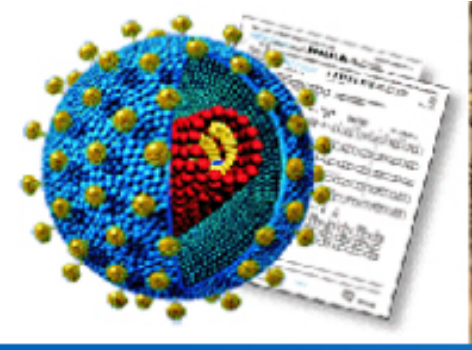



# Overview of Efficacy Study Design Strategies for new Systemic PrEP Products

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# Framework for Design Choices

1. Type of new product
2. Choice of control/standard

- Populations and known efficacy
- Superiority and non-inferiority
- Scientific rationale and ethical basis

# Type of new product

- New daily oral drug
  - Higher or equivalent efficacy
  - Risks and benefits
    - More effective drug, fewer side effects, higher adherence
    - Avoid first line treatment drugs, lower risk of community resistance
    - Expanded options, choice
- Longer acting formulation (injectable, less frequent oral dose)
  - Higher efficacy
  - Risks and benefits
    - Increased adherence and convenience
    - Safety concerns
- New dosing strategy for TDF/FTC (e.g. coitally dependent)
  - Equivalent efficacy
  - Risks and benefits
    - Likelihood of active drug at time of exposure
    - Decreased drug exposure and cost

# Choice of control

- Active control: Daily TDF/FTC

  Arm 1: Daily TDF/FTC

  Arm 2: New systemic drug or dosing strategy

- Placebo control:
  - "Add-on" design
    - All study participants have access to daily TDF/FTC

    Arm 1: Daily TDF/FTC + placebo

    Arm 2: Daily TDF/FTC + new systemic drug
  - Standard of care
    - No access to TDF/FTC

    Arm 1: Placebo

    Arm 2: New systemic drug

# Possible PrEP Scenarios

| Control | Experimental | | |
|---|---|---|---|
| | New daily oral drug | New longer acting drug | New TDF/FTC dosing strategy |
| **Active: Daily TDF/FTC provided as a study drug** | Scenario A | Scenario B | Scenario C |
| **Placebo add-on to daily TDF/FTC** | Scenario D | Scenario E | Scenario F - N/A |
| **Placebo** | Scenario G | Scenario H | Scenario I |

# Populations: Current Efficacy Results

| Study | Risk/Gender | Adherence | # of Events | Efficacy; 95% CI |
|---|---|---|---|---|
| Partners PrEP<br>Kenya, Uganda | Discordant heterosexual couples | ~80% | 13 vs. 52 | 75% (55%, 87%) |
| TDF2<br>Botswana | Heterosexual Men & Women | ~80% | 9 vs. 24 | 63% (22%, 83%) |
| iPrEx<br>Peru, Brazil , Ecuador (82%) | MSM | ~50% | 48 vs. 83 | 42% (18%, 60%) |
| FemPrEP<br>South Africa, Kenya (98%) | Heterosexual Women | ~35% | 33 vs. 35 | 6% (-69%, 41%) |
| VOICE<br>South Africa (81%) | Heterosexual Women | To be reported | To be reported | To be reported |

# Possible PrEP Scenarios

| Control | Experimental | | |
|---|---|---|---|
| | New daily oral drug | New longer acting drug | New TDF/FTC dosing strategy |
| Active: Daily TDF/FTC provided as a study drug | **Scenario A** | Scenario B | Scenario C |
| Placebo add-on to daily TDF/FTC | Scenario D | Scenario E | |
| Placebo | Scenario G | Scenario H | Scenario I |

# Scenario A: Daily new drug vs. Daily TDF/FTC

- Example: Maraviroc vs. TDF/FTC in MSM
- Assumes daily TDF/FTC is a standard of care, and is provided by the study
- Non-inferiority trial
  - Requires high adherence to daily regimen
  - Requires strong evidence of efficacy of new agent, since some participants are not receiving TDF/FTC
  - Prohibitively large trial under alternative of 1.0; more feasible if new drug expected to be slightly better than TDF/FTC

# Possible PrEP Scenarios

| Control | Experimental | | |
|---|---|---|---|
| | New daily oral drug | New longer acting drug | New TDF/FTC dosing strategy |
| **Active: Daily TDF/FTC provided as a study drug** | Scenario A | **Scenario B** | Scenario C |
| **Placebo add-on to daily TDF/FTC** | Scenario D | Scenario E | |
| **Placebo** | Scenario G | Scenario H | Scenario I |

# Scenario B: Longer Acting drug vs. Daily TDF/FTC

- Daily TDF/FTC assumed as standard of care
- Risk/benefit profile of longer acting drug
  - May have higher efficacy: better protection
  - Potential to preserve first line treatment drugs
  - May have more safety risk
- Superiority design justified if higher sustained drug levels
  - Example: Injectable vs. daily TDF/FTC in heterosexual women
  - Evidence of safety and potential for efficacy
  - Standard of care for maintaining adherence
- Non-inferiority design
  - Example: Longer acting vs. daily TDF/FTC in heterosexual couples
  - Requires safety and proof-of-concept for efficacy for new drug
  - Requires best real world achievable adherence
  - Feasibility of the trial depends on the margin set for non-inferiority (given setting where proven effective)

