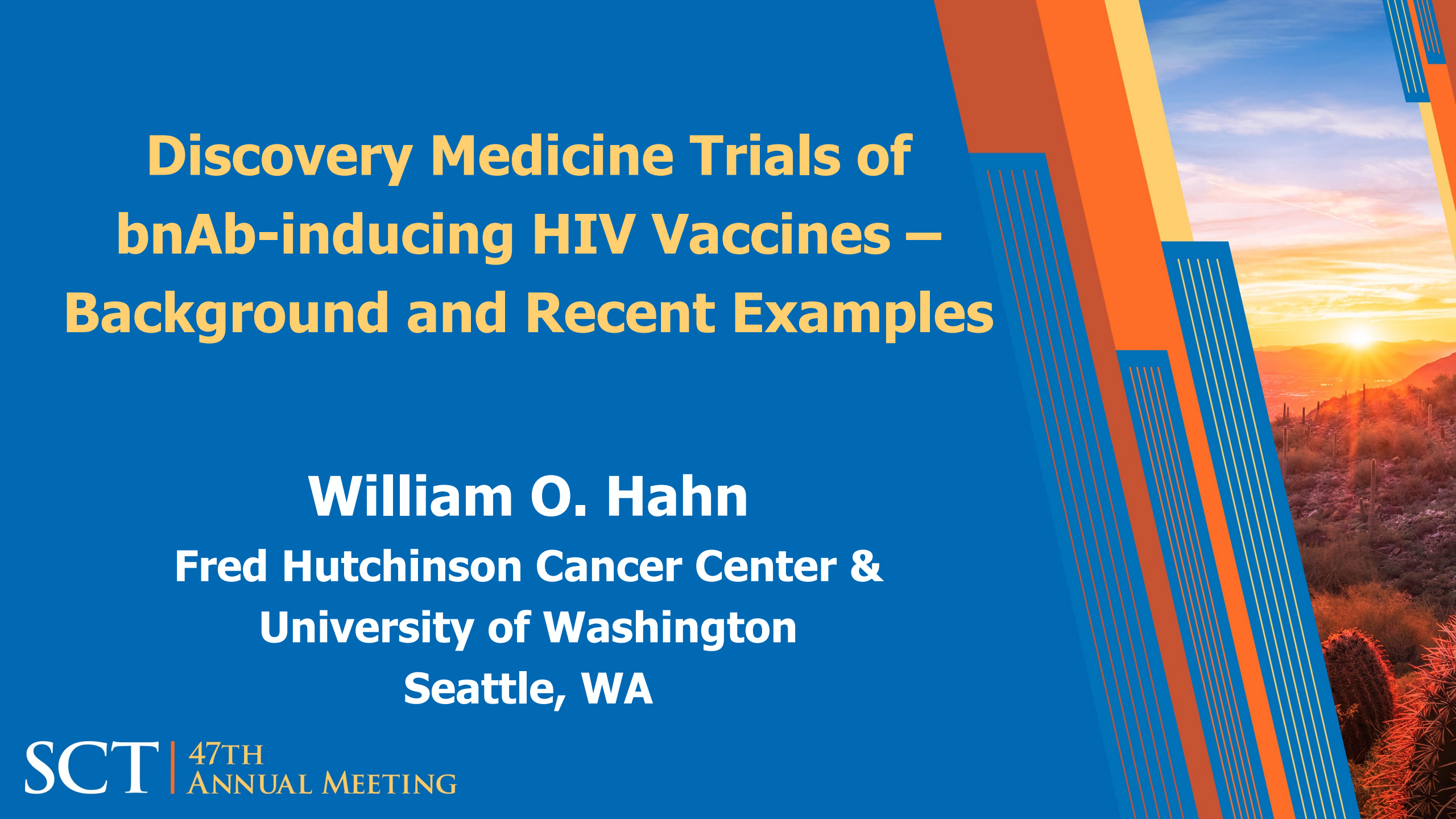

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Disclosures:

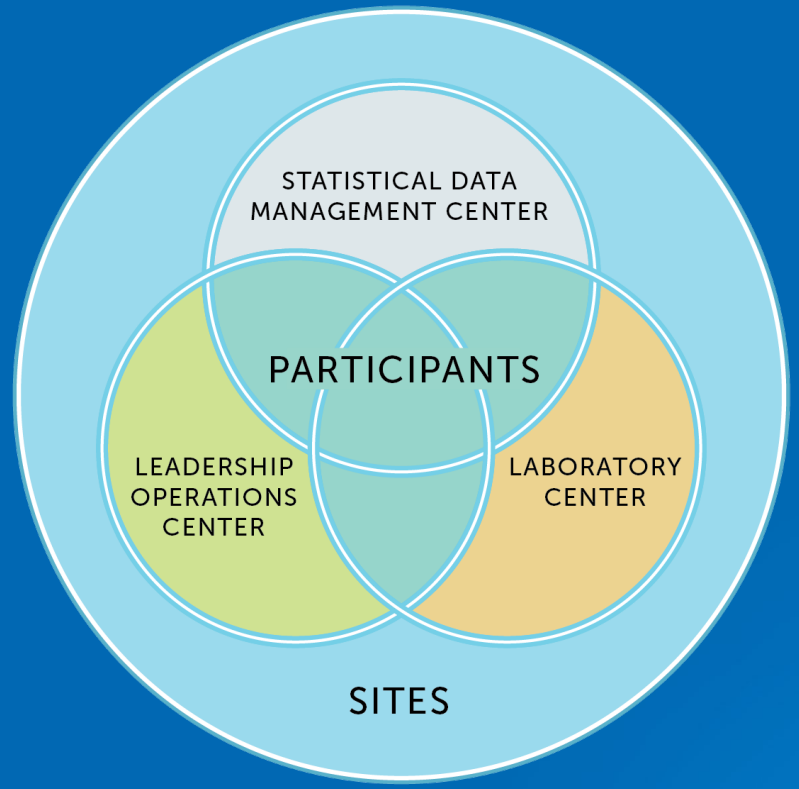
No disclosures

Outline

- Who are we? (the HVTN)
- Brief background on current HIV
- Introduction to biology behind sequential immunization strategies

HIV Vaccine Trials Network

- The HIV Vaccine Trials Network (HVTN) is the largest publicly funded global clinical trials program dedicated to vaccines (currently HIV and TB).
- The network conducts all phases of clinical trials.
- The HVTN is funded by the National Institute of Allergies and Infectious Disease (NIAID) at the US National Institutes of Health (NIH).
- To learn more www.hvtn.org



Clinical Research Sites (CRSs)
Leadership Operations Center (LOC)
Statistical and Data Management Center (SDMC)
Laboratory Center (LC)

Since founding in 2000, involved in seven Phase 2b or 3 studies

Year End	2007	2007	2009	2013	2020	2021	2021	2023	2024
Trial, Product/ Clade	**STEP**, MRK-Ad5, B	**Phambili**, MRK-Ad5, B	**Thai Prime-Boost/RV 144**, ALVAC-AIDSVAX, B/E	**HVTN 505**, DNA+Ad5, A/B/C	**Uhambo/ HVTN 702**, ALVAC/gp120 MF59 boost	**Imbokodo/ HVTN705**, Ad26 Mosaic/gp140 clade C boost	**AMP Studies**, VRC01 monoclonal antibody	**Mosaico/ HVTN706**, Ad26 Mosaic/gp140 mosaic boost	**PrEPVacc**, DNA-HIV-PT123 (clade C) with AIDSVAX, B/E or with MVA A/E, CN54gp140
Location	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US	South Africa	Thailand	US	South Africa	Malawi, Mozambique, South Africa, Zambia, Zimbabwe	Botswana, Brazil, Kenya, Malawi, Mozambique, Peru, South Africa, Switzerland, Tanzania, US, Zimbabwe	Argentina, Brazil, Italy, Mexico, Peru, Poland, Puerto Rico, Spain, United States	South Africa, Tanzania, Uganda
Number of Trial Participants	3,000	801	16,402	2,500	5,400	2,600	1,924 / 2,699	3,900	1,512

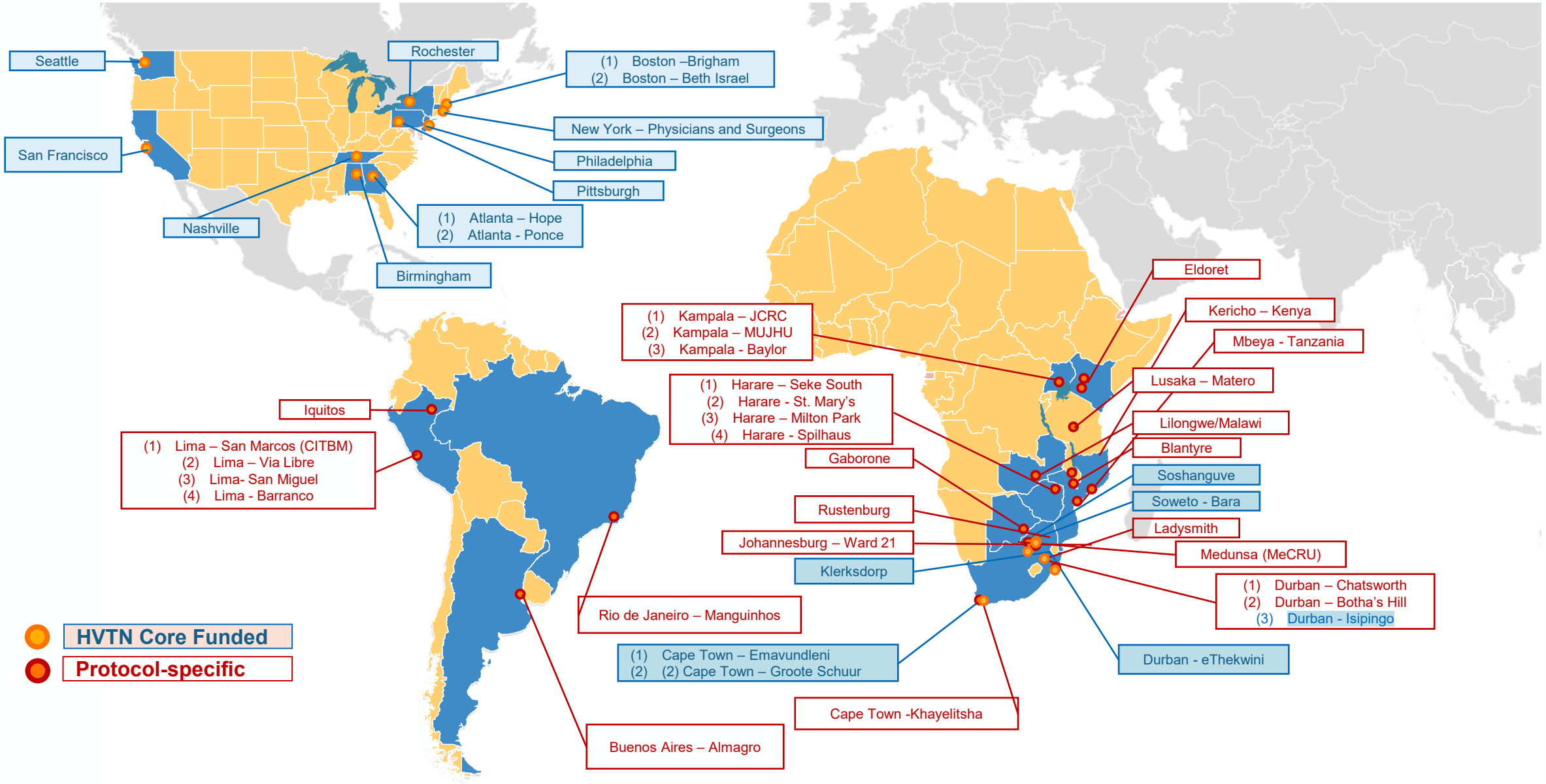
Long track record of working with Industry Partners, including Phase I work (see next slide)

Slide adapted from AVAC

Recent Partnerships in Phase I:

Trial		Last Enrollment
• HVTN137	DYNAVAX	• 2023
• HVTN142:	Vir	• 2024
• HVTN304 + 305	INOVIO POWERING DNA MEDICINES	• 2023
• HVTN302	moderna	• 2022
• HVTN319	uvaxbio	• 2025
• HVTN318	Oncovir	• 2025

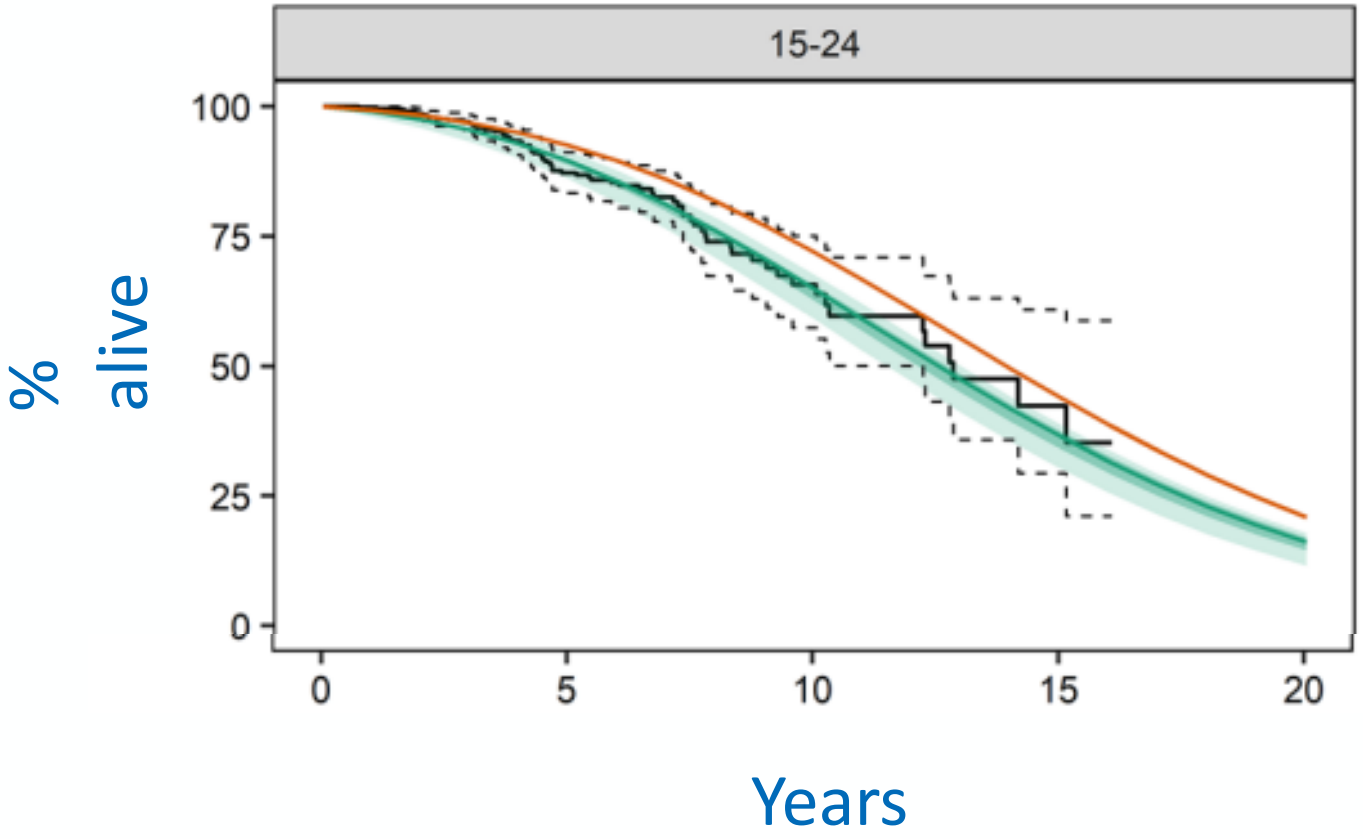
HVTN Clinical Trial Sites



HVTN HIV and TB Protocols by Phase 2000 - 2026

Phase	# Protocols
Phase 1, 1b, 1/2	92
Phase 2, 2a	6
Phase 2b, 2b/3, 3	8
Observational	22
TOTAL	**128**

