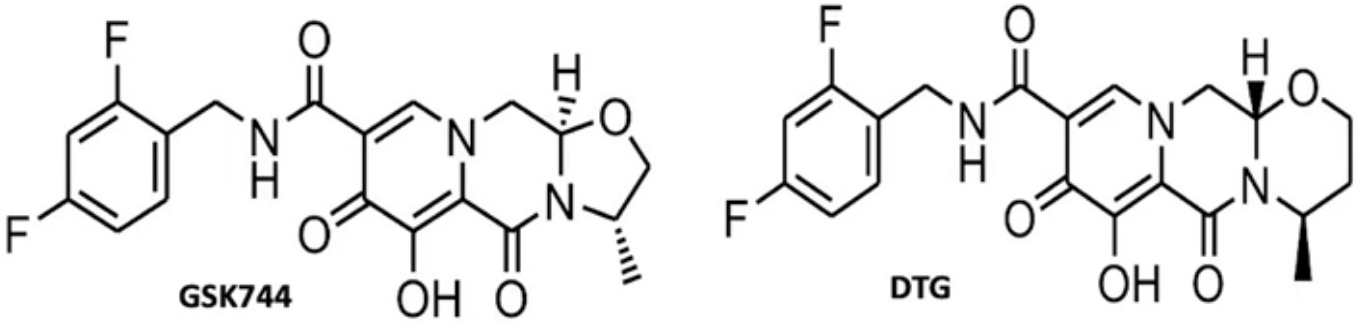
Practice changing articles…in the clinic!

RACHEL SAFRAN, MD FACP AAHIVS

Disclosures

- I have no relevant financial disclosures.
- I do conduct clinical research trials, but will not be discussing any of those investigational products:
  - Gilead
  - GSK
  - Merck
  - AstraZeneca

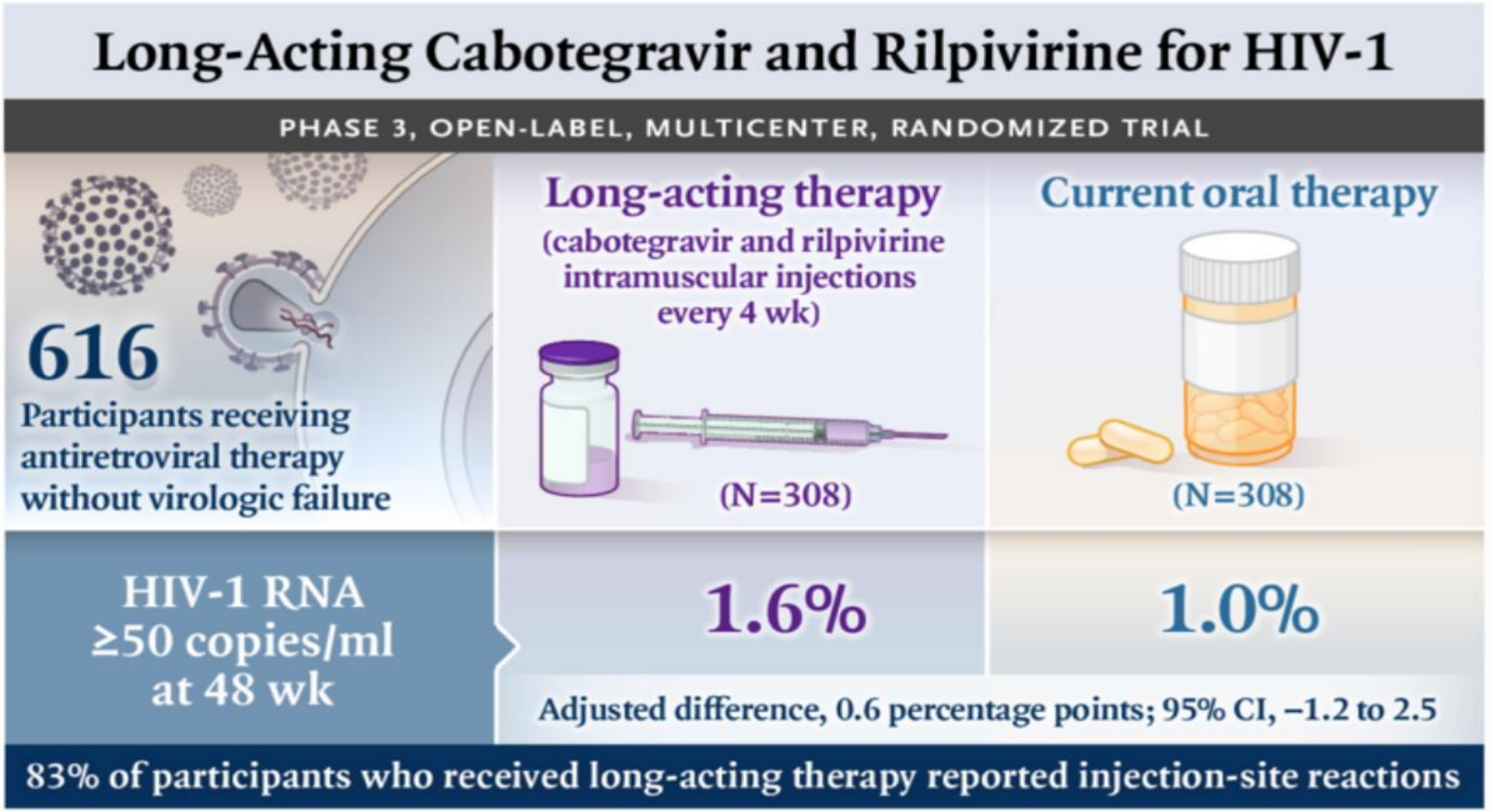
Long Acting HIV Treatment and Prevention



Cabotegravir

FLAIR – First Long Acting Injectable Regimen

The NEW ENGLAND JOURNAL of MEDICINE



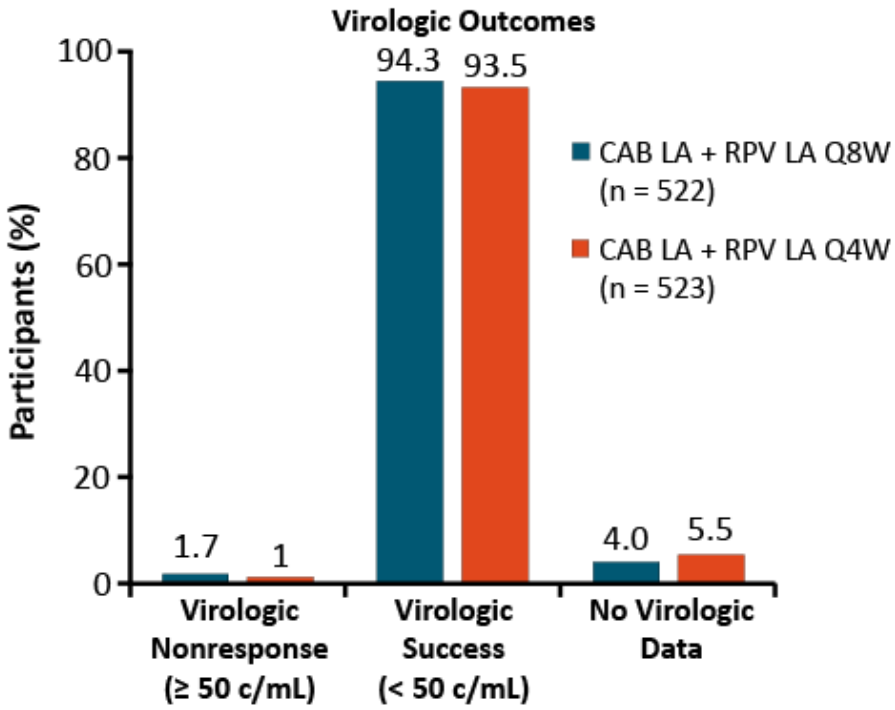
N Engl J Med 2020; 382:1124-1135

Monthly treatment with CAB/RPV

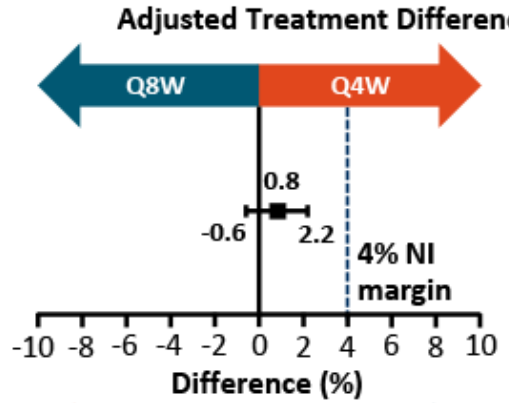
Month 1	Month 2	Month 3
Oral therapy lead-in	Initiation injections	Continuation injections

https://cabenuvahcp.com/dosing/once-monthly/

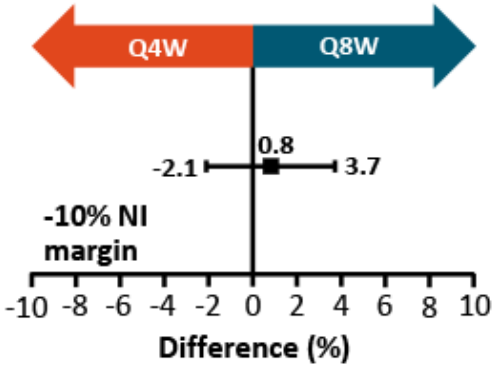
ATLAS-2M



*Based on Cochran-Mantel-Haenszel analysis adjusting for prior CAB + RPV exposure.



