

AVAC

Global Advocacy for HIV Prevention

HIV Prevention Research Process: The Basics ... and more

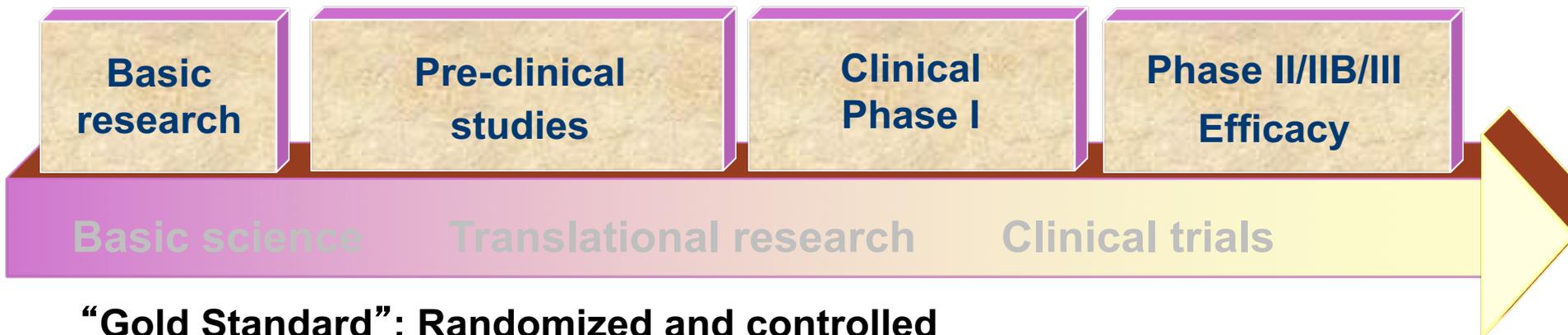
Fellows Workshop 2018

From the lab to you: the research process

- Preclinical research (concept, lab, animal studies)
- Clinical (human) research
 - Phase 1: smaller safety studies,
 - Phase 2: larger, longer, look at safety and immunogenicity
 - Phase 2b/3: even larger, look at safety and efficacy

After effectiveness results.....