Reminder:
Untreated HIV is a highly lethal disease in young people



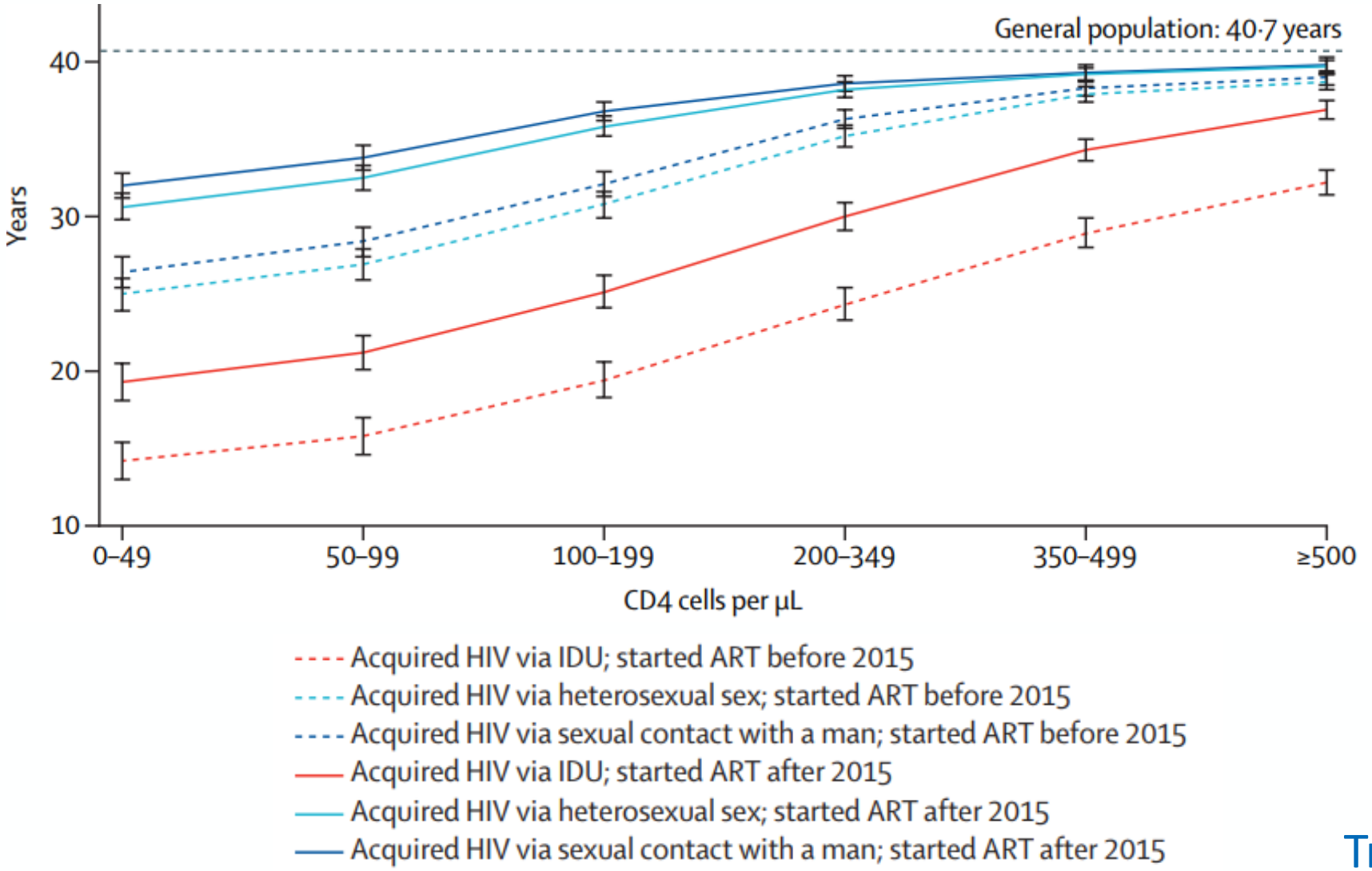
Median survival for young person (age 15-24) after acquisition with untreated HIV is ~12 years

Glabius et al., J AIDS Soc 2021

San Francisco Chronicle 1993 (Founded in 1979)

Caption “[t]he men in white are the surviving members of the original San Francisco Gay Men’s Chorus. The others [in black] represent those lost to HIV”

Treated HIV has essentially normal life expectancy

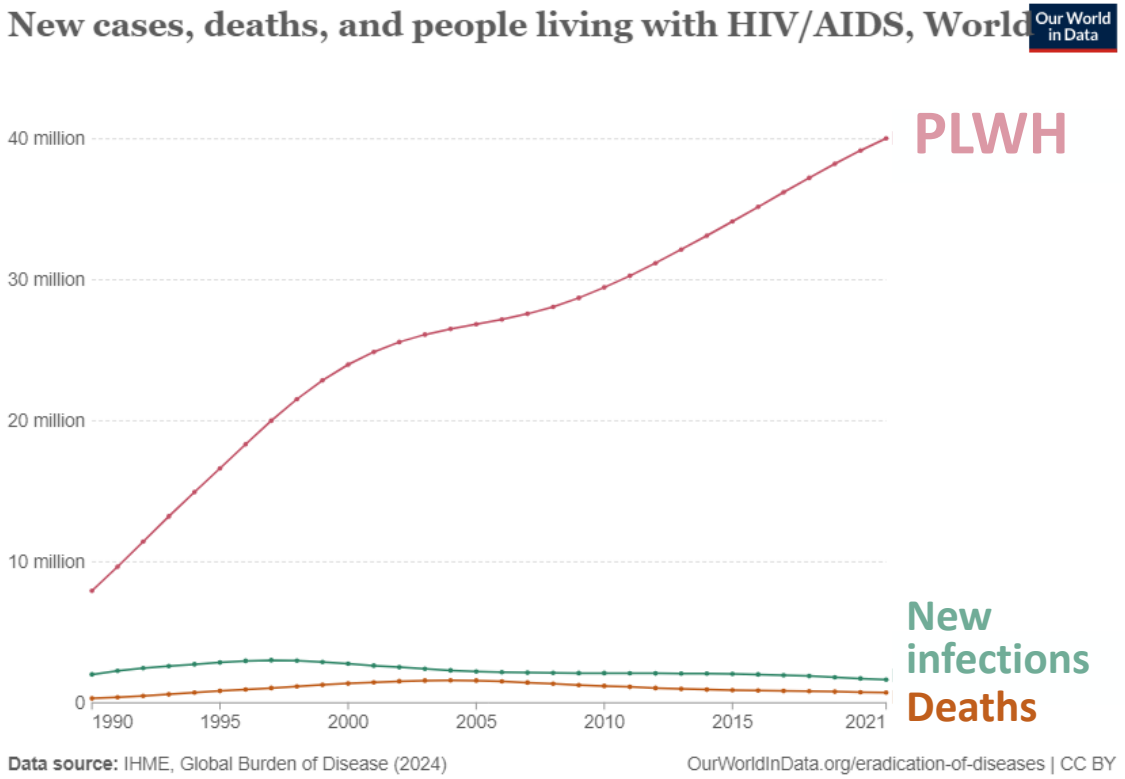


If diagnosed before HIV is advanced and treated with antiretrovirals, life expectancy following acquisition of HIV is essentially normal

Trickey et al., Lancet HIV 2023

HIV Epidemiology:

- HIV: a major global public health issue: 42.3 million deaths to date; Ongoing transmission in all countries.
- 2023: Estimated 39.9 million people living with HIV, 65% of whom are in the WHO African Region.
- In 2023: estimated 630 000 deaths from HIV-related causes and an estimated 1.3 million people acquired HIV (>3000 infections per day)



https://www.who.int/news-room/fact-sheets/detail/hiv-aids

Costs of HIV

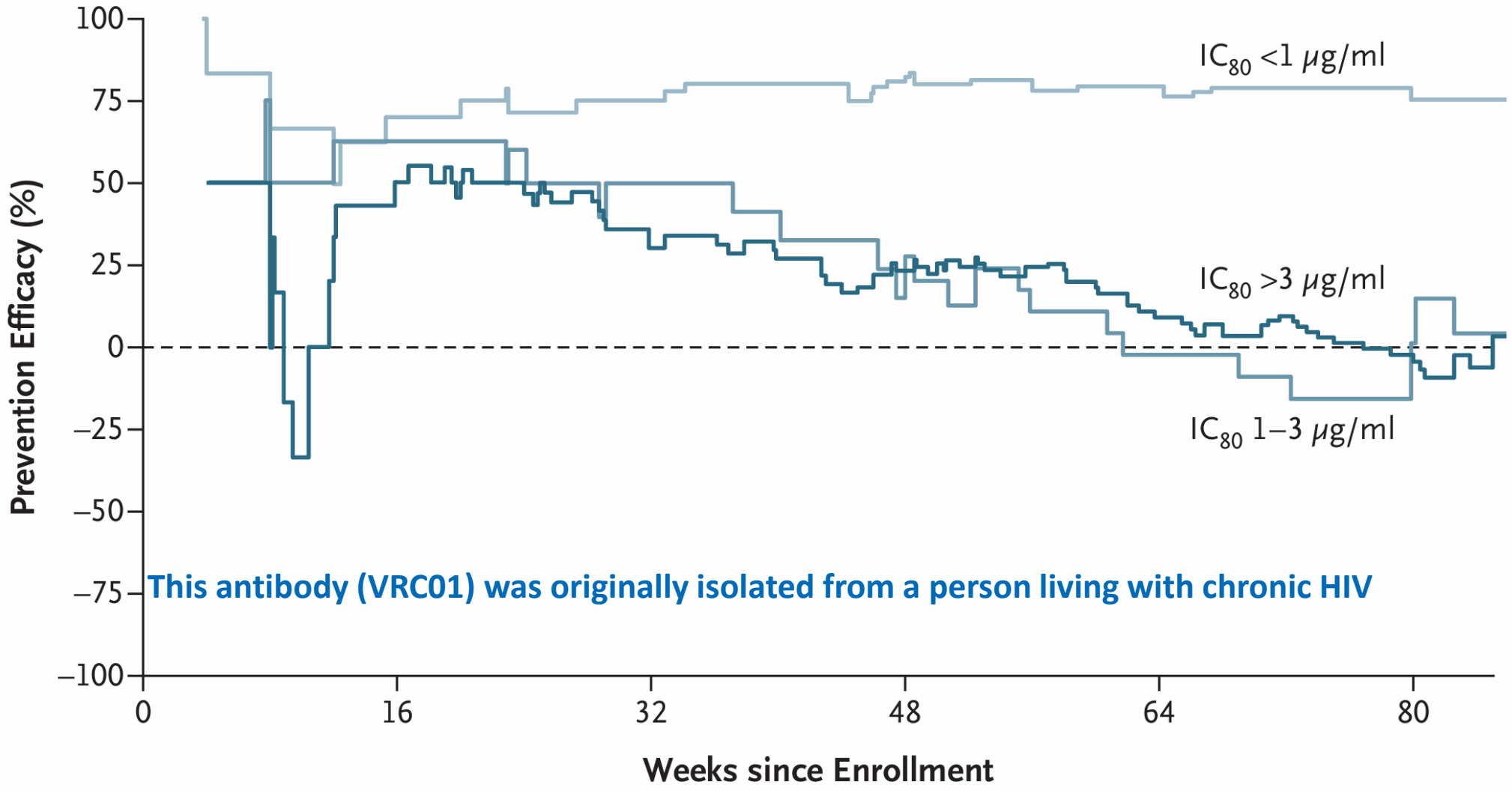
- In US, 2025 retail cost per month of front-line HIV agent (“Biktarvy” or bictegravir/TAF/FTC) is $4200 USD per month, $~50,000/year
- The average lifetime HIV-related medical cost for a person with HIV in the US is estimated to be $420,285 discounted and $1,079,999 undiscounted. [3]

[1]Skyquest. HIV Drugs Market Size, By Distribution Channel(Hospitals Pharmacies, Retail Pharmacies, and Online Pharmacies), By Region - Industry Forecast 2024-2031. Report ID: SQMIG35I2310 | Region: Global | Published Date: July, 2024.
[2]https://www.hiv.gov/federal-response/funding/budget#:~:text=Federal%20Domestic%20HIV%2FAIDS%20Programs, Congress%20through%20the%20appropriations%20process.
[3]**Estimated Lifetime HIV–Related Medical Costs in the United States.** Bingham, Adrienna PhD; Shrestha, Ram K. PhD; Khurana, Nidhi PhD; Jacobson, Evin U. PhD; Farnham, Paul G. PhD. Author Information*Sexually Transmitted Diseases* 48(4):p 299-304, April 2021.

Where is the field at with an HIV Vaccine?

Trying to make clinical trials fit biology

Antibody Mediated Protection (AMP):
Antibodies Alone can Prevent HIV



This antibody (VRC01) was originally isolated from a person living with chronic HIV

Corey et al., NEJM 2022

1862: Darwin's Christmas Orchid Story

1862: Darwin receives "Christmas" orchid from Madagascar.

Darwin notes that it has long tube before nectar reaching nectar.

He hypothesizes **something has evolved to drink nectar** and serves as pollinator.

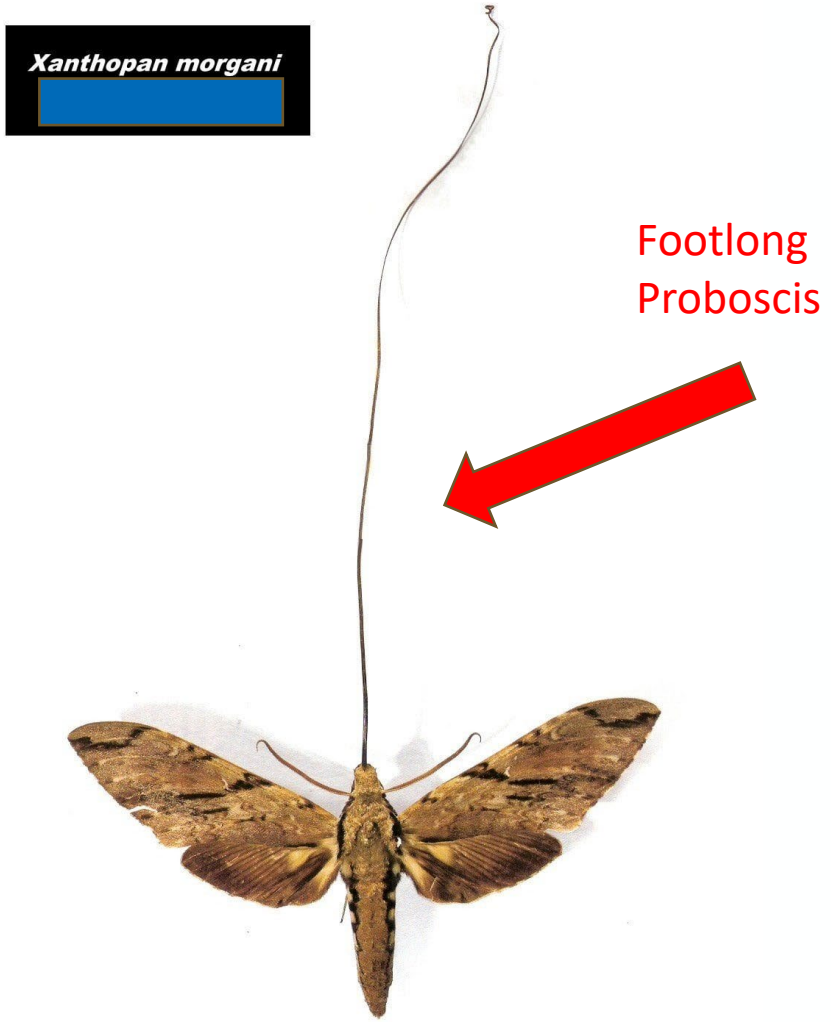
Darwin's Orchid (*Angraecum sesquipedale)*

Nectar sits about a foot down

https://www.theguardian.com/science/lost-worlds/2013/oct/02/moth-tongues-orchids-darwin-evolution

1907: Pollinator with long proboscis identified

Four decades later (1907), “Hawk Moth” (*Xanthopon morganii*) with footlong proboscis identified



https://www.theguardian.com/science/lost-worlds/2013/oct/02/moth-tongues-orchids-darwin-evolution