Primary endpoint (HIV-1 RNA ≥ 50 c/mL): CAB LA + RPV LA Q8W noninferior to Q4W



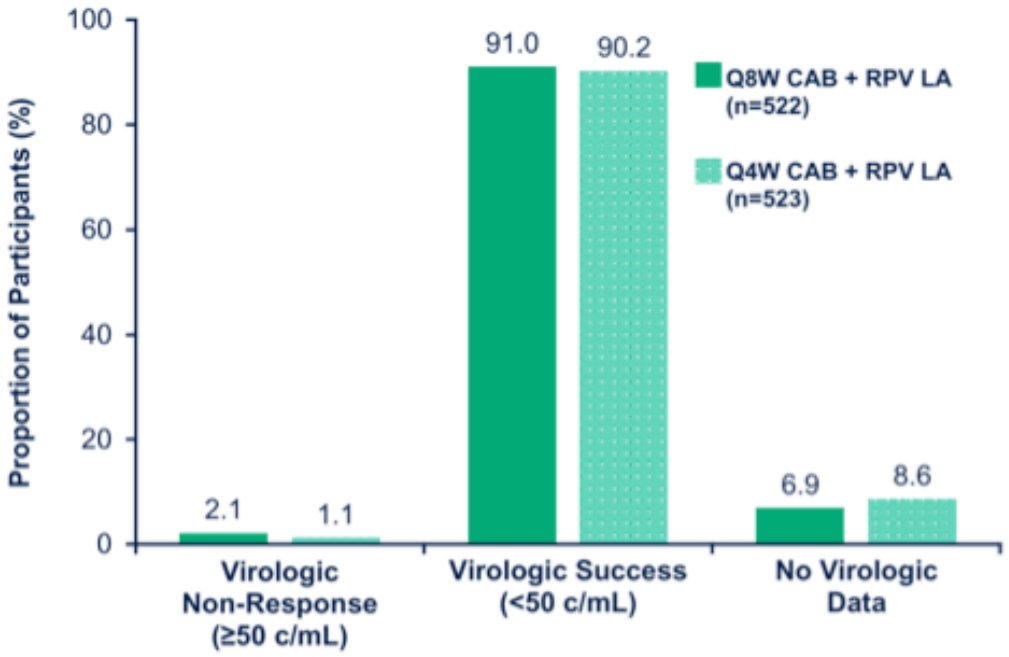
Key secondary endpoint (HIV-1 RNA < 50 c/mL): CAB LA + RPV LA Q8W noninferior to Q4W

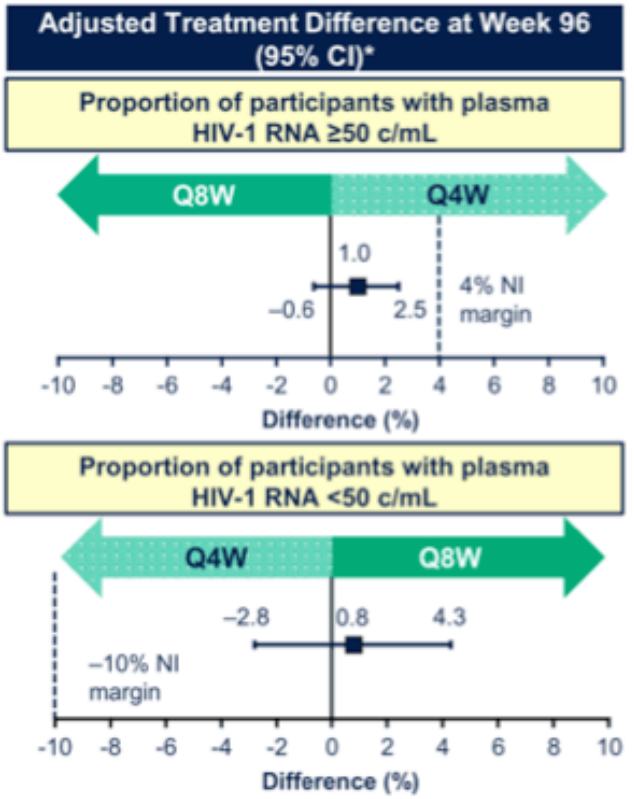
Overton. CROI 2020. Abstr 34. Reproduced with permission.

Slide credit: clinicaloptions.com

Lancet 2021 Dec 19;396(10267):1994-2005.

ATLAS-2M Week 96: Virologic Snapshot Outcomes for ITT-E: CAB + RPV LA Continued to Maintain High Levels of Viral Suppression





*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

AIDS 2022 Feb 1;36(2):185-194

ATLAS-2M Week 96: Snapshot Outcomes at Week 96 (ITT-E Population)

	Q8W* (n=522)	Q4W* (n=523)
HIV-1 RNA <50 c/mL	475 (91.0)	472 (90.2)
Adjusted† difference (95% CI)	0.8 (–2.8, 4.3)	
HIV-1 RNA ≥50 c/mL	11 (2.1)	6 (1.1)
Adjusted† difference (95% CI)	1.0 (–0.6, 2.5)	
Data in window not below threshold	2 (0.4)	2 (0.4)
Discontinued for lack of efficacy	8 (1.5)	3 (0.6)
Discontinued for other reason while not below threshold	1 (0.2)	1 (0.2)
No virologic data	36 (6.9)	45 (8.6)
Discontinued study due to AE or death‡	17 (3.3)	17 (3.3)
Discontinued study for other reason	16 (3.1)	27 (5.2)
On study but missing data in window	3 (0.6)	1 (0.2)

AIDS 2022 Feb 1;36(2):185-194

INNOVATION

U.S. FDA Approves CABENUVA (rilpivirine and cabotegravir) for Use Every Two Months, Expanding the Label of the First and Only Long-Acting HIV Treatment

CABENUVA offers virologically suppressed adults living with HIV an injectable treatment option administered as few as six times a year.

INITIATION		CONTINUATION			
MONTH 1	MONTH 2	MONTH 3	MONTH 4	MONTH 5	MONTHS 6, 8, AND BEYOND
Administer the first CABENUVA injections (1 LA cabotegravir 600 mg/3 mL and 1 LA rilpivirine 900 mg/3 mL). Administer the second set of initiation injections 1 month later.			For duration of treatment, administer CABENUVA injections (1 LA cabotegravir 600 mg/3 mL and 1 LA rilpivirine 900 mg/3 mL) every 2 months.		

