Conference on Retroviruses and Opportunistic Infections (CROI) Round Up!

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AETC AIDS Education & Training Center Program Southeast

Disclosures

I have no disclosures.

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30th

CROI2023

Conference on Retroviruses and Opportunistic Infections

FEBRUARY 19–22 • SEATTLE, WASHINGTON

#CROI2023

CONFERENCE PLATFORM

CROI 2023 OPENING SESSION

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Objectives

- Discuss the new data from CROI in 3 contexts
  - HIV Morbidity and Mortality
  - HIV and Depression
  - Prophylactic STI Treatment

Trends in mortality in people living with HIV in an international cohort (RESPOND)

Trends in mortality in people living with HIV in an international cohort (RESPOND)

Presented by Erich Tusch on behalf of the RESPOND cohort consortium

Disclosures: none

Tusch E, Pelchen-Matthews A, Peters L, et al. Trends in mortality in people living with HIV in an international cohort (RESPOND). 30th CROI, Conference on Retroviruses and Opportunistic Infections, February 19-22, 2023, Seattle. Abstract 870.

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RESEARCH ARTICLE Open Access

Changes in mortality rates and causes of death in a population-based cohort of persons living with and without HIV from 1996 to 2012

Oghenowede Eyawo[1,2], Conrado Franco-Villalobos[1], Mark W. Hull[1], Adriana Nohpal[3], Hasina Samji[4], Paul Sereda[1], Viviane D. Lima[1], Jeannie Shoveller[1,5], David Moore[1], Julio S. G. Montaner[1,6], Robert S. Hogg[1,2*] and for the Comparative Outcomes And Service Utilization Trends (COAST) study

Outcomes

- Primary outcome – death from any cause.
- Utilized ICD9 and ICD10 codes for death
- Computed Age-standardized mortality rates (ASMR)