- Open-label, 3b, post-licensure Phase 4 marketing studies



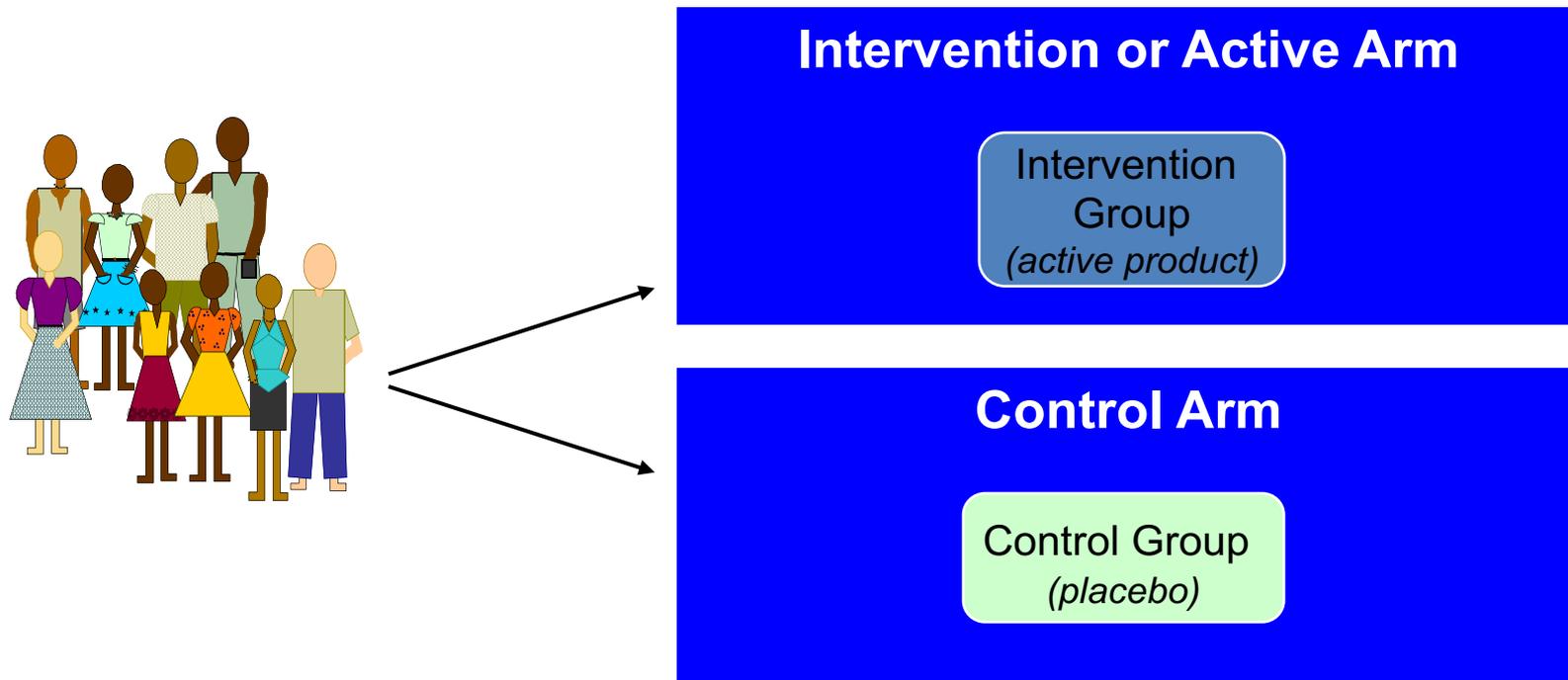
“Gold Standard”: Randomized and controlled

How are clinical trials conducted?

- The “gold standard” in research is a randomized and controlled study (RCT)
- Three key concepts:
 - Controlled
 - Randomized
 - Double-blind

