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COUNTERFACTUAL ESTIMATION OF CAB-LA EFFICACY AGAINST PLACEBO USING EXTERNAL TRIAL DATA

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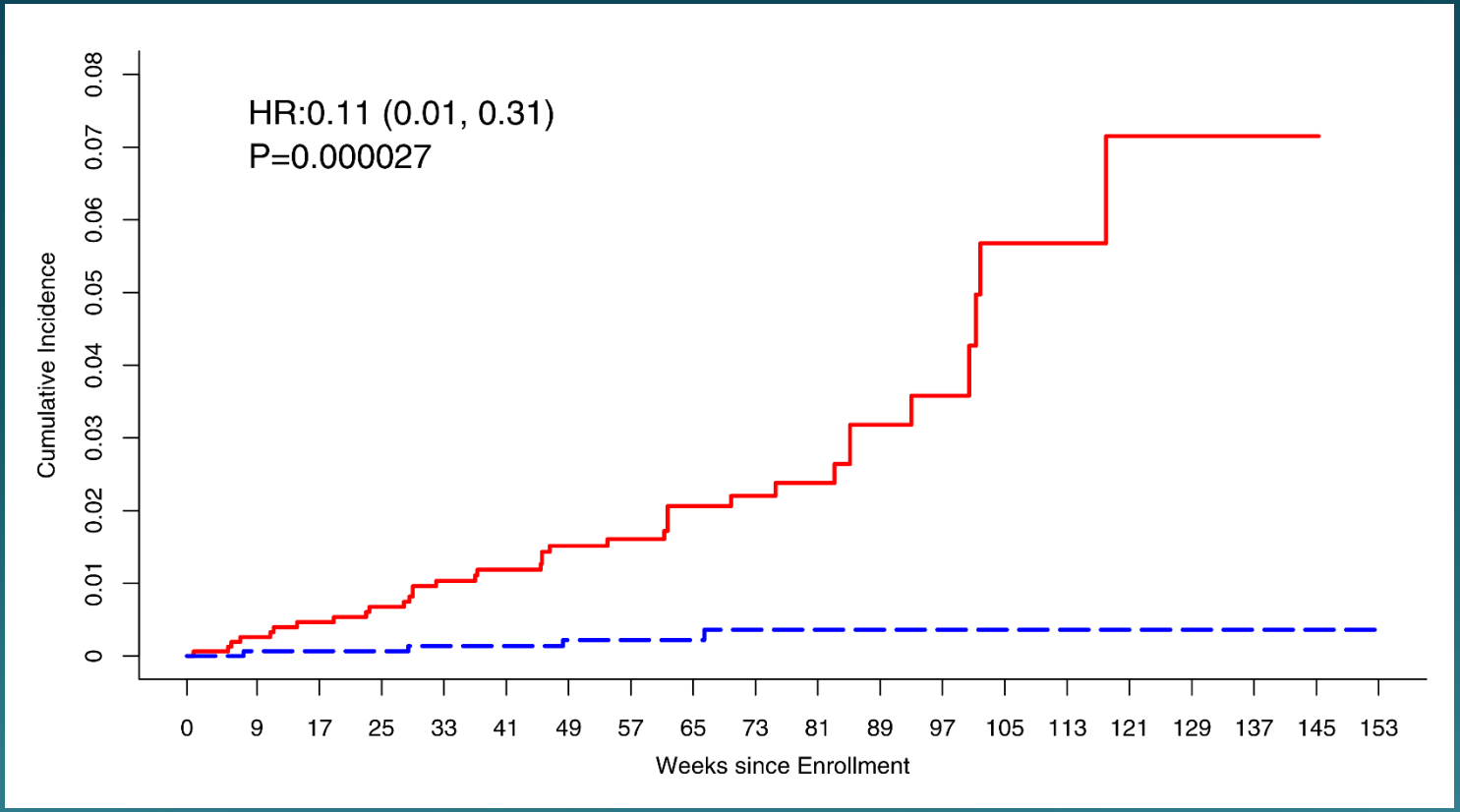
Disclosure: None

HPTN 084: CAB-LA Superior to FTC/TDF

	CAB-LA	TDF/FTC
HIV infections/Person Years	4/1953	36/1939
HIV incidence (95% CI)	0.20 (0.06, 0.52)	1.85 (1.3, 2.57)



*Women in the CAB-LA group had **89%** 95%CI(69%, 99%) **lower risk of HIV infection,** compared to TDF/FTC group*

What is the efficacy of CAB-LA compared to placebo?