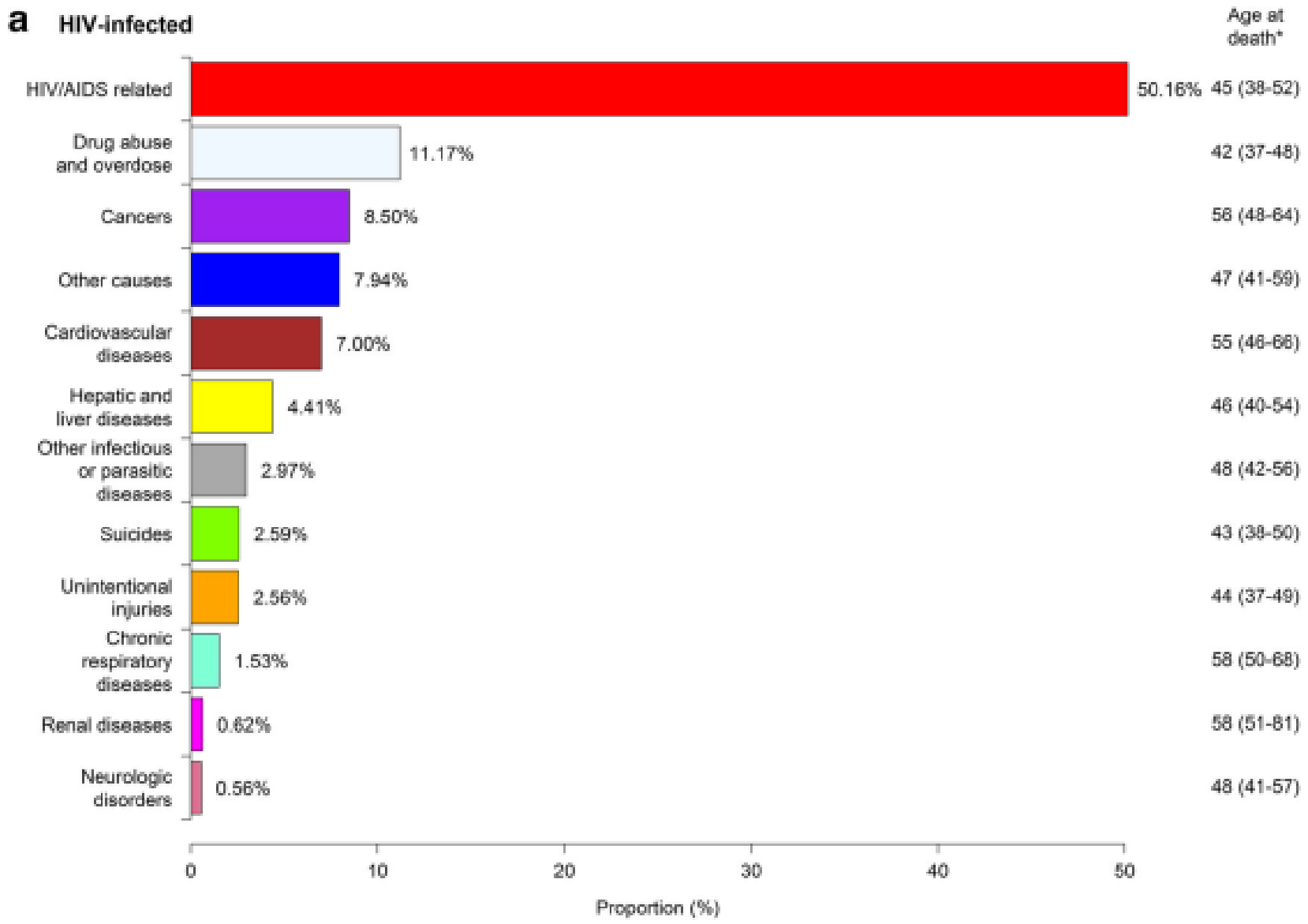
Methods

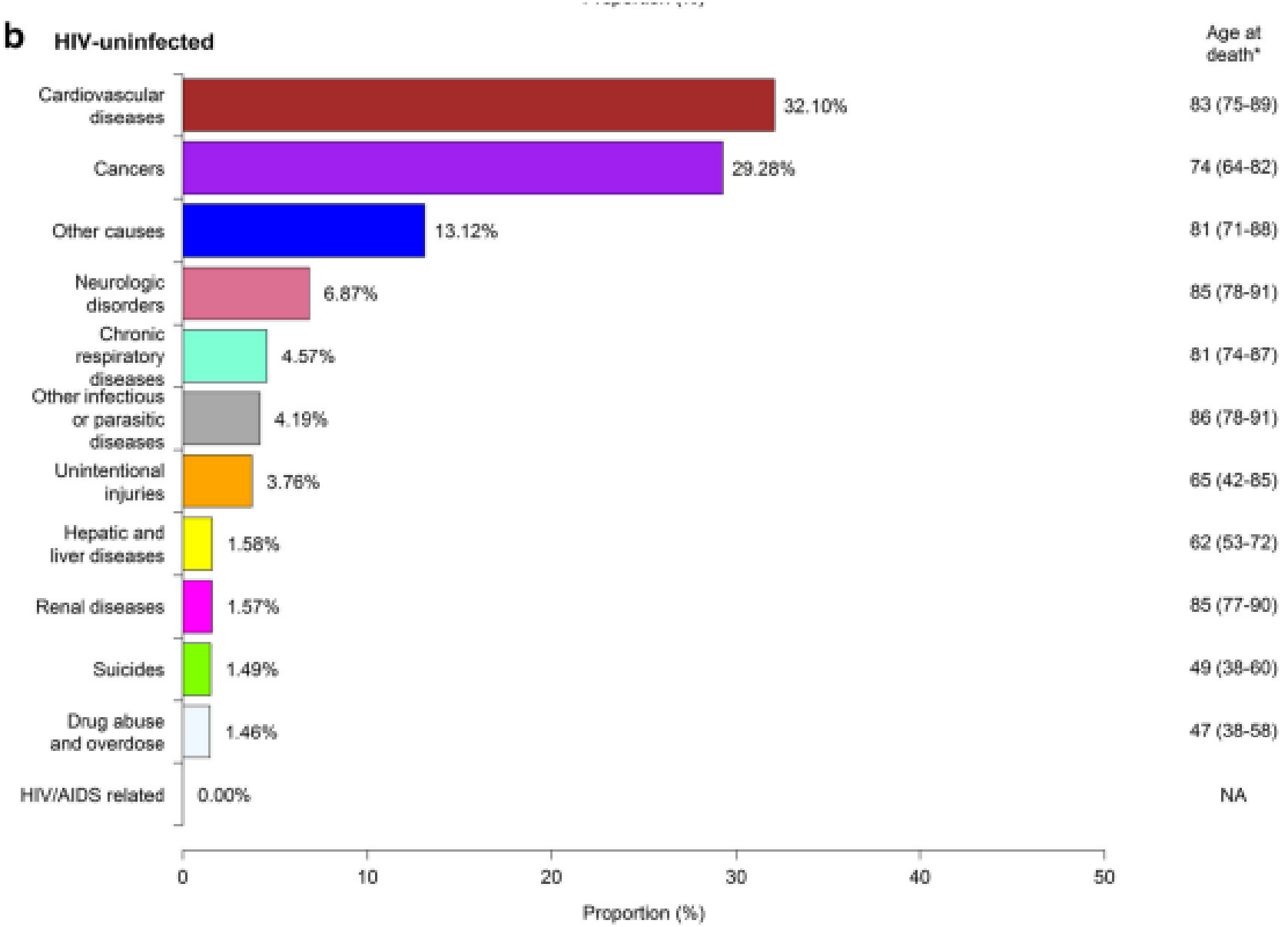
- Used data from the Comparative Outcomes and Service Utilization Trends (COAST) study
- Study period April 1, 1996 – March 31, 2013
- Comparisons between groups were performed using Chi-square test or Fisher exact test for categorical variables and Kruskall-Wallis test for continuous variables.
- Test of trend over time were performed using Kendall rank correlation.

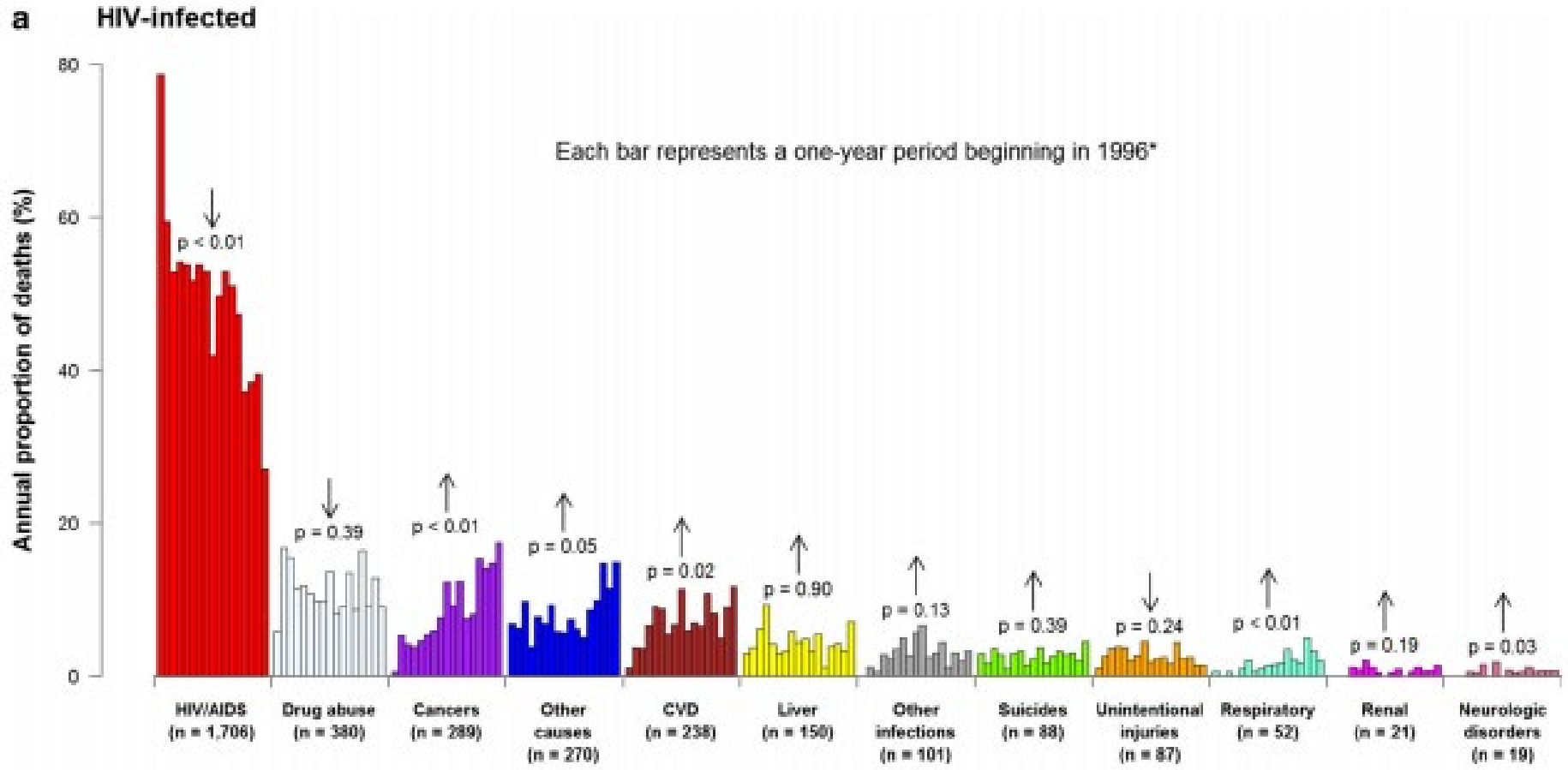
Table 2 Characteristics of study participants

Characteristics	Entire sample, n (%)			Dead, n (%)		
	HIV+ (*N* = 13729)	HIV- (*N* = 510313)	*p*-value	HIV+ (*N* = 3401)	HIV- (*N* = 47647)	*p*-value
Age at study entry, median (Q1, Q3) years	38 (32, 46)	36 (24, 50)	<0.001	41 (34, 49)	71 (59, 78)	<0.001
Age at death, median (Q1, Q3) years				46 (39, 55)	80 (69, 87)	<0.001
Sex						
Male	11017 (80.25)	256440 (50.25)	<0.001	2716 (79.86)	24394 (51.20)	<0.001
Female	2712 (19.75)	253873 (49.75)		685 (20.14)	23253 (48.80)	
Follow-up time, median (Q1, Q3) years	7.22 (2.96, 12.97)	12.70 (4.76,16.75)	<0.001	3.91 (1.16, 7.60)	8.42 (4.25, 12.58)	<0.001
Antiretroviral therapy ever?						
Yes	10165 (74.04)			2377 (69.89)		
No	3564 (25.96)	–		1024 (30.11)	–	

