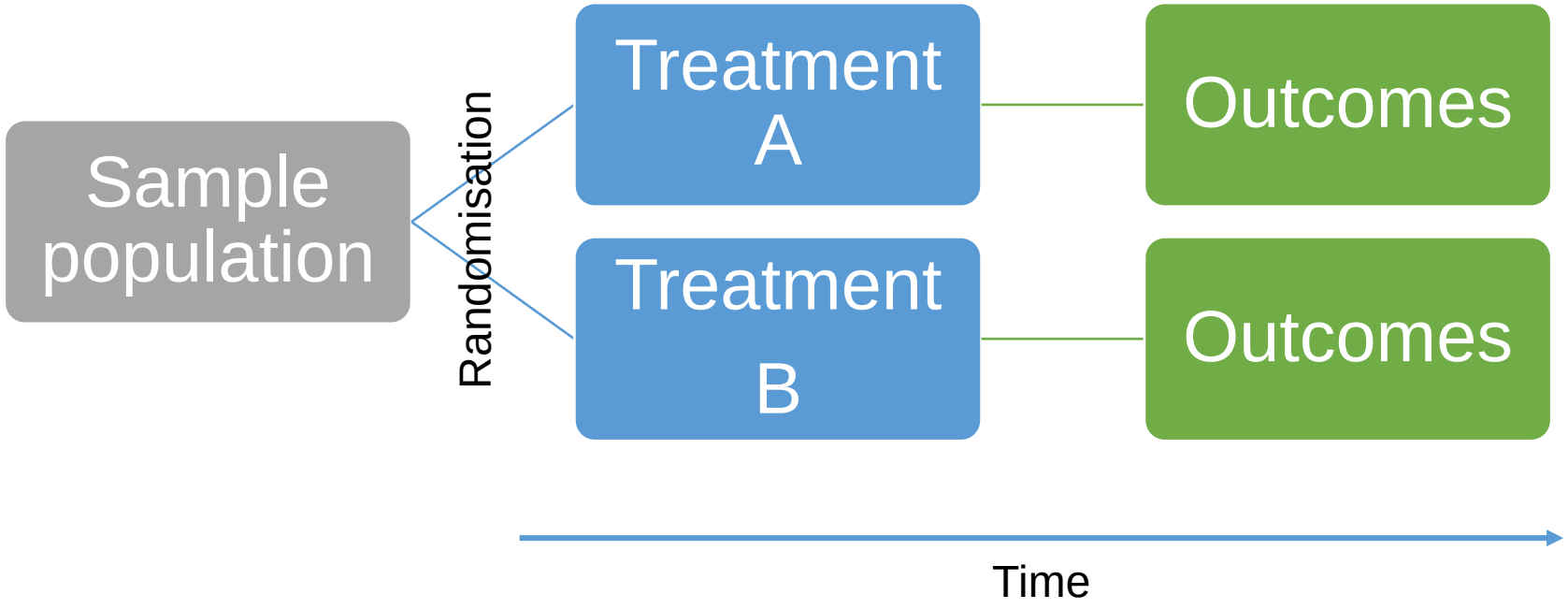
Overview of designs of recently completed HIV prevention trials

Sinéad Delany-Moretlwe, MBBCh PhD DTM&H
University of the Witwatersrand
IAS, July 2023

The basic structure of an RCT



Any differences in outcomes are attributed to the trial therapy

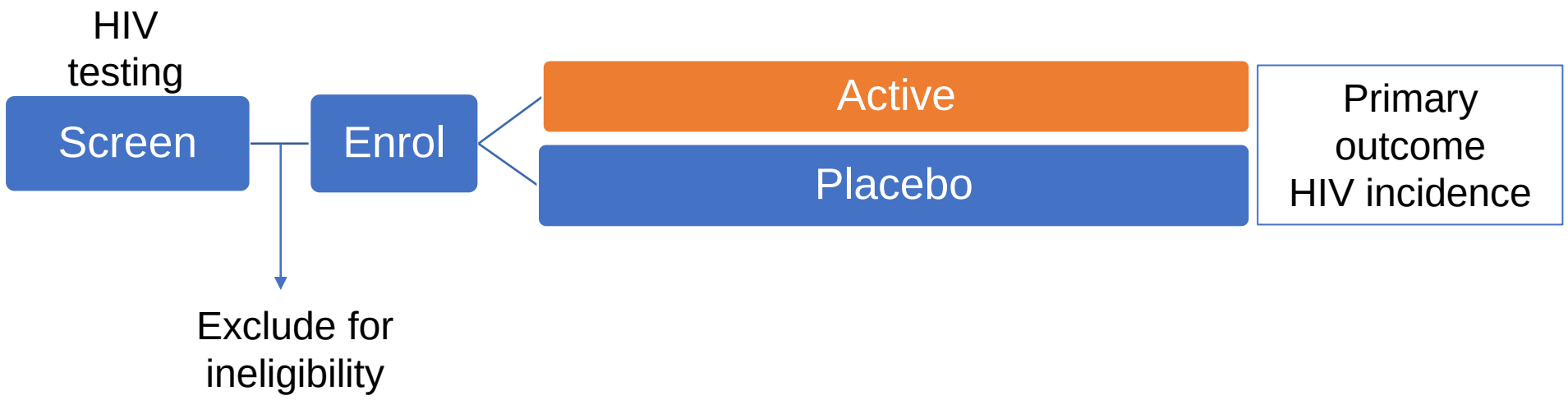
Results from a limited sample are used to make inferences about treatment in the general population