Delany-Moretlwe R4P 2021 LB 1479

Prevention trials in 2016-2020 in Africa

- HPTN 084: PrEP
  - Randomized controlled trial of CAB-LA versus TDF/FTC
- AMP women (HVTN 701/HPTN 085): Monoclonal Ab
  - Randomized controlled trial of VRC-01 versus ***placebo***
- ECHO: Long-acting contraceptives and HIV
  - Randomized controlled trial of DMPA-IM vs. Copper IUD vs. Levonorgestrel Implant
  - Contraceptives not HIV prevention agents: treated as ***equivalent to placebo***
- HIV Vaccine trial: HVTN 702
  - Randomized controlled trial of ALVAC-gp120 vaccine vs ***placebo***

Corey NEJM 2021; ECHO Consortium Lancet 2019; Gray NEJM 2021

Goal

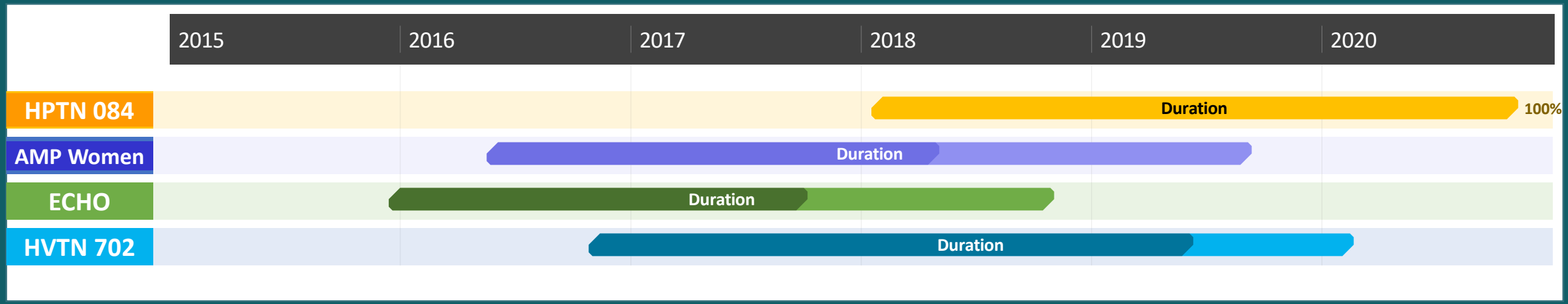
- Use “placebo” data from women
  - Enrolled in a randomized clinical trial
  - Prospectively measured HIV incidence
  - Very similar inclusion criteria
  - Similar clinical trial standard of care/prevention
- To estimate the HIV incidence rate that would have been seen in a placebo arm of HPTN 084 = “counterfactual placebo”
- To estimate the reduction in relative risk of HIV-infection for CAB-LA relative to placebo

Note: Use of TDF/FTC PrEP was permitted in all three external studies, but uptake documented in <5% of follow-up

Three counterfactual comparisons

Country	HPTN 084	AMP Women placebo	ECHO	Vaccine placebo
Botswana	46	47		
Eswatini	80		502	
Kenya	31	27	901	
Malawi	113	59		
South Africa	653	341	5768	1884
Zimbabwe	391	145		
Total women	1614	638	7829	1884

Concurrency of Trial Follow-up



Statistical Methods

- ITT estimate, including all follow-up
- "Direct standardization" to HPTN 084 using country-standardized person years (Age-standardized person years for South African comparison)
- Use analysis weights to match person-years of follow-up in external study to the person-years distribution in HPTN 084