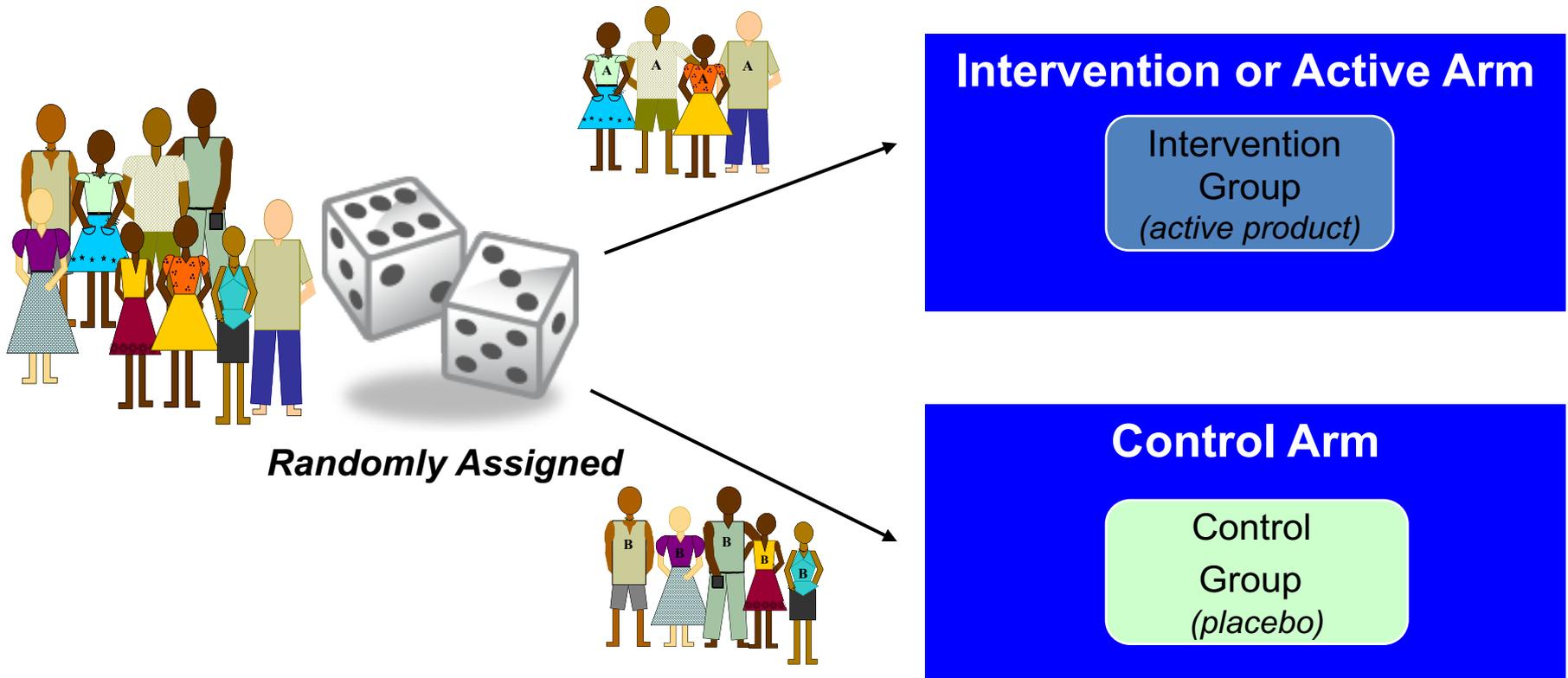
Randomized Controlled Trial

- Looks at the effect of an intervention/product in a trial setting – factors are more controlled than in real life
- Involves a minimum of 2 arms (study groups)