2 IM injections at separate gluteal sites (opposite sides or 2 cm apart) during same visit

https://cabenuvahcp.com/dosing/every-2-month/

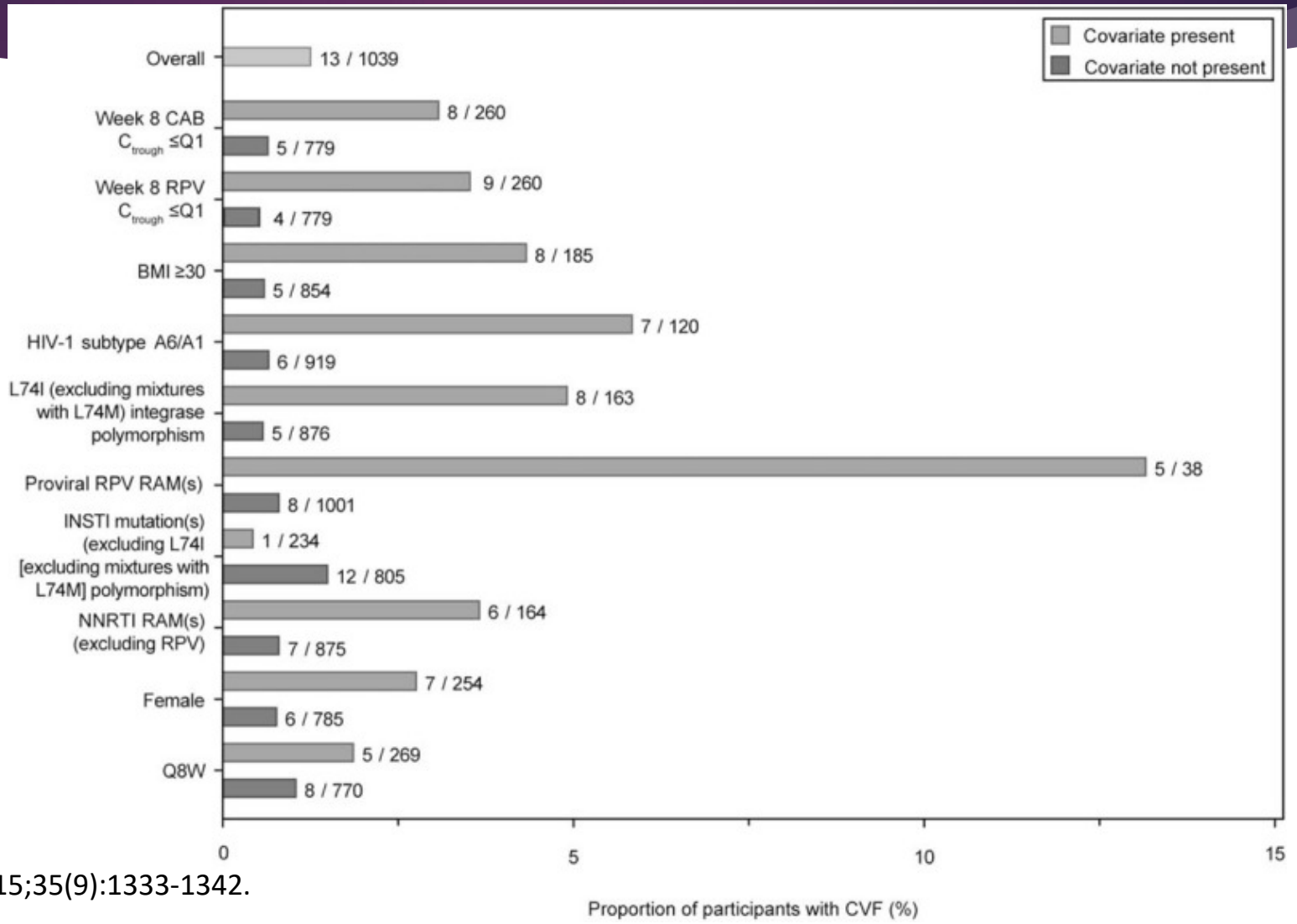
Which of the following patients is the most *appropriate* candidate for CAB/RPV-LA?

A. 34y/o cisgender MSM with history of limited adherence, last HIV RNA viral load 30 copies.
B. 50y/o TGW suppressed on BIC/FTC/TAF with diabetes, HTN, and CKD (CrCl 35mL/min) and BMI 35.
C. 22y/o cisgender MSM suppressed on DOL/ABC/3TC with epilepsy that is controlled with levetiracetam and phenytoin.
D. 30y/o cisgender female suppressed on DOL + FTC/TAF who is 2months pregnant.
E. 60y/o cisgender MSM suppressed on RPV/FTC/TAF with history of chronic Hepatitis B.

New HHS Recommendation – Sept 2022

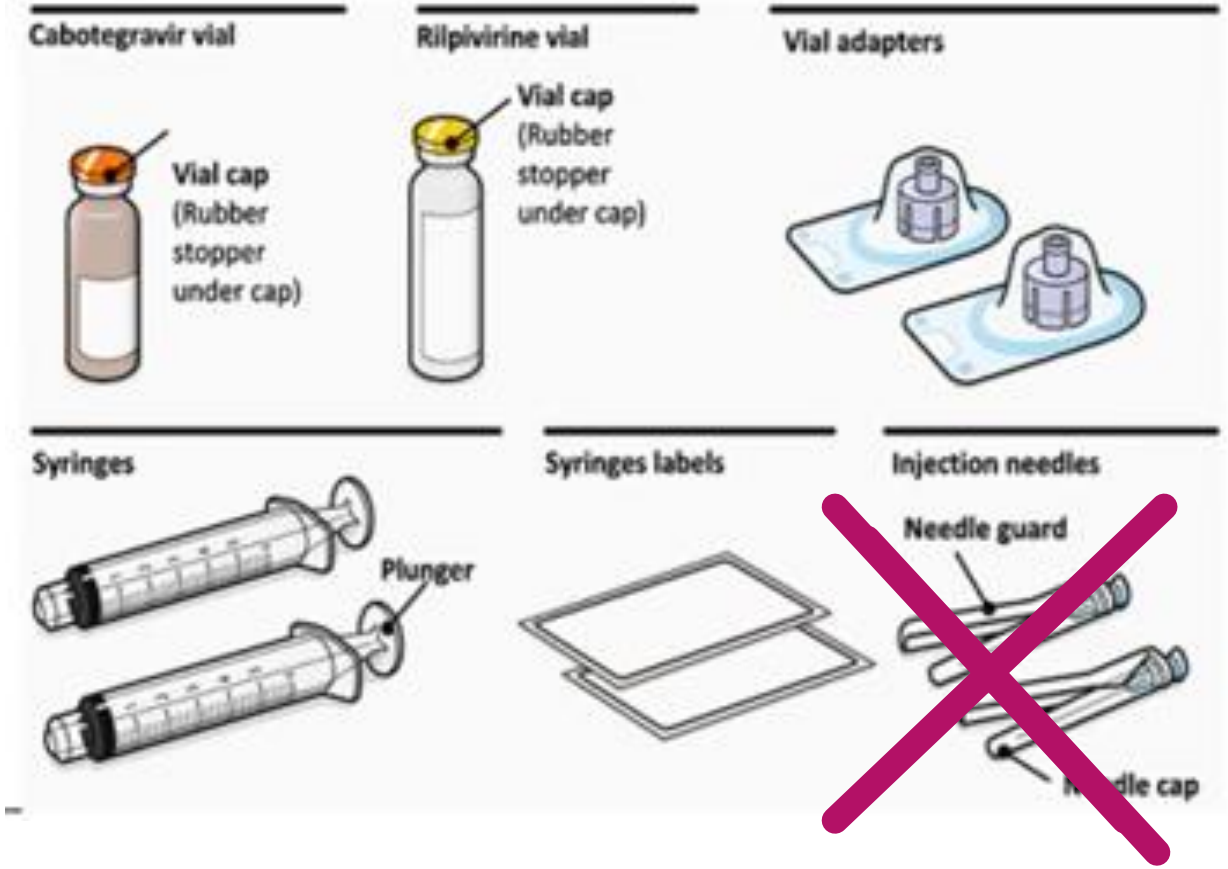
- The panel recommends against use of long acting ART regimen of intramuscular CAB and RPV in people who have detectable viral load due to suboptimal adherence to ART and who have ongoing challenges with retention in HIV care, except in a clinical trial (AIII).

Clinical predictors of failure



AIDS 2021 Jul 15;35(9):1333-1342.