Legend: Q1, 25th percentile; Q3, 75th percentile


a
HIV-infected
Age at death*
HIV/AIDS related
50.16%
45 (38-52)
Drug abuse and overdose
11.17%
42 (37-48)
Cancers
8.50%
58 (48-64)
Other causes
7.94%
47 (41-59)
Cardiovascular diseases
7.00%
55 (46-66)
Hepatic and liver diseases
4.41%
46 (40-54)
Other infectious or parasitic diseases
2.97%
48 (42-56)
Suicides
2.59%
43 (38-50)
Unintentional injuries
2.56%
44 (37-49)
Chronic respiratory diseases
1.53%
58 (50-68)
Renal diseases
0.62%
58 (51-81)
Neurologic disorders
0.56%
48 (41-57)
0
10
20
30
40
50
Proportion (%)


b
HIV-uninfected
Age at death*
Cardiovascular diseases
32.10%
83 (75-89)
Cancers
29.28%
74 (64-82)
Other causes
13.12%
81 (71-88)
Neurologic disorders
6.87%
85 (78-91)
Chronic respiratory diseases
4.57%
81 (74-87)
Other infectious or parasitic diseases
4.19%
86 (78-91)
Unintentional injuries
3.76%
65 (42-85)
Hepatic and liver diseases
1.58%
62 (53-72)
Renal diseases
1.57%
85 (77-90)
Suicides
1.49%
49 (38-60)
Drug abuse and overdose
1.46%
47 (38-58)
HIV/AIDS related
0.00%
NA
0
10
20
30
40
50
Proportion (%)



Trends in mortality in people living with HIV in an international cohort (RESPOND)

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Background & Methods

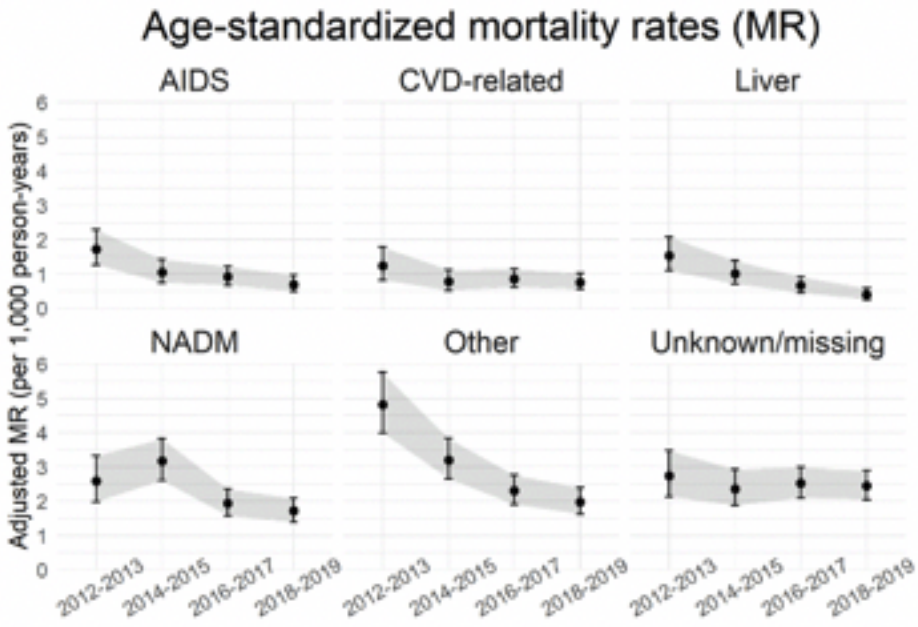
- Mortality rates in people living with HIV have declined due to effective antiretroviral treatment (ART) (1).
- Aging, coinfections, and comorbidities may also drive changes in mortality (2).
- We investigated recent patterns in mortality to **identify opportunities to reduce mortality**.

- The **RESPOND** cohort consortium was initiated in 2017 and includes over 33,000 people living with HIV from 17 cohorts across Europe and Australia.
- Prospective follow up from 2012 to 2019. Participants before 2017 enrolled retrospectively.
- **Age-standardized mortality rates** were compared over time.
- **Risk factors for all-cause mortality** investigated with multivariable Poisson regression.

(1) Smith CJ, et al. The Lancet. 2014
(2) Pelchen-Matthews A, et al. AIDS. 2018

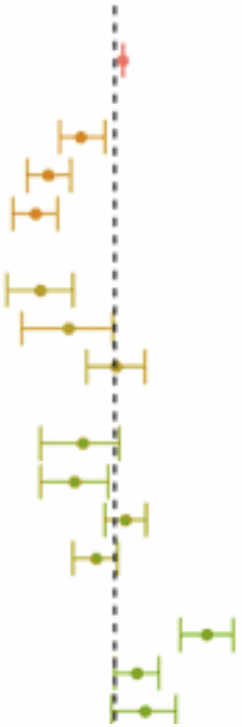
Results

- 33,598 participants
- 167,930 PYFU (median 4.8; IQR 3.1–8.0)
- 1,700 (5.1%) died
- Age-adjusted cause-specific mortality **decreased** for all causes except unknown/missing



All-cause mortality univariable and multivariable time-updated Poisson regressions

Covariate	Level	IRR (95% CI)	aIRR (95% CI)
Age (per one year)		1.05 (1.05–1.06)	1.05 (1.05–1.06)
Time period (ref. 2012–2013)			
	2014–2015	0.84 (0.73–0.97)	0.81 (0.71–0.94)
	2016–2017	0.71 (0.62–0.81)	0.66 (0.58–0.76)
	2018–2019	0.66 (0.58–0.76)	0.61 (0.53–0.7)
Race/Ethnicity (ref. White)			
	non-White	0.38 (0.31–0.46)	0.63 (0.51–0.77)
	Unknown	0.63 (0.47–0.83)	0.75 (0.56–0.99)
	Prohibited	0.76 (0.64–0.9)	1.01 (0.84–1.21)
Region (ref. Central West)			
	Central East	0.84 (0.65–1.06)	0.82 (0.63–1.03)
	East	1.31 (1.08–1.56)	0.78 (0.63–0.96)
	North / Australia	0.89 (0.79–1.01)	1.07 (0.94–1.22)
	South	0.84 (0.74–0.96)	0.89 (0.77–1.02)
HIV transmission risk (ref. MSM)			
	Injection drug use	3.08 (2.73–3.47)	1.78 (1.51–2.1)
	Heterosexual contact	1.11 (0.98–1.25)	1.15 (1–1.32)
	Other/unknown/missing	1.49 (1.22–1.81)	1.21 (0.98–1.47)