Randomized Controlled Trial

Participants are randomized



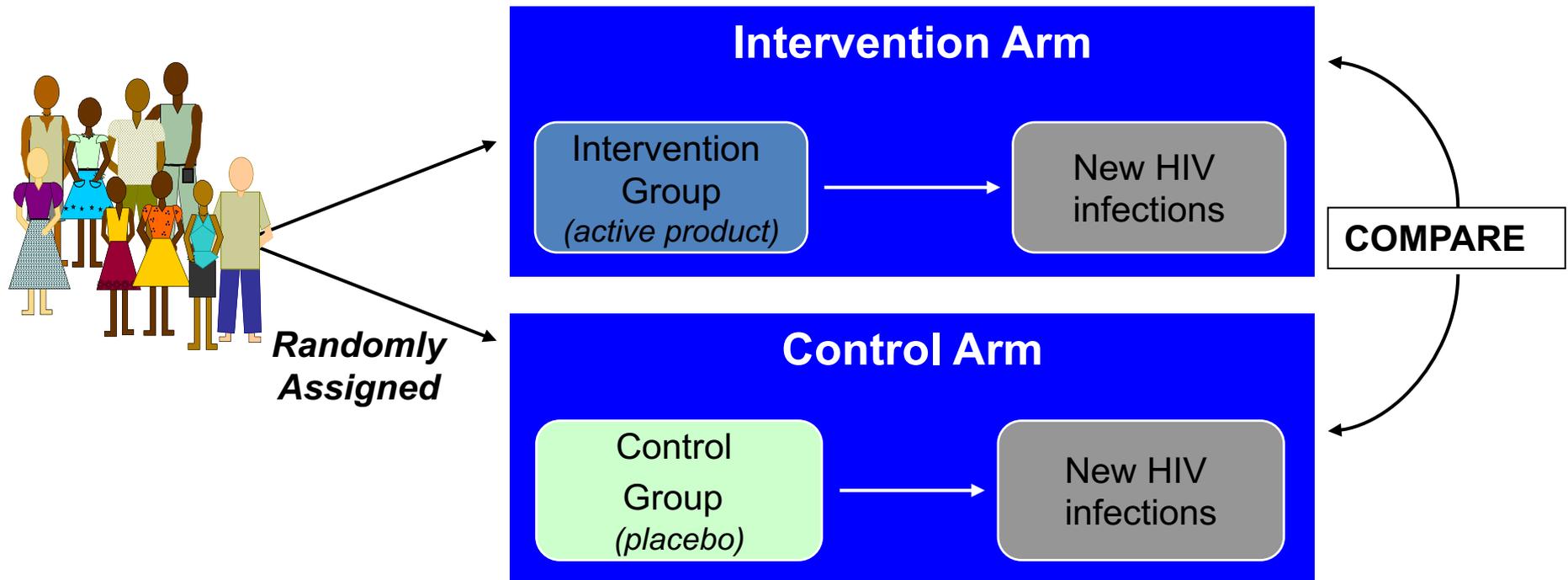
Double-Blinded RCT

The trial is double-blinded:

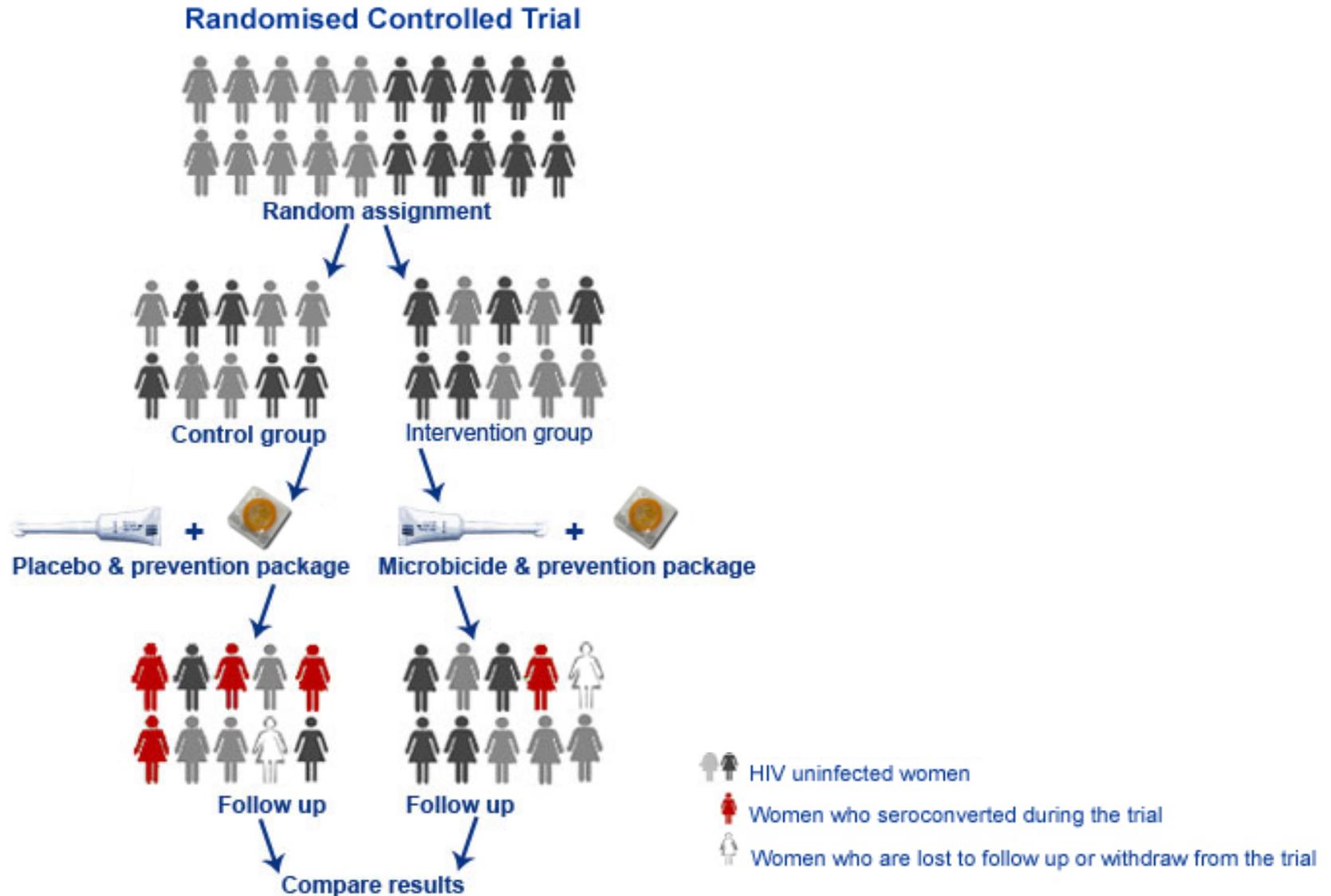
- Neither participants nor researchers know whether each participant is in the active or control arm(s)
- Less potential for bias
- Data unblinded at the end of study to compare between groups