BMI >30 use a 2in needle

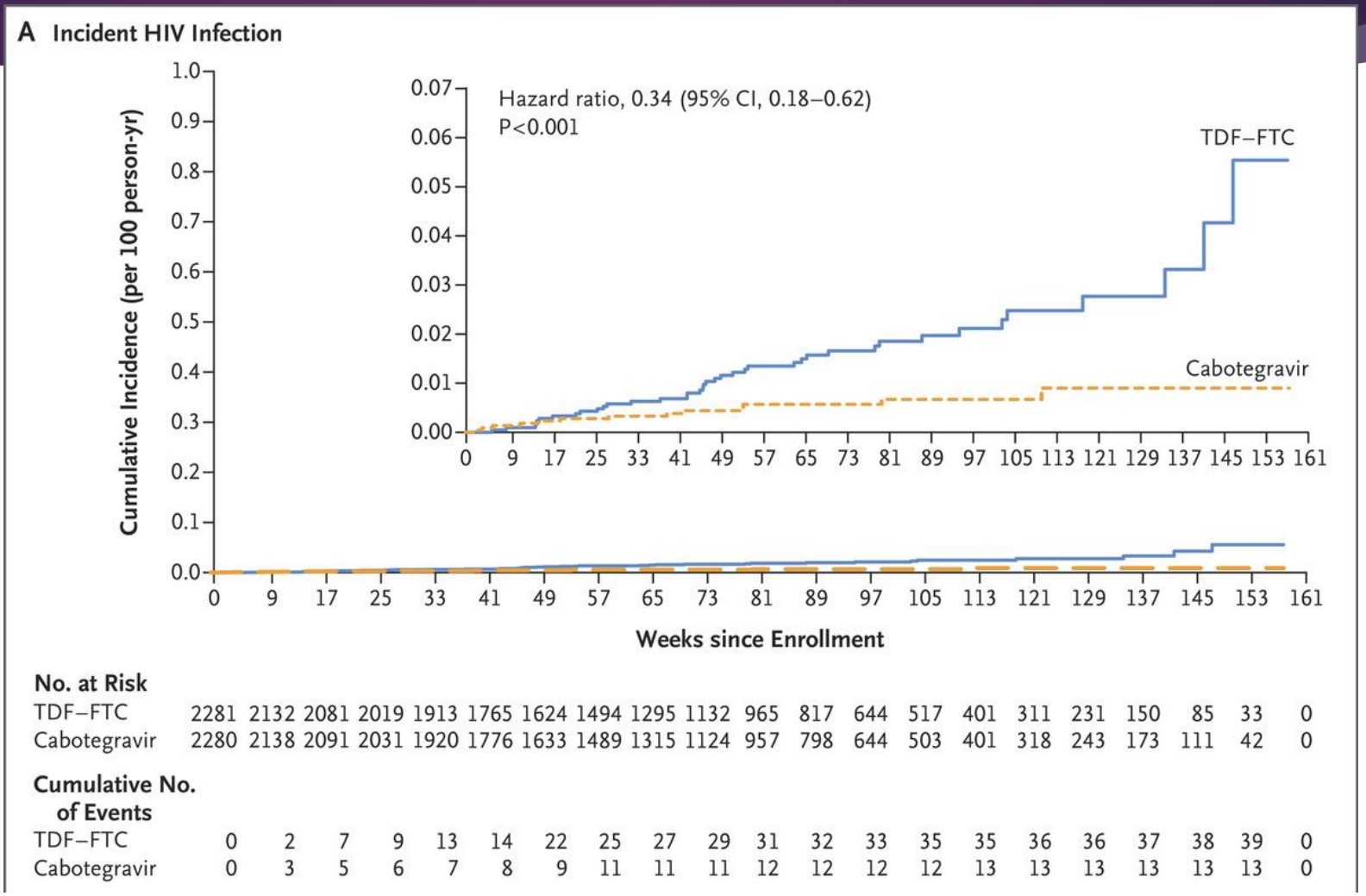


Things to consider

- Patient interest/desire
- Hepatitis B immunity/history
- Co-morbidities and drug-drug interactions
- Insurance and drug acquisition
- Refrigeration
- Adherence and scheduling

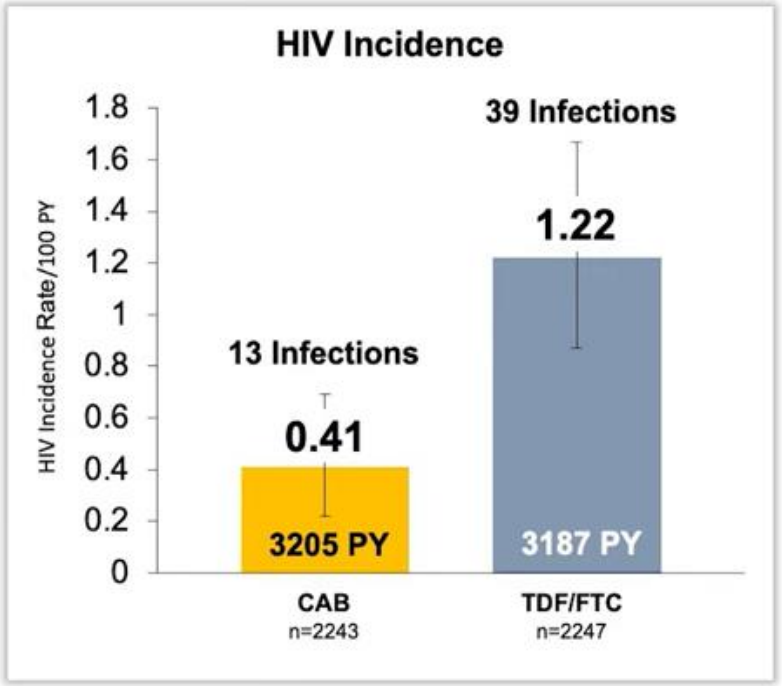
FDA approves first
injectable treatment for HIV
pre-exposure prevention
FDA

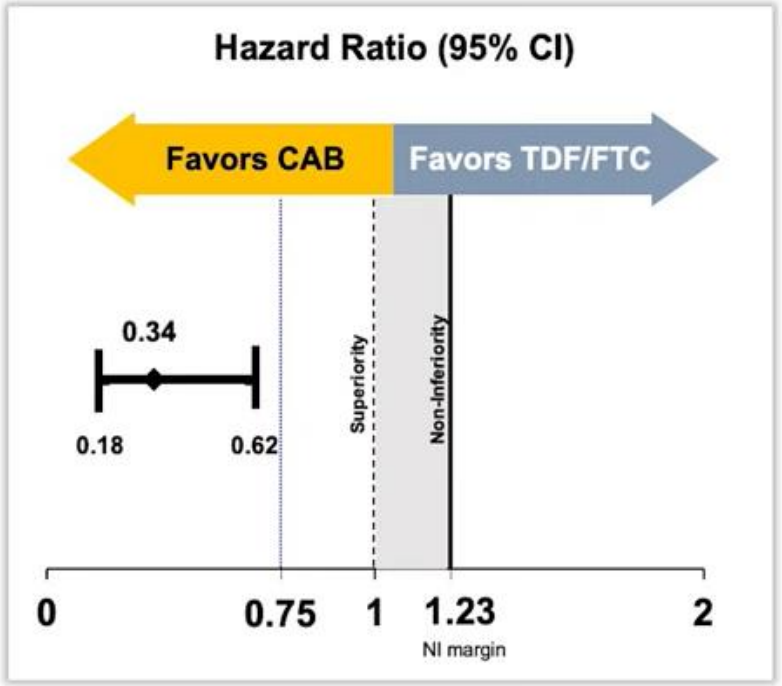
HPTN-083



N Engl J Med 2021 Aug 12;385(7):595-608

CAB-LA for HIV Prevention (PrEP)

