Designing HIV Vaccine Efficacy Trials in the PrEP Era

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Background

- Results of PrEP trials and FDA approval of Truvada in July 2012 have changed the landscape for HIV prevention
  - Increasing numbers of vaccine and non-vaccine prevention trial participants may be using PrEP for HIV prevention
  - Increasing interest in combination prevention strategies
Potential Mutual Enhancements of Vaccine and PrEP Efficacy (Scott Hammer/Magda)

• PrEP may improve vaccination
  ♦ PrEP during vaccination phase may protect before vaccine-induced protective immunity has matured
  ♦ PrEP during vaccination and immediately post-vaccination may protect activated CD4+ T cells
  ♦ PrEP intra-cellularly at the site of vaccination may make it easier for vaccination to abort infection at the site, and viral antigen expression may adjuvant vaccine-induced immunity

• Vaccination may improve PrEP
  ♦ Vaccine may protect during periods of low PrEP adherence

• PrEP/Vaccine may improve each other
  ♦ Threshold for virus escape (from both vaccine and PrEP) may increase
Outline

- Vaccine efficacy trial designs that account for background PrEP use

- Vaccine efficacy trial designs that assign PrEP as a study intervention

Vaccine efficacy trial designs that account for background PrEP use

Context: PrEP not yet standard of care for the efficacy trial population, and interest centers on studying the vaccine with no or limited PrEP use

Example: HVTN 505
• A Phase 2, randomized, placebo-controlled trial to evaluate the safety and effect on post-HIV acquisition viremia of a multiclade HIV-1 DNA plasmid vaccine followed by a multiclade HIV-1 recombinant adenoviral vector vaccine in HIV-uninfected, adenovirus type 5 neutralizing antibody negative, circumcised men and transgender women, who have sex with men in the US

• n = 1350 ppts, randomized 1:1 (vaccine:placebo) and followed for at least 12 months post-enrollment
  – Began enrolling May, 2009

• Primary vaccine activity endpoint: setpoint viral load
  – Study not powered to assess the vaccine effect on HIV acquisition
In 2010, iPrEx results showed that daily oral tenofovir reduced the risk of HIV acquisition by 44% (95% CI: 15-63%) in an international MSM population.

The RV144 Thai vaccine efficacy trial had also recently been published showing 31% vaccine efficacy (VE) (95% CI: 1.1 - 52.1).

At the time, about half of the planned $n = 1350$ HVTN 505 participants had been enrolled.
505 Design Modification

• Chosen following input from community, trial participants, site investigators, study team, and funding agency

• Add monitoring for PrEP, and increase to n = 2200 to allow
  – HIV acquisition as co-primary endpoint
    • 80% power to detect VE = 50%
    – 20% PrEP uptake assuming TE-PrEP = 44%

• Trial stopped due to efficacy futility on April 22, 2013

TE = treatment efficacy = 1 – relative risk
Impact of PrEP Use on Vaccine Efficacy
Trial Sample Size

• In general, the lower underlying HIV incidence due to background PrEP requires enlarging a trial
  ♦ e.g. in HVTN 505, allowing for up to 20% background PrEP use assuming 44% efficacy necessitated a ~9% increase in sample size
Impact of PrEP Use on Trial Sample Size*

Trials sized to detect 40% VE with 90% power (1-sided 0.025-level log-rank). Calculations assume PrEP does not affect vaccine efficacy.

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* Sample sizes for two-arm trial; placebo group incidence absent PrEP use is 4% annually. Trials sized to detect 40% VE with 90% power (1-sided 0.025-level log-rank). Calculations assume PrEP does not affect vaccine efficacy.
Measuring PrEP Use: Two-Phase Sampling Design (e.g., HVTN 505)

To enable assessment of PrEP-related objectives, e.g. VE by PrEP use:

- Two-phase design measures ‘cheap proxy’ data in everyone and ‘expensive gold-standard data’ in a selected sample

- **Phase I:** Self-reported use for all trial participants

- **Phase II:** ARV concentrations in plasma or mucosal specimens for selected participants:
  - All HIV-infected ppts at and just prior to diagnosis
  - All ppts self-reporting PrEP use
  - Random sample of ppts not self-reporting use
  - All ppts in the immunogenicity cohort, at the primary immunogenicity time point
  - All ppts at enrollment (for case-only assessment of PrEP modification of VE)
Vaccine efficacy trial designs that include PrEP as study intervention

*Context:* PrEP not yet standard of care for the efficacy trial population, but there is interest in designs that assign it to some or all participants
Illustration: Phase 2b Vaccine Efficacy Trial Design (Gilbert et al., 2011)

- Consider Stage 1 of the two-stage Phase 2b efficacy trial design being planned for southern Africa
  - Enroll ppts over 18 months (halved accrual first 6 months), equal allocation to treatment arms, follow for 18 months
  - Test bi-monthly for incident infection
  - Assumed HIV incidence is 4% annually, absent Vaccine or PrEP
  - Power trial to detect VE = 40% using 1-sided log-rank test with 2.5% type I error