Randomized Controlled Trial

- Goal is to assess if the active study product really works, by comparing to the control
- HIV prevention research: compare new HIV infections in the study arms to determine if the intervention prevented infection and/or progression to disease



Measuring effectiveness



RCT Summary

1. One group of participants uses the test product or strategy (active arm)
2. Other group does not use the test product or strategy at all (control arm)
3. All participants get standard prevention tools
4. At the end, researchers compare outcomes (such as numbers of new HIV infections) in each group
5. If fewer people got HIV in the active arm than in the control arm, that would suggest that the test strategy reduced HIV risk

Safeguards in clinical trials

- International Ethical Standards
- National Regulatory Bodies
- Institutional Review Boards (IRBs)/Ethics Review Committees
- Community/stakeholder input – governed by Good Participatory Practice (GPP) guidelines
- Informed Consent
- Adverse event monitoring
- Data Safety and Monitoring Boards (DSMBs/IDMC)
- Community Involvement

➔ From Research to Rollout: Evaluations that move a product to the "real world"

Post-trial access

- Intervention provided to trial participants and, sometimes, their communities, after the trial is over and before a product is available for widespread use.

Open label extensions

- Intervention made available, often for a specific time frame, in the context of a follow-on study protocol in which participants from the previous randomized controlled trial (RCT) know that they are receiving the active intervention.
- Gather information about how a product works in people who are now aware of the potential benefit.

Open label / implementation studies

- Research protocols similar to above but enrolling new participants—e.g., those who were not previously enrolled in the RCTs and who might be in open label extensions (OLEs).

Demonstration projects

- "Road test" use of new option in real-world settings—not in trial site.
- Can address both infrastructure needs to deliver intervention and ways individuals integrate it into daily activities and decision making.
- Can help answer core questions about which populations will gain greatest benefit from new interventions, how best to provide those tools and ensure that people use them as directed, and how to integrate new tools with existing methods and health systems.