1992: Darwin's Original Hypothesis Confirmed

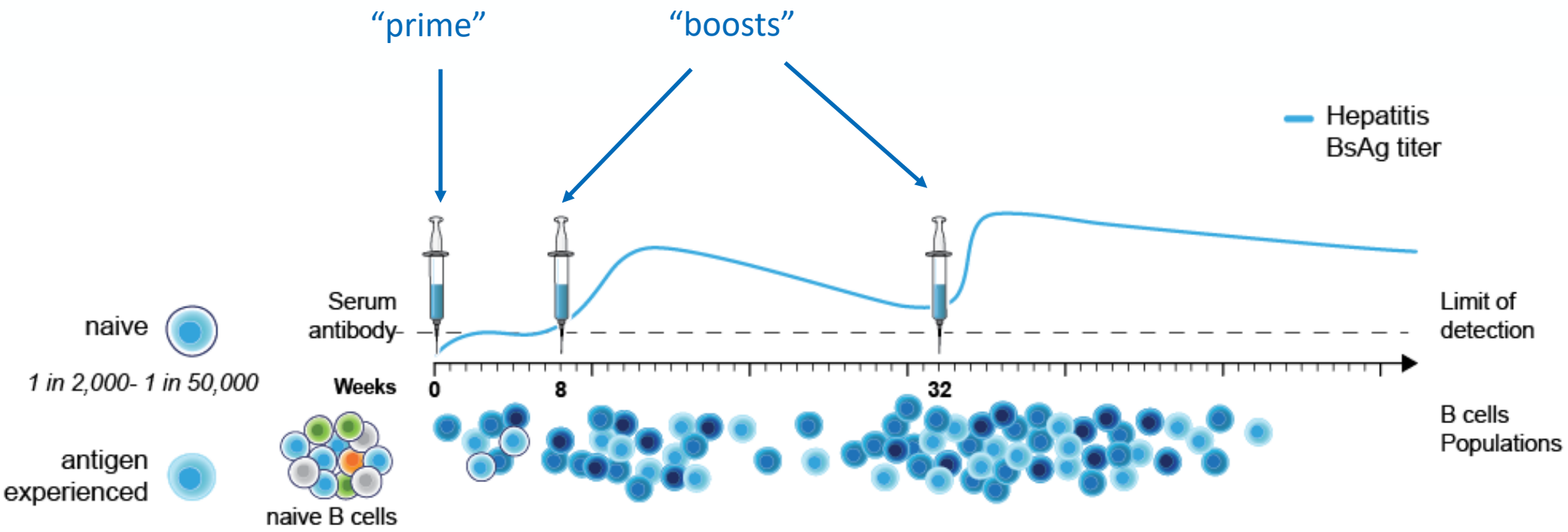
Not until 1992 was direct confirmation of Hawk Moth feeding on Christmas Orchids observed in wild

We know these "moths" (antibodies) exist: we are trying to identify correct flowers to induce their evolution

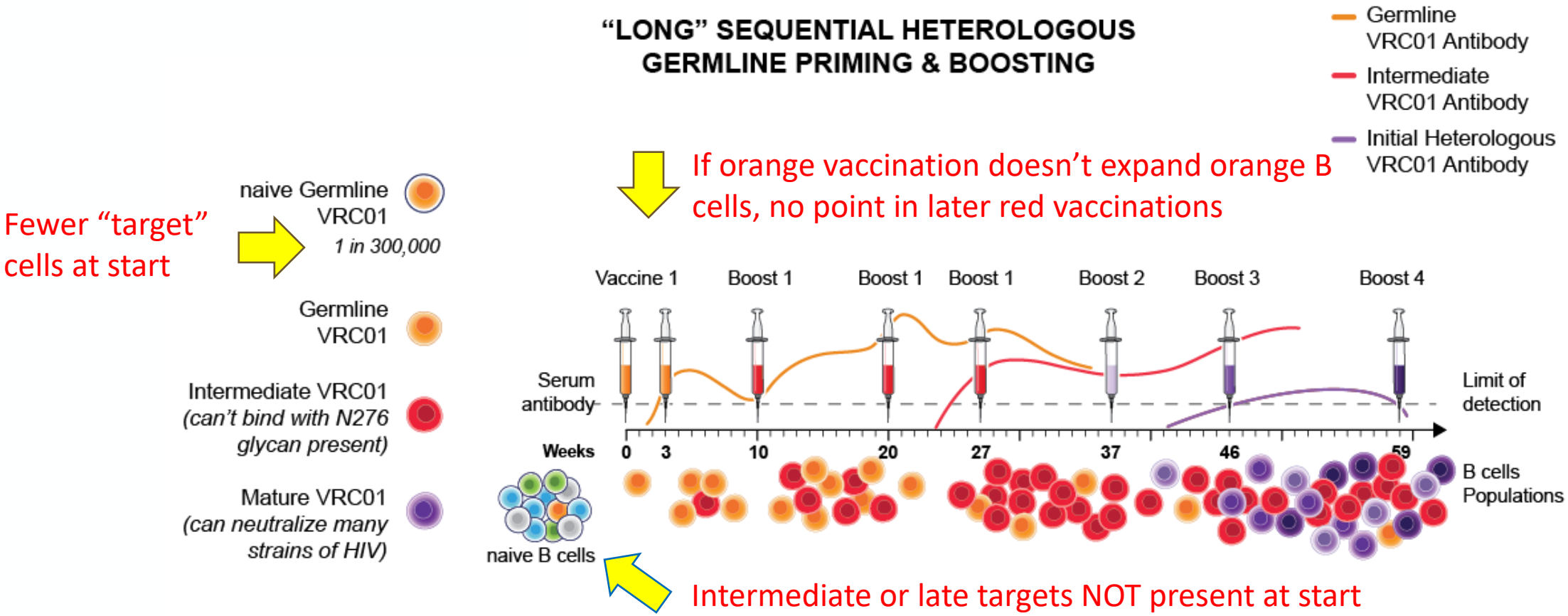
https://www.theguardian.com/science/lost-worlds/2013/oct/02/moth-tongues-orchids-darwin-evolution

Conventional Vaccination Schedule with Recombinant Protein

Example: Hepatitis B Vaccine



Proof of concept sequential immunization (in preclinical models): how to get bNabs in serum



Challenges: First-in-Human HVTN115 Example

- Complete Regimen with four different products worked out, >5 years development time
- Large size (“n”=107)
- Supported with extensive toxicology studies
- Started 2017-Completed 2023
- Met primary immunologic endpoint (elicited binding antibodies)
- 218 pages for protocol
- 57 I/E criteria-> screen to enroll ~3:1

Concept didn’t work at all because **step 1** didn’t work, no justification for further development of gp120 monomer

Study arm	N	Month 0 (Day 0)	Month 2 (Day 56)	Month 4 (Day 112)	Month 8 (Day 224)	Month 12 (Day 364)
Part A						
Group 1	12	20 mcg CH505TF	20 mcg CH505TF	20 mcg CH505TF	20 mcg CH505TF	20 mcg CH505TF
Group 2	12	100 mcg CH505TF	100 mcg CH505TF	100 mcg CH505TF	100 mcg CH505TF	100 mcg CH505TF
Group 3	12	400 mcg CH505TF	400 mcg CH505TF	400 mcg CH505TF	400 mcg CH505TF	400 mcg CH505TF
Group 4	6	placebo	placebo	placebo	Placebo	placebo
Total Part A	42 (36/6)					

Study arm	N	Month 0 (Day 0)	Month 2 (Day 56)	Month 4 (Day 112)	Month 8 (Day 224)
Part B					
Group 5	20	400 mcg CH505TF	400 mcg CH505w53	400 mcg CH505w78	400 mcg CH505w78
Group 6	20	400 mcg CH505TF	400 mcg CH505TF, CH505w53	400 mcg CH505TF, CH505w53, CH505w78	400 mcg CH505w53, CH505w78
Group 7	20	400 mcg CH505 M5	400 mcg CH505 M5	400 mcg CH505 M5	400 mcg CH505 M5
Group 8	5	placebo	placebo	placebo	placebo
Total Part B	65 (60/5)				
Total Part A & Part B	107 (96/11)				

What did we learn?

- Need to focus on stepwise evaluation (A *then* B *then* C)
- Time/Speed is a critical factor (“fail faster”)
- Don’t need such large “n”
- Focus on what really matters (B cells, not binding antibodies)
- Need to engineer flexibility into clinical designs

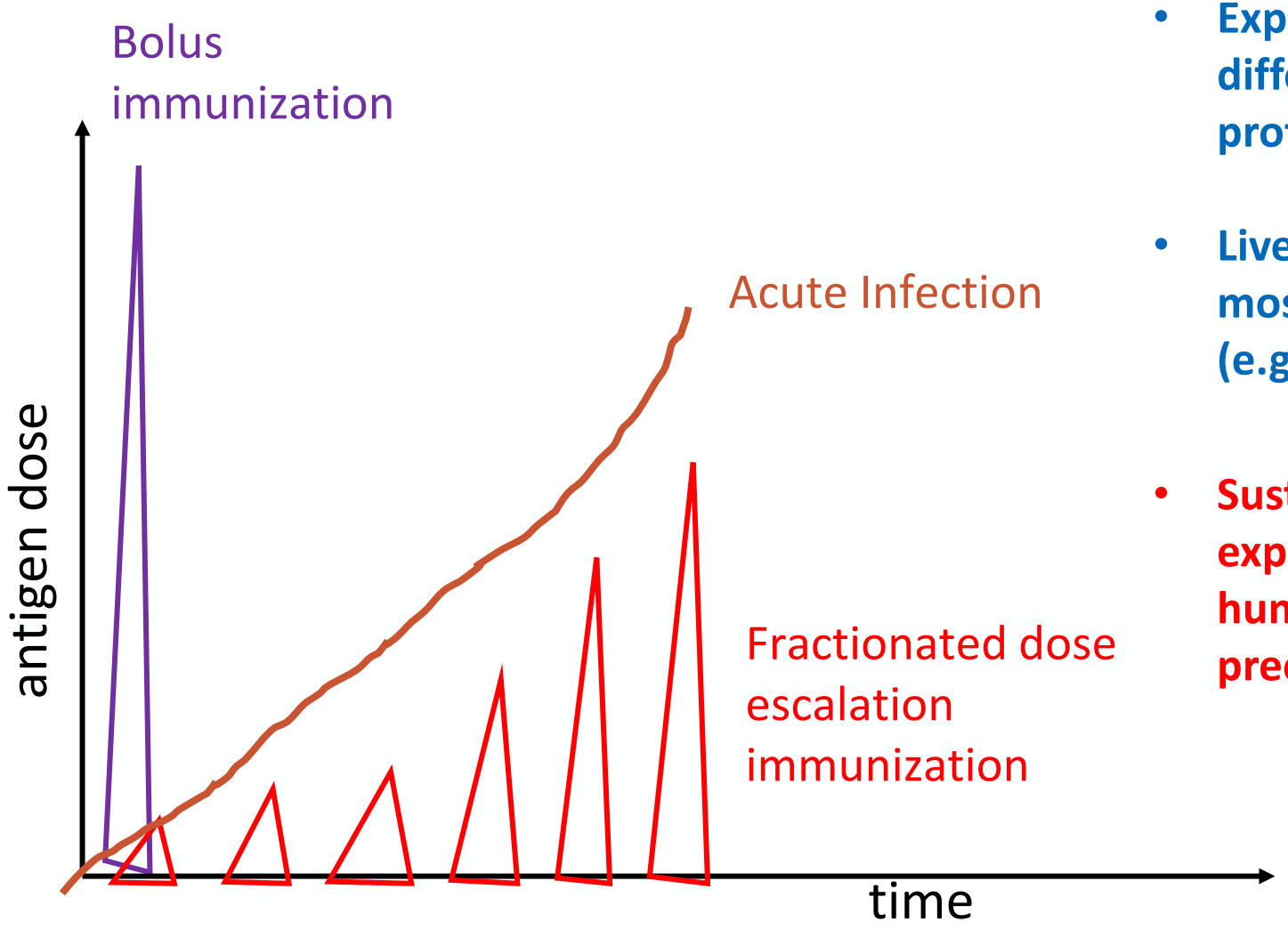
HVTN300 First "Discovery Medicine Trial"

- Simplified I/E criteria→ better screen/fail ratio
- Faster enrollment
- Streamlined protocol
- Started 2022-> finished 2023
- Smaller "n" (12)
- No placebos
- Primary endpoint: antibodies capable of neutralizing autologous viruses and inducing multiple bNab classes
- 87 pages for protocol; streamlines regulatory reviews

N	Protein antigen	Adjuvant	Route	Month 0 (Day 0)	Month 2 (Day 56)	Month 4 (Day 112)	Month 8 (Day 224)	Month 12 (Day 364)
12*	CH505 TF chTrimer (300 mcg)	3M-052-AF (5 mcg) + Alum (500 mcg)	IM	✓	✓	✓	✓	✓

Summary of lots of immunology:
Worked, but not well enough to advance in clinical development.

Does Mimicking Antigen Exposure Typical During Acute Infection With a Vaccine Improve Immune Responses?



- **Exposure to antigen over time different between infection and protein immunization**
- **Live virus vaccines typically induce most robust immune responses (e.g. yellow fever vaccine)**
- **Sustained antigen/adjuvant exposure leads to enhanced humoral outcomes in several preclinical models**

Tam et al., *PNAS* 2016 PMID 27702895
Cirelli et al. *Cell* 2019 PMID 31080066
Cirelli and Crotty 2017 PMID 28738289
Irvine et al. *Adv Drug Deliv Rev* 2020 PMID 32598970

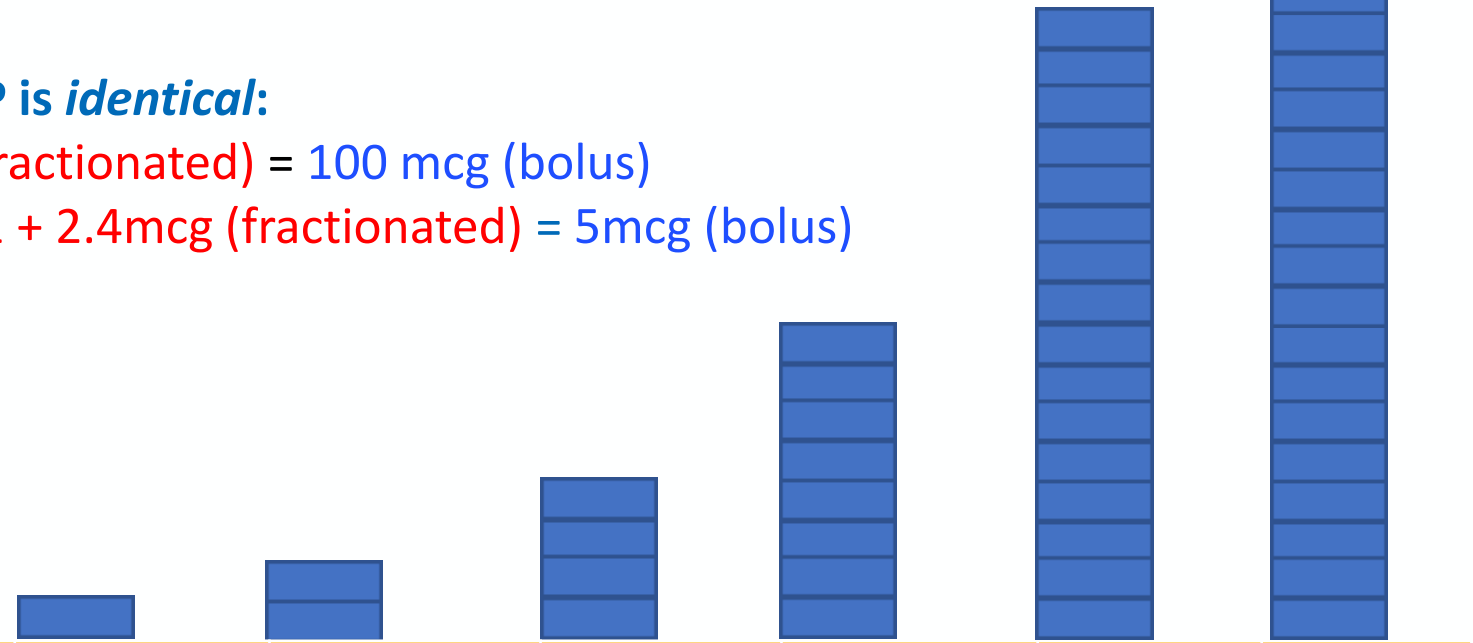
Operationalizing Fractionated Escalating Priming in Discovery Medicine Trial