Placebo-controlled trials

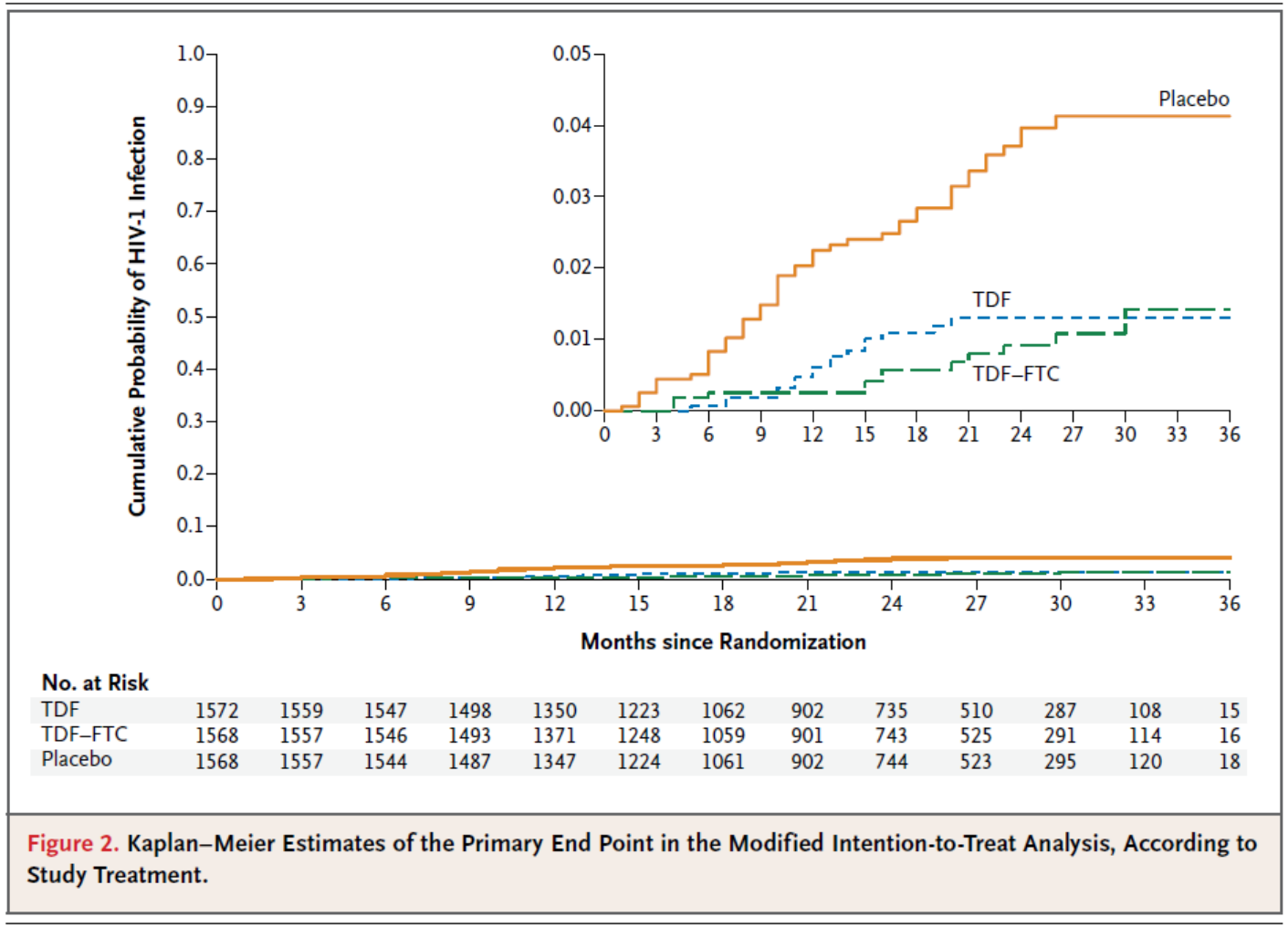
Ethical guidance permits the use of placebo-controlled trials when