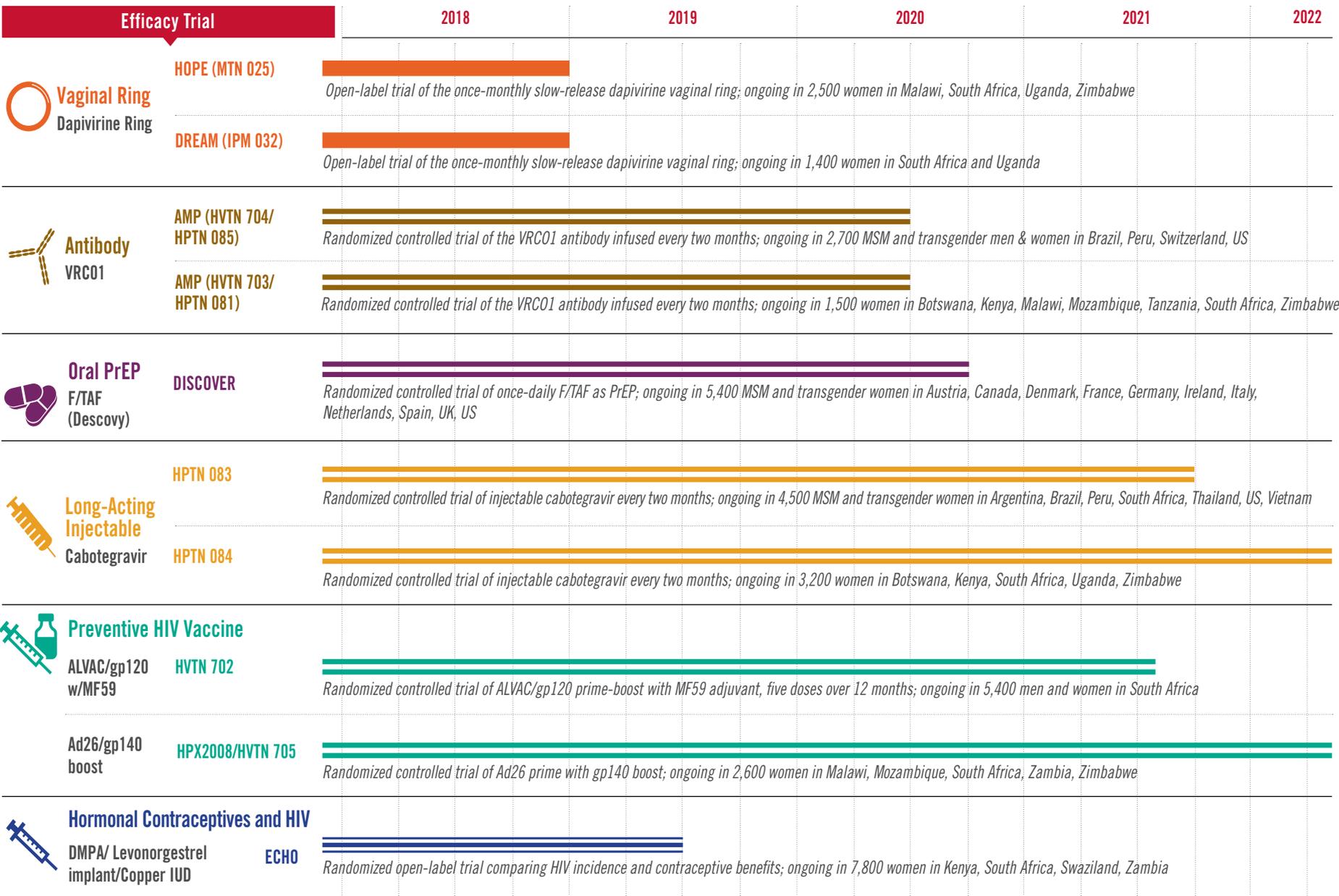
Product introduction

- Complex process of formally making new options widely available. Can include:
 - Meeting complex regulatory requirements, prequalification by WHO, and various country-specific requirements.
 - Overcoming logistical challenges, such as production scale-up, supply and logistics issues that come with manufacturing and introducing a new product.
 - Building awareness of and demand for new prevention methods in relevant communities through education, marketing, promotion and other activities.
 - Working with health ministries, funding agencies and implementing partners to ensure that new interventions are integrated with other proven strategies and health systems.

Scale-up

- Process of ramping up access to new options for all who need them. Scale-up requires mobilization of sufficient resources for procurement, distribution, delivery, worker training and other costs associated with rollout; quick identification and resolution of potential bottlenecks; and engagement with at-risk communities to ensure a sense of ownership over the scale-up.

Times they are a changin'
(for trial design now that there's PrEP)



Open-label
 Randomized Controlled
 Open-label and Randomized
 Ongoing

Research pipeline (not efficacy)

- Rectal microbicides
- MPTs (Multi-Prevention Technologies)
- Implants
- Long-acting injectables
- Cure
- Vaccines
- Broadly neutralizing antibodies

“In clinical trials, PrEP should be provided on-site (as part of SoC) to all participants only in countries with national guidelines on PrEP.”