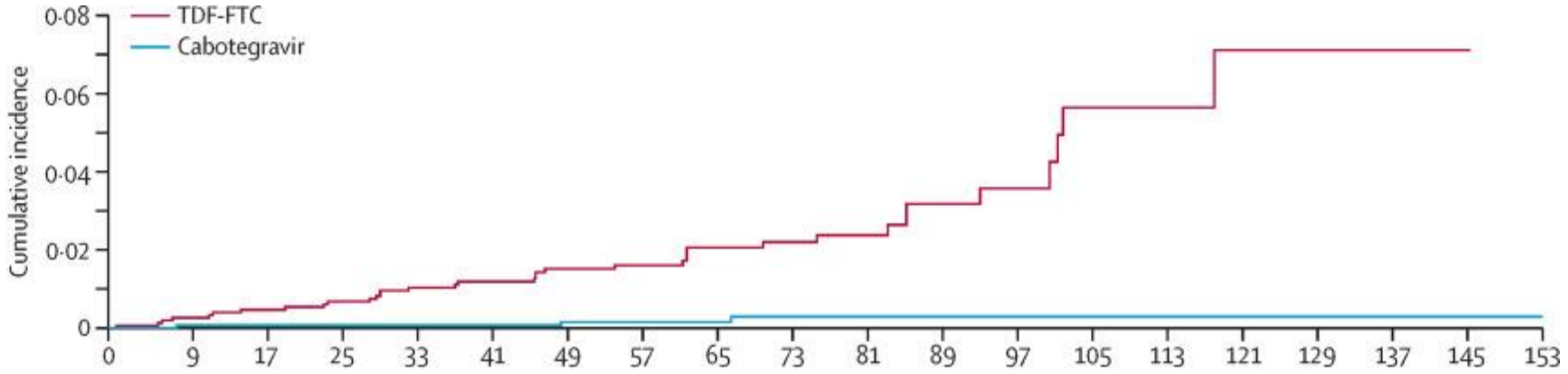




CI, confidence interval

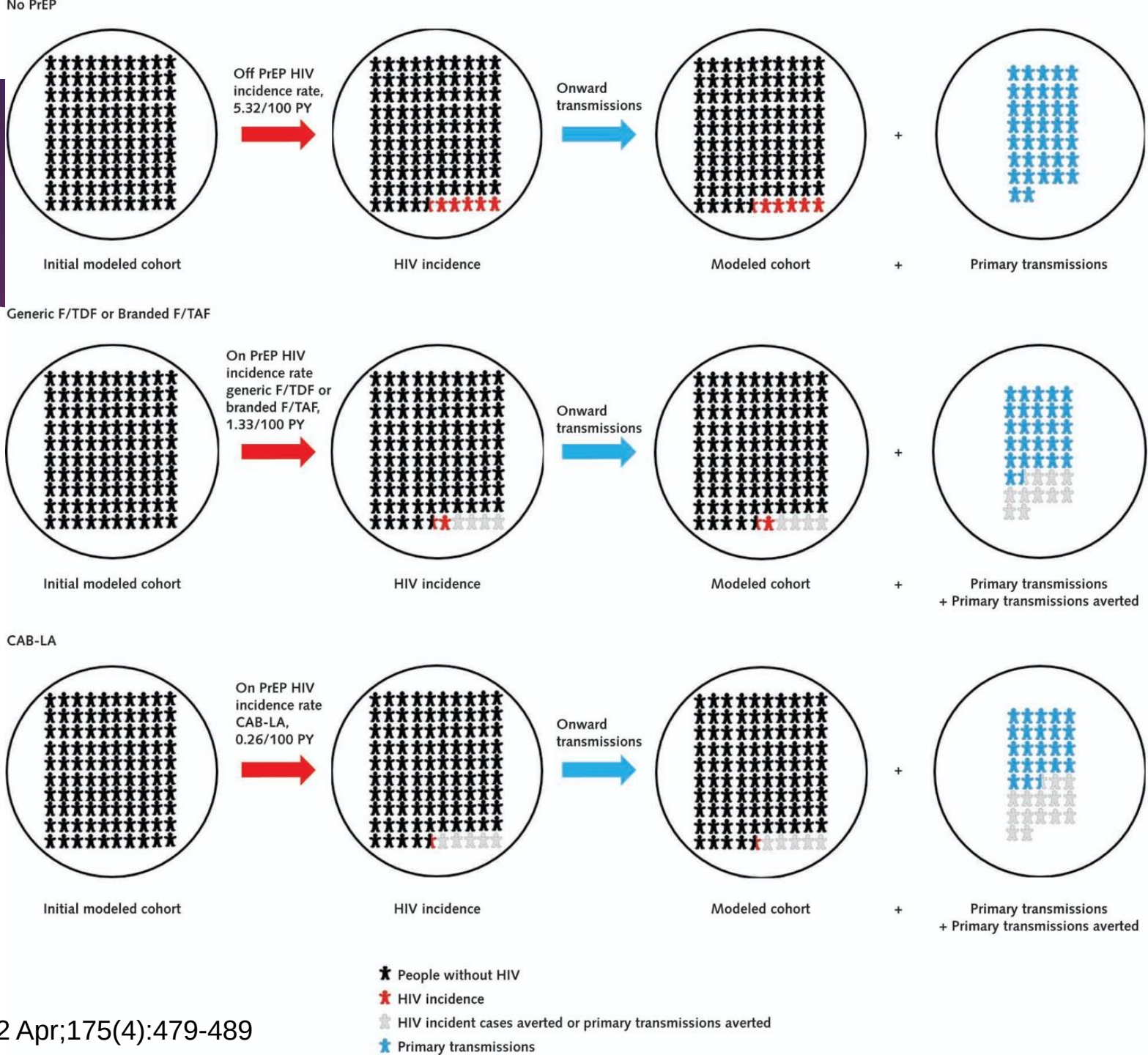
N Engl J Med 2021 Aug 12;385(7):595-608

HPTN-084



Number at risk																			
TDF-FTC	1610	1490	1429	1410	1353	1260	1160	984	800	656	485	306	201	115	70	63	52	22	3	0
Cabotegravir	1614	1488	1441	1429	1371	1279	1181	988	801	647	482	304	204	116	67	58	50	23	3	2
Cumulative number of events																			
TDF-FTC	0	4	7	10	15	17	21	22	26	27	28	31	32	35	35	36	36	36	36	36
Cabotegravir	0	1	1	1	2	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4

Lancet 2022 May 7;399(10337):1779-1789.



Ann Intern Med 2022 Apr;175(4):479-489

Is it ready for primetime?

Ann Intern Med 2022 Apr;175(4):479-489

A common case

- 68y/o post menopausal cisgender female presents for urgent care follow up after acute cystitis. Symptoms resolved after a 3 day course of TMP/SMX but this is her 4th UTI in the last year and she asks what else she can do to prevent this from happening.
- No known drug allergies
- Normal renal function
- Current medications:
  - Alendronate weekly
  - Pravastatin 20mg daily
  - Estradiol vaginal cream 3x per week

What would you recommend?

A. Nitrofurantoin 100mg daily
B. Trimethoprim-sulfamethoxazole 40mg/200mg daily
C. Trimethoprim-sulfamethoxazole 40mg/200mg M/W/F
D. Cephalexin 250mg daily
E. Fosfomycin 3g every 10 days
F. Methenamine Hippurate 1g BID
G. D-mannose 2g daily
H. Referral to urology

THE SPOKESMAN-REVIEW
Spokane, Washington Est. May 19, 1883

NEWS > HEALTH

Pills and powders aim to replace cranberry juice as go-to prevention for UTIs

Oct. 3, 2022 | Updated Mon., Oct. 3, 2022 at 4:48 p.m.

D-mannose for preventing and treating urinary tract infections.

- D mannose is a sugar that can help prevent bacterial adherence to uroepitheial cells.
- Review of 7 RCTs with 719 patients - treatment and prevention
  - Little to no evidence to support or refute use of D-mannose
  - Very difficult to analyze because studies investigated different D-mannose preparations, different populations, and different control groups.

Cochrane Database Syst Rev. 2022 Aug 30;8:

Methenamine hippurate for preventing urinary tract infections

Methenamine hippurate ***may*** be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis. It does not appear to work in patients with neuropathic bladder or in patients who have renal tract abnormalities. The rate of adverse events was low, but poorly described. ***There is a need for further large well-conducted RCTs to clarify this question, particularly for longer term use.***

Cochrane Database Syst Rev. 2012 Oct 17;10(10)

ALTAR Study

ALternative **T**o prophylactic **A**ntibiotics for the treatment of **R**ecurrent UTIs in women

BMJ 2022;376:o533

thebmj Visual abstract

Non-antibiotic alternatives for treatment of urinary tract infections (UTIs)

Summary

Methenamine hippurate could be an appropriate non-antibiotic alternative to prophylactic antibiotics for women with recurrent UTIs, informed by patient preferences and antibiotic stewardship

Study design

Randomised non-inferiority trial | Open label | Recruited women from eight centres across the UK

Population

240 adult women with recurrent UTIs requiring prophylactic treatment

- Median average 6 UTIs in 12 months before trial entry in both groups
- Peri-/post-menopausal: 59%
- Average age: 50 years

Comparison

Experimental

Methenamine hippurate
Taken twice daily for 12 months

120

Control

Antibiotic prophylaxis
Nitrofurantoin, trimethoprim, or cefalexin taken daily for 12 months

120

Outcomes

Incidence of symptomatic, antibiotic treated UTIs over the 12 month treatment period

		Absolute difference in UTI incidence ‡ 90% CI	
		0	1
		0.5	
Modified intention-to-treat *	205	1.38	0.89
Intention-to-treat	240	1.40	0.88
Per protocol †	170	1.29	0.87

No difference | Non-inferiority margin

* All participants observed for ≥ six months
† Participants who achieved ≥90% adherence
‡ Methenamine hippurate minus antibiotic prophylaxis

https://bit.ly/bmj-altar

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Take home points

- Methenamine was cheaper, but dose twice daily
- Patients in the antibiotic arm had higher rates of resistant E Coli detected (72% vs 56%)
- Adverse drug reactions only report in the antibiotic arm
- *All 4 admissions related to UTI were in the methenamine arm*

Opinion time – what is the "best" method for colon cancer screening?