1. There is **no effective standard treatment** (prevention) for the condition under study
2. Withholding treatment poses **negligible risks to participants**
3. Compelling methodological reasons for using a placebo AND withholding treatment **does not pose a serious harm to participants**
4. Compelling methodological reasons for using a placebo AND research is intended to develop interventions that can be implemented in the population from which participants are drawn AND the trial **does not require participants to forgo treatment that they would otherwise receive**

Placebo-controlled trials



Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women



No. at Risk

TDF	1572	1559	1547	1498	1350	1223	1062	902	735	510	287	108	15
TDF–FTC	1568	1557	1546	1493	1371	1248	1059	901	743	525	291	114	16
Placebo	1568	1557	1544	1487	1347	1224	1061	902	744	523	295	120	18

Figure 2. Kaplan–Meier Estimates of the Primary End Point in the Modified Intention-to-Treat Analysis, According to Study Treatment.

HIV incidence was 75% lower in the TDF/FTC group and 67% lower in the TDF group compared to placebo

Baeten, NEJM 2012

Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women

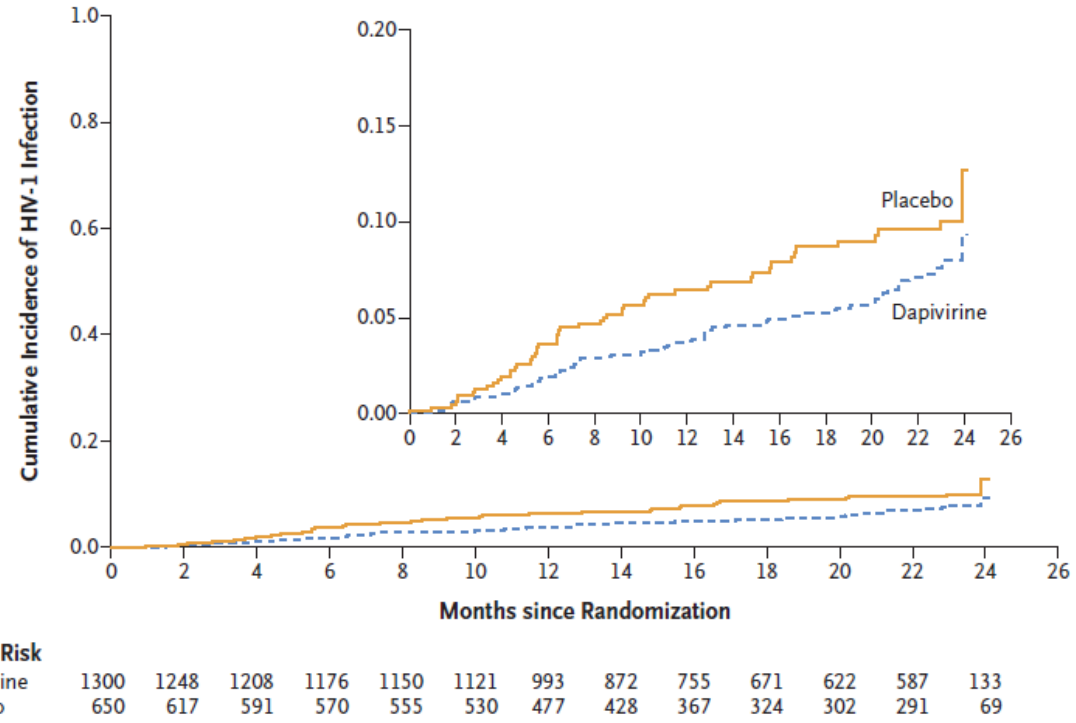


Figure 2. Time to Seroconversion, on the Basis of Confirmed Trial End Points, in the Modified Intention-to-Treat Population.

Shown are data in the analysis window up to the end of the week 104 (last product-use visit). Eight participants in the dapivirine group and nine in the placebo group had longer follow-up time, including one participant in the dapivirine group and four in the placebo group who had seroconversion at the exit visit. The inset shows the same data on an enlarged y axis. HIV-1 denotes human immunodeficiency virus type 1.

HIV-1 incidence was 31% lower in the dapivirine group than in the placebo group (hazard ratio, 0.69; 95% confidence interval, 0.49 to 0.99; P = 0.04).