“Advocates cannot influence the products that are studied or trial designs.”

Research Complexity in Post-Placebo Era

- Active control (instead of placebo control)
- Double-dummy double-blind trials
- Open-label trial
- Non-inferiority trials
- Superiority trials

Research in the Post-Placebo Era

Placebo-Controlled Trial

Experimental



VS.

Placebo



Double-Dummy Double-Blind*

Experimental

Placebo

Placebo

Active

DISCOVER
(Oral F/TAF)



+



VS.



+



HPTN 083;
HPTN 084
(Long-acting
Cabotegravir)



+



VS.



+



Open-Label With Active Arm*

Not in use
in today's
PrEP trials,
considered
for HPTN 084.

Active



VS.

Experimental



Open-Label
Extension

Product
Introduction

If the experimental product is shown to be safe and effective, trial designers may decide to give all participants access to the active product, or products, if multiple are shown to be safe and effective.

Licensure
Demonstration
projects
Rollout
Scale-up

All of these designs are randomized, meaning that participants are assigned to a study arm by chance. This protects against bias, whether the participant knows what he or she is receiving or not.

Percolating Pipeline in PrEP Era

| Strategy | Trial | # | Population | Status | Location | PrEP Status |
|-----------------------------------------------------------------|-----------------------|-------|-----------------------------|--------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Oral PrEP: Daily oral F/TAF | Discover | 5,000 | MSM & transgender | Fully enrolled | Canada, Denmark, Germany, Ireland, Italy, Netherlands, Spain, UK, US | Oral TDF/FTC as part of active control in double-dummy, double-blind design |
| bNAb: VRC01 infused every 2 months | HVTN 704/HPTN 085 | 2,700 | MSM & transgender | Enrolling | Brazil, Peru, Switzerland, US | Access to oral FTC/TDF PrEP offered at no drug cost to every participant |
| | HVTN 703/HPTN 081 | 1,500 | Sexually active women | Enrolling | Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe | Oral TDF/FTC discussed in IC, risk reduction counseling sessions, and referral systems |
| Vax: ALVAC/gp120 MF59 adjuvant boost, 5 doses in 12 months | HVTN 702 | 5,400 | Sexually active women & men | Enrolling | South Africa | |
| Vax: Ad26/Mosaic + gp140 boost, 4 doses in 12 months | HPX2008/HVTN705 | 2,600 | Sexually active women | Enrolling | Malawi, Mozambique, South Africa, Zambia, Zimbabwe | |
| Long-acting injectable: cabotegravir every two months | HPTN 083 | 4,500 | MSM & transgender | Enrolling | Argentina, Brazil, Peru, South Africa, Thailand, US | Oral TDF/FTC as part of active control in double-dummy, double-blind design |
| | HPTN 084 | 3,200 | Sexually active women | Enrolling | Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe | |
| HC/HIV: evaluating 3 contraceptives for possible increased risk | ECHO | 7,800 | Sexually active women | Enrolling | Kenya, South Africa, Swaziland, Zambia | Both PEP and PrEP will be offered, either onsite or by rererral, per local standard of care/national policy |
| Ring/PrEP: dapivirine ring and oral TDF/FTC | MTN 034/IPM 045/REACH | 300 | Sexually active women | Planned start early 2018 | Kenya, South Africa, Uganda, Zimbabwe | Open-label cross-over; all will try both ring and oral, then choose |

Research in the Post-Placebo Era

- [Advocate's Guide to Research Terms in the Post-Placebo Era](#)
- [HIV Prevention Trial Terms: An Advocate's Guide](#)
- Px Pulse podcasts:
 - [PrEP and Trial Design — A no brainer for some](#)
 - [Testing Long-Acting PrEP, Easier Said Than Done](#)
 - [Standard of Care in the Era of PrEP](#)