Evolving Designs for HIV Prevention Trials

AVAC
25 Years and Counting

There are more biomedical strategies available for HIV prevention than ever before.

- Daily oral PrEP is rolling out around the world.
- Voluntary medical male circumcision continues to be scaled up.
- Injectable cabotegravir is now available as pre-exposure prophylaxis in the U.S. and Australia
- Antiretroviral treatment (ART) for people living with HIV is available "on demand" in many countries— effective ART is good for people's health and can help reduce the risk of passing on the virus.

At the same time, research is continuing. Today's ARV-based prevention options require high levels of adherence (e.g., taking a pill every day). Additional options, such as a vaccine, neutralizing antibody or longer-acting forms of PrEP would be important new strategies. Trials must be able to test these new tools, and meet ethical standards by providing participants with the best available prevention package. Now that daily oral PrEP is rolling out, and other PrEP methods may soon reach the market, the prevention package provided to trial participants may need to include these options.

The first table below defines trial designs under discussion. The second table describes the design of actual ongoing trials.

Table 1: Overview of Different Trial Comparison Types

Trial Comparison Type	Definition	Examples in HIV Prevention
Placebo control	When one group of trial participants uses a new tool (one that is being tested, such as a vaccine or a pill), and another group uses a placebo (a dummy version of the one being tested). Examples of a placebo include a sugar pill or a saline injection or a ring without any drug inside it.	All past oral PrEP, vaginal ring, vaccine, AMP efficacy trials ***Randomized, blinded trials***
Active control	When one group of trial participants uses an HIV prevention product (such as oral PrEP) or strategy (such as circumcision) already known to work. A second trial group uses a new tool that is being tested (like long-acting injectable PrEP). This way, researchers can compare a strategy already known to work to a new one—to find out if the new one is (1) better, (2) just as good or (3) not as good as the one that works. (See also ***non-inferiority*** and ***superiority.***)	DISCOVER, HPTN 083/084 ***Randomized trials that can be blinded or open-label.***
External control	The FDA has begun to consider the efficacy of an experimental product compared to "external controls". External controls the FDA will consider are "current estimates [of background incidence rates of HIV] from sites involved in recent clinical trials, cross-sectional HIV surveillance surveys, and from high quality local epidemiology data."	Not done in HIV px yet, but proposed by FDA to Gilead for their TAF for PrEP for cisgender women Planned for PURPOSE 1 and PURPOSE 2 ***Randomized trials that can be blinded or open-label.***
Counterfactual	Relies on historical cohort data to provide an estimation of incidence that can be used to compare what happens in a group of participants using a new intervention.	Open-label extension (OLEs) from oral PrEP and vaginal ring efficacy trials ***Open-label and not randomized***

Additional definition of trial design terms, including those noted above in ***bold italics***:

- An Advocate's Guide to Research Terms in the Post-Placebo Era
- HIV Prevention Trial Terms: An Advocate's Guide

Background document on counterfactuals:

- "Threshold-crossing": A Useful Way to Establish the Counterfactual in Clinical Trials?, Clin Pharmacol Ther. 2016 Dec; 100(6): 699–712.

Background documents on ethical guidelines:

- HPTN Ethics Guidance for Research, February 2020
- *Why ethics guidance needs to be updated for contemporary HIV prevention research*, *JIAS*
- *HIV prevention research and COVID-19: putting ethics guidance to the test*, *BMC Medical Ethics*
- UNAIDS/WHO Ethical Considerations in HIV Prevention Trials, January 2021
- *Revised UNAIDS/WHO Ethical Guidance for HIV Prevention Trials*, *JAMA*

Table 2: Efficacy Trials for Islatravir, F/TAF and Lenacapavir

Trial/Product	Status	Developer	Total Trial Size and population	Active Arm Size	Control Arm	Countries	Control Arm(s) and Efficacy Endpoint(s)
IMPOWER-022 **Monthly Oral Islatravir** *(along with a daily oral placebo pill)*	Discontinued in September 2022	Merck	4,500 cisgender women, 16-45 years-old –90% in Eastern & Southern Africa; 10% in US	2,250	2,250 *receive daily oral F/TDF and monthly oral placebo pill*	Eswatini, Kenya, Malawi, South Africa, Uganda, US, Zambia, Zimbabwe	**Active-control**: Randomized, double-dummy/double-blind superiority comparison of ISL to F/TDF. Plus, secondary analysis using recency data from screened participants as **external control**.
IMPOWER-024 **Monthly Oral Islatravir** *(along with a daily oral placebo pill)*	Discontinued in September 2022	Merck	1,500 cisgender men and transgender women who have sex with men, ≧ 16 years-old	1,000	500 *receive daily oral F/TDF and monthly oral placebo pill*	Kenya, South Africa, US	**External control**: Compare observed incidence rate in ISL arm to background incidence based on: ■ Recency assay performed on screened population ■ Local surveillance data (where available)
PURPOSE 1 **Daily Oral F/TAF** *Daily Oral F/TAF (along with placebo injection every six months)*	Recruiting	Gilead	5,010 cisgender AGYW, 16-25 years-old	2,004	1,002 *receive daily oral F/TDF and placebo injection* every six months	South African and Uganda	**External control**: Both F/TAF and LEN compared to background incidence via: ■ Recency assay ■ Plasma/DBS adherence-efficacy ■ Surveillance or clinical trial data ■ STI-HIV incidence
Six-monthly Injectable Lenacapavir *(along with daily oral placebo pill)*		Gilead		2,004			
PURPOSE 2 **Six-monthly Injectable Lenacapavir** *(along with a daily oral placebo pill)*	Recruiting	Gilead	3, 000 cisgender men who have sex with men, transgender women, transgender men, gender non-binary individuals, ≧ 16 years-old	2,000	1,000 *receive daily oral F/TDF and monthly oral placebo pill*	Brazil, Peru, South Africa, US	**External control**: LEN compared to background incidence via background HIV via: ■ Recency assay ■ Plasma/DBS adherence-efficacy ■ Surveillance or clinical trial data ■ STI-HIV incidence