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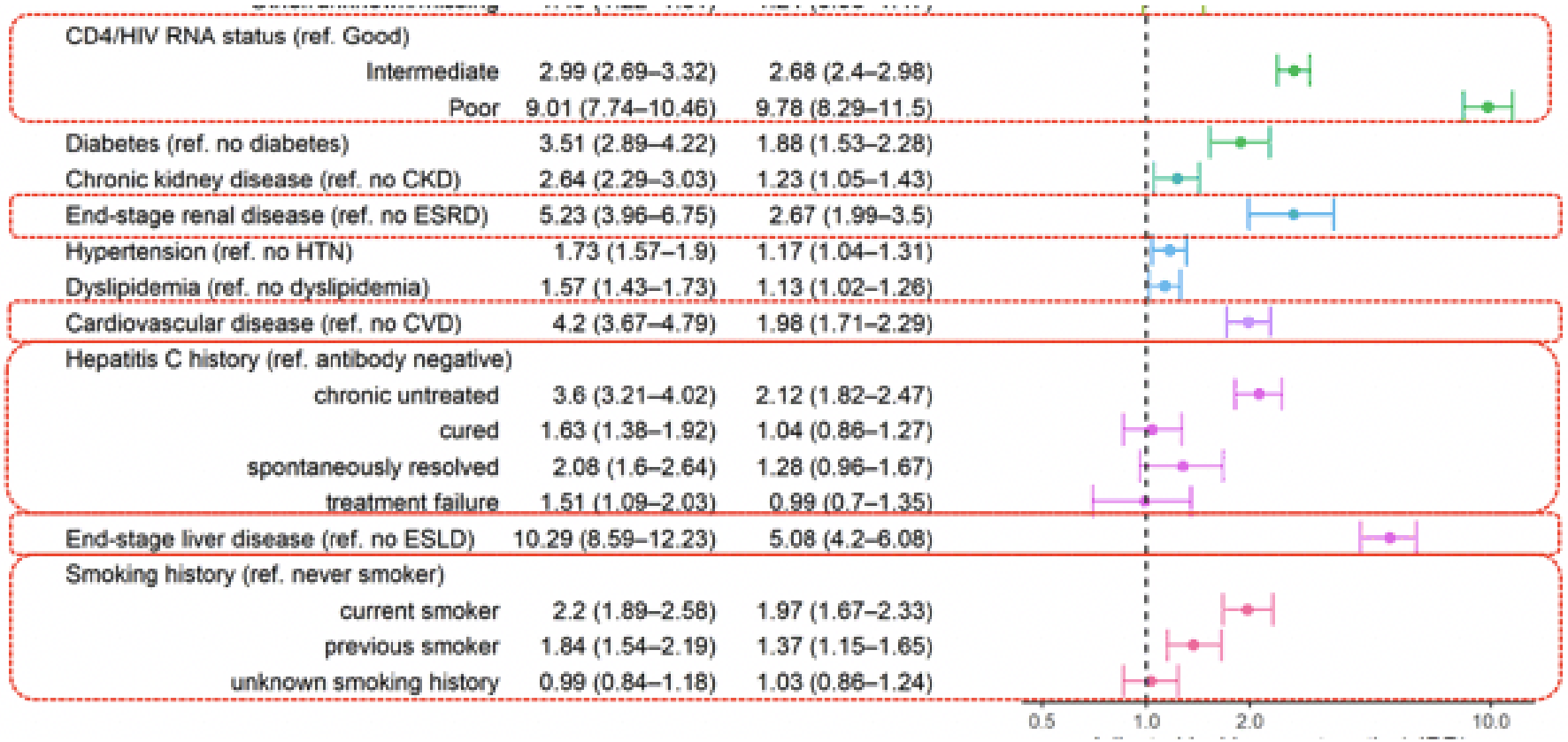

CD4/HIV RNA status (ref. Good)		
Intermediate	2.99 (2.69–3.32)	2.68 (2.4–2.98)
Poor	9.01 (7.74–10.46)	9.78 (8.29–11.5)
Diabetes (ref. no diabetes)	3.51 (2.89–4.22)	1.88 (1.53–2.28)
Chronic kidney disease (ref. no CKD)	2.64 (2.29–3.03)	1.23 (1.05–1.43)
End-stage renal disease (ref. no ESRD)	5.23 (3.96–6.75)	2.67 (1.99–3.5)
Hypertension (ref. no HTN)	1.73 (1.57–1.9)	1.17 (1.04–1.31)
Dyslipidemia (ref. no dyslipidemia)	1.57 (1.43–1.73)	1.13 (1.02–1.26)
Cardiovascular disease (ref. no CVD)	4.2 (3.67–4.79)	1.98 (1.71–2.29)
Hepatitis C history (ref. antibody negative)		
chronic untreated	3.6 (3.21–4.02)	2.12 (1.82–2.47)
cured	1.63 (1.38–1.92)	1.04 (0.86–1.27)
spontaneously resolved	2.08 (1.6–2.64)	1.28 (0.96–1.67)
treatment failure	1.51 (1.09–2.03)	0.99 (0.7–1.35)
End-stage liver disease (ref. no ESLD)	10.29 (8.59–12.23)	5.08 (4.2–6.08)
Smoking history (ref. never smoker)		
current smoker	2.2 (1.89–2.58)	1.97 (1.67–2.33)
previous smoker	1.84 (1.54–2.19)	1.37 (1.15–1.65)
unknown smoking history	0.99 (0.84–1.18)	1.03 (0.86–1.24)

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(NEURO)INFLAMMATORY BIOMARKERS MEDIATE THE ASSOCIATION BETWEEN HIV AND DEPRESSION

Mudra Rakshasa-Loots, A et al. (NEURO)INFLAMMATORY BIOMARKERS MEDIATE THE ASSOCIATION BETWEEN HIV AND DEPRESSION. CROI 2023 Feb 20 – 23.

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BACKGROUND

- People with HIV are at increased risk for depression, though the underlying mechanisms for this are unclear.
- In the general population, depression is associated with peripheral and central inflammation.
- Since HIV infection may elicit (neuro)inflammation, **we hypothesised that (neuro)inflammatory biomarkers would mediate the association between HIV and depressive symptoms.**

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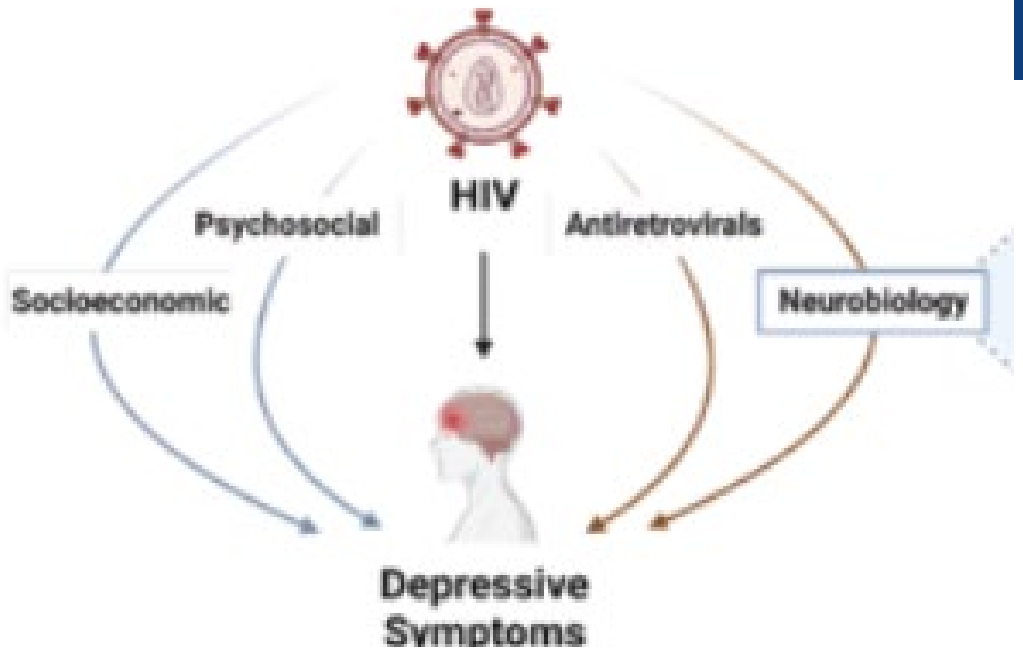
In a sample of 125 people living with HIV and 79 people without HIV, the biomarkers MIG and TNF-α in plasma and MIP1-α and IL-6 in CSF mediated the association between HIV status and depressive symptoms.

