# ExMed Protocols: Overview for Communities

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# Understanding the ExMed Studies

- ExMed = Experimental Medicine
- Exploratory in nature
- These are *vaccine* studies with a 300-series number (HVTN 300, 301, etc.).
- They are generally much smaller than our traditional Phase 1 studies.
- They may not always use a placebo/control group.

# Some key study features

- Often first-in-human studies and often using novel adjuvants
- Use of additional procedures to get a different look at immune responses – e.g. leukapheresis, fine needle aspiration (biopsy of the lymph nodes in the upper arm, close to the injection site)
- May test approaches to make all vaccines better rather than a specific product (for example, fractional dosing)

# Why do we need ExMed studies?

- AMP Studies proved that bnAbs can be protective. How do we induce them through vaccination?

- B cells that make bNabs develop along a particular path. It is important to test the start of a vaccine strategy (“prime”) before moving on to test the final regimen. Are you on the right path? Do you need to make adjustments to the vaccine regimen?

# Sample Primary Objectives

| Primary Objectives | Endpoints |
|---|---|
| 1. To assess the safety and tolerability of the vaccine/adjuvant regimen | a) Local and systemic reactogenicity signs and symptoms will be collected for a minimum of 7 days following vaccination. |
| | b) Serious adverse events (SAEs), medically attended adverse events (MAAEs), adverse events of special interest (AESIs) and adverse events (AEs) leading to early participant withdrawal or permanent discontinuation will be collected throughout the study and for 12 months following vaccination. Additionally, all adverse events will be collected for 30 days after any receipt of study vaccination. |
| 2. To determine the expansion of CD4 binding site (CD4-bs) cross-reactive B cells including VRC01-class B cells following immunization with either bolus or fractionated dosing. | a) Frequency of CD4-bs-specific B cells will be determined by flow cytometry. |
| | b) Frequency of VRC01-like BCR sequences will be determined by VH/VL sequencing of sorted B cells. |

# Sample Secondary Objectives & Endpoints

| Secondary Objectives | Endpoints |
|---|---|
| 1. To determine the quality and quantity of Env-specific binding antibodies (Abs) elicited by vaccination with either bolus or fractionated dosing. | Response rate, magnitude, epitope-specificity, and avidity of Env-specific serum IgG binding antibodies. |
| 2. To determine whether the fractionated dose vaccination approach increases the frequencies of CD4-bs-specific B cells, (including VRC01-like B cells) compared to the traditional bolus dose delivery. | Frequency of CD4-bs B cells and BCR sequences of isolated CD4-bs and VRC01-class memory B cells induced post-immunization with the traditional bolus dosing versus the fractionated dose delivery approach and induced following a “low” or “high” dose second dose. |
| 3. To determine neutralizing properties of vaccine-induced Abs after each immunization. | Response rate and magnitude of serum antibody neutralization of the vaccine strain, and a panel of CD4-bs bnAb precursor-sensitive viruses, as measured by TZM-bl assay. |
| 4. To determine whether the fractionated dose vaccination approach, when compared with the traditional bolus dose delivery, increases the frequencies of CD4-bs-specific B cells, and/or induces genetic changes associated with the development of broadly neutralizing antibodies (bnAbs). | Analysis of CD4-bs-specific B cell frequencies and BCR sequences, as described in Primary Objective 2, with comparisons between fractionated dosing and traditional bolus dosing. |

# Sample Exploratory Objective

To conduct analyses related to furthering the understanding of HIV, immunology, vaccines, and clinical trial conduct, including but not exclusive to B cell repertoire analysis (including analysis of rare B cell lineages associated with bnAb precursors), and assessment of lymph node aspirate for germinal center activity, including cellular phenotyping and mutational frequency analysis suggestive of somatic hypermutation and affinity maturation following immunization.

# Sample study schema: HVTN 300

A protein vaccine given with a 2-adjuvant combo:
study is fully enrolled (n=12) and in follow-up

| | | | Time after first injection visit | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Procedure | Screening visit(s) | First injection visit | 2 weeks | 2 months | 2½ months | 4 months | 4½ months | 8 months | 8½ months | 12 months | 12½ months | 18 months | 2 years |
| **Injection** | | √ | | √ | | √ | | √ | | √ | | | |
| Medical history | √ | | | | | | | | | | | | |
| Complete physical | √ | | | | | | | | | | | √ | |
| Brief physical | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | | |
| Blood drawn | √ | √ | √ | | √ | √ | √ | √ | √ | √ | √ | √ | |
| **Lymph node cell collection** | | | | | | | √ | | | | | | |
| **Leukapheresis*** | | √ | | | | | | | √ | | | | |
| Pregnancy test** | √ | √ | | √ | | √ | √ | √ | √ | √ | | √ | |
| HIV testing | √ | | | | | √ | | √ | | √ | | √ | |
| Risk reduction counseling | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | |
| Interview/questionnaire | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

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# Sample study schema: HVTN 301

A protein vaccine given with a 2-adjuvant combo, given in traditional “bolus” dosing, or divided into fractionated dosing: study is still under regulatory review and not yet final

| BOLUS DELIVERY ARM | | | |
|---|---|---|---|
| Group | n | First injection visit | Final injection visit 3 months later |
| 1 | 12 | Medium dose | Lower dose |
| 2 | 12 | Medium dose | Higher dose |
| 3 | 2 | Placebo | Placebo |
| All groups will receive injections at 2 visits scheduled 3 months apart. Lymph node cell collections at 2 timepoints post-vaccination. | | | |

| FRACTIONATED DELIVERY ARM | | | |
|---|---|---|---|
| Group | n | First dose divided into smaller amounts at 6 injection visits | Final injection visit 3 months later |
| 4 | 12 | Medium dose | Lower dose |
| 5 | 12 | Medium dose | Higher dose |
| 6 | 2 | Placebo | Placebo |
| The first dose will be divided into 6 smaller amounts [2 visits per week (Monday and Thursday) for 3 weeks]. The second dose will be given about 3 months later and will be given all at once. Lymph node cell collections at 2 timepoints post-vaccination. | | | |

# Sample study schema: HVTN 305

**A DNA vaccine at a lower and higher dose given intradermally with electroporation, and a protein vaccine boost with a 2-adjuvant combo given intramuscularly: study is still under regulatory review and not yet final**

| Group # | Number of People | Products | Dose | Where | How | First injection visit | 1 mont h later | 3 months later | 6 months later |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 9 | DNA vaccine | Lower dose | Skin of both upper arms | Needle & syringe + EP | X | X | X | |
| 2 | 18 | DNA vaccine | Higher dose | Skin of both upper arms | Needle & syringe + EP | X | X | X | |
| 3 | 18 | DNA vaccine | Higher dose | Skin of both upper arms | Needle & syringe + EP | X | X | X | |
| | | Protein vaccine | -- | Muscle of both upper arms | Needle & syringe | | | X | X |

- Group 1 is the first-in-human use of this vaccine.
- All participants get leukapheresis at 2 timepoints
- Groups 2 and 3 get lymph node biopsy at 2 timepoints.

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# Community Engagement

- Sites are held to all the same requirements.
- Protocol teams continue to have community representation: CAB members and community education/recruitment staff.
- HVTN committee review process for protocol development continues to have community representation at every level.

- Biggest difference is in the Informed Consent form and any supplemental materials: we are providing details about the additional procedures, showing pictures if relevant, etc.

# Acknowledgements


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# THANK YOU

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