Visit schedule: Six visits over three weeks (e.g. Mon/Thurs or Tues/Fri)

Total dose of both adjuvant and protein NP is *identical*:

Protein NP: 2+5+10+15+20+48 mcg (fractionated) = 100 mcg (bolus)

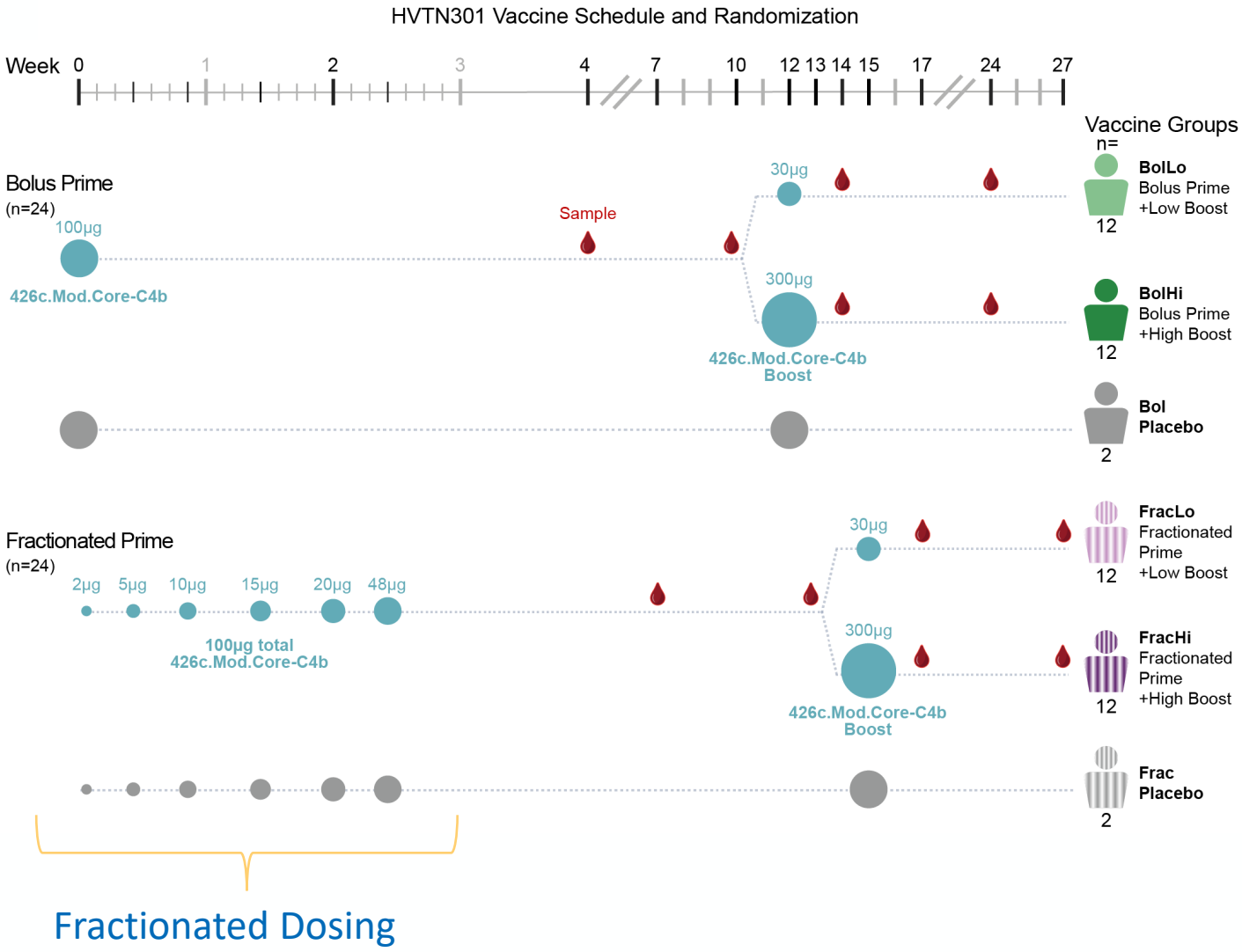
3M-052-AF: 0.1 + 0.25 + 0.5 + 0.75 + 1 + 2.4mcg (fractionated) = 5mcg (bolus)



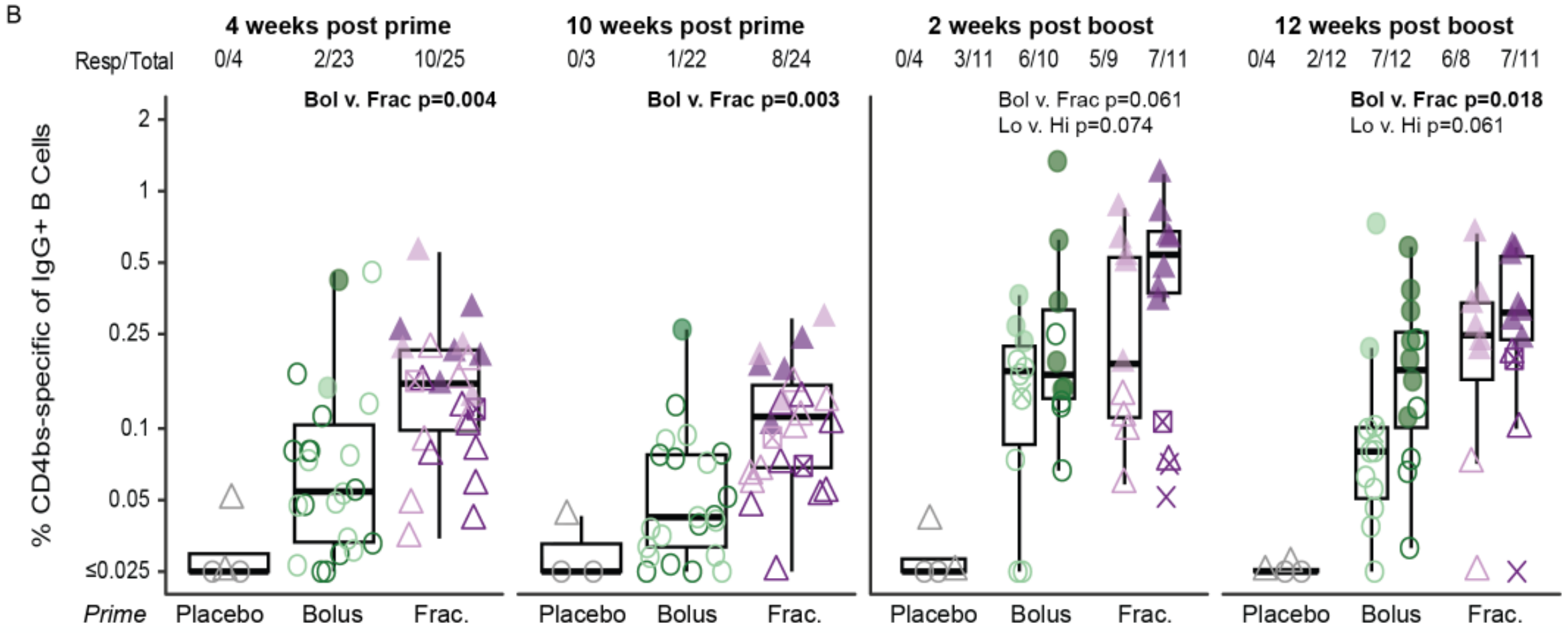
	D0	D3	D7	D10	D14	D17
426c.Mod.Core-C4b dose	2 mcg	5 mcg	10 mcg	15 mcg	20 mcg	48 mcg
3M-052 AF dose	0.1 mcg	0.25 mcg	0.5 mcg	0.75 mcg	1 mcg	2.4mcg

First-in-Human HVTN301 Example

- Two doses of “step 1”
- Designed to answer immunologic question
- Primary endpoint is cells, not antibodies
- Minimal toxicology supporting (no formal toxicology study of either fractionated dosing or protein)
- Started in Q4 2022
- Vaccinations Complete Q3 2023

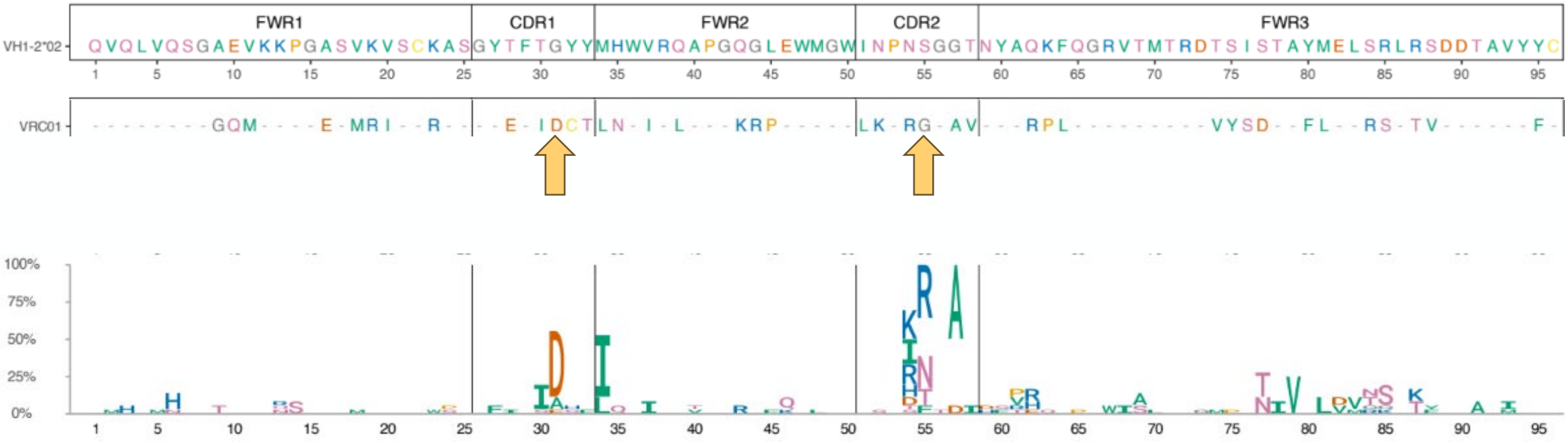


Vaccine Elicited B cells with the desired characteristics, more with Fractionated Prime



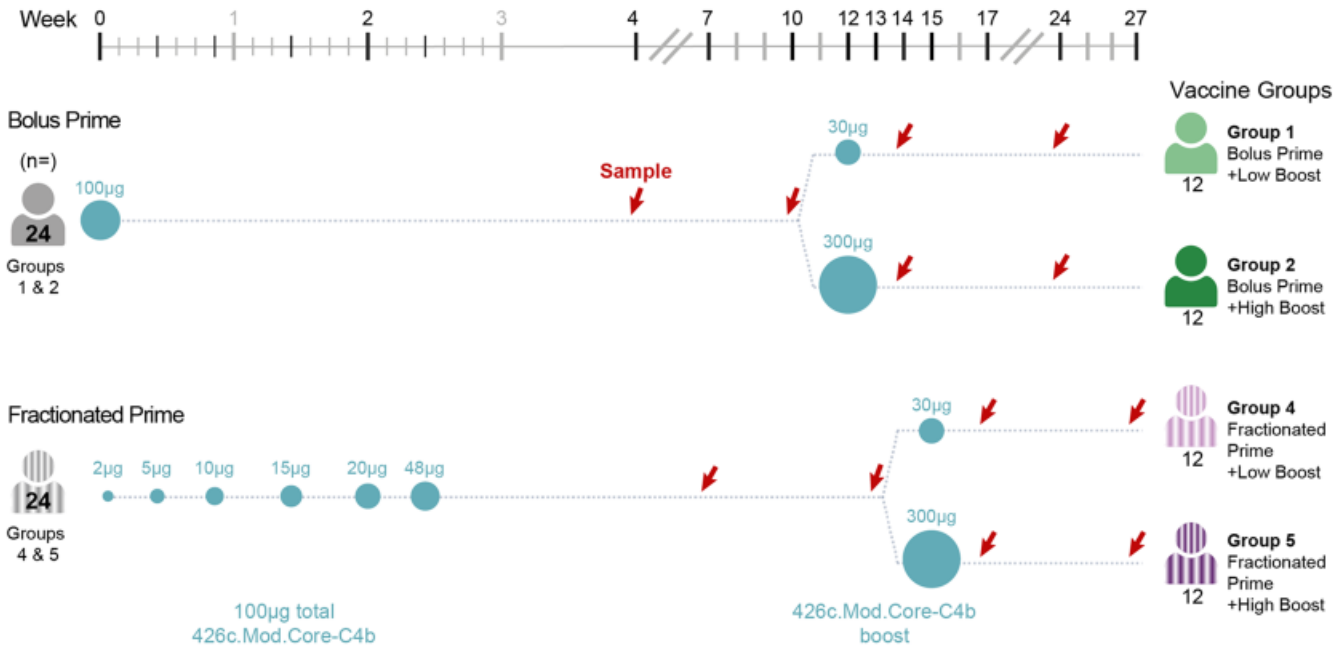
Vaccine Elicits Lots of CD4bs targeting B cells: Fractionated> Bolus

Some of these cells have correct characteristics: Fractionated> Bolus



All participants in original HVTN301 offered option to participate in optional boost study using 300mcg of GT1.1 with 5mcg 3M-052 AF/Alum

Original 301



402-602 days from last dose of 426.mod.core (or placebo)

GT1.1 boost

GT1.1. Boost:

27 participants from original cohort (including original placebo recipients) consent to receive GT1.1 x 2 doses three months apart

Vaccinations Complete Q2 2025

Primary Immunologic Endpoint of Trials: BCR Sequence Definitions

VRC01 Class Definition: HVTN325

- VH1-2
- 5 amino acid long CDR3

Jardine et al., Science 2016

BG18 Class Definition: HVTN144

Category of BG18-class BCR precursor	Criteria
Type I Must satisfy criteria 1 or 2 (examples shown in notes below)	1. HCDR3 length ≥ 20 amino acids (aa), D3-3 gene in I(T/S)IFGVVII reading frame, D gene starts at position† 3-6 within HCDR3 2. HCDR3 length ≥ 20 aa and (F/Y/W)G starting at position† 6-9 and one of the following: a. D3-3 in VL(A/R)FLEWLLY reading frame with the underlined position starting directly after the (F/Y/W)G b. D3-10*01 in VLLWFGELL reading frame with the underlined position starting directly after the (F/Y/W)G c. D3-10*02 in ITMFGELL reading frame with the underlined position starting directly after the (F/Y/W)G
Type II Must satisfy criteria 1-4	1. N332 epitope-specific 2. VL3-25, VL3-1, or VL3-10 light chain (LC) 3. HCDR3 length ≥ 20 aa 4. Does not meet BG18 type I criteria
Type III Must satisfy criteria 1-4	1. N332 epitope-specific 2. HCDR3 length ≥ 20 aa 3. Binding orientation similar to BG18 as determined by Cryo–electron microscopy (Cryo-EM) with light chain straddling the variable loop 1 (V1) loop and HCDR3 interacting with conserved residues at the base of the V3 loop and ß19 4. Does not meet BG18 type I or type II criteria

Notes: Examples of BG18 type I HCDR3 sequences are shown below. The D gene is underlined and the (F/Y/W)G motif is bold.

