How Can a Significant Outcome of One Trial Impact Ongoing or Future Trials?

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Next Steps for HIV Prevention in Women: Tenofovir Gel and Beyond

Joint Civil Society and MTN Community Working Group Meeting
8 October, 2011, Cape Town
Overview

- Placebo-controlled trials
- After the placebo: What then?
- Determining Standards of Prevention
- How can one trial impact another?
- DSMB reviews
- What happened in VOICE?
- Tenofovir gel: What do we need to be prepared for?
What is a placebo-controlled trial?

- A type of study that aims to determine how effective a treatment or intervention is compared to “no treatment at all.”
- One group of participants uses the active treatment and another group uses a placebo
  - Placebos look the same but do not contain an active product.
Why a placebo-controlled trial?

- Considered the gold standard
  - Best way to determine if a new drug or product is safe and effective

- Important for licensure
  - Regulators usually want to see data from a placebo-controlled trial

- Conducted when there is not already an approved product widely available and/or no clear evidence supporting a new indication
  - All HIV prevention trials currently use a placebo
How does it work?

- Participants in a trial are similar in age, risk, etc.
- They are randomly assigned to a study group like a roll of a dice
- Neither the researchers nor the participants knows the group they are in
Example: ASPIRE Study Design

Women will be randomized to use either a ring containing dapivirine or one with no active drug.
What’s an HIV prevention package?

3,476 Women

- HIV prevention package + Placebo ring 1,738 women
- HIV prevention package + Dapivirine ring 1,738 women
What’s an HIV prevention package?

- Researchers want to make sure that participants have access to prevention methods that we know can work to reduce the risk of HIV.
  - Called “standards of prevention”
- All women receive HIV counseling, condoms, risk reduction counseling, and treatment for STIs at each clinic visit.
- Participants are still at risk of HIV infection, because none of these methods are perfect, and the trials are conducted in areas with high HIV rates.
How do we determine efficacy?

- At the end of a study, we compare the number of HIV infections that occurred among women who received an active product with the number of HIV infections that occurred among women in the placebo group.

- If there are significantly fewer HIV infections in the group using the active product compared to the placebo, this means it is more effective for reducing the risk of HIV than a placebo.
What if we had an effective product?

- Would we still use a placebo?
- Would the standards of prevention change?
Alternative study designs

- Say we had an effective product, we might design future studies to compare the known active product to a new, unproven product, instead of a placebo.

- In the HIV treatment world, placebo-controlled trials are no longer conducted.
Redefining the standard of prevention

- In the future, it could also be possible to add an active product to the standard prevention package used in a trial.
- What is considered “standard” in one country may not be the same in another country, especially if that intervention is not available.
New Questions for HIV Prevention

- When is it no longer ethical to have a placebo group in an HIV prevention study?
  - Is it when a trial has found a product effective?
  - One trial or two trials?
  - How effective?
  - Or when that product has been approved and is available?

- Should the drug or intervention be part of the prevention package?
  - Should HIV prevention study participants receive this new effective prevention product if is not available in the community?
  - Who decides?
What if there is an ongoing trial?

If one trial has a significant outcome – either a positive or a negative finding, what happens to other trials in the field?

- Should the trial stop testing the product?
- Is there still valuable information to be gained by continuing?
- What decisions need to be made with future trials?
Several years ago, three research groups started clinical trials to find out whether circumcising adult men could prevent some of them from becoming infected with HIV.

The trials were done in South Africa (in an area known as Orange Farm), Kenya, and Uganda.
Responding to External Information

- The Orange Farm trial stopped early because results were very favorable to circumcision.
- Could the other two trials (in Kenya and Uganda) continue ethically?
- The DSMB recommended **continuing** because:
  - Studies were nearly finished and could either agree with or disagree with the Orange Farm result.
- Both studies confirmed the result in this case.
Why does a study or an arm of a study stop early?