CONCLUSIONS

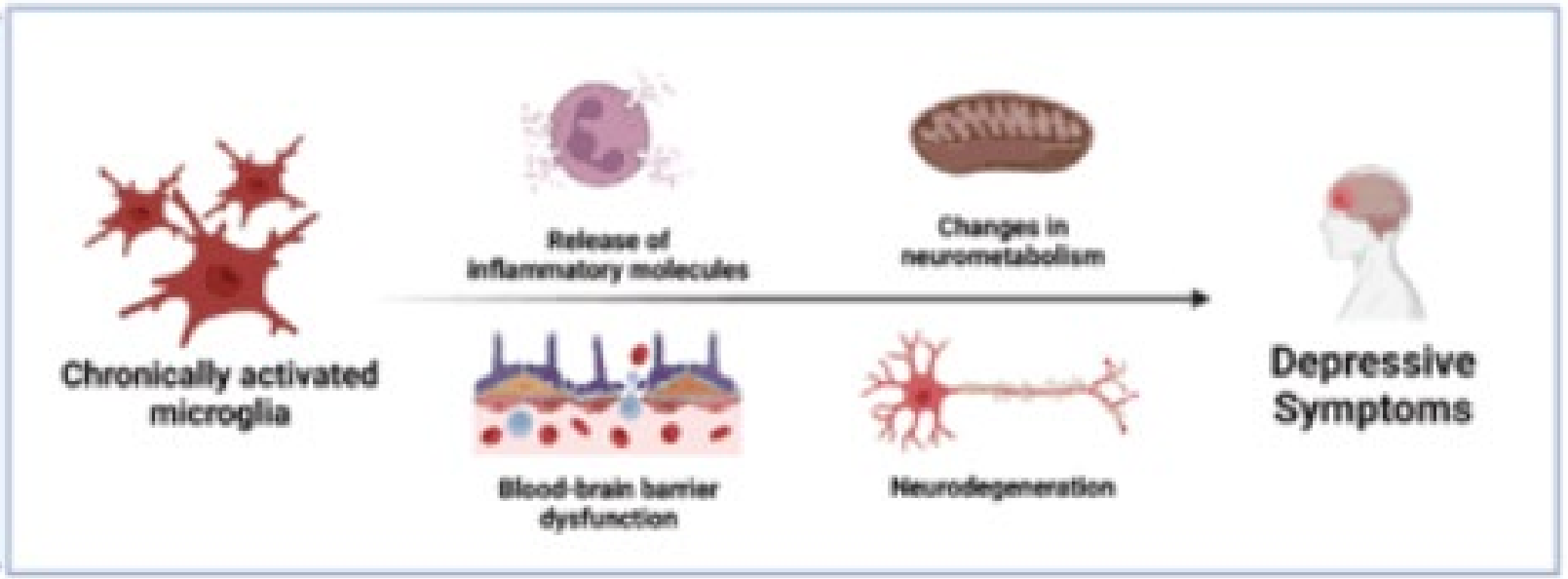
- Four biomarkers of inflammation – MIG and TNF-α in plasma, and MIP1-α and IL-6 in CSF – are potential mediators of the association between HIV status and depressive symptoms.
- Some limitations of the study include: analyses restricted to participants without severe depressive symptoms (PHQ-9 > 15); lack of gender and ethnic diversity limits generalisation.

GET IN TOUCH: arish.mudrarakshasa@ed.ac.uk or j.vera@bsms.ac.uk



HYPOTHESIS

Biomarkers of systemic and central nervous system inflammation mediate the association between HIV and depressive symptoms



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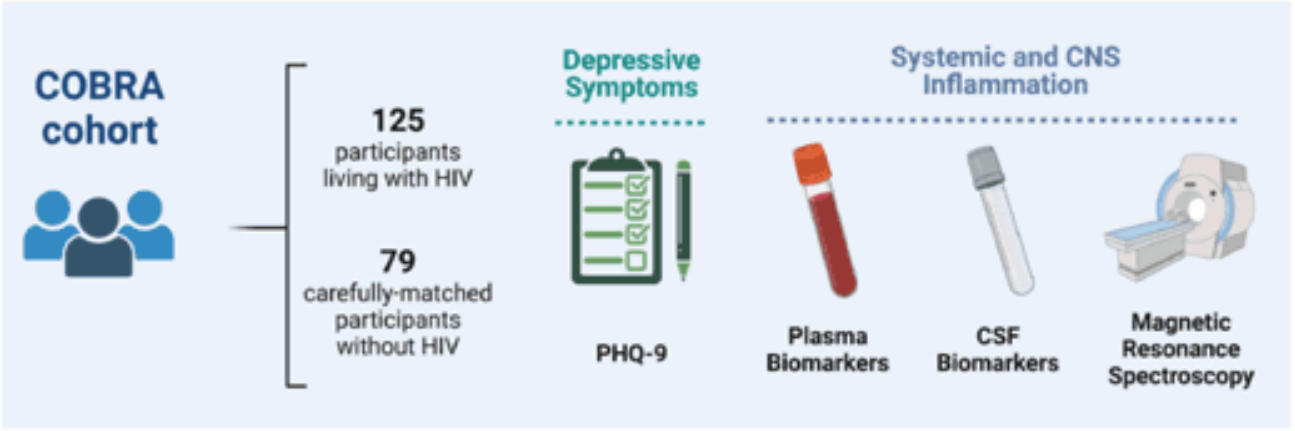
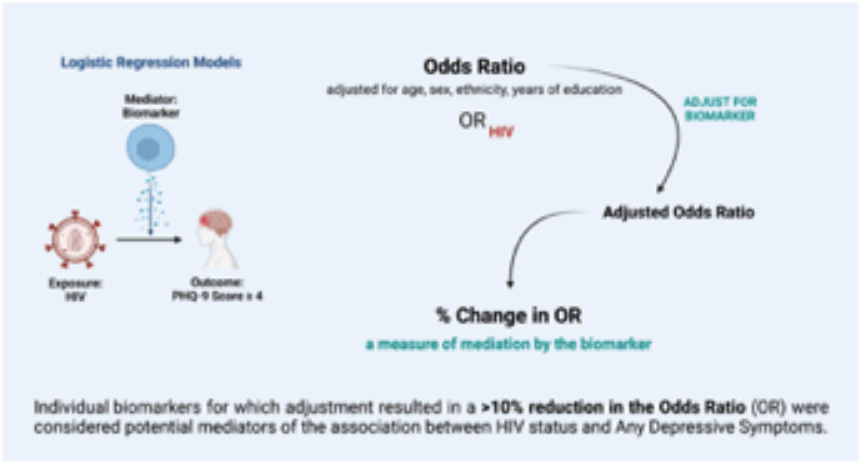
Methods



Biomarker	
Magnetic Resonance Spectroscopy	Myo-inositol Choline
Soluble biomarkers *measured in all participants, where possible*	CRP I-FABP Kyn:Trp Index Neopterin NFL sCD14 sCD16 sCD163
Soluble biomarkers *measured in a subset of participants*	IL-6 IP-10 MCP-1 MIG MIP1α RANTES TNF-α



Individual biomarkers for which adjustment resulted in a **>10% reduction in the Odds Ratio** (OR) were considered potential mediators of the association between HIV status and Any Depressive Symptoms.