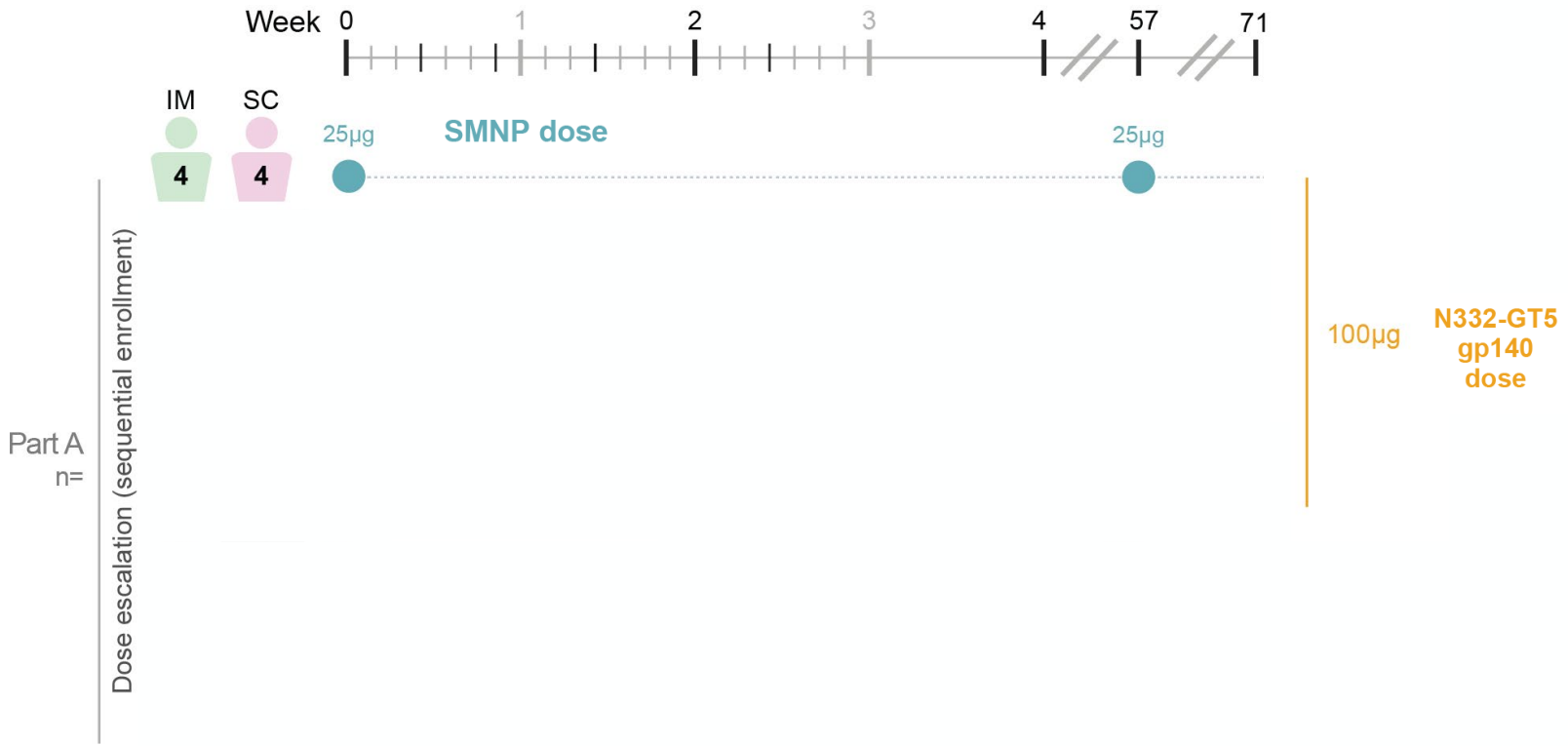
- CARNAITIFGVVIIGEYYYYGMDV type I criterion 1: In this example D3-3 is starting at position 5.
- CARNAIRI**YG**VLAFLEWLLYGMDV type I criterion 2a: In this example (F/Y/W)G is starting at position 8.
- CARNAIRI**YG**LLWFGELLYYGMDV type I criterion 2b: In this example (F/Y/W)G is starting at position 8.
- CARNAIRI**YG**ITMFGELLYYGMDV type I criterion 2c: In this example (F/Y/W)G is starting at position 8.
- BG18 type I definition does not require the presence of all or any specific amino acid in the D gene, including the amino acid at the starting position.

†Refers to position within the HCDR3 defined as the number of amino acids after the second cysteine in the antibody V_H gene

Steichen et al., Science 2016

Recent Trial Design: Both Protein and Adjuvant First in Human
Careful dose escalation before formal immunogenicity comparison

Part A:
Goal to identify maximum tolerated dose IM and SC



Part B:
Formally compare immunogenicity of fractionated prime* to bolus prime

Amanda Woodward Dav

New HVTN Discovery Medicine Trials

1. Simplification
2. Smaller “n”
3. Test immunologic concepts, precise B cell definitions

Better, faster, cheaper-> pick two

(we picked better and faster…. These are not cheap trials on a per participant basis)

Are these concepts only HIV-specific?

- In theory, germline targeting/sequential immunization technique could be applied to any disease potentially modifiable by an antibody

- Non-intuitive examples outside of infectious disease
  - heroin/fentanyl (Kolma et al., Vaccines 2025)
  - nicotine (Mendez et al., Brain Sci 2025)
  - malignancies (Hou et al., Cancers 2026)
  - carcinogens (Tompa et al., Canc Letters 1979)

Acknowledgements

Discovery Medicine Trials of bnAb-inducing HIV Vaccines – Statistical Perspectives & Challenges

Yunda Huang, PhD

Fred Hutchinson Cancer Center &

University of Washington

Seattle, WA

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Disclosures

- No disclosures.

Summary of HVTN DiscoMed Clinical Trials by bnAb Site

- HVTN 322 OPT4 mRNA + OPT4 glycan shielded mRNA (Duke)
- HVTN 326 OPT4 NP prime + OPT4 glycan shielded mRNA + Q23.17 mRNA (Duke)

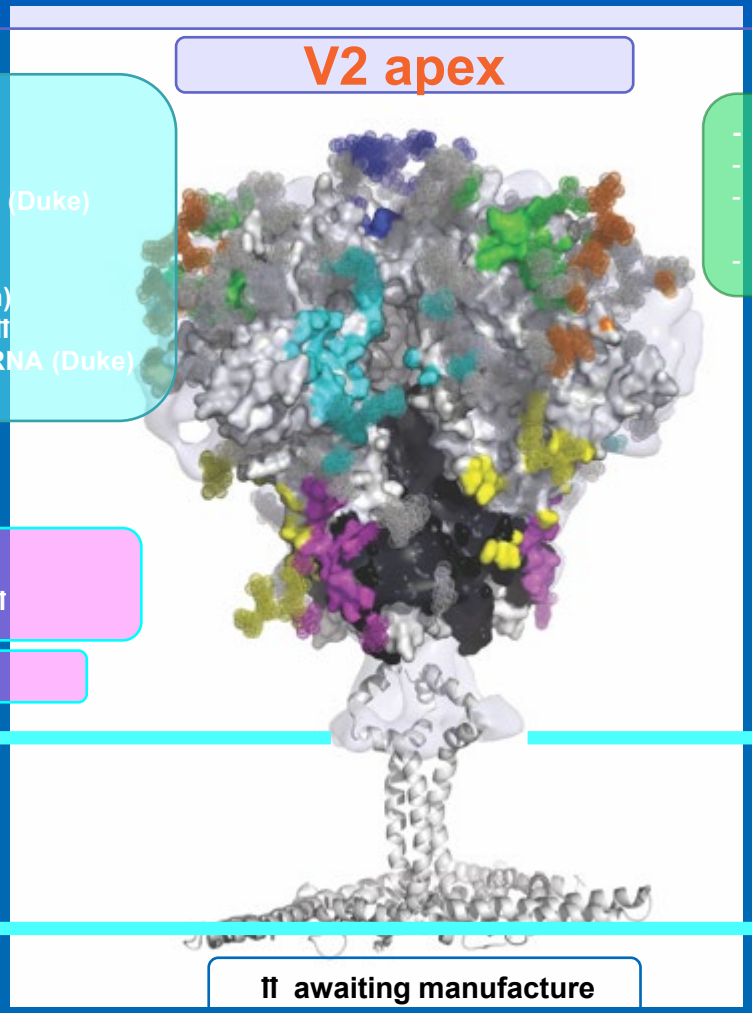
V2 apex

- HVTN 301 426c Core NP (Hutch) + GT1.1 (Amsterdam)
- HVTN 302 mRNA BG505 (Scripps)
- HVTN 305 eOD-GT8 DNA (Wistar)
- HVTN 312 CH505M5 mRNA + CH505 TF mRNA + CH505 w24 mRNA (Duke)
- HVTN 313 Clade C NFL delta Gly4 trimer (Scripps)
- HVTN 319 UFOSApNP (Uvax Bio)
- HVTN 320 426c Core NP + HxB2 Core NP, both 3M-052/alum (Hutch)
- HVTN 323 self-amplifying 426c core NP + HXB2 NP mRNA (Hutch) ††
- HVTN 324 CH505M5 NP + CH505 TF NP/mRNA + CH505 w24 NP/mRNA (Duke)
- HVTN 325 426c Core NP + HxB2 Core NP, both SMNP (Hutch)

CD4 binding site

- HVTN 144 N332-GT5 gp140 trimer (Scripps)
- HVTN 307 V3G CH848 Pr-NP1 + V3G CH848 mRNA trimer (Duke)
- HVTN 321 CH848 10.17 DS DT V1 swap mRNA + CH848 10.17 DS WT with N133/N137 intact mRNA (Duke)
- Infant V3G NP (Duke)

V3 glycan



- non-PEG MPER liposome (Duke) ††

MPER

Fusion peptide

†† awaiting manufacture

Outline

- Phase 1 Discovery Medicine vaccine trials vs. Phase 1 licensure-track vaccine trials
- Study design
- Data analyses
  - Analysis cohort
  - Analysis approaches
- Summary

	Discovery Medicine phase 1 trials*	Licensure-track phase 1 trials
Primary Objective	**Mechanistic learning**: initiate and characterize bnAb developmental pathways; safety	Safety, tolerability, and basic immunogenicity to support advancement

*Martin TM et al. Curr Opin HIV AIDS. 2023; Maciel et al. npj Vaccines 2025

	Discovery Medicine phase 1 trials*	Licensure-track phase 1 trials
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Intervention Strategy	Sequential, prime-boost multi-dose regimens; evolving vaccine constructs	Fixed candidate products; predefined dosing regimens

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Target Outcome	Characterizing complex immune processes, specific immune signatures	Binding antibody, neutralization antibody titers (if applicable), reactogenicity

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Intervention Strategy	Sequential, prime-boost multi-dose regimens; evolving vaccine constructs	Fixed candidate products; predefined dosing regimens
Target Outcome	Characterizing complex immune processes, specific immune signatures	Binding antibody, neutralization antibody titers (if applicable), reactogenicity
Decision Rules	Adaptive, data-driven advancement based on immune signatures and pathway evidence; safety	Advancement based on acceptable safety and adequate immunogenicity

*Martin TM et al. Curr Opin HIV AIDS. 2023; Maciel et al. npj Vaccines 2025

Scientific Operation Implications

- Fast and abbreviated interim immunogenicity data reports for timely decision making
- Quick sharing of early immunogenicity data to labs and vaccine developers
- Ongoing cross-protocol analyses to speed product development

Study Design Implications

	Discovery Medicine phase 1 trials*	Licensure-track phase 1 trials
Endpoints	High-dimensional immune measures (e.g., B-cell receptor sequencing)	Standard immunogenicity endpoints and safety outcomes

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Study Design Implications

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Multiplicity Handling	Managed via prioritization, and signal detection approaches; less stringent control	Minimal multiplicity concerns; endpoints are few and predefined

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Multiplicity Handling	Managed via prioritization, and signal detection approaches; less stringent control	Minimal multiplicity concerns; endpoints are few and predefined
Sample Size Rationale	Driven by need to detect mechanistic signals	Small cohorts sufficient to assess safety and basic immune response

*Martin TM et al. Curr Opin HIV AIDS. 2023; Maciel et al. npj Vaccines 2025

Study Design Implications

	Discovery Medicine phase 1 trials*	Licensure-track phase 1 trials
Endpoints	High-dimensional immune measures (e.g., B-cell receptor sequencing)	Standard immunogenicity endpoints and safety outcomes
Multiplicity Handling	Managed via prioritization, and signal detection approaches; less stringent control	Minimal multiplicity concerns; endpoints are few and predefined
Sample Size Rationale	Driven by need to detect mechanistic signals	Small cohorts sufficient to assess safety and basic immune response
Design Structure	Adaptive and iterative; cohort expansion, regimen modification, or addition common	Dose-escalation with fixed scheme

*Martin TM et al. Curr Opin HIV AIDS. 2023; Maciel et al. npj Vaccines 2025

Dose Escalation & Sample size in DiscoMed Trials

- **Rapid identification of maximum tolerable & immunogenic dose.**
- **Smaller sample size (e.g., n=3 to 12 per treatment group)**
- **Conceptually similar to the 3+3 design used in cancer therapeutic trials**
  - However, exact 3+3 design is not used in preventive vaccine trials given the lower tolerance for adverse events in healthy populations

Controls or Placebos in DiscoMed Trials

- **Traditionally, placebos are important for**
  - Blinding, especially in safety assessments
  - Controlling background immune response variability
- **Reduced reliance on placebos in DiscoMed trials**
  - Limited value of placebos in safety evaluation given small sample sizes; safety pauses are incorporated in phase 1 evaluations
  - B-cell receptor sequencing endpoints are highly specific to vaccine-induced signals; resource intensive.
  - Baseline (pre-vaccination) readouts are used as internal references

Outline

- Phase 1 Discovery Medicine vaccine trials vs. Phase 1 licensure-track vaccine trials
- Study design
- **Data analyses**
  - Analysis cohort
  - Analysis approaches
- **Summary**

Sequential Immunizations

Trial	N	# vaccinations
300	51	5
301	53	2 bolus; 6 FD+1 bolus
301 boost	27	2
302	108	3
304	20	4 or 6
305	46	4

Sequential Immunizations Over 3-12 Months

Trial	N	# vaccinations	Vaccination series duration
300	51	5	12 months
301	53	2 bolus; 6 FD+1 bolus	3 months; 3.75 months
301 boost	27	2	3 months
302	108	3	6 months
304	20	4 or 6	6 months
305	46	4	10 months

Sequential Immunizations Over 3-12 Months

Trial	N	# vaccinations	Vaccination series duration	Trial duration/ppt
300	51	5	12 months	24 months
301	53	2 bolus; 6 FD+1 bolus	3 months; 3.75 months	30 months
301 boost	27	2	3 months	12 months
302	108	3	6 months	12 months
304	20	4 or 6	6 months	18 months
305	46	4	10 months	18 months

Analysis Cohorts

Safety Analysis – **Modified Intent-to-treat (MITT)** cohort: All randomized and enrolled participants, regardless of the number of vaccinations received.

Immunogenicity Analysis

Primary: **Dynamic Per-Protocol (DPP) cohort** -- for the analysis of immunogenicity at a given time-point, all MITT participants who received all intended protocol-specified vaccinations prior to the given time-point.

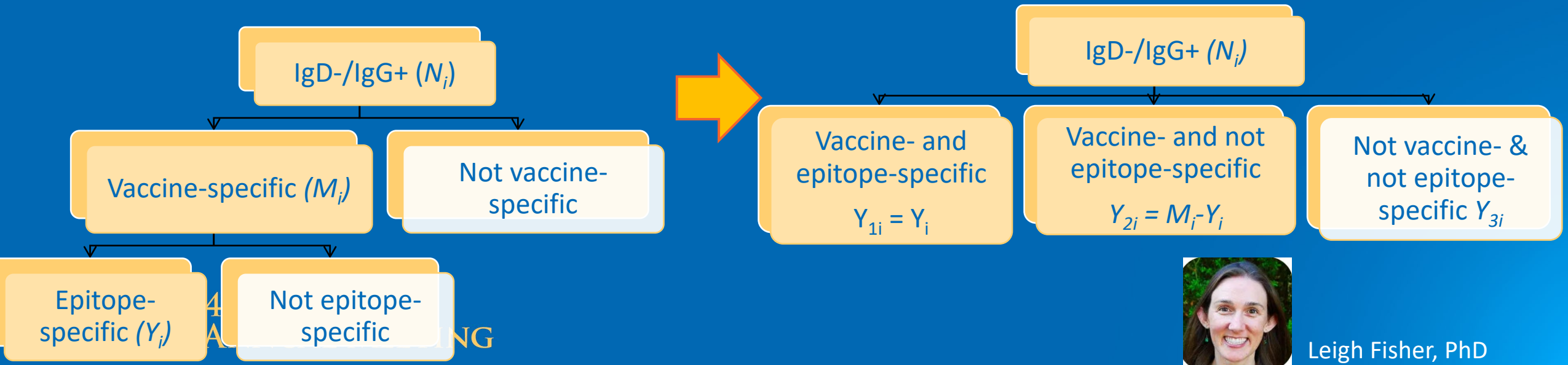
Secondary: **Full Per-Protocol (FPP) cohort** -- for the analysis of immunogenicity at any time-points, all MITT participants who received all intended vaccinations of the entire protocol-specified vaccination series.

