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

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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  • while binding us to infeasible trial sizes because they rely on outdated trials of limited relevance to today.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

1 - 2
Efficacy Threshold
Upper 95% C.I. = 5/100PY

Historical Pregnancy Rate per 100 PY

~85

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• Historical Reference of Pregnancy Rate without Contraception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• Confidence that the difference between the two is sufficiently large to justify use of historical reference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?

“What 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

Community Transmitters
Risk Behavior
HIV Incidence Index vs. Pearl Index

Infection Threshold

0.7

HIV Incidence without PrEP (CI)

HIV INFECTIONS per 100 PY

OC Failure Rate < 5

1-2

PEARL INDEX: PREGNANCIES per 100 PY

OC Failure Rate < 5

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

Pregnancy Rate: No Contraception

~ 85
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_aLdQXhIERSo71lKgpes3w