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.
- The Dapivirine Vaginal Ring and injectable cabotegravir are in regulatory review and could be made available in the months ahead.
- 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 two additional 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

<table>
<thead>
<tr>
<th>Trial Comparison Type</th>
<th>Definition</th>
<th>Examples in HIV Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo control</td>
<td>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.</td>
<td>All past oral PrEP, vaginal ring, vaccine, AMP efficacy trials. <strong>Randomized, blinded trials</strong></td>
</tr>
<tr>
<td>Active control</td>
<td>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 <strong>non-inferiority and superiority</strong>.)</td>
<td>DISCOVER, HPTN 083/084 Planned for IMPOWER-22 <strong>Randomized trials that can be blinded or open-label.</strong></td>
</tr>
<tr>
<td>External control</td>
<td>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.”</td>
<td>Not done in HIV px yet, but proposed by FDA to Gilead for their TAF for PrEP for cisgender women Planned for IMPOWER-24, PURPOSE 1 and PURPOSE 2 <strong>Randomized trials that can be blinded or open-label.</strong></td>
</tr>
<tr>
<td>Counterfactual</td>
<td>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.</td>
<td>Open-label extension (OLEs) from oral PrEP and vaginal ring efficacy trials <strong>Open-label and not randomized</strong></td>
</tr>
</tbody>
</table>

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 documents on counterfactuals:


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

<table>
<thead>
<tr>
<th>Trial/Product</th>
<th>Status</th>
<th>Developer</th>
<th>Total Trial Size and population</th>
<th>Active Arm Size</th>
<th>Control Arm</th>
<th>Countries</th>
<th>Control Arm(s) and Efficacy Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMPOWER-022</strong>&lt;br&gt;Monthly Oral Islatravir&lt;br&gt;(along with a daily oral placebo pill)</td>
<td>On hold. Related islatravir studies showed lower lymphocyte and CD4+ T cell counts in some participants.</td>
<td>Merck</td>
<td>4,500 cisgender women, 16-45 years-old – 90% in Eastern &amp; Southern Africa; 10% in US</td>
<td>2,250</td>
<td>2,250 receive daily oral F/TDF and monthly oral placebo pill</td>
<td>Eswatini, Kenya, Malawi, South Africa, Uganda, US, Zambia, Zimbabwe</td>
<td><strong>Active-control:</strong> Randomized, double-dummy/double-blind superiority comparison of ISL to F/TDF. Plus, secondary analysis using recency data from screened participants as external control.</td>
</tr>
</tbody>
</table>
| **IMPOWER-024**<br>Monthly Oral Islatravir<br>(along with a daily oral placebo pill) | On hold. Related islatravir studies showed lower lymphocyte and CD4+ T cell counts in some participants. | 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**<br>Daily Oral F/TAF<br>Daily Oral F/TAF (along with placebo injection every six months) | On hold. Related to concerns about compatibility of the glass vials with the lenacapavir solution. | 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 |
| **PURPOSE 2**<br>Six-monthly Injectable Lenacapavir<br>(along with a daily oral placebo pill) | On hold. Related to concerns about compatibility of the glass vials with the lenacapavir solution. | 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 |