Outline

- Phase 1 Discovery Medicine vaccine trials vs. Phase 1 licensure-track vaccine trials
- Study design
- **Data analyses**
  - Analysis cohort
  - **Analysis approaches**
- **Summary**

Comparison of B-cell Phenotyping (BCP) Data

- **Goal:** Compare vaccine-induced BCP responses (#cell counts and %) between groups, accounting for uncertainties in both the numerators and denominators of the reported frequencies (e.g., % epitope-specific IgG+ memory B-cells)
- **Approach:** Restructure the hierarchical data and model cell subset counts directly using a Dirichlet-Multinomial model
  - Estimates differences on the rates of any cell subsets, with credible intervals
  - Easily translates the results into cell counts
  - Flexibly incorporates assay measurement errors, zero-inflation, more cell-subsets



Leigh Fisher, PhD

Computational Analysis of B-cell Receptor (BCR) Sequences

Heavy chain: CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG …
Light chain: GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTGGGCTCCAGGGTGAGGCTTGGTACAGCCTGGGGG …

- **Sequence annotation (IgBLAST)**
  - Accessible in R via Bioconductor package igblastr
- **Databases**
  - Annotated Antibody Sequences for HIV-1 (DAASH)
- **Statistical and computational tools**
  - Visualization of BCR repertoire landscapes
  - Formal comparison of BCR repertoire features
  - Predicting antibody structures and functions

Ollivier Hyrien, PhD

Challenges of BCR Sequencing Data Analysis

- **BCR-sequencing data set = large, complex, and requires specialized bioinformatics processing before statistical analysis**
  - **Few definitions of bnAb-class signatures are universally accepted**
    - VRC01-class is well-defined: CD4 binding site + VH1-2*02/04 + 5 AA-long light chain CDR3
    - E.g., HJ16-class not well-defined;
  - **Dealing with many, complex scientific questions and non-standard statistical endpoints**
    - Discrete, multinomial endpoints (e.g., germline genes, CDR3 lengths)
    - Latent clonal relationships between B cells lead to non-independent observations

Ollivier Hyrien, PhD

Role of Modeling

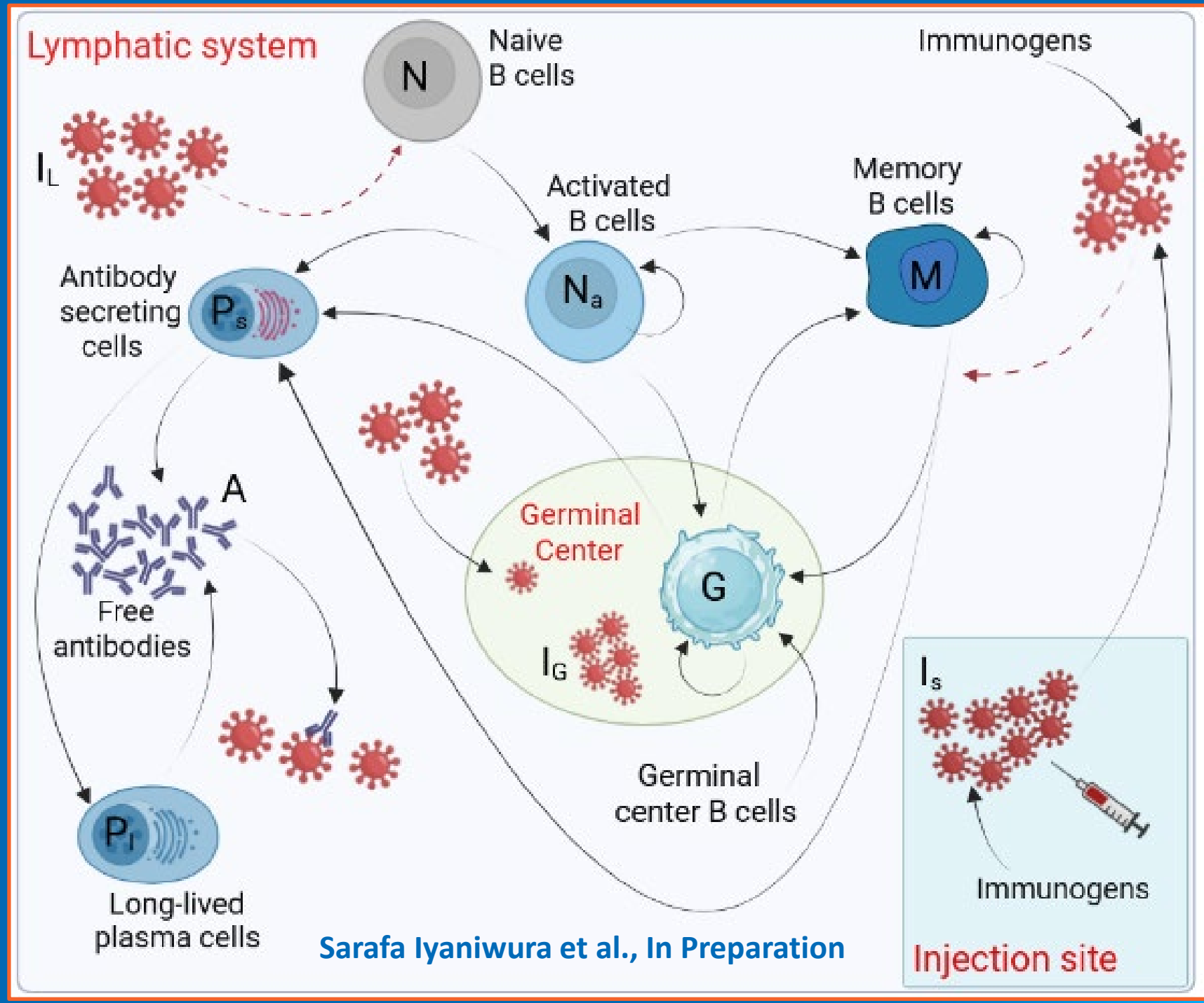
- **Growing interest in quantitative immune system models**
- **Approaches:**
  - Ordinary Differential Equation (ODE) models
  - Stochastic/Systems Immunology Models

- **Potential applications:**
  - Predict immune response trajectories
  - Optimize dose, timing, and sequence of immunogens
  - Reduce experimental search space
- Limitations: predictive performance still under evaluation

Schematic diagram of B-cell dynamics.

- injection site (I_s),
- lymphatic compartments (I_L),
- germinal center (I_G).
- immunogen-specific naïve B cells (N), activated B cells (N_a),
- germinal center B cells (G),
- short-lived antibody secreting cells (P_s), long-lived plasma B cells (P_l),
- memory B cells (M),
- free antibodies (A).

Black arrows indicate transfer of immunogens between compartments or differentiation of cells. Red dashed arrows represent activation of naïve and memory cells by immunogens.



Summary

- **Novel approaches to clinical trial design and data analysis are needed for the development of bnAb-inducing HIV vaccines**
  - Early identification and elimination of ~7/17 (41%) unsuccessful immunogens evaluated in HVTN's phase 1 discovery medicine trials since 2020.
- **Initial success has been observed in the induction of bnAb precursor B-cell responses** (Caniels et al., *Science* 2025; Willis et al, *Science* 2025)
- **Safety of candidate bnAb-inducing immunogens have been evaluated in >600 participants of discovery medicine trials.**

Acknowledgements

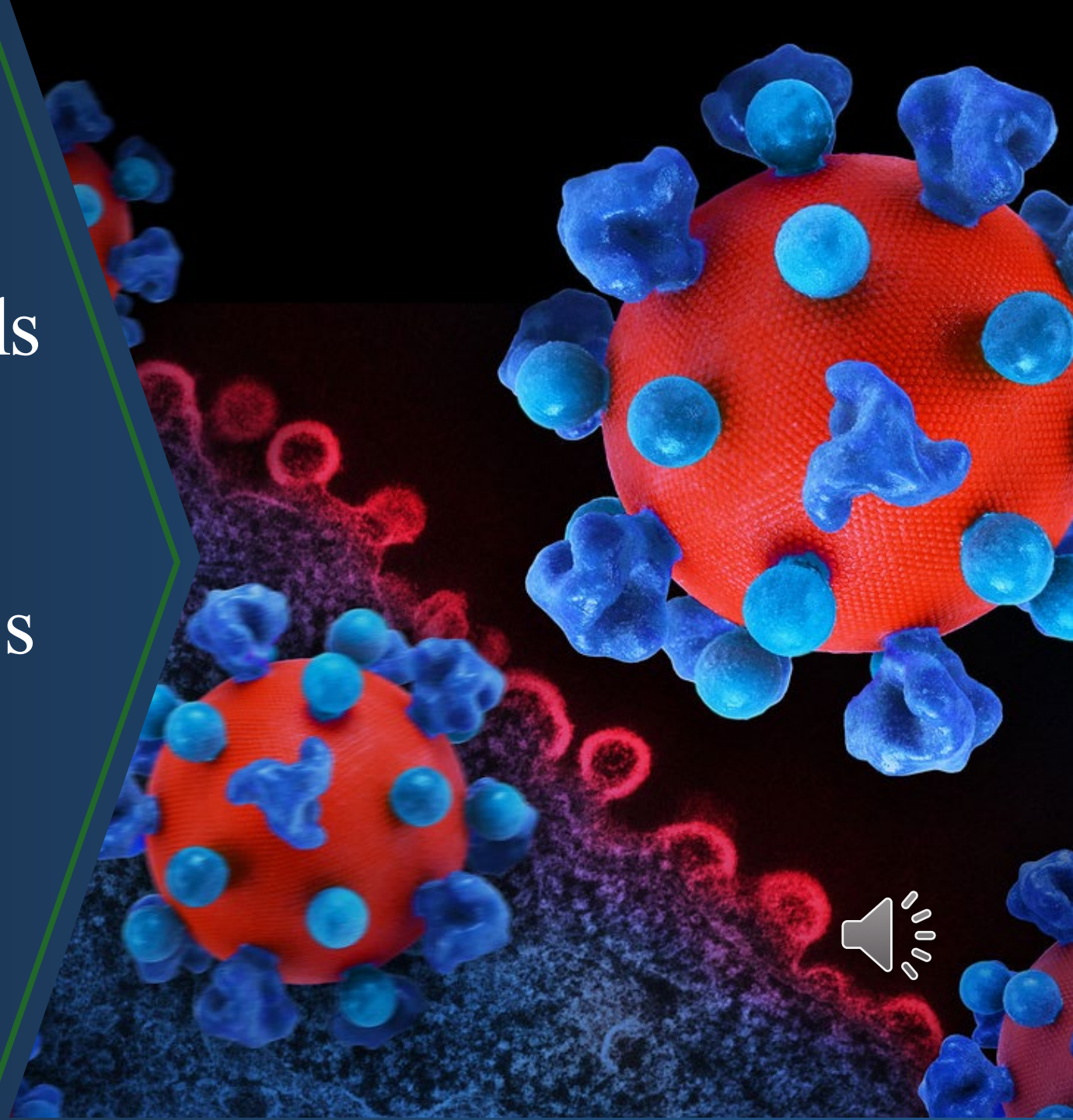
NIH National Institute of Allergy and Infectious Diseases

HIV VACCINE TRIALS NETWORK

Study teams, site investigators/staff, pharmacists, community members & TRIAL PARTICIPANTS!

National Institute of Allergy and Infectious Diseases

Discovery Medicine Trials of bnAb-inducing HIV Vaccines – Regulatory Perspective and Lessons



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Division of Acquired Immunodeficiency Syndrome (DAIDS)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)

Disclaimer & Disclosure

The views and opinions expressed in this presentation are the speaker's own and do represent the official policy of the NIH, DHHS, or any other government agency or official.

No relevant financial disclosures.

Agenda

- History
- Discovery Medicine Program
- FDA Engagement
- Current Approach

Classic Drug/Vaccine Development

- Trials look at a single or a combination of products in a single study
- Products do not change over the course of the study
- The drug(s)/vaccine(s) are regulated by FDA under a single IND

Non-iterative DAIDS HIV Vaccine Trial

Group	N	Week 0 (Month 0)	Week 8 (Month 2)	Week 16 (Month 4)
1	12	Immunogen A	Immunogen A	Immunogen A
2	12	Immunogen A	Immunogen A	Immunogen A
3	12	Immunogen A	Immunogen A	Immunogen A
4	12	Immunogen A	Immunogen A	Immunogen A
Total	48 (adult participants without HIV)			

HVTN Discovery Medicine Program

- Gaining knowledge to facilitate iterative advancement in vaccine development
- Ability to expand study scope based on early immune response data
- Current trials are not planned to progress immediately to Phase 2 and beyond

Martin TM, Robinson ST, Huang Y. Curr Opin HIV AIDS. 2023

HVTN Discovery Medicine Program

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Martin TM, Robinson ST, Huang Y. Curr Opin HIV AIDS. 2023

HVTN Discovery Medicine Program

- Addition of immunogens and/or adjuvants to on-going trials
  - Testing a series of immunogens where the manufacturing and CMC would be available sequentially in time and the clinical protocol will be amended to incorporate each new immunogen as it becomes available
  - Testing priming regimen(s) and prospectively planning for a boost immunogen from a series of existing immunogens that is to be chosen based on immunogenicity data from the primed participants

Non-iterative DAIDS HIV Vaccine Trial

Group	N	Week 0 (Month 0)	Week 8 (Month 2)	Week 16 (Month 4)	Week 24 (Month 6)
1	12	Immunogen A	Immunogen A	Immunogen A	Immunogen B
2	12	Immunogen A	Immunogen A	Immunogen A	Immunogen B
3	12	Immunogen A	Immunogen A	Immunogen A	Immunogen B
4	12	Immunogen A	Immunogen A	Immunogen A	Immunogen B
Total	48 (adult participants without HIV)				

History of FDA Engagement

- Type C Meeting, Q1 2024
  - DAIDS proposed the use of adaptive trial design[1] for HVTN Discovery Medicine Program Trials

1. Adaptive Trial Design for Clinical Trials of Drugs and Biologics, Guidance for Industry, November 2019

Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2019
Biostatistics

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry

History of FDA Engagement

- Type C Meeting, Q1 2024
  - DAIDS proposed the use of adaptive trial design[1] for HVTN Discovery Medicine Program Trials
  - FDA did not agree with the proposed use of Adaptive Trial Design and requested additional information and requested a Type B Meeting
- Informal Scientific Presentation to CBER/OVRR, Q3 2024
  - DAIDS worked with OVRR to plan a 90 minute presentation by leaders in HIV vaccine development
- Type B Meeting, Q2 205
  - Worked with FDA on adapting Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial, Guidance for Industry[2] to work for Discovery Medicine Program

1. Adaptive Trial Design for Clinical Trials of Drugs and Biologics, Guidance for Industry, November 2019

Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2022

Current Approach

- Umbrella Trial Design
  - Single-trial infrastructure, design and protocol to evaluate multiple products
  - Each product is submitted under its own "secondary" IND with the umbrella trial and master protocol submitted under the "primary" IND
- Trials currently ongoing under an active IND
  - Submit a Type D meeting request to the current IND
- New trials that will be submitted to a future new IND
  - Submit a Type B pre-IND meeting request

