Non-inferiority Trials of new PrEP Interventions

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Motivation for Non-Inferiority PrEP Trials

- Existing effective intervention with substantial proven efficacy
- New product with favorable profile compared to existing intervention
## Motivation for Non-Inferiority PrEP Trials

<table>
<thead>
<tr>
<th>Study and setting</th>
<th>Risk/Gender</th>
<th>Adherence (test of plasma)</th>
<th># of Events</th>
<th>Efficacy; 95% CI</th>
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Profile of new PrEP product choices

- **New daily oral drug**
  - Somewhat higher or similar efficacy
  - Motivation
    - Fewer side effects, higher adherence
    - Avoid first line treatment drugs
    - Lower risk of community resistance

- **Longer acting formulation (e.g. injectable)**
  - Somewhat higher or similar efficacy
    - Increased adherence and convenience
  - Safety concerns

- **New dosing strategy for TDF/FTC (eg coitally dependent)**
  - Equivalent efficacy
    - Increased ‘coverage’ (active drug at time of exposure)
    - Decreased cost and side effects
## Possible PrEP Trial Scenarios

<table>
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<th>Control</th>
<th>Experimental</th>
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<tr>
<td>Daily TDF/FTC as an Active Control</td>
<td>Scenario A</td>
</tr>
<tr>
<td>Placebo add-on to Daily TDF/FTC</td>
<td>Scenario D</td>
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New product choices in PrEP

• New daily oral drug
  • Somewhat higher or similar efficacy
  • Motivation
    • Fewer side effects, higher adherence
    • Avoid first line treatment drugs
    • Lower risk of community resistance

• Longer acting formulation (e.g. injectable)
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• New dosing strategy for TDF/FTC (eg coitally dependent)
  • Equivalent efficacy
    • Increased ‘coverage’ (active drug at time of exposure)
    • Decreased cost and side effects
What is the question?

Superiority
• “Is new PrEP drug better than Placebo?”
• Scientific: Does new PrEP drug provide a clinically meaningful benefit?

Non-inferiority
• “Is new PrEP drug the same as FTC/TDF?”
• Scientific: Is new PrEP drug not unacceptably worse than FTC/TDF?
2010 FIFA WORLD CUP

GROUP A
- SOUTH AFRICA
- MEXICO
- URUGUAY
- FRANCE
- GROUP A WINNER
- GROUP B 2ND PLACE

GROUP B
- ARGENTINA
- NIGERIA
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FTC/TDF
Placebo

Winner: FTC/TDF
FTC/TDF
Placebo
Winner: FTC/TDF
New drug candidate
FTC/TDF
Placebo

Winner: FTC/TDF

New drug candidate
FTC/TDF
Placebo

Winner: FTC/TDF
New drug candidate
Dual Goals of Non-Inferiority Trials

1. Direct evaluation of the clinical efficacy/safety of Experimental relative to Standard
2. Contribute evidence to the evaluation of efficacy/safety of Experimental relative to Placebo

(Constancy assumption)

“The presumption that the historical estimates of effectiveness of the active standard apply under the conditions of the NI trial”
Factors invalidating Constancy Assumption
(New PrEP vs. FTC/TDF NI Trial vs. Trials of TDF/FTC vs Placebo)

- Patient characteristics
  e.g., Participants with different risk characteristics in NI Trial

- Use of supportive care
  e.g., Enhanced prevention SOC attenuates effect of FTC/TDF in NI Trial

- Dose, schedule, level of adherence
  e.g., Lower adherence to FTC/TDF in NI trial

- Efficacy and safety endpoints
  ~ well-defined & reliable ~ clinically meaningful ~ sensitive
What is the question?

**Non-inferiority**

- "Is the new PrEP drug the same as FTC/TDF?"
- **Scientific:** Is new PrEP drug **not unacceptably worse** than FTC/TDF?
- **Statistical design:** Can we rule out that a new PrEP drug is worse than FTC/TDF by **fixed margin**?
  - "Rule out" = not in the 95% confidence interval
Example: Maraviroc (new PrEP) vs. TDF/FTC (Standard)

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The challenge for a NI PrEP trial

- FTC/TDF is a PrEP regimen that provides a clinically meaningful protection
- Do not want to replace with a meaningfully less effective intervention

⇒ Reliable evaluation of benefit-to-risk profile of new PrEP interventions
  - Requires development of rigorous evidence-based NI margins.
1. Base on the effect of FTC/TDF estimated from historical trials

   *But the constancy assumption likely is invalid* due to differences between NI and Historical Trial (i.e. iPrEx) in:
   - baseline patient characteristics
   - supportive prevention standard of care
   - HIV risk factors
   - level of adherence to FTC/TDF

2. Preserve a specified percentage of the active control's effect

   Ethically cannot do a placebo controlled trial
“Setting the margin” for unacceptably worse

- A recommended approach
  1. Use lower 95% bound of existing evidence of efficacy as established “known benefit”.
  2. Preserve a fixed amount of known benefit e.g. 50%

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<th>Study and setting (% of total population)</th>
<th>Risk/Gender</th>
<th># of Events</th>
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<th>Efficacy = (1-RR)</th>
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RR

- 0.40 42% reduction
- 0.58 “known benefit”
- 0.82 “No benefit”
- 1.0 0%
“Setting the margin” for unacceptably worse

- A recommended approach
  1. Use upper 95% bound of existing evidence of efficacy as established “known benefit”
  2. Preserve a fixed amount of known benefit e.g. 50%

\[
\text{NI Margin} = \frac{1}{0.90} = 1.10
\]
A NI trial of Maraviroc vs. FTC/TDF

- Design: upper bound of 95% CI to rule out $RR = 1.10$
- Assume Maraviroc is slightly more effective (i.e. 25%)

10% increase
"Not clinically worse"

Non inferiority Trial HIV infection Duration
Maraviroc 133/3200 2 yr follow-up
TDF/FTC 153/3200 2.25/100 person years

$RR = 0.87 (0.69, 1.09)$
Interpretation of NI trials

“On the basis of the data alone, cannot distinguish between well conducted trial [with high adherence] where new drug found not unacceptably worse vs. a trial with low adherence that fails to find a true difference”

Non-inferiority trial

• ITT analysis anti-conservative
• As treated analysis can be biased in either direction
Summary of challenges:

- Reliance on historical trial results, the constancy assumption and known efficacy lead to very large trials
- Interpretation of results intrinsically unclear
- Inconsistency of PrEP efficacy results
- Risk/Benefit analysis for NI trials clearly easier for a product with a clear advantage over FTC/TDF
“Non-inferiority trials with non-rigorous margins allow substantial risk for accepting inadequately effective experimental regimens, leading to the risk of erosion in quality of health care...

Due to the inherent uncertainties in non-inferiority trials, alternative designs should be pursued whenever possible.”

Fleming TR, Odem-Davis K, Rothmann MD, Shen YL  “Some essential considerations in the design and conduct of non-inferiority trials.”  Clinical Trials 8: 432-439, 2011
ACKNOWLEDGEMENTS

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