Trial Design Takes a Step in the Post PrEP Era: What will Gilead's study of F/TAF among cisgender women tell us about next gen PrEP and next gen trial design

November 13, 2019

Trial Design Options?

- FDA regulations [21 CFR 314.126] cite five different kinds of controls: placebo, no-treatment, dose-comparison, active, and historical control
- Active controlled trials with noninferiority comparisons rely on historical information as do historical controls and can suffer from similar biases.
- For HIV prevention, NI trials may be:
  - no more rigorous than other historical (or external) controls
  - while binding us to infeasible trial sizes because they rely on outdated trials of limited relevance to today.

What About Oral Contraceptives? Trial Design/Endpoint

- Active-Controlled or Single Arm Trials
- Endpoint = Pearl Index: number of pregnancies per 100 woman years, a measure to summarize contraceptive effectiveness
- Products typically have less than 1.5-2 unintended pregnancies per 100 PY
- EMA requires sufficient sample size to guarantee the width of the 95% C.I. for the Pearl Index to be no larger than 1
- This standard is based on historical evidence and confidence that pregnancy will occur with a reliably high frequency in a targeted population and time period

Pearl Index
Used for OC Trials

Contraceptive Failure Rate per 100 PY

Historical Pregnancy Rate per 100 PY

1 - 2

~85

Efficacy Threshold
Upper 95% C.I. = 5/100PY

Pregnancies per 100 Person-Years

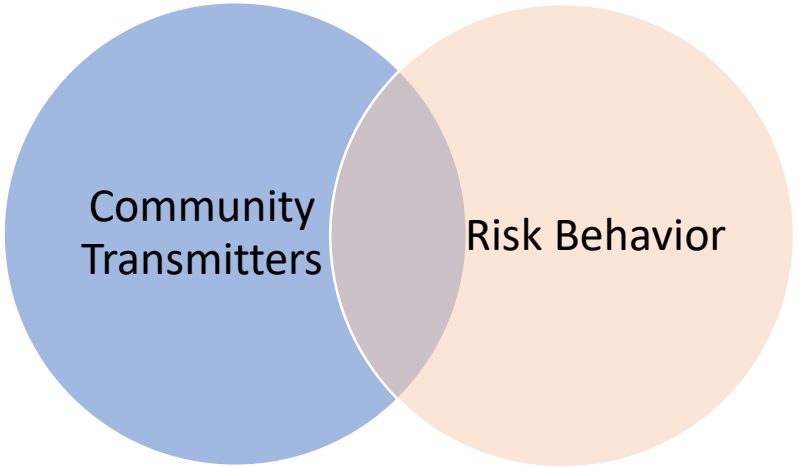
Pearl Index: Essential Components

- Contraceptive Failure Threshold:
  - Acceptable amount of failures in a defined population over a defined time period
  - Acceptable failure rate is clinically defined/chosen
- Historical Reference of Pregnancy Rate without Contraception
  - Counterfactual estimate of pregnancy rate had the population studied received no PrEP
- Confidence that the difference between the two is sufficiently large to justify use of historical reference

What about a “Pearl Index” for HIV Prevention ?

“HIV Incidence Index”

- HIV incidence is much lower than pregnancy rate.
  - It is variable and population dependent
  - Difficult to predict future HIV rates using only baseline factors or patient history.
- For a reliable high HIV incidence must have:
  - A population with risk behaviors
  - A high prevalence of potential transmitters



HIV Incidence Index vs. Pearl Index

Reliable Estimate of HIV Incidence of PrEP
Use TWO methods: Epidemiologic Data, Predictions based on STI rate or screen failures, etc.

Infection Threshold

0.7 — **5**

HIV Incidence without PrEP (CI)

HIV INFECTIONS per 100 PY

OC Failure Rate < 5

1-2

Pregnancy Rate: No Contraception

~ 85

PEARL INDEX: PREGNANCIES per 100 PY

Trial Design Proposal for HIV Prevention Trials

- Active-Controlled Trials with F/TDF or current standard
- Compare safety of the two regimens and estimates of HIV seroconversions powered for a level of precision but not for traditional non-inferiority
- Define a stringent threshold of an acceptable rate of HIV infection, (e.g., 0.8-1.0 per 100 PY)
- Define an acceptable difference between new agent and F/TDF (e.g., 0.5/100 PY)
- Choose trial sites with high-risk individuals: epidemiologic and other data
- Use two or more methods to estimate HIV incidence off PrEP. Examples:
  - Collect data on Rectal GC and other STIs to assess risk of HIV (based on previous correlations)
  - Look at epidemiologic seroconversion data from the same site areas/time period

Discussion

- **Chat**
  - Use the chat feature to send a question or message to the host and panelists.

- **Question & Answer**
  - The Q&A window allows you to ask questions to the host and panelists.
  - Click Q&A to open the Q&A window.
  - Type your question into the Q&A box. Click **Send**.

Upcoming Webinars

November 15th, 1-2pm ET

PK, PD and F/TAF: What does an advocate need to know about the pharmacology of safety and efficacy and today's PrEP drugs

https://zoom.us/webinar/register/WN_aLdQXhlERI2o7tlKGpes3w