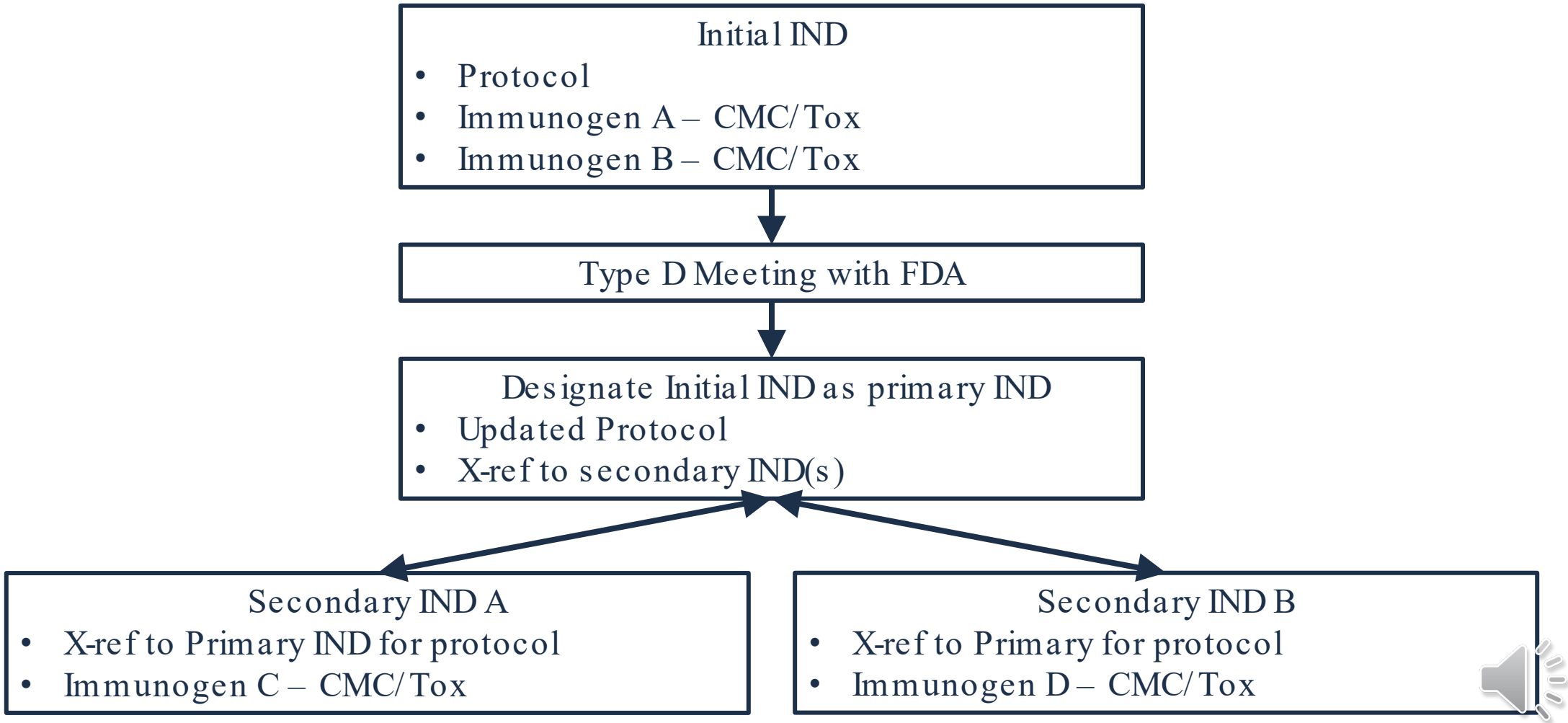
HVTN Discovery Medicine Examples

Discovery Medicine Umbrella Trial Example

Current Protocol Schema

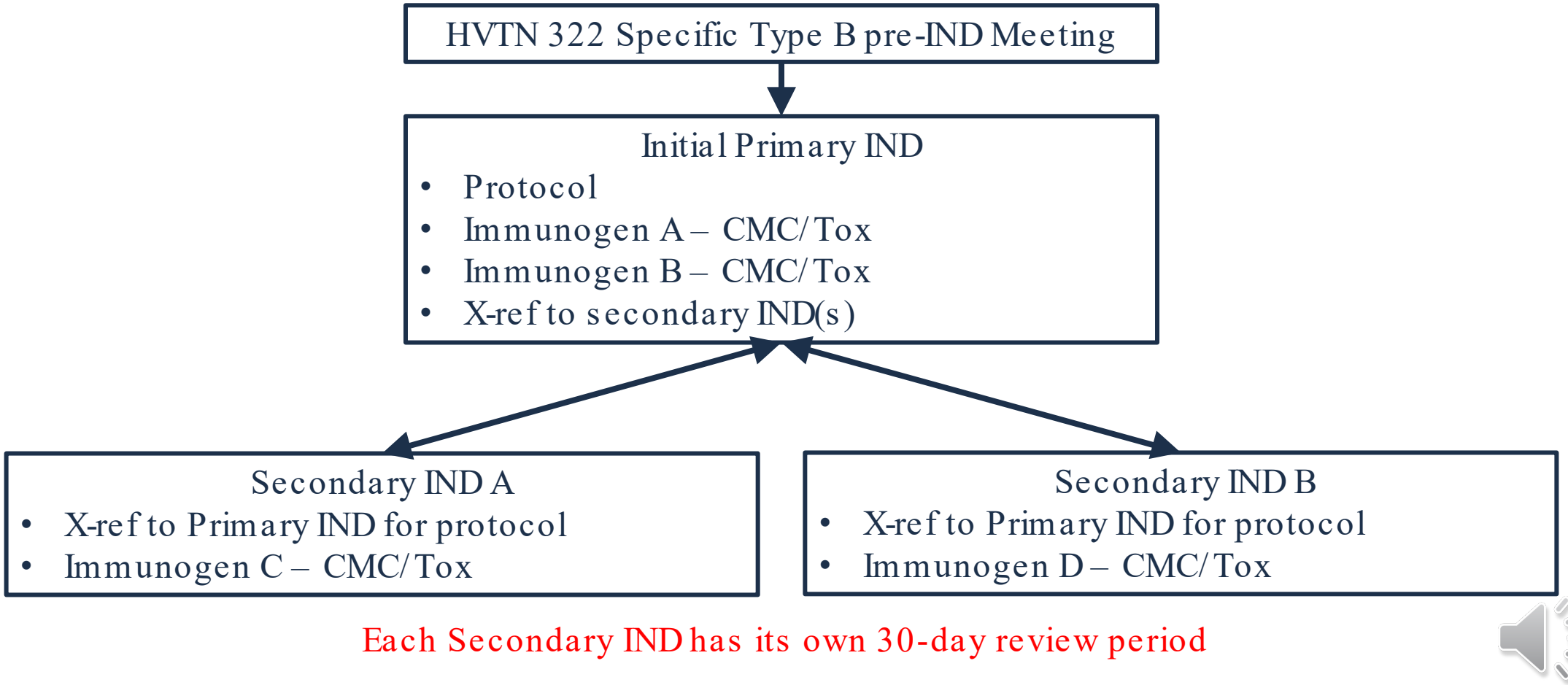
Group	N	Week 0 (Month 0)	Week 8 (Month 2)	Week 16 (Month 4)	Week 24 (Month 6)
1	12	Immmunogen A	Immunogen A	Immunogen A	Immunogen B
2	12	Immunogen A	Immunogen A	Immunogen A	Immunogen B
3	12	Immunogen A	Immunogen A	Immunogen A	Immunogen B
4	12	Immunogen A	Immunogen A	Immunogen A	Immunogen B
Total	48 (adult participants without HIV)				

Type D: Existing IND



Each Secondary IND has its own 30-day review period

Type B: pre-IND



Each Secondary IND has its own 30-day review period

Limitations and Conclusions

- Development of an effective HIV Vaccine has been unsuccessful for 40+ years, a new approach was necessary
- Our current approach is still on a case-by-case basis with the FDA
- May not be relevant to other drugs and biologics

- The FDA is willing to work within the regulations and guidances when there is an unmet need

Acknowledgements

All our trial participants

HIV VACCINE TRIALS NETWORK

ACTG

HPTN HIV Prevention Trials Network

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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- Mark Mishkin, M.P.H. – Deputy Branch Chief
- Yette Asfaw – Health Specialist
- Nikita Daniel, M.S. – Scientific Program Coordinator

Thank you

craig.sturgeon@nih.gov

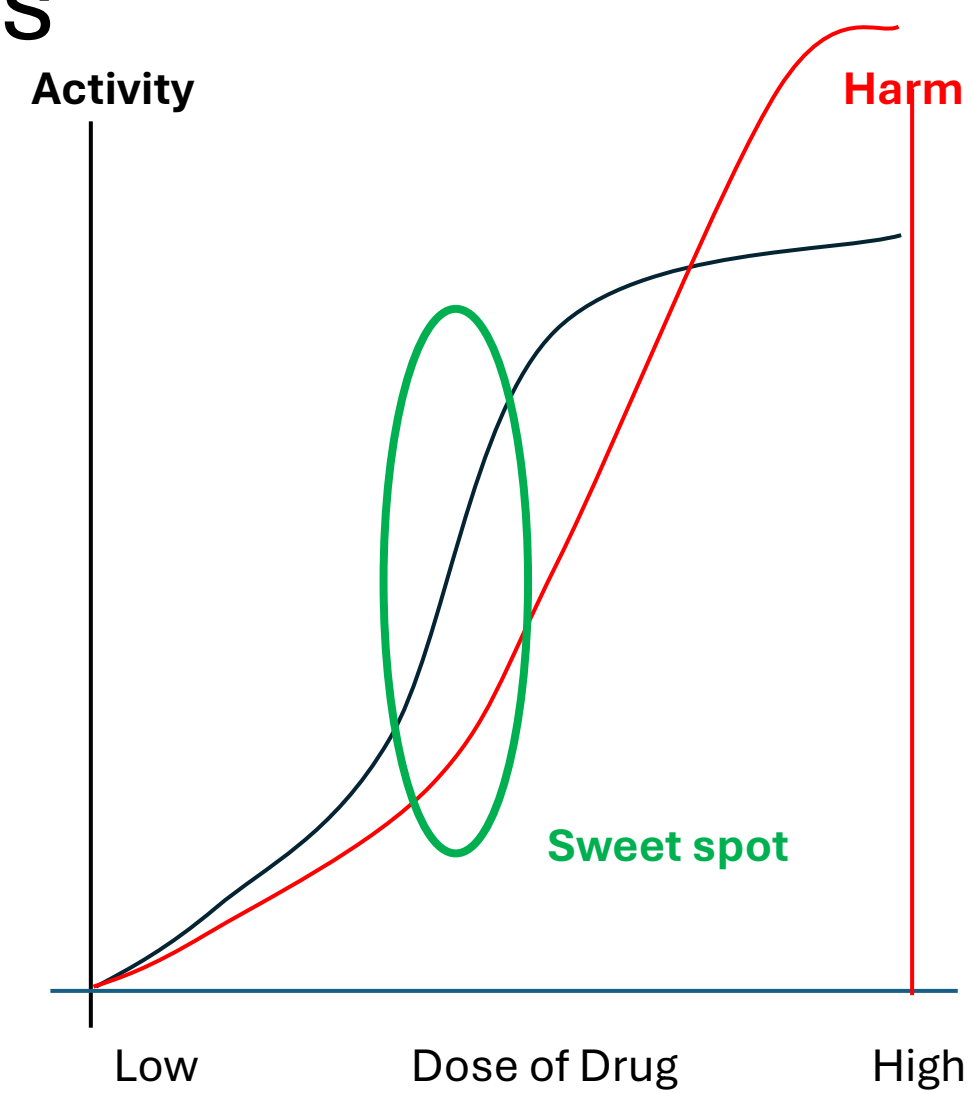
Discussion

Dean Follmann

NIH Alumnus

Drug Early Phase Studies

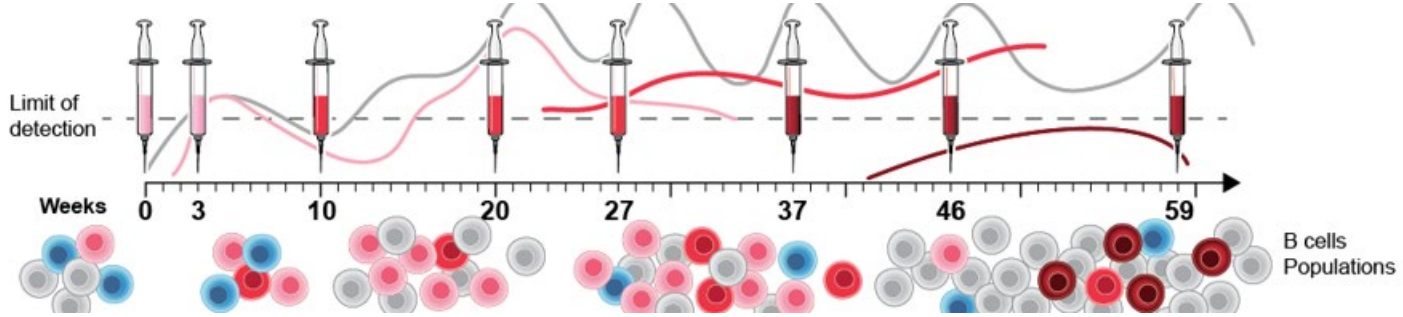
- Select a dose in humans that
  - Produces high biological activity
  - Has an acceptable safety profile
- Up/down dose selection



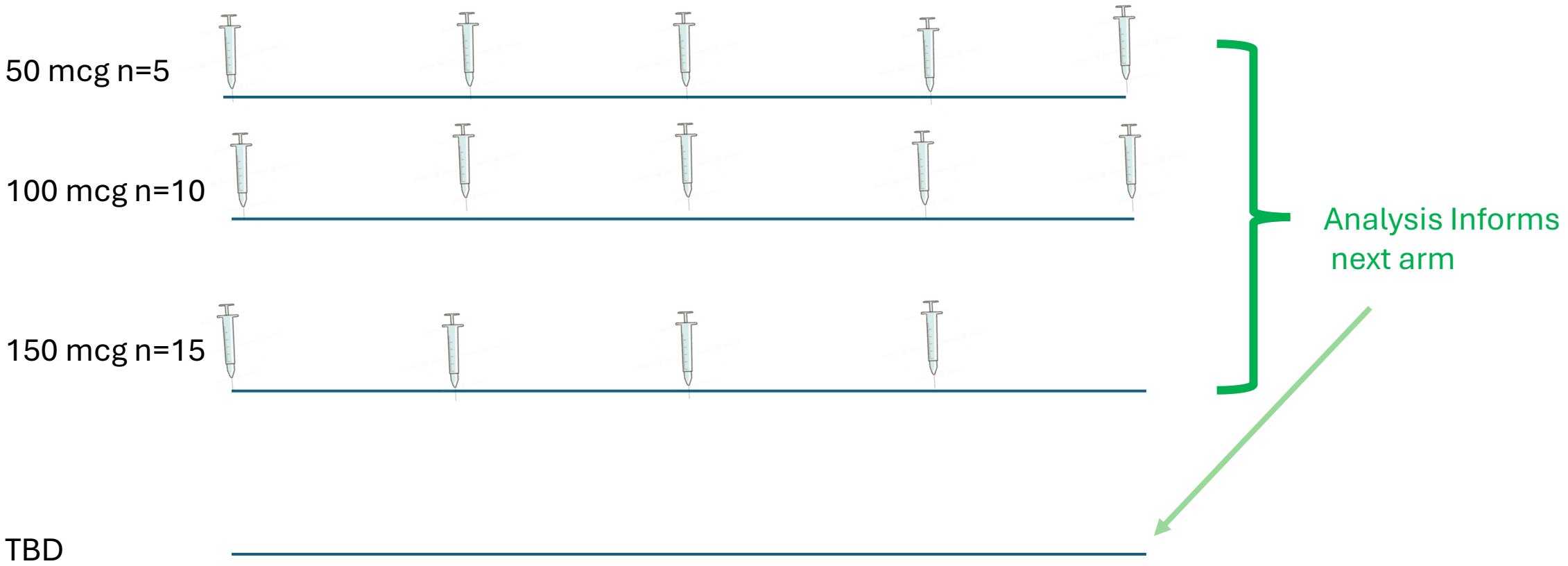
HIV Vaccine Early Phase Studies

- Develop a complex sequential vaccine regimen that involves
  - Immunogen (what your immune system recognizes)
  - Dose (amount of immunogen)
  - Timing (interval between shots)
  - Adjuvants (other chemical that increases immune response)
- Goal to train “the right” naïve B-cells