STUDY START (ACTUAL)

2012-07-24

PRIMARY COMPLETION (ACTUAL)

2015-07-03

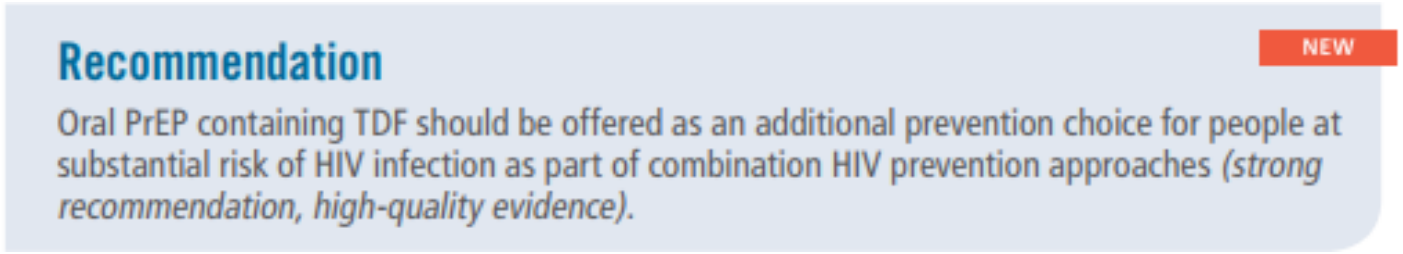
STUDY COMPLETION (ACTUAL)

2015-12

Nel, NEJM 2016

TDF/FTC: a new option for prevention

- WHO 2015 recommendation



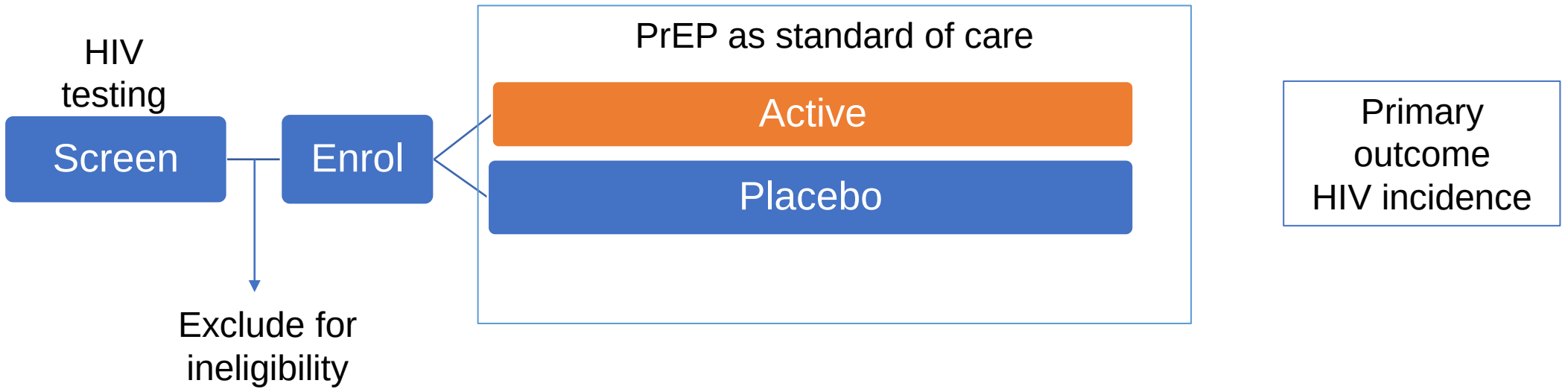
Recommendation NEW

Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches *(strong recommendation, high-quality evidence)*.

- Variable implementation
  - TDF/FTC licensed for PrEP in limited number of countries initially
- For trials, access initially variable and site specific
- Placebo-controlled trials no longer justifiable