- Final analysis when all participants reach 18 months follow-up

- Determine n to ensure 50% probability that sufficient infections are observed to address each primary objective with 90% power
PrEP Assumptions

• In evaluating TE-PrEP and TE-Vaccine + PrEP, null hypothesis is $H_0: \ TE \leq 30\%$ [vs. for vaccine, $H_0: \ TE-Vaccine \leq 0\%$]
  ♦ Consistent with null used in PrEP trials

• Design study assuming vaccine and PrEP are additive, i.e., with $RR = 1 - TE$:
  ♦ Additivity: $RR\text{-Vaccine+PrEP} = RR\text{-Vaccine} \times RR\text{-PrEP}$
  ♦ Antagonism: $RR\text{-Vaccine+PrEP} > RR\text{-Vaccine} \times RR\text{-PrEP}$
  ♦ Synergy: $RR\text{-Vaccine+PrEP} < RR\text{-Vaccine} \times RR\text{-PrEP}$

• Interventions are double-blinded and primary analyses are intention-to-treat
  ♦ Secondary analyses include evaluating TE-PrEP in the adherent subgroup
Potential Primary Objectives and Study Designs

<table>
<thead>
<tr>
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| 1. Evaluate TE-Vaccine+PrEP  
2. Evaluate TE-Vaccine  
3. Compare TE-Vaccine vs. TE-Vaccine+PrEP                                      | **Design A:**  
• Vaccine               + PrEP  
• Vaccine-placebo + PrEP  
• Vaccine              + PrEP-placebo  
• Double placebo        |
| 1. Evaluate TE-Vaccine+PrEP  
2. Evaluate TE-Vaccine  
3. Compare TE-Vaccine vs. TE-Vaccine+PrEP                                      | **Design B:**  
• Vaccine               + PrEP  
• Vaccine              + PrEP-placebo  
• Double placebo        |
| 1. Evaluate TE-Vaccine in the context of PrEP                                    | **Design C:**  
• Vaccine               + PrEP  
• Vaccine-placebo + PrEP  
• Vaccine              + PrEP-placebo        |
| 1. Evaluate TE-Vaccine in the context of PrEP                                    | **Design D:**  
• Vaccine               + PrEP  
• Vaccine-placebo + PrEP        |
| 1. Evaluate TE-Vaccine+PrEP                                                      | **Design E:**  
• Vaccine               + PrEP  
• Double placebo        |
Secondary Objectives

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<td><strong>Design D:</strong>&lt;br&gt;• Vaccine + PrEP&lt;br&gt;• Vaccine-placebo + PrEP</td>
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<td>1. Evaluate TE-Vaccine+PrEP</td>
<td><strong>Design E:</strong>&lt;br&gt;• Vaccine + PrEP&lt;br&gt;• Double placebo</td>
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If TE-PrEP = 60%:

- N = 7,600 for Design A
- N = 5,700 for Design B
- N = 13,800 for Design C
- N = 9,200 for Design D
- N = 1,400 for Design E

*Assume TE-Vaccine = 40% and the Vaccine & PrEP work additively
Summary of Results

• **Relative sample sizes**
  – Designs C and D evaluating Vaccine in the context of PrEP are the largest, due to the reduced underlying HIV incidence
  – Design E assessing combination prevention is smallest
  – Designs A, B assessing efficacy of Vaccine alone and with PrEP, and comparing these efficacies, are intermediate in size

• Designs A, B address 3 primary questions; Designs C, D, E each address only one objective

• Designs D, E pose challenges for breadth of vaccine licensure indication given that the vaccine is only studied in combination with PrEP
Establishing Non-inferiority of the Vaccine

- May be of interest to establish non-inferiority of Vaccine vs. Vaccine + PrEP, i.e. to demonstrate

  \[ \text{RR-Vaccine} \leq C \times \text{RR-Vaccine+PrEP} \]

  where \( C > 1 \) is non-inferiority margin
  ♦ Vaccine alone could spare toxicities and expense of PrEP

- Double-placebo arm would be necessary, given lack of prior evidence of Vaccine + PrEP efficacy

- Designs A and B that include Vaccine + PrEP, Vaccine, Double-placebo arms could address both superiority and non-inferiority objectives
Non-Inferiority, cont’d.

- Establishing non-inferiority may only be justified if low PrEP efficacy is anticipated.