  to fight multiple HIV strains

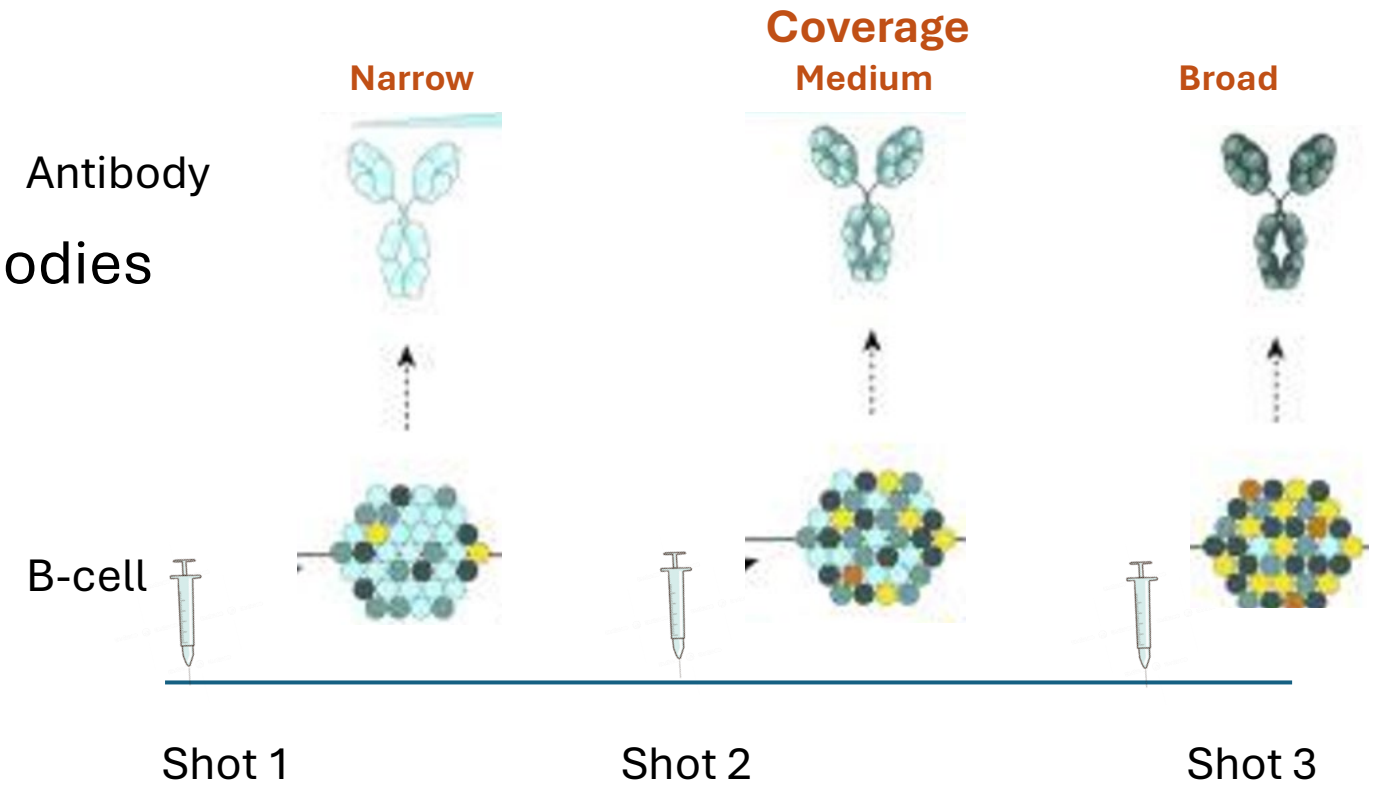


FDA Accepts Design Flexibility



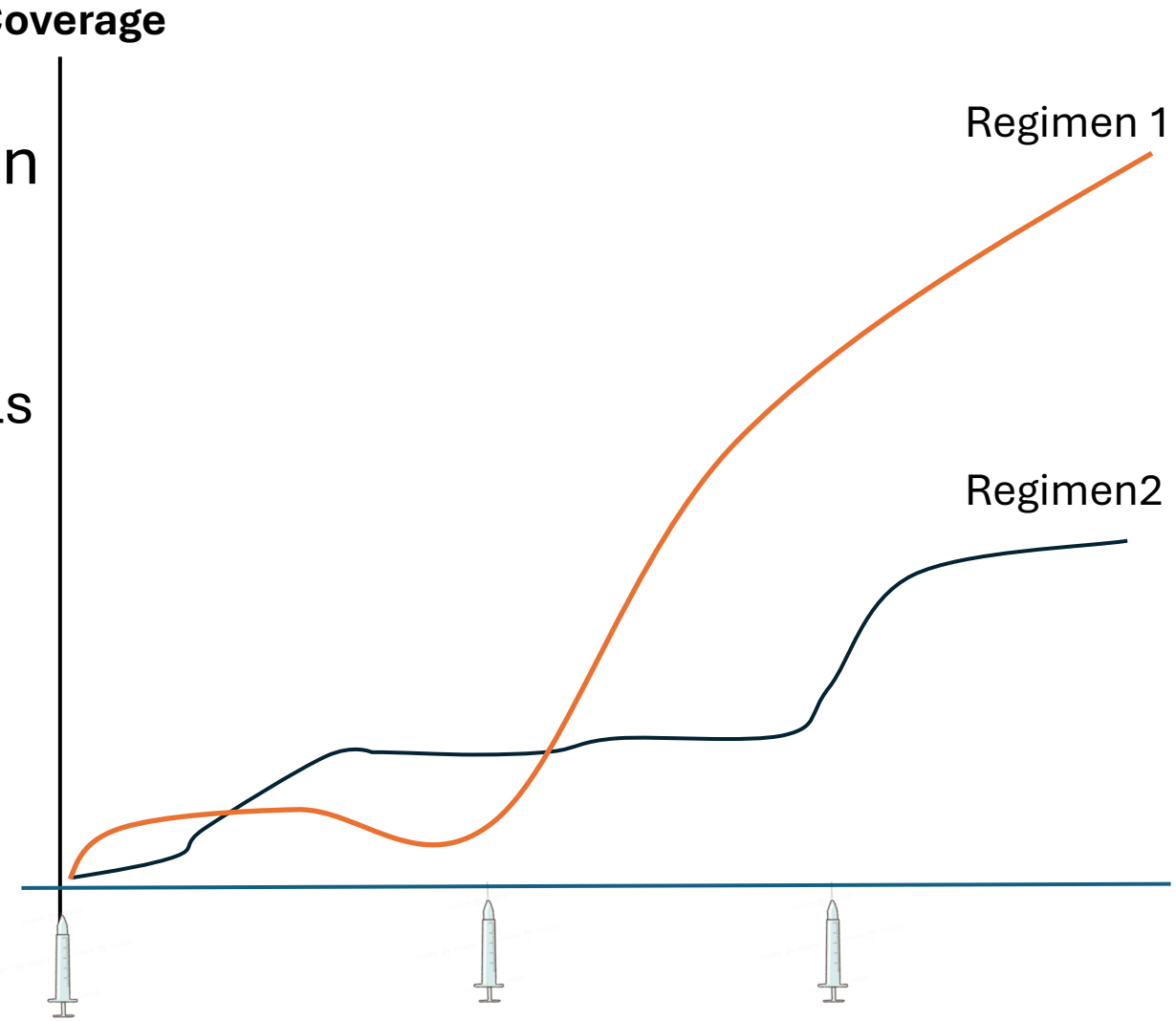
Training B-cells to fight multiple HIV strains

- Successive shots push the right B-cells to hypermutate in the receptor region
- Daughter cells can mutate as well
- Leads to broadly neutralizing antibodies



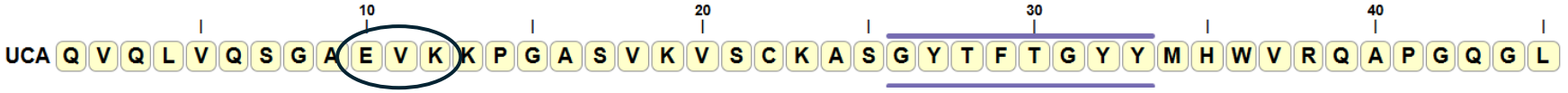
HIV Vaccine Early Phase Studies

- Develop a complex vaccine regimen
  - Coax out rare B-cells
  - Encourage mutations
  - Refine into broadly neutralizing B-cells



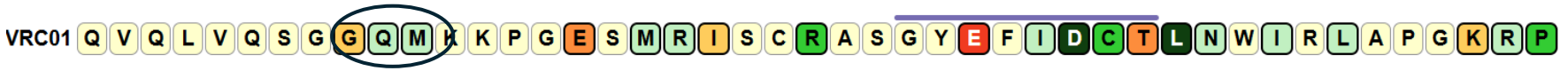
Develop B-cells to fight multiple HIV strains

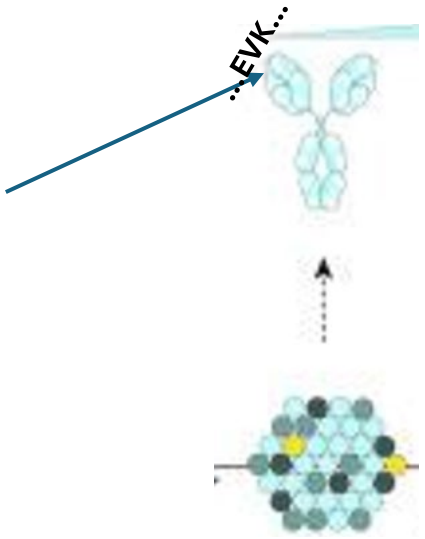
Rare B-cell



Sequential Immunization Induces Mutations

Broadly Neutralizing B cell





Narrow

Antibody

B-cell

BROAD

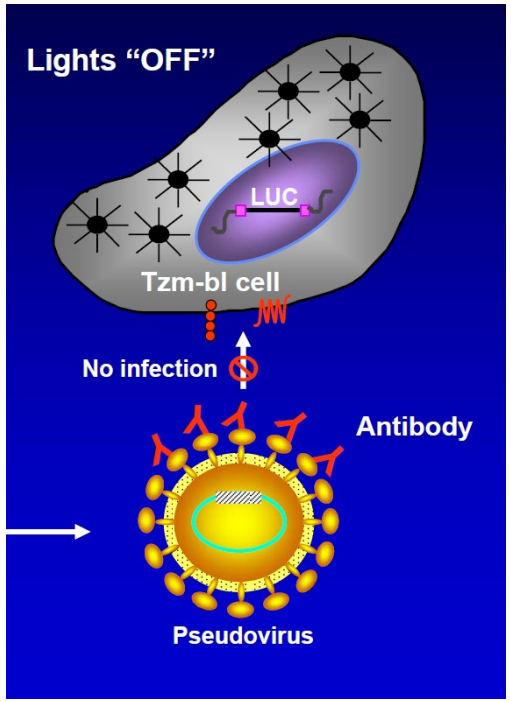
Antibody

B-cell

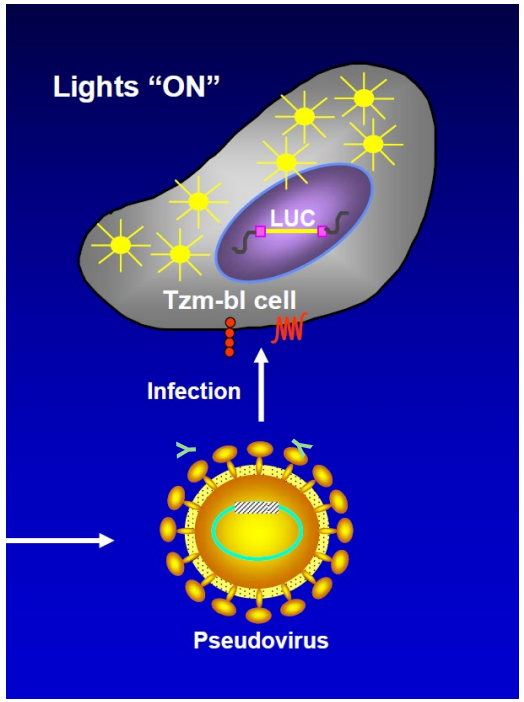
How do you analyze letters?

- Draw serum (with antibodies) following immunization
- Mix serum with virus and infectable cells
- Cells light up if virus gets inside
- Measure dilution when cells turn on
- Multiple reads for multiple viruses

Person	Virus 1 titer	Virus 2 Titer	Virus 3 Titer
Sally	1:1000	1:500	1:2000
Edward	1:100	1:10	1:10



Antibodies Work

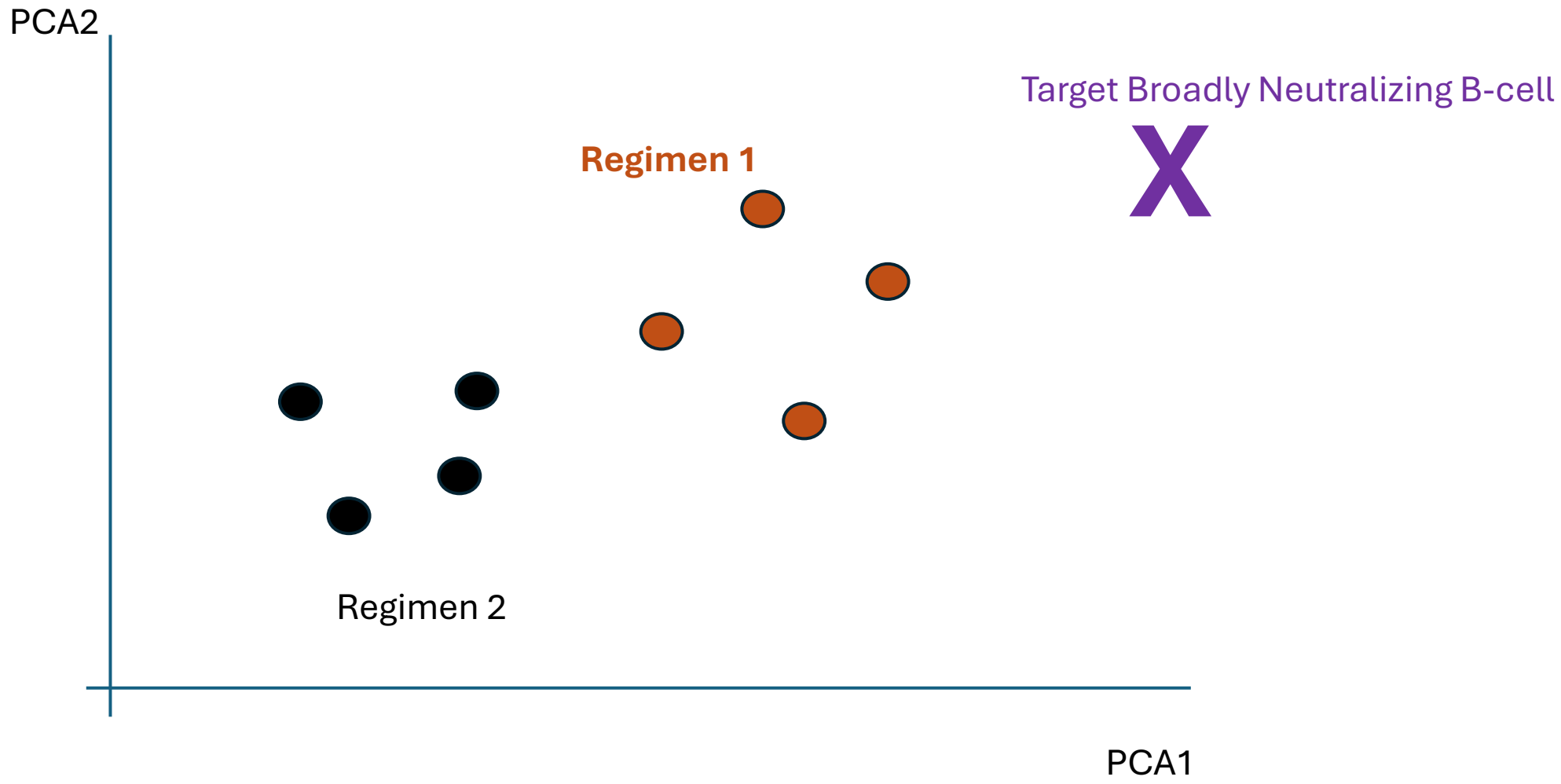


Antibodies Fail

How do you analyze letters?

- Text can be converged into a high dimensional vector **X**
  - “I saw a cowboy herding cats” => **X** = (0.15, 1.30, 2.28, . . . , -13.11)
  - “QVLQLVQ” => **X** = (0.25, 1.01, -0.28, . . . , 11.31)
- Statistically reduce the dimension of **X**
  - Neural network
  - Elastic net
- Measure how close an antibody is to the target antibody in the low dimensional space

Dimension Reduction of Letters to Vector



Summary

- Discovery medicine arms are complex
  - Timing, dose, immunogen, adjuvant can all be changed
- Impact is complex
  - Not drug in blood but coaxing a specific immune response
- Analysis is complex
  - How to analyze letters
- Strategy is ambitious
- Results so far are quite promising