METHODS

- *N* = 204: 125 people with HIV, 79 people without HIV in the COmorBidity in Relation to AIDS (COBRA) study, a prospective cohort of adults living with HIV in London and Amsterdam were included. (PMID: 29596425)
- **Depressive symptoms** were measured using the Patient Health Questionnaire (PHQ-9). A total PHQ-9 score ≥ 4 was considered as "Any Depressive Symptoms".
- **Systemic and central nervous system inflammation** was measured using blood plasma, CSF, and brain MRS imaging biomarkers.

Results:

We included 204 participants (125 with HIV, 79 without HIV, median [interquartile range (IQR)] age 57 years [51-62], 93% male, 92% White) with PHQ-9 score and at least one biomarker available. Both groups had similar baseline characteristics. All people with HIV were on antiretroviral therapy and had HIV-RNA viral load < 200 copies/mL. The prevalence of Any Depression was significantly higher amongst participants with HIV than those without HIV (26.4% vs 11.4%, p = 0.02). The OR (95% confidence interval) for Any Depression in the full sample (N = 204), adjusted for sociodemographic factors but before adjusting for biomarkers, was 3.27 (1.46, 8.09). Of the biomarkers analysed, plasma MIG (-15.0%), plasma TNF-α (-11.4%), CSF MIP1-α (-21.0%), and CSF IL-6 (-18.0%) met our criteria for >10% reduction in OR associated with HIV status for Any Depression.


Putamen
FWM
Plasma
CSF
% Change in Odds Ratio
Outcome: "Any Depressive Symptoms"
Choline
Myo-inositol
NFL
Neopterin
CRP
Kyn:Trp
sCD16
I-FABP
sCD14
sCD163
MIP1α / CCL3
IL-6
RANTES / CCL5
MIG / CXCL9
MCP-1 / CCL2
IP-10 / CXCL10
TNF-α
Neurometabolites
Soluble biomarkers (in full sample)
Soluble biomarkers (in subset)

CONCLUSIONS

- Four biomarkers of inflammation – MIG and TNF-α in plasma, and MIP1-α and IL-6 in CSF – are potential mediators of the association between HIV status and depressive symptoms.
- Some limitations of the study include: analyses restricted to participants without severe depressive symptoms (PHQ-9 > 15); lack of gender and ethnic diversity limits generalisation.

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Effect of Common Antiretroviral Combinations on Depressive Symptoms in Women with HIV

Parra-Rodriguez L, O'Halloran J, Wang Y, et al. Effect of common antiretroviral combinations on depressive symptoms in women with HIV. 30th CROI, Conference on Retroviruses and Opportunistic Infections, February 19-22, 2023, Seattle. Abstract 469.

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Open Forum Infectious Diseases

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PMCID: PMC9487706
PMID: 36147597

Changes in Quality of Sleep, Mood, and Other Neuropsychiatric Symptoms After Switching Dolutegravir/Lamivudine/Abacavir to Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in a Randomized Study of People With Human Immunodeficiency Virus With Poor Sleep Quality: GESIDA 10418

Alfonso Cabello-Úbeda, Alicia González Baeza, Jesús Troya García, Sara de La Fuente Moral, María Novella Mena, Adriana Pinto Martínez, Rafael Micán, Miguel Górgolas, Guillermo Cuevas Tascón, Alberto Díaz de Santiago, José Sanz Morerno, David Rial Crestelo, Carmen Busca Arenzana, José Ignacio Bernardino Serna, Mariana Díaz Almirón, Joanna Cano, Herminia Esteban, and Ignacio Pérez-Valero✉

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Methods

- The DETOX study included 2 consecutive design phases.
- In phase one, participants who reported poor quality of sleep in the Pittsburgh Sleep Quality Index (PSQI) were randomized to switch at baseline from DTG/3TC/ABC to DRV/COBI/FTC/TAF (immediate switch arm) or to continue 4 weeks with DTG/3TC/ABC and then switch to DRV/COBI/FTC/TAF (deferred switch arm).
- In phase 2, participants from both arms completed 8 weeks of follow-up after their switch to DRV/COBI/FTC/TAF.

Objectives

- Primary: compare changes in the quality of sleep, measured with the PSQI from baseline to week 4 between study arms.
- Secondary
  - Compare changes in patient-reported neuropsychiatric symptoms detected and quantified, using HADS and DETOX questionnaires, from baseline to week 4
  - Evaluate changes in quality of sleep using HADS/DETOX
  - Viral suppression on switching regimens

Table 1.

Baseline Characteristics

Variable	Delayed Switch[a] Arm n = 35	Immediate Switch[a] Arm n = 37	*P* Value
Age, mean (SD)	46.1 (10.5)	48.4 (11.5)	.379
Gender: male, n (%)	29 (82.9)	32 (86.5)	.669
Ethnicity: Caucasian, n (%)	26 (74.3)	28 (75.7)	.915
Toxic habits[b], n (%)	20 (57.1)	24 (64.9)	.502
Illicit drug use, n (%)	6 (17.1)	15 (40.5)	**.023**[c]
Years since HIV diagnosis, mean (SD)	12.2 (10.3)	13.1 (10.3)	.720
Years of HIV undetectability, mean (SD)	5.3 (5.0)	5.56 (4.0)	.798
Years on DTG/3TC/ABC, mean (SD)	3.1 (1.6)	2.7 (1.25)	.205
CD4 nadir, mean (SD)	358 (232.5)	230 (215)	.482
Previous AIDS diagnosis, n (%)	5 (14.3)	7 (18.9)	.598
Current CD4 cell count, mean (SD)	727.4 (315.7)	611.1 (190.9)	.067
Positive anxiety screen: HADs, n (%)	21 (60)	19 (51.4)	.424
Positive depression screen: HADs, n (%)	10 (28.6)	7 (18.9)	.307