WHO, 2015

Placebo-controlled trials

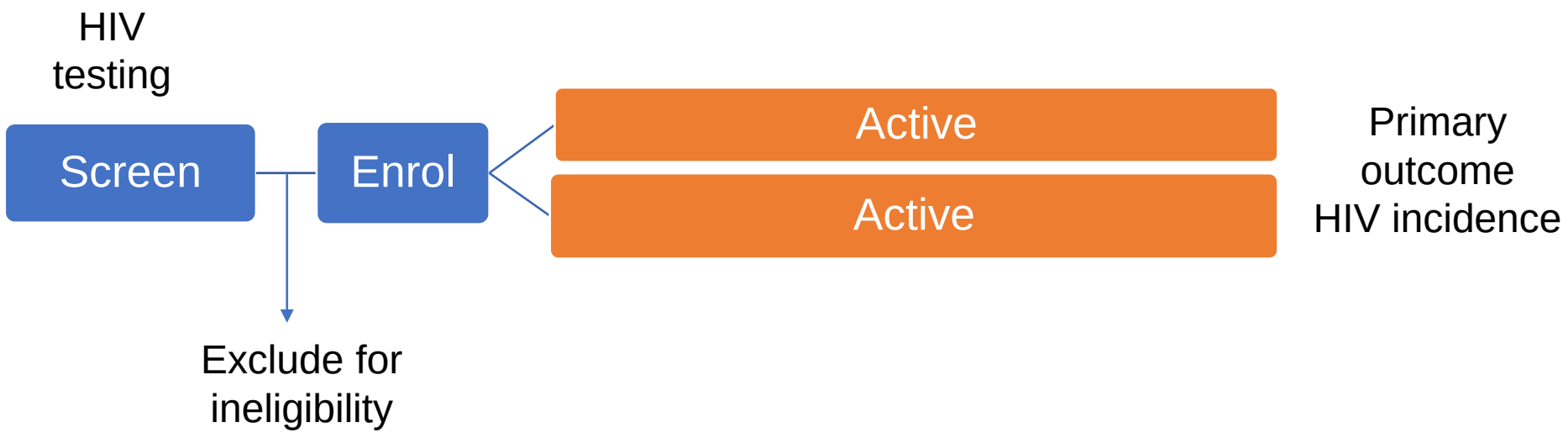


PrEP uptake when offered as standard of care:

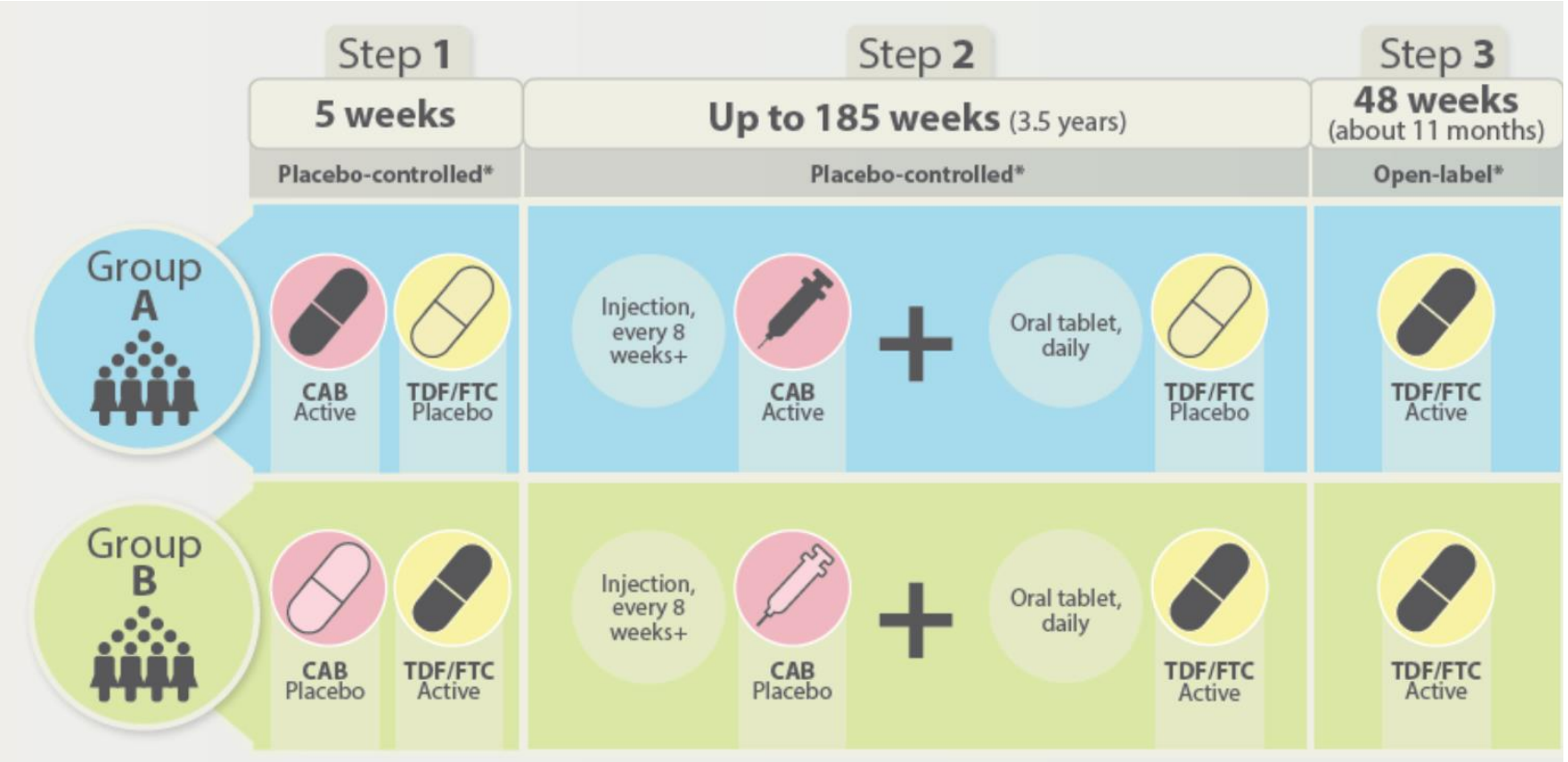
- HVTN 805/HPTN 081 AMP 0.5%
- HVTN 702 2-3%
- ECHO 17%

Mgodi JAIDS 2021; Gray, NEJM 2021; Beesham, JIAS 2020

Active controlled trials

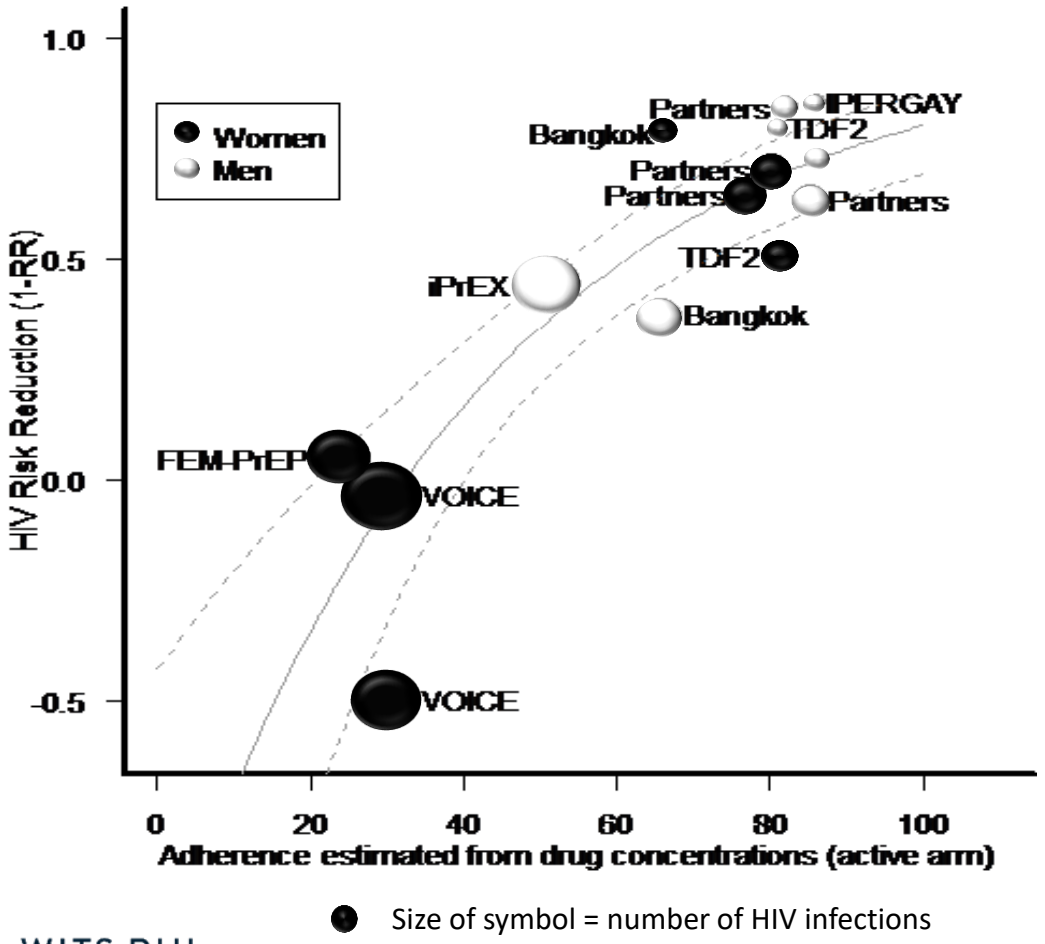


HPTN 083/084 study design: active control



HIV, (pregnancy testing in HPTN 084) and safety assessments at each product administration visit; additional post injection safety visits
Real-world adherence counselling support aligned with national guidelines

Influence of varying effectiveness estimates for TDF/FTC



- MSM
  - Meta-analysis estimate of effectiveness 55% (34-69%)
  - Adherence range 55-85%
- Women
  - Meta-analysis estimate of effectiveness 36% (-8%–62%)
  - Adherence range: 20%-80%
- HPTN 083 designed as a non-inferiority trial while HPTN 084 was designed as a superiority trial

WITS RHI

Hanscom, 2016

HPTN 083 and HPTN 084 stopped prematurely by DSMB for efficacy

HPTN 083

- Cisgender men and transgender women who have sex with men
- 4,566 participants
- Argentina, Brazil, Peru, US, South Africa, Thailand, Vietnam (43 sites)

Results: **66% reduction in HIV infections** in CAB-LA arm compared to TDF/FTC.

HPTN 084

- Cisgender women 18 to 45 years
- 3,224 participants
- Uganda, Kenya, Malawi, Zimbabwe, Eswatini, South Africa, Botswana (20 sites)

Results: **88% reduction in HIV infections** in CAB-LA arm compared to TDF/FTC.

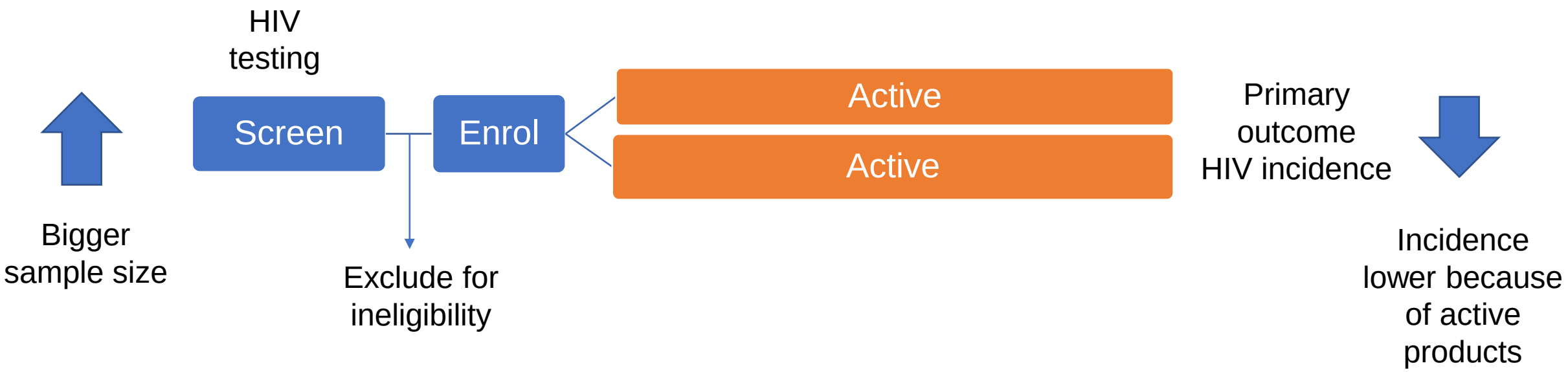
CAB generally safe and well-tolerated

CAB-LA likely confers an adherence advantage

Regulatory approvals in USA, Australia, Zimbabwe, South Africa, Malawi, Botswana

Landovitz, NEJM 2021; Delany-Moretlwe, Lancet 2022

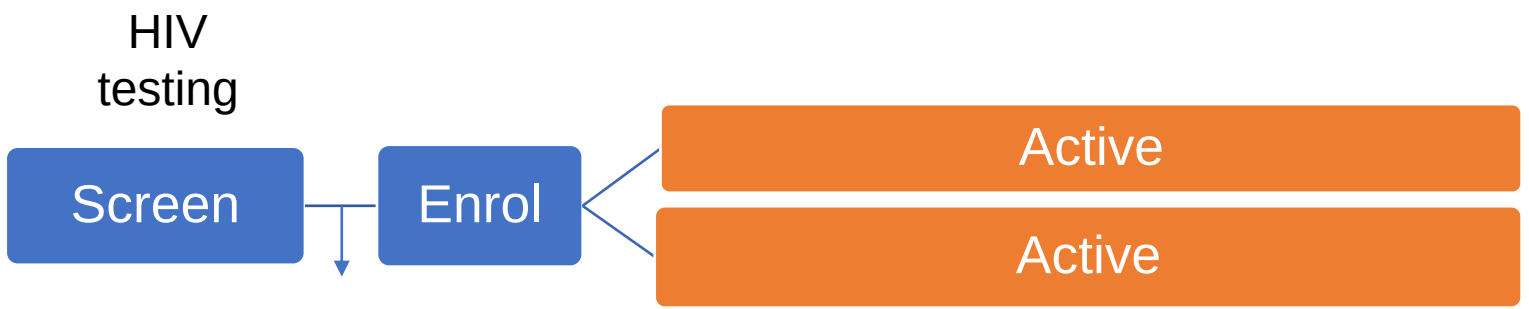
Active controlled trials



e.g. HPTN 083/4 HIV incidence across both groups ~1%

Landovitz, NEJM 2021; Delany-Moretlwe, Lancet 2022

Using a counter-factual approach to estimate new PrEP efficacy

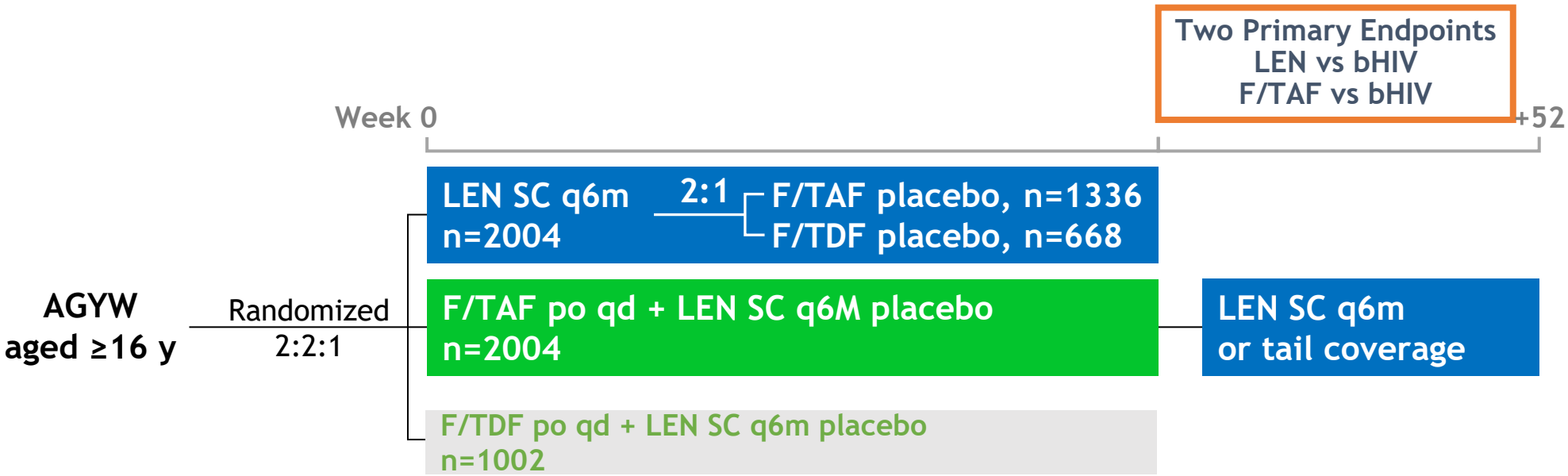