A. Colonoscopy
B. Flexible sigmoidoscopy
C. Annual fecal based testing
D. Every 3 year fecal based testing
E. Something else

Controversy or caution?

ORIGINAL ARTICLE

Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death

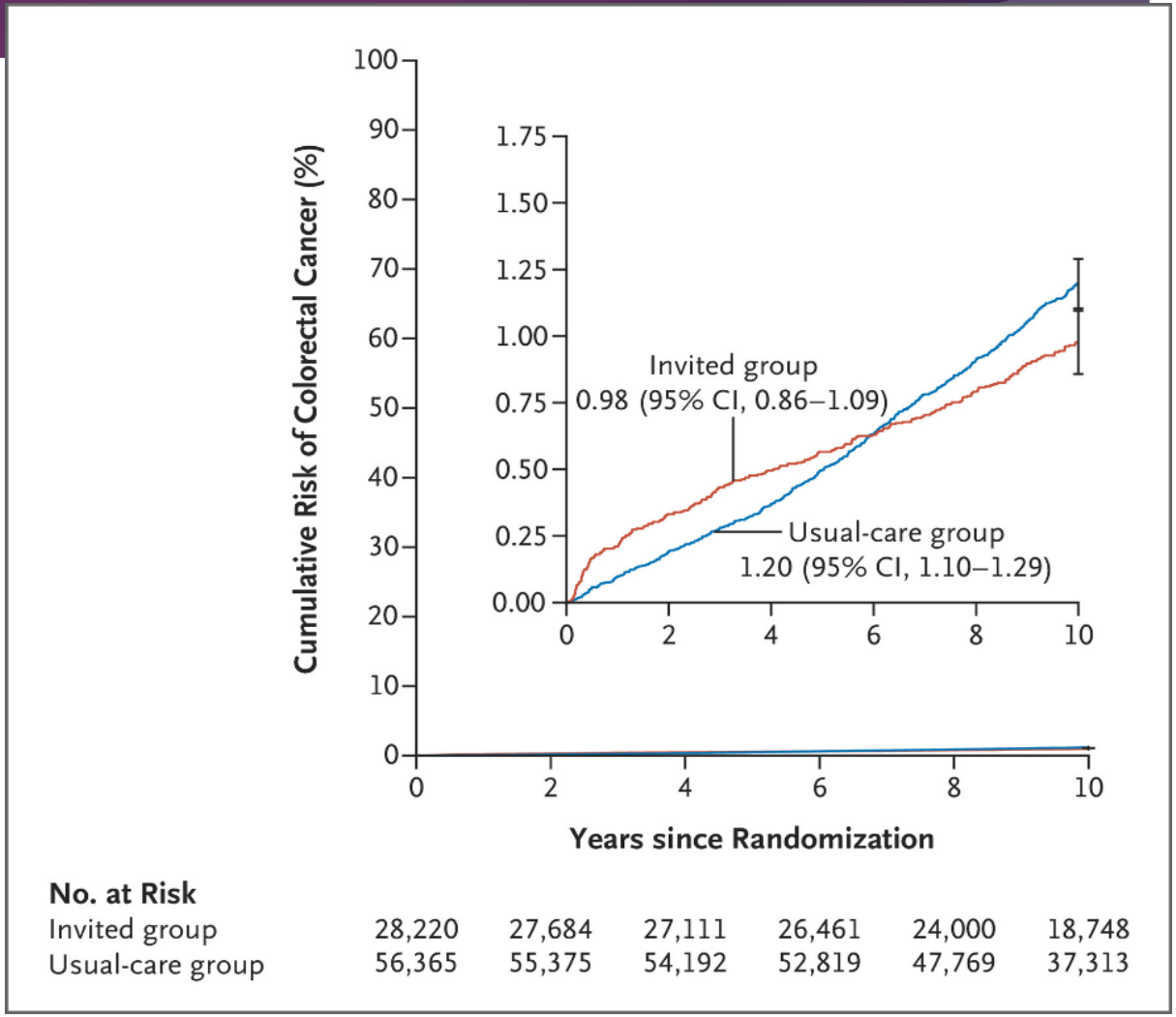
Michael Bretthauer, M.D., Ph.D., Magnus Løberg, M.D., Ph.D., Paulina Wieszczy, Ph.D., Mette Kalager, M.D., Ph.D., et al., for the NordICC Study Group*

N Engl J Med 2022; 387:1547-1556

NORDICC Study

- Participants age 55-64 were invited to a single screening colonoscopy vs usual care.
- Presumptively healthy men and women in Poland, Norway, Sweden and the Netherlands.
- **Found 18% lower 10yr risk of developing colon cancer…but NO significant effect on death from colorectal cancer.**

Cumulative Risk of Colorectal Cancer at 10yrs (intention to screen)



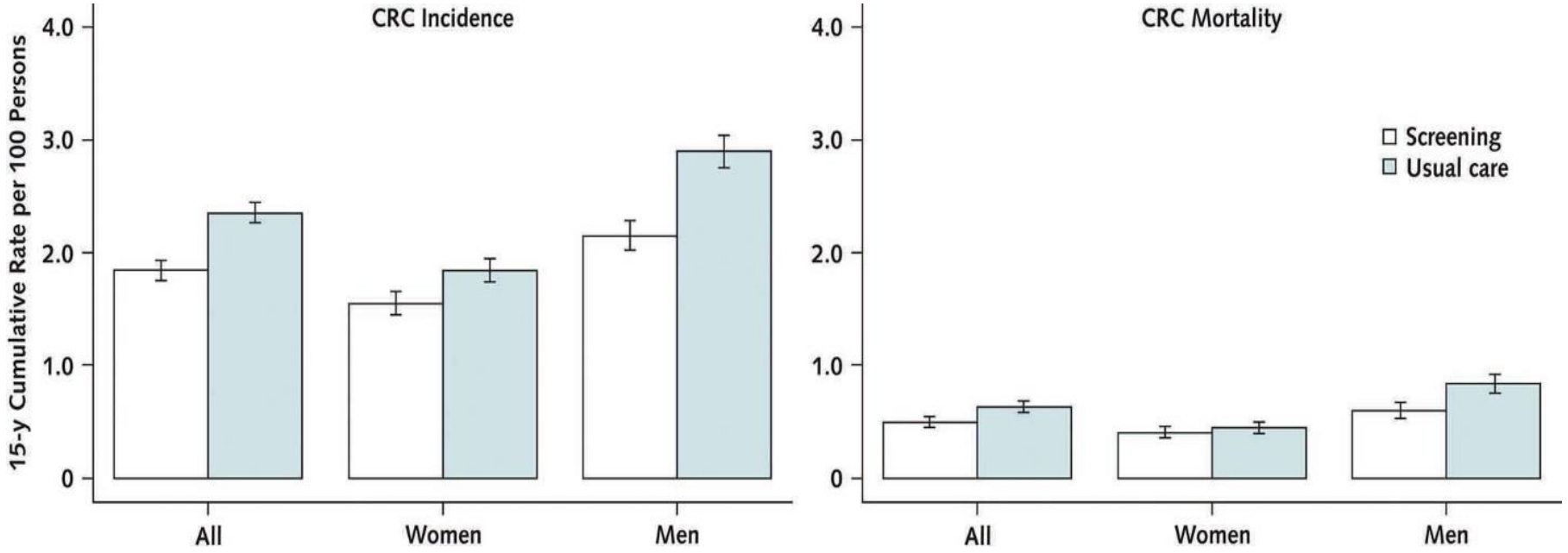
N Engl J Med 2022; 387:1547-1556

Flex sigs maybe?