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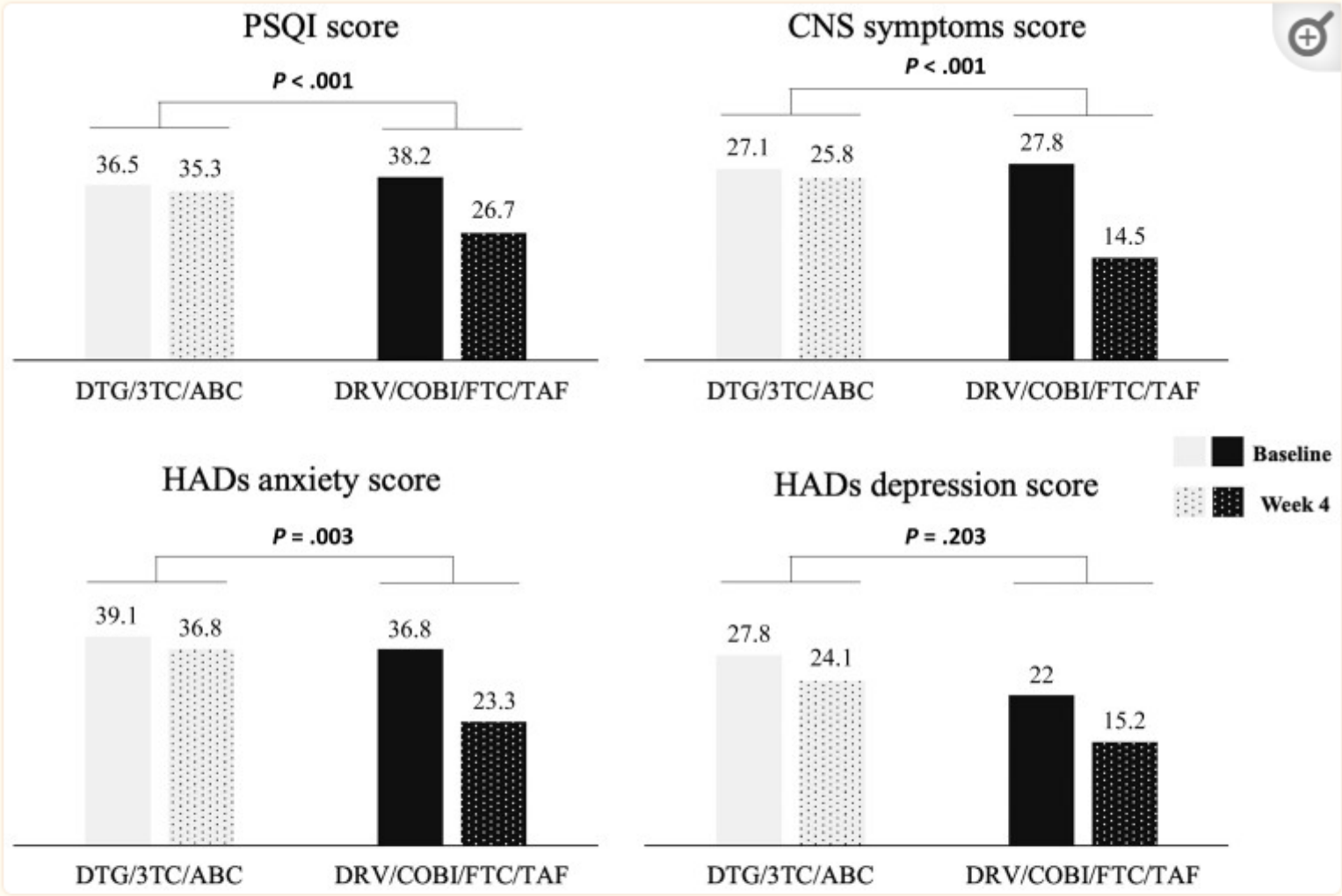

Figure 1.

Baseline and week 4 results of the Pittsburgh Sleep Quality Index (PSQI), the Hospital Anxiety and Depression scale (HADS) anxiety and depression subscales, and the central nervous system (CNS) symptoms scores in each study arm, for the intention-to-treat population. ABC, abacavir; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; 3TC, lamivudine.

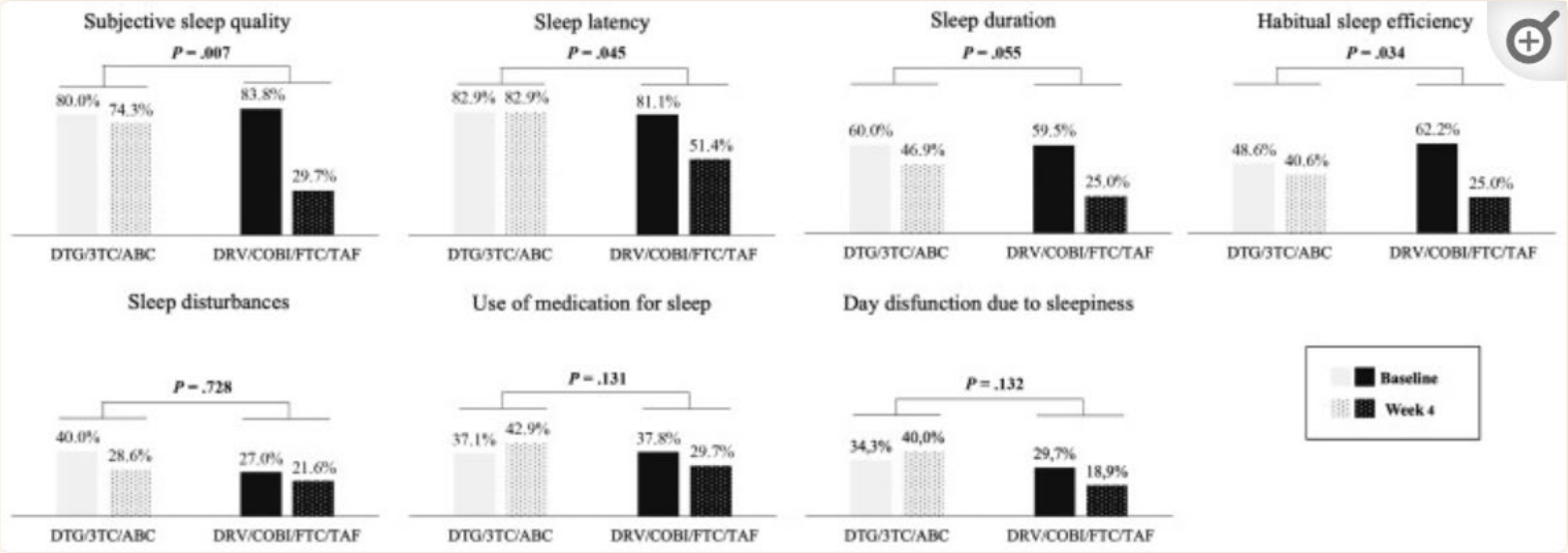

Figure 2.

Proportion of participants reporting moderate-severe disturbances in the Pittsburgh Sleep Quality Index components in each study arm at baseline and at week 4 for the intention-to-treat population. ABC, abacavir; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; 3TC, lamivudine.

Effect of Common Antiretroviral Combinations on Depressive Symptoms in Women with HIV

Parra-Rodriguez L, O'Halloran J, Wang Y, et al. Effect of common antiretroviral combinations on depressive symptoms in women with HIV. 30th CROI, Conference on Retroviruses and Opportunistic Infections, February 19-22, 2023, Seattle. Abstract 469.

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BACKGROUND

- Modern antiretroviral therapy (ART) has been associated with neuropsychiatric adverse events including depression.

- We examined the combined effect of ART regimens on somatic (e.g. sleep/appetite disturbances) and non-somatic (e.g. sadness) depressive symptoms in women with HIV (WWH).