Counterfactual HIV incidence: HIV incidence in a similar population not exposed to intervention

Multiple approaches to assessing counterfactual incidence

Primary outcome assessment involves comparison of incidence in trial with counterfactual placebo incidence

Design for LEN and F/TAF for PrEP in AGYW



Goal: Evaluate the efficacy and safety of both LEN and F/TAF for PrEP

- External control: bHIV in those not on PrEP

bHIV based on recency assay in screened population

Alternative methods include Adherence-Efficacy Back-calculation with Plasma and recent clinical trial data from ECHO, HVTN 702, and HPTN 084

Internal active control:

F/TDF

- bHIV, background HIV incidence.

Slide courtesy of M. Das

Summary

- Randomised controlled trials are considered most rigorous method for assessment of effectiveness of new interventions
- In the absence of effective PrEP, placebo-controlled trials were justified
- Following the demonstration of TDF/FTC as PrEP, new agents compared to effective PrEP i.e. active controls
- As long-acting highly effective PrEP agents are approved, alternative trial designs using counterfactual approaches are likely to be needed to estimate HIV efficacy of new PrEP agents

Acknowledgements

HPTN 083/4 teams including

- Raphael Landovitz,
- Beatriz Grinstejzn,
- Mina Hosseinpour,
- Deborah Donnell,
- Jim Hughes and Brett Hanscom

The Forum for Collaborative Research HIV prevention trials in women working group

NIAID, BMGF, ViiV Healthcare and Gilead who funded HPTN 083/4