HPTN
HIV Prevention
Trials Network

Developing Placebo Counterfactuals for PrEP Studies

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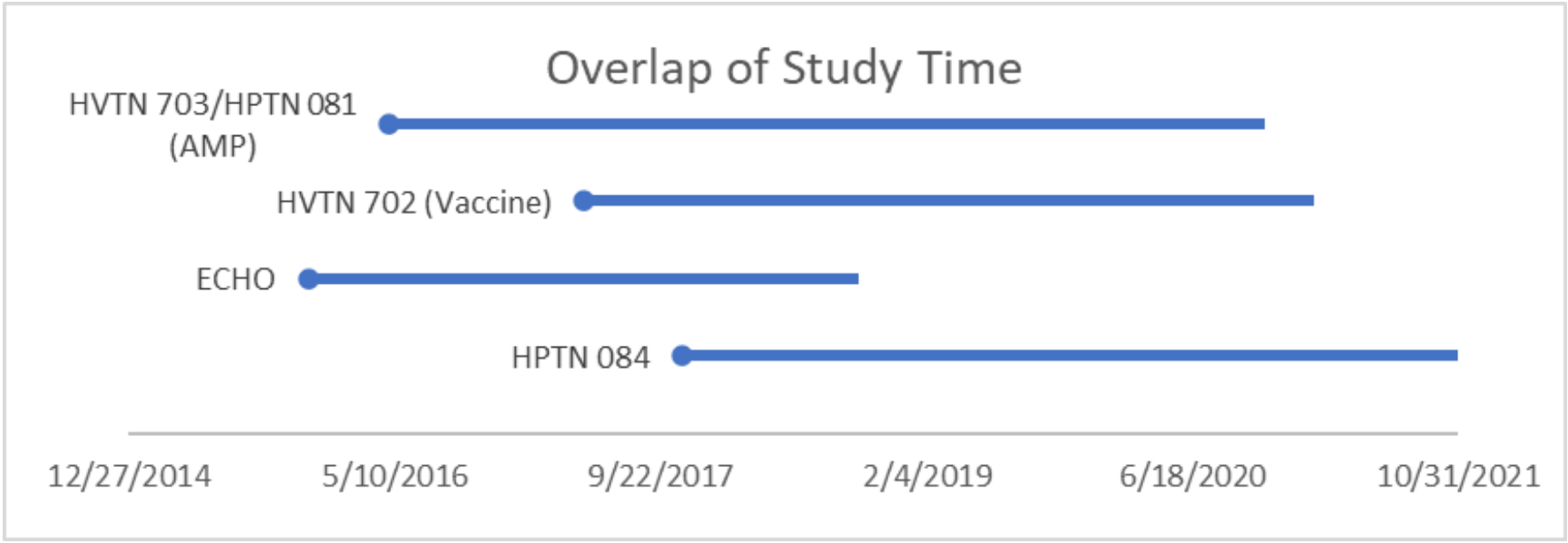
Introduction

- Current PrEP trials use an “active” control arm
  - HPTN 083/084 use TDF/FTC control
- Nonetheless, there is interest in understanding the effect of new PrEP agents versus placebo
  - Supplementary evidence of efficacy
  - Understanding population impact

Introduction

- External, contemporaneous trials with placebo arms may be used to form a “counterfactual” placebo arm for an active control trial
  - Overlap in populations
  - Overlap in time
  - Overlap in eligibility criteria

	HPTN 084	**ECHO**	**HVTN 702**	**AMP (HVTN 703/HPTN081)**
Study design description	Compare HIV incidence between PrEP options; 1:1 randomization to TDF/FTC daily pills or CAB LA injectable; double blind, double dummy	Compare HIV incidence between contraceptive options; 1:1:1 randomization to DMPA, copper IUD, or LNG implant; open- label	Determine efficacy of an HIV vaccine candidate for HIV prevention; 1:1 randomization to placebo or vaccine; double blind	Determine efficacy of mAb for HIV prevention; 1:1:1 to VRC01 30mg / VRC01 10mg / Placebo; double blind
Sites	Botswana, eSwatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe	eSwatini, Kenya, South Africa, and Zambia	South Africa	Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe
Population	HIV-seronegative women aged 18–45 years	HIV-seronegative women aged 16-35 years	HIV-seronegative men and women aged 18–35 years	HIV-seronegative women aged 18–40 years
Sample size	Target: N = 3200 PY = 7125	Included: N= 7103 PY = 9594	Included: N =1886 Y = 2782	Included: N = 1393 PY = 2266


Overlap of Study Time
HVTN 703/HPTN 081
(AMP)
HVTN 702 (Vaccine)
ECHO
HPTN 084
12/27/2014
5/10/2016
9/22/2017
2/4/2019
6/18/2020
10/31/2021

Methods

- Target trial (e.g. HPTN 084)
  - s subgroups (sites/countries/regions)
  - m_i = person-years in subgroup i
  - O = observed HIV incidence in experimental arm in s subgroups
- External trial (e.g. ECHO)
  - Same s subgroups (sites/countries/regions)
  - I_i = HIV incidence in (placebo arm of) subgroup i

$$\mathrm{cP} = \left. \sum_i m_i I_i \middle/ \sum_i m_i \right.$$

Methods

- Counterfactual relative risk (cRR)
  - Compare cP to observed incidence in the target trial across the s subgroups
  - cRR = O/cP
- Confidence intervals for cP, cRR may be computed on log scale

Example – ECHO and HPTN 084

- HIV-uninfected women in SSA
- 1:1:1 randomization to DMPA, copper IUD, or LNG implant; open- label
- No difference between arms – combine all arms
- Overlapping countries with HPTN 084: eSwatini, Kenya, South Africa

Country	084 Person Years	ECHO Incidence (%/yr)	Expected 084 incidence (%/yr)
Kenya	65	1.36	3.50
South Africa	802	4.64	
Eswatini	77	4.97	

- cP = 4.44%/yr (95% CI: 4.02 – 4.89)

Summary

- Further stratification could be done by age or other demographics, though the data start to get thin.
- Counterfactual estimates do not have the strength of evidence of a randomized comparison
  - Combine with other evidence e.g. adherence and HIV incidence in active control arm
- Utility of this approach may decline as contemporaneous placebo arm data become less available

Collaborators

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