15-Year Benefits of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality : A Pooled Analysis of Randomized Trials

NORCAP – Norwegian Colorectal Cancer Prevention
PLCO – US
UKFSST – UK
SCORE - Italy

Ann Intern Med . 2022 Oct 11. Online ahead of print



Ann Intern Med . 2022 Oct 11. Online ahead of print

	Intention to screen analysis*			
	Rate Ratio	*95% CI*	*Rate Difference§*	*95% CI*
CRC Incidence				
Trial†				
NORCCAP	0.78	(0.68-0.90)	0.56	(0.24-0.87)
PLCO	0.80	(0.74-0.86)	0.45	(0.30-0.60)
UKFSST	0.76	(0.70-0.82)	0.64	(0.45-0.83)
SCORE	0.82	(0.71-0.95)	0.50	(0.15-0.85)
Pooled analysis				
All	0.79	(0.75-0.82)	0.53	(0.43-0.64)
Location				
Distal	0.68	(0.64-0.72)	0.48	(0.40-0.56)
Proximal	0.93	(0.86-1.00)	0.08	(0.01-0.15)
Sex‡				
Women	0.85	(0.79-0.92)	0.29	(0.15-0.42)
Men	0.74	(0.70-0.79)	0.80	(0.63-0.96)
CRC mortality				
Trial†				
NORCCAP	0.78	(0.61-1.00)	0.17	(0.00-0.34)
PLCO	0.76	(0.69-0.83)	0.14	(0.06-0.21)
UKFSST	0.72	(0.62-0.84)	0.21	(0.11-0.31)
SCORE	0.81	(0.62-1.06)	0.15	(-0.03-0.33)
Pooled analysis				
All	0.76	(0.69-0.83)	0.17	(0.11-0.22)
Location‖				
Distal	0.63	(0.53-0.74)	0.13	(0.09-0.18)
Proximal	0.92	(0.78-1.08)	0.02	(-0.02-0.06)
Sex‡				
Women	0.88	(0.76-1.01)	0.06	(-0.01-0.13)
Men	0.69	(0.61-0.78)	0.29	(0.20-0.37)

Ann Intern Med . 2022 Oct 11. Online ahead of print

Don’t forget fecal tests!

Acceptability of alternative technologies compared with fecal immunochemical test and/or colonoscopy in colorectal cancer screening: A systematic review.

21 studies with findings suggesting FIT is *more acceptable* as a screening modality than colonoscopy or flexible sigmoidoscopy.

J Med Screen . 2022 Aug 29. Online ahead of print.

TARGET-C *(Comparison of Colonoscopy, Fecal Immunochemical Test, and Risk-Adapted Approach in a Colorectal Cancer Screening Trial)*

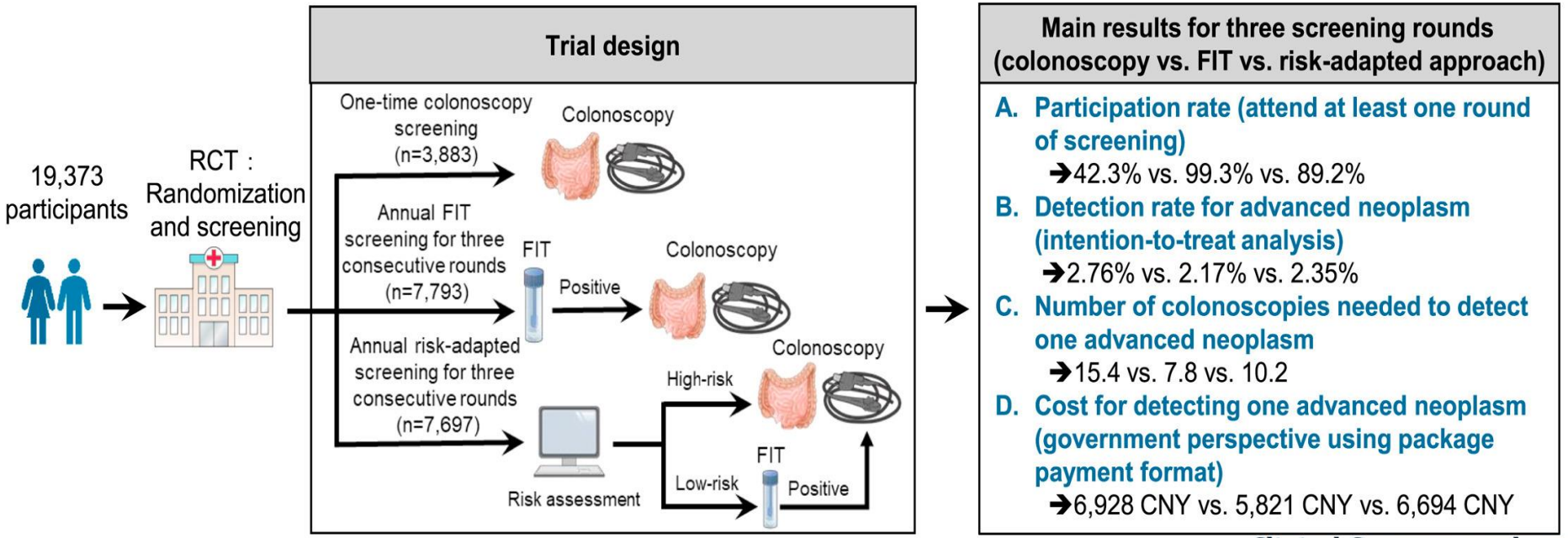
- Randomly allocated 19,373 participants into 1 of 3 screening arms
  - 1 time colonoscopy
  - Annual FIT
  - Annual risk adapted screening

Modified AsiaPacific Colorectal Screening (APCS) score

- Age (0: 50–54 years; 1: 55–64 years; 2: 65–74 years)
- Sex (0: female; 1: male)
- Family history of CRC among first-degree relatives (0: absent; 1: present),
- Cigarette smoking (0: nonsmoker; 1: current or past smoker)
- Body mass index (0: <23kg/m^2; 1: >23kg/m^2)

Clin Gastroenterol Hepatol. 2022 Aug 11; online ahead of print.

Colonoscopy *vs.* fecal immunochemical test (FIT) *vs.* risk-adapted approach in colorectal cancer screening



Clinical Gastroenterology and Hepatology

Clin Gastroenterol Hepatol. 2022 Aug 11; online ahead of print.

Take home message

- NORDICC - INVITATION to colonoscopy seems less effective as a population based screening of asymptomatic, average risk people.
- But may not truly estimate the effect of the procedure itself so perhaps more important is to study the acceptability and cost effectiveness of alternatives.

The best colorectal cancer screening test for a patient is the one they will complete.

Beverage Bonuses

COFFEE SAVES LIVES!

Association of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Coffee Consumption With All-Cause and Cause-Specific Mortality [A Large Prospective Cohort Study]

Ann Intern Med. 2022; 175(7):909-917.