# Possible PrEP Scenarios

| Control | Experimental | | |
|---|---|---|---|
| | New daily oral drug | New longer acting drug | New TDF/FTC dosing strategy |
| **Active: Daily TDF/FTC provided as a study drug** | Scenario A | Scenario B | **Scenario C** |
| **Placebo add-on to daily TDF/FTC** | Scenario D | Scenario E | |
| **Placebo** | Scenario G | Scenario H | Scenario I |

# Scenario C: Alternate TDF/FTC dosing vs. Daily TDF/FTC

- Example: Coitally dependent vs. Daily TDF/FTC.
- Risk/Benefit
  - Likelihood of effectiveness for preventing HIV when exposed
  - Lower TDF/FTC exposure
- Non-inferiority setting
  - Establish alternate dosing strategy is acceptable alternative to daily
- Superiority of alternate dosing
  - Substantial reduction in HIV infections as a result of alternate (lower) dosing
- Priority only if non-daily dosing became a *de facto* standard of usage for TDF/FTC as PrEP

# Possible PrEP Scenarios

| Control | Experimental | | |
|---|---|---|---|
| | New daily oral drug | New longer acting drug | New TDF/FTC dosing strategy |
| **Active daily TDF/FTC control provided as a study drug** | Scenario A | Scenario B | Scenario C |
| **Placebo add-on to daily TDF/FTC** | **Scenario D** | **Scenario E** | |
| **Placebo** | Scenario G | Scenario H | Scenario I |

# Possible PrEP Scenarios

| Control | | Experimental | | |
|---|---|---|---|---|
| | | New daily oral drug | New longer acting drug | New TDF/FTC dosing strategy |
| **Active: Daily TDF/FTC provided as a study drug** | | Scenario A | Scenario B | Scenario C |
| **Placebo add-on to daily TDF/FTC** | TDF/FTC is available | **Scenario D** | **Scenario E** | |
| | TDF/FTC is provided by study | | | |
| **Placebo** | | Scenario G | Scenario H | Scenario I |

# Scenarios D&E:
# Add-on new daily vs. TDF/FTC alone
# Add-on longer acting vs. TDF/FTC alone

- Placebo controlled trial, TDF/FTC available to all study participants
  - Option 1: TDF/FTC provided as a study drug
    - Example: TDF/FTC + maraviroc vs. TDF/FTC + placebo in women
    - Does not preserve first line treatment drugs
  - Option 2: TDF/FTC in (changing background) real-world PrEP
    - Example: Injectable active vs. Injectable placebo in US MSM
    - Assess actual TDF/FTC use and drug-drug interactions
    - Likely appropriate for HIV vaccine and microbicide products
- Superiority
  - Does not require daily TDF/FTC to be highly efficacious
  - Plausible that longer acting could be more efficacious
  - Context of trial determines most relevant question

# Possible PrEP Scenarios

| Control | Experimental | | |
|---|---|---|---|
| | New daily oral drug | New longer acting drug | New TDF/FTC dosing strategy |
| **Active: Daily TDF/FTC provided as a study drug** | Scenario A | Scenario B | Scenario C |
| **Placebo add-on to daily TDF/FTC** | Scenario D | Scenario E | |
| **Placebo** | **Scenario G** | **Scenario H** | Scenario I |

# Scenarios G&H:
# New daily oral vs. placebo
# New longer acting vs. placebo

- Placebo possible where:
  - Community does not support TDF/FTC for PrEP but strong argument to support new drug
  - In a group unwilling or unable to take daily TDF/FTC
    - ***New drug needs to overcome these barriers***
- Superiority design
  - Example: Injectable active vs. injectable placebo in FemPrEP-like population
  - Highest achievable adherence (long acting preferable)
  - Likely need to establish super-superiority (rule out less than 30% efficacy)

# Possible PrEP Scenarios

| Control | Experimental | | |
|---|---|---|---|
| | New daily oral drug | New longer acting drug | New TDF/FTC dosing strategy |
| **Active: Daily TDF/FTC provided as a study drug** | Scenario A | Scenario B | Scenario C |
| **Placebo add-on to daily TDF/FTC** | Scenario D | Scenario E | |
| **Placebo** | Scenario G | Scenario H | **Scenario I** |

# Scenario I
# New TDF/FTC dosing vs. Placebo

- Example: Faster/longer acting TDF/FTC vs. placebo in FemPrEP-like population
- Superiority design
  - Daily TDF/FTC not practical or effective in a setting/population
  - Proof of concept that new dosing strategy will improve efficacy
  - Example:
    - Coitally dependent tenofovir gel effective in Caprisa 004;
    - Daily use of tenofovir gel not effective in VOICE

# Conclusion

- Both superiority and non-inferiority designs are possible design paths
- Design enmeshed with context:
  - Existing evidence (population & selected comparison)
  - Best available knowledge of safety and potential efficacy for new drug
- Principle of distributed justice: studies need to address the greatest unmet need