- Study teams define **stopping rules** before the study starts.
- DSMBs reviewing blinded data use these as a guide to determine whether a study should continue, be modified or stop before its scheduled end.
- A Data Safety Monitoring Board (DSMB) is a group of independent experts that conducts routine reviews of blinded data while a trial is ongoing:
  - Are there safety concerns?
  - Will the trial be able to answer the study questions?
  - Do any of the study questions already have clear answers?
  - Should the trial keep going, stop early or be modified.
VOICE
A Randomized Placebo Controlled Trial

5,000 Women

Tablet (3,000)
- Truvada (1,000)
- Tenofovir (1,000)
- Placebo Tablet (1,000)

Vaginal Gel (2,000)
- Tenofovir Gel (1,000)
- Placebo Gel (1,000)

Five study groups
DSMB Reviews of VOICE

- There have been 5 face-to-face reviews to date:
  - May and Sept 2011 were reviews of efficacy
  - Until Sept. 16 review, recommended to continue with no changes each time

- Met by conference call soon after results released of Partners PrEP and TDF2 studies (July 2011)
  - Recommended VOICE continue with no changes
  - Decided to hold next full review earlier than planned
DSMB Review Sept 16 2011

- No safety concerns with any of the products
- Stop testing oral tenofovir tablet because it will not be possible to demonstrate it is effective for reducing HIV in the women in the trial
  - Oral tenofovir no better than a placebo
- The other arms of the study should continue
  - To determine whether oral Truvada tablet or tenofovir gel are effective
VOICE Study Post DSMB

Sept. 16 DSMB – closed the oral tenofovir arm because not possible to show it is effective in VOICE

No concerns about safety of any product

Five study groups

- Tablet (3,000)
  - Truvada (1,000)
  - Tenofovir (1,000)
  - Placebo Tablet (1,000)

- Vaginal Gel (2,000)
  - Tenofovir Gel (1,000)
  - Placebo Gel (1,000)
The DSMB for VOICE

- National Institute of Allergy and Infectious Diseases (NIAID) Prevention Trials DSMB reviews VOICE
  - 10 members, including 3 from Africa (1 of whom is a bioethicist)

- At any time, the DSMB could recommend the study be modified or stopped due to product effectiveness, product safety or futility (the study cannot answer the questions it was designed to).

- Next review is Nov. 15
The buzz about tenofovir gel......

- A lot of talk about what if tenofovir gel is found effective in VOICE or FACTS 001
  - How will this impact ongoing or planned trials?
  - Will this mean no more placebo?
  - Will this mean changing the standard of prevention?
  - When will the gel be available?

- But what if tenofovir gel is not effective?
  - DSMB review or final study results could find this
But……

- But what if tenofovir gel is **not** effective?
  - A VOICE DSMB review or the final study results could find this
VOICE may not find gel effective

- Remember HPTN 035 and MDP 301?
  - HPTN 035 found PRO 2000 30 % effective but this was not statistically significant
    - Confidence interval 7 to 54 %
  - MDP 301 was a larger Phase III trial that did not find it effective at all
- More than one trial is needed to confirm a result or to help get closer to the truth
What were the results of CAPRISA 004?

- VOICE and FACTS 001 are hoping to confirm the results of CAPRISA 004.

- Tenofovir gel was found to be 39% more effective than placebo gel for protecting against HIV when used before and after sex.

- But the true effectiveness may be low as 6% and as high as 60% (confidence interval).
CAPRISA 004

Tenofovir gel was 39% more effective than placebo gel for protecting against HIV when used before and after sex.

According to the confidence interval, the true level of risk reduction might be as low as 6% or as high as 60%.

<table>
<thead>
<tr>
<th>Study result</th>
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<tbody>
<tr>
<td>Placebo Gel</td>
<td>60 infections</td>
</tr>
<tr>
<td>Tenofovir Gel</td>
<td>38 infections</td>
</tr>
<tr>
<td>39% fewer</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>6%</td>
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<td>39%</td>
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Confidence Interval

No protection

Full protection
Managing expectations

- VOICE or FACTS may confirm the results of CAPRISA 004, but that could also mean that these studies find tenofovir gel reduces the risk of HIV by only 6%, 15% or 20%

- Would tenofovir gel still be considered for approval?

- We need to be sure that in all the buzz about tenofovir gel we include this as a possibility

- Important to manage expectations
Questions about tenofovir gel

What if it is effective?
☐ Will placebo-controlled trials still be ethical?
☐ Should it be introduced into the standard HIV prevention package?
☐ What if available in one country and not another?
☐ How will all this affect ASPIRE?

What if it’s not effective?
Acknowledgements

MTN is funded by NIAID (5U01AI068633), NICHD and NIMH, all of the U.S. National Institutes of Health