- E.g. suppose Vaccine is non-inferior to Vaccine+PrEP if it preserves 50% of the efficacy on the log scale, i.e.

  \[ RR_{\text{Vaccine}} \leq 1.65 \times RR_{\text{Vaccine+PrEP}}, \]

  where \( 1.65 = \exp(0.5). \)

Assuming Vaccine and PrEP additively and TE-Vaccine = 40%, Vaccine is non-inferior only if

\[ 0.6 \leq 1.65 \times 0.6 \times RR_{\text{PrEP}}, \]

i.e. TE-PrEP \( \leq 39\% \)
Use of PrEP-placebo

• Given adherence issue, may be of interest to capture behavioral effects of PrEP provision in future studies

• If high PrEP efficacy has been established, use of PrEP-placebo may be considered unethical

• In the four-arm design A, PrEP-placebo could be replaced with no further intervention
  – Maintains the blind as to Vaccine receipt
  – TE-PrEP and TE-Vaccine+PrEP then capture the impact of participants’ knowledge as to PrEP receipt
Accommodating PrEP Unwillingness

• Fewer ppts may be willing to be randomized to PrEP than to vaccine
  ♦ Advantageous to use two-stage randomization, first to vaccine vs. vaccine-placebo, then PrEP-willing ppts to PrEP vs. PrEP-placebo
Two-Stage Randomization

1. Vaccine + PrEP

2. Vaccine + PrEP-placebo

2a. Vaccine

3. Vaccine-placebo + PrEP

4. Vaccine-placebo + PrEP-placebo

4a. Vaccine-placebo
Two-Stage Randomization

Evaluate efficacy of Vaccine-Alone:

- Compare 2+2a vs. 4+4a

1. Vaccine + PrEP

2. Vaccine + PrEP-placebo

2a. Vaccine

3. Vaccine-placebo + PrEP

4. Vaccine-placebo + PrEP-placebo

4a. Vaccine-placebo
Two-Stage Randomization

Evaluate efficacy of PrEP Alone:

- Compare 3 vs. 4
Two-Stage Randomization

Evaluate efficacy of Vaccine+PrEP:

- Compare 1 vs. 4
Advantages of the Two-Stage Randomization

• Increases the number of eligible participants

• Allows the design to achieve its objectives with the smallest-possible n
  • Eg if 2/3 are PrEP-willing, the n = 7,600 ppt Design A could be reduced to n = 6,900 using two-stage randomization
Accommodating Participants Desiring to Use PrEP

• Some participants may have a strong desire to use PrEP and therefore be unwilling to be randomized to PrEP/PrEP-placebo

• An alternative two-stage randomization queries about desire to use PrEP, willingness to be randomized to PrEP, or unwillingness to use PrEP at stage 2
Alternative Two-Stage Randomization

Desiring PrEP
1a. Vaccine + PrEP

1. Vaccine + PrEP

Vaccine -Placebo

PrEP -willing

2. Vaccine + PrEP -placebo

PrEP -unwilling

2a. Vaccine

Vaccine -Placebo

Desiring PrEP
3a. Vaccine-placebo + PrEP

3. Vaccine-placebo + PrEP

PrEP -willing

4. Vaccine-placebo + PrEP -placebo

PrEP -unwilling

4a. Vaccine-placebo
Alternative Two-Stage Randomization

1. Vaccine + PrEP
2. Vaccine + PrEP -placebo
3. Vaccine-placebo + PrEP
4. Vaccine-placebo + PrEP -placebo
5. Vaccine-placebo

Groups 1a and 3a do not contribute to primary evaluation of TE-Vaccine+PrEP, or TE-PrEP.

They can be used in secondary analyses comparing PrEP efficacy versus effectiveness.
Implications of the Alternative Two-Stage Randomization

- Maximizes the number of eligible participants
- However, a larger sample size is required because data from participants desiring PrEP are not used for primary analyses
Discussion (1)

- ARV use measured using plasma or mucosal samples may have error
  - e.g., Current assays using plasma samples can only detect ARV use within last 14 days

- Two-phase sampling methodology not well-developed to handle this problem
  - Existing methodology needs extension to accommodate error-prone phase II data
• Licensure complexities with Designs D and E
  ♦ Under Design D where PrEP is assigned to all ppts, would future licensure of the vaccine be restricted to ppts who take PrEP?
  ♦ Under Design E where Vaccine+PrEP is studied, would the vaccine be licensed only when co-administered with PrEP?

• Designs A and B advantageous by directly providing the needed data to
  ♦ Assess efficacy of Vaccine alone
  ♦ Assess efficacy of combination prevention
  ♦ Compare efficacy of Vaccine alone vs. combination prevention
  ♦ Design A also assesses efficacy of PrEP alone and compares efficacy of Vaccine alone vs. PrEP alone
Discussion (3)

• For the 4-arm Design A, two-stage randomization can be used to minimize sample size and include PrEP-unwilling participants
  – Additional inclusion of PrEP-desiring participants allows data from these subjects to contribute data to analyses comparing PrEP efficacy vs. effectiveness

• Given adherence issue, consideration warranted of unblinded PrEP provision in future trials
  – To capture the impact of participants’ knowledge of PrEP provision on efficacy