Annals of Internal Medicine®

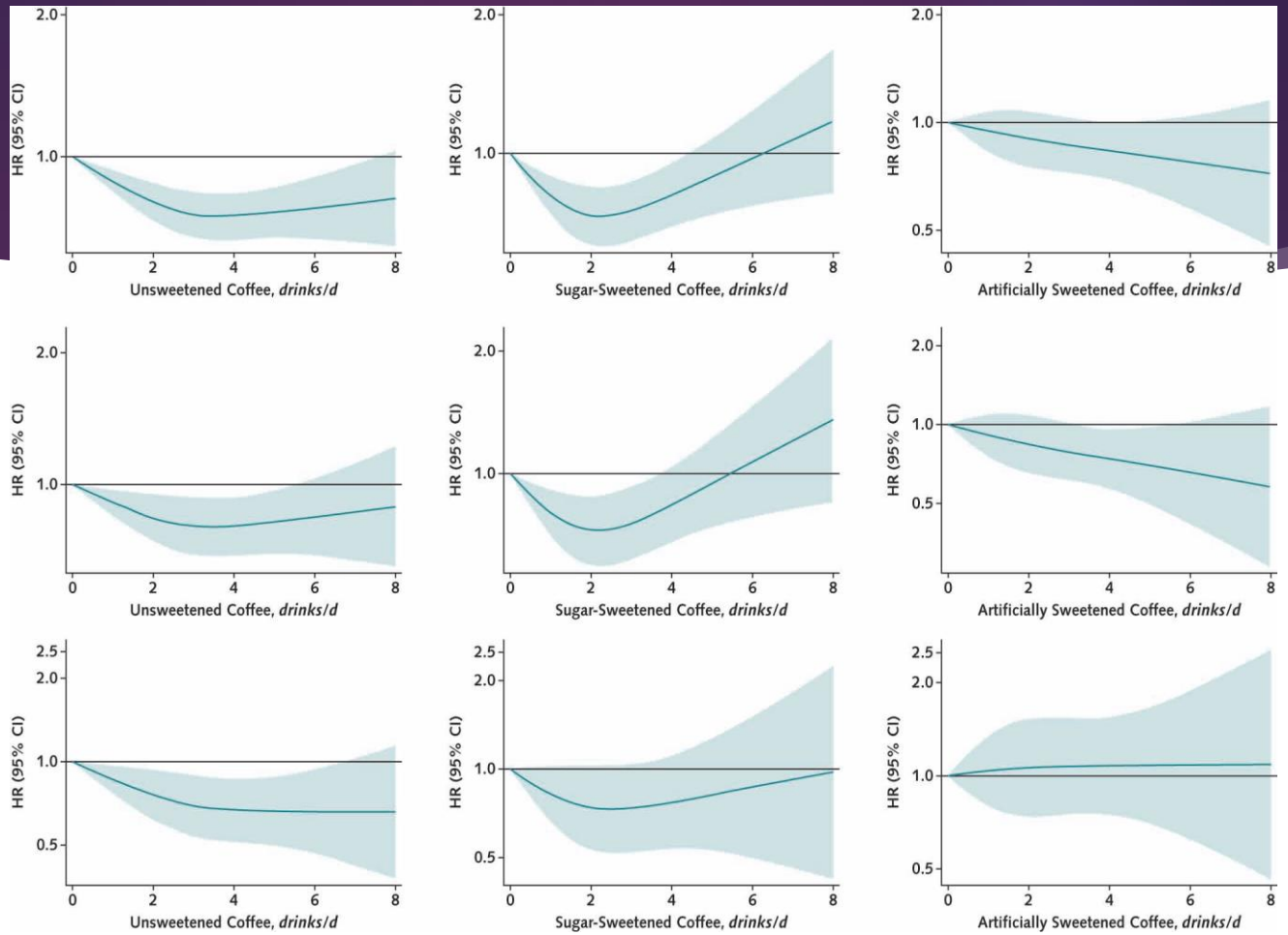


Figure Legend:

Multivariable Cox regression model with penalized splines adjusted for age, sex, Townsend deprivation index, education level, ethnicity, smoking status, pack-years of smoking, physical activity level, body mass index, waist circumference, hypertension, diabetes, depression, family history of CVD, family history of cancer, long-standing illness, cholesterol-lowering drug use, blood pressure drug use, vitamin and mineral supplement use, and intake of total energy, total sugar, fresh fruit, vegetables, red meat, processed meat, alcohol, tea, milk, sugar-sweetened beverages, and artificially sweetened beverages. CVD = cardiovascular disease; HR = hazard ratio.

"Although we cannot definitively conclude that drinking coffee reduces mortality risk, the totality of the evidence does not suggest a need for most coffee drinkers—particularly those who drink it with no or modest amounts of sugar—to eliminate coffee. So drink up—but it would be prudent to avoid too many caramel macchiatos while more evidence brews."

Ann Intern Med. 2022; 175(7):909-917.

Don’t like coffee?

Tea Consumption and All-Cause and Cause-Specific Mortality in the UK Biobank [A Prospective Cohort Study].

Ann Intern Med. 2022; 175(9):1201-1211.

Annals of Internal Medicine®

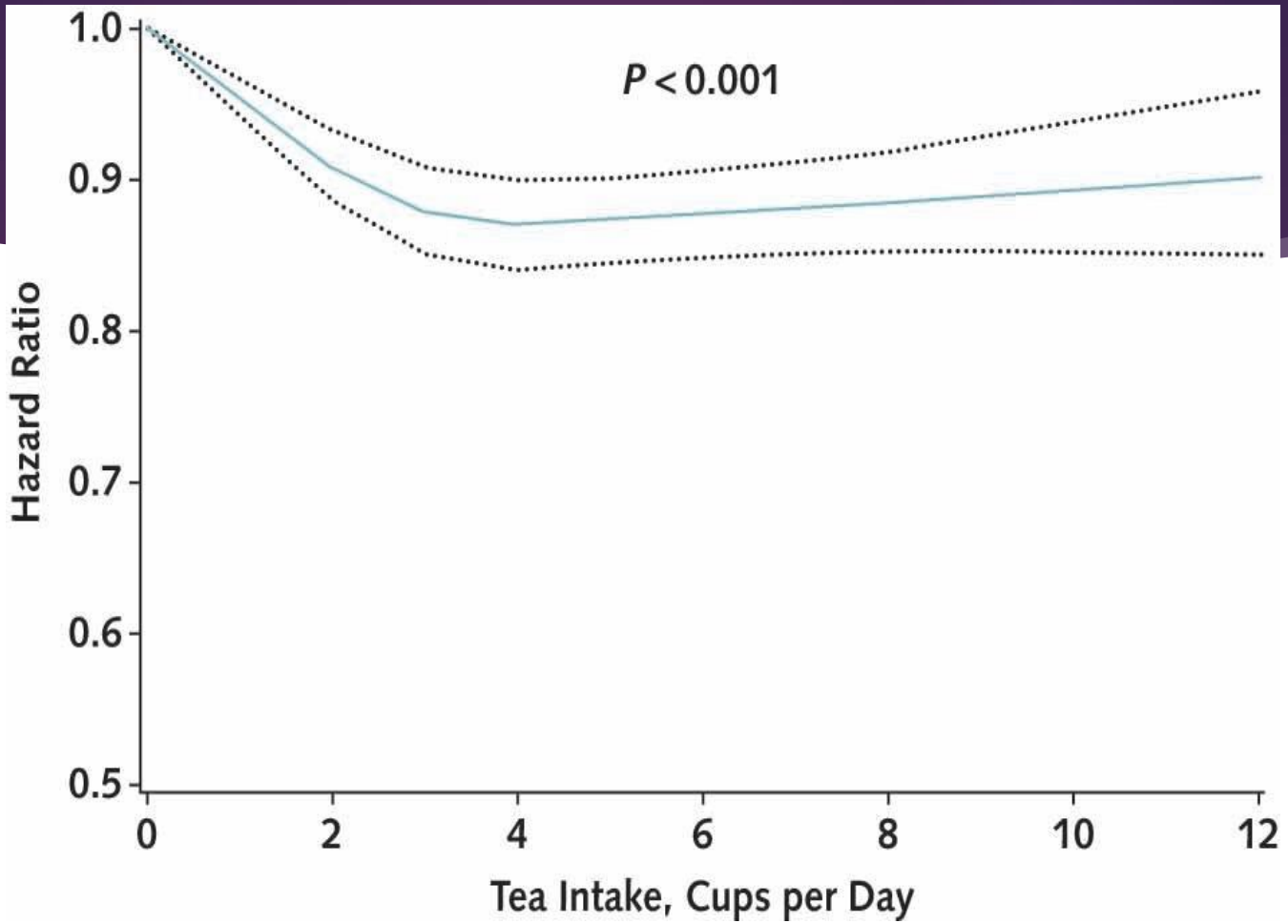


Figure Legend:

*** Hazard ratio was adjusted for age; sex; race and ethnicity (White, Black, Asian, mixed, or other race), assessment center, Townsend deprivation score, general health status (excellent, good, fair, or poor), cancer (yes or no), cardiovascular disease (yes or no), diabetes (yes or no), BMI (kg/m2), tobacco smoking (25-level variable including current smoking status, smoking intensity [current and former smokers], time since quitting [former smokers], and cigar and pipe use [current and former smokers]); physical activity (>10 minutes of moderate or vigorous activity; days per week); alcohol intake (never drinker, former drinker, infrequent drinker [<1 drink per week], occasional drinker [>1 drink per week but <1 drink per day], moderate daily drinker [1 to 3 drinks per day]), or heavy drinker [>3 drinks per day]; coffee intake (cups per day); and dietary intake including vegetables (tablespoons per day), fruits (pieces per day), red meat (beef, lamb, and pork; 0 to 1, 1.5, 2, 2.5, 3 to 21 times per week as quintiles), and processed meat (0, <1, 1, 2 to 4, 5 to 6, and ≥7 times per week). The solid line represents hazard ratio; the dotted line represents 95% CI.**

Thank you!

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