E.g. For HPTN 084 and AMP women

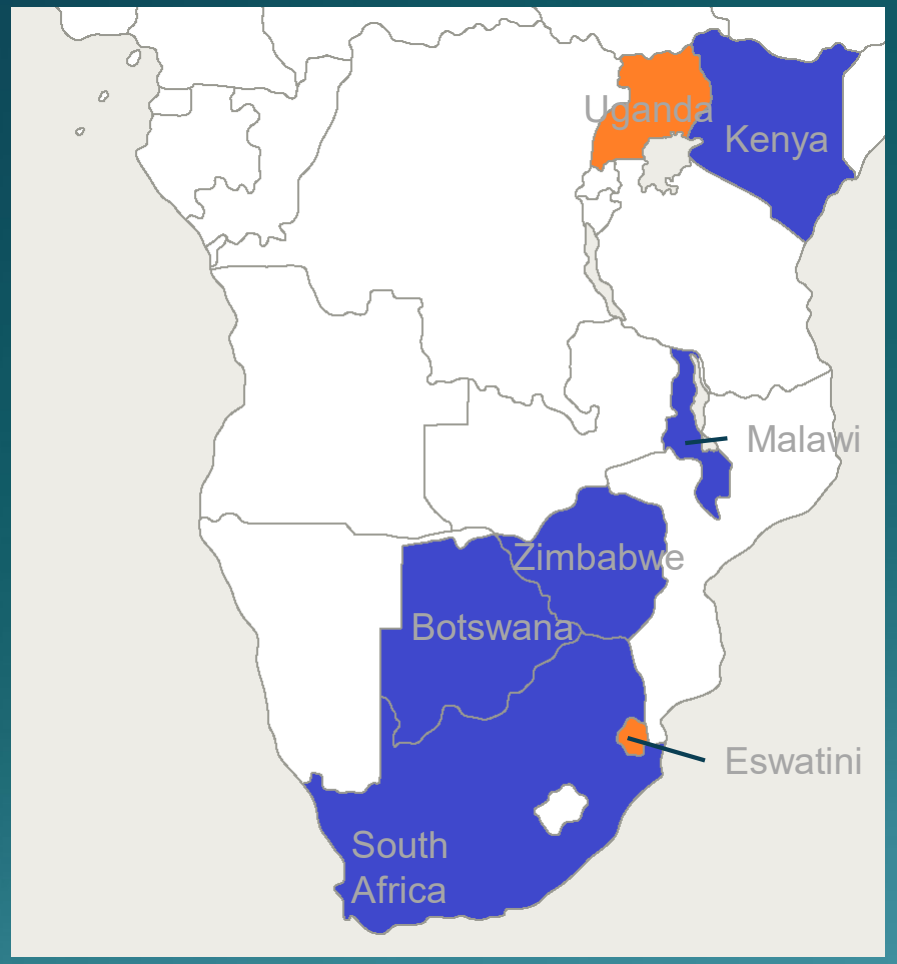
	HPTN 084		AMP women	
	PY	%	PY	%
Botswana	69.4	4%	97.3	8%
Kenya	50.4	3%	52.3	4%
Malawi	144.9	9%	110.1	9%
South Africa	722.7	47%	637.2	54%
Zimbabwe	559.9	36%	272.3	23%
Total	1956.3		1202.5	

Results: Comparing Baseline Age and STI

Variable		Five country		Three country		South Africa	
		HPTN 084 CAB-LA	Weighted AMP Women	HPTN 084 CAB-LA	Weighted ECHO	HPTN 084 CAB-LA	HVTN 702 placebo
Age Category	18-24	46%	38%	57%	63%	61%	61%
	25-29	26%	32%	22%	26%	21%	23%
	30-39	24%	30%	18%	12%	16%	16%
	>=40	4%	1%	2%	0%	2%	0%
Baseline Gonorrhea		7%	5%	7%	5%	7%	5%
Baseline Chlamydia		20%	15%	24%	20%	25%	21%

Efficacy Results

Counterfactual study	CAB-LA Incidence	Counterfactual Placebo Incidence	Efficacy of CAB-LA versus Placebo (95% CI)
Five Country (AMP Women)	0.19	2.62	**93% (76%-98%)**
Three Country (ECHO)	0.23	4.47	**95% (79%-99%)**
South Africa (HVTN 702 Vaccine)	0.28	4.21	**93% (73%-98%)**



Conclusion

- Placebo-based ITT efficacy of CAB-LA extraordinarily high (93-95%) in women; consistent across different settings in Africa with moderate and high HIV incidence

- Successfully constructed a counterfactual placebo using data from external trials, with overlapping follow-up in time and place; illustrates a potential approach for estimating efficacy in future prevention trials with no placebo arm