METHODS

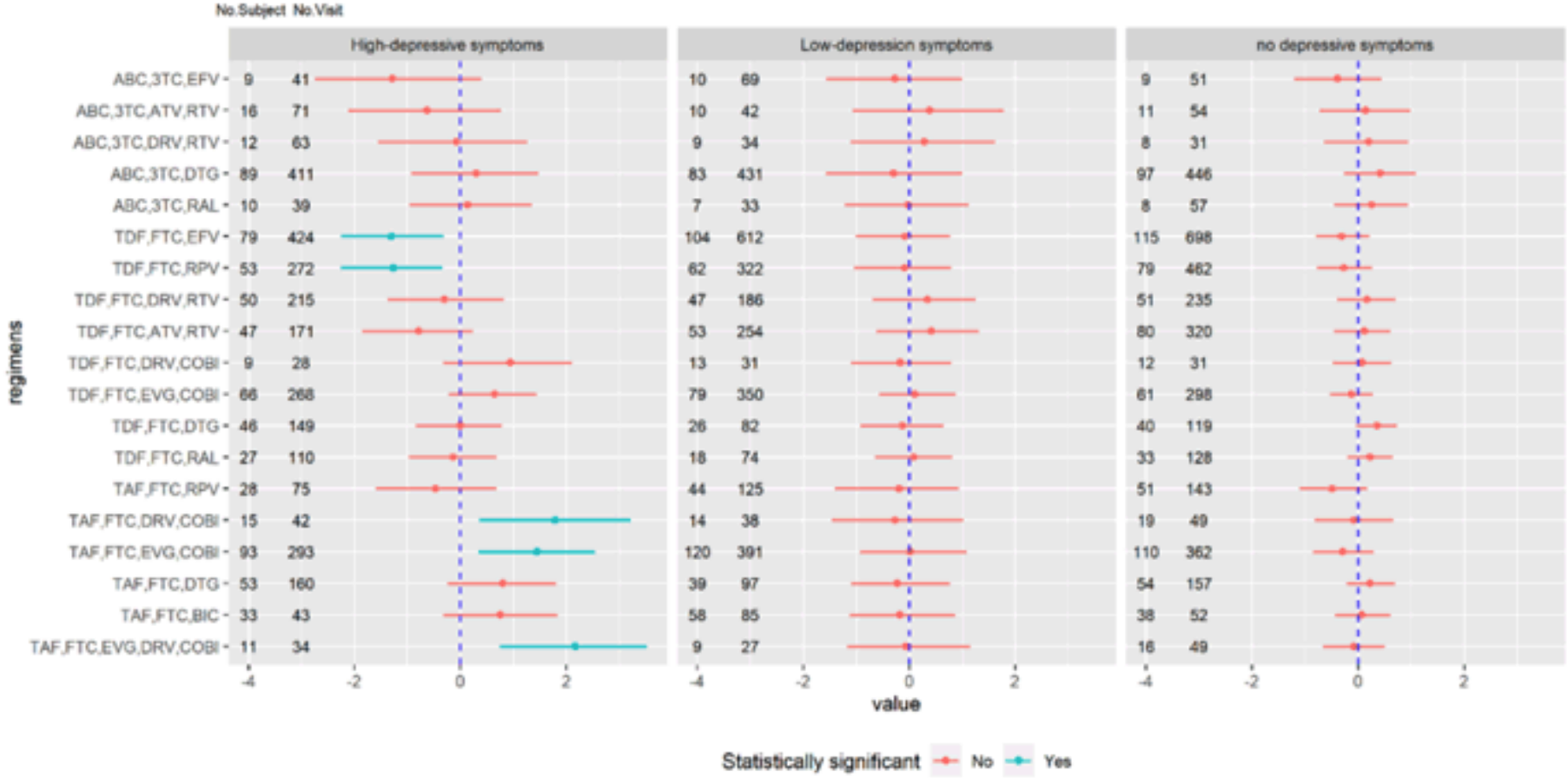
- Women's Interagency HIV Study (WIHS) participants with ≥2 study visits receiving contemporary ART regimens were divided into three groups using longitudinal Center for Epidemiologic Studies Depression (CES-D) scale scores:
  - High-depression (CES-D ≥16 on ≥50% of visits)
  - Low-depression (CES-D ≥16 on < 50% of visits)
  - Never depressed (CES-D < 16 for all visits)

- Novel Bayesian machine learning methods building upon a subset-tree kernel approach were developed to estimate the combined effects of ART regimen on somatic and non-somatic depressive symptoms in each group after controlling for relevant covariates.

Total Sample (n=1,538)	High-depression (n=459) Mean (SD)	Low-depression (n=500) Mean (SD)	Never depressed (n=579) Mean (SD)	p-value
Year of Age, n (%)				0.307
25-35	44 (10)	62 (12)	52 (9)	
36-45	122 (27)	141 (28)	171 (30)	
45-55	214 (47)	204 (41)	242 (42)	
>55	79 (17)	93 (19)	114 (20)	
Race/ethnicity, n (%)				0.031
White (Non-Hispanic)	65 (14)	49 (10)	45 (8)	
African-American (Non-Hispanic)	319 (69)	356 (71)	438 (76)	
Hispanic	60 (13)	78 (16)	82 (14)	
Highest level of education: complete high school, n (%)	280 (61)	330 (66)	432 (75)	<0.001
Average household income/year: <= $12000, n (%)	274 (60)	266 (53)	252 (44)	<0.001
Lowest CD4 (cells per mm^3), median (IQR)	272 (321)	273.5 (296.5)	278 (286.5)	0.980
Current CD4 (cells per mm^3), median (IQR)	559 (478.5)	574 (397)	613 (411)	0.102
Depressive symptoms (CES-D)	23.9 (11.3)	11.3 (8.9)	4.4 (4.2)	<0.001
Recent heavy alcohol use, n (%)	89 (19)	90 (18)	74 (13)	0.009
Current smoking status, n (%)	226 (49)	173 (35)	180 (31)	<0.001
Recent marijuana use, n (%)	124 (27)	85 (17)	87 (15)	<0.001
Recent Crack, cocaine, and/or heroin use, n (%)	69 (15)	28 (6)	26 (4)	<0.001

Table 1. Baseline characteristics

Figure 1. Combined effects of different ART regimens according to frequency on somatic depressive symptoms by group



ABC: Abacavir, 3TC: Emtricitabine, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide, EFV: Efavirenz, RPV: Rilpivirine, ATV: Atazanavir, DRV: Darunavir, RTV: Ritonavir, COBI: Cobicistat, RAL: Raltegravir, EVG: Elvitegravir, DTG: Dolutegravir, BIC: Bictegravir.

All models controlled for: study enrollment site; age; race/ethnicity; years of education; exposure time of ART drugs used prior to 2014 (drugs used less than 100 times in the database are not included); average household income; CD4 count; body mass index; substance use (crack, cocaine and/or heroin use; marijuana; smoking; alcohol); menopausal status; diabetes; and undetectable viral load.

RESULTS

- In the high-depression group, the combination of TAF with either a cobicistat-boosted INSTI or PI was associated with greater somatic symptoms, while no difference was observed with TDF in these combinations.

- In the same group, TDF combined with an NNRTI was associated with fewer somatic symptoms of depression.

- ART regimens were not associated with somatic symptoms in the low- or no-depression groups.

- No relationship was found between ART and non-somatic symptoms in any group.

CONCLUSIONS

- Somatic depressive symptoms were observed more frequently among WWH who received TAF with a cobicistat-boosted INSTI or PI, but no relationship was found between depressive symptoms and TDF or un-boosted INSTIs or PIs.

- Our findings suggest complex associations between ART and depression, such that ART combinations rather than individual agents are associated with depressive symptoms.

- Future studies should consider complete drug regimens when assessing the risk of long-term neuropsychiatric complications of ART.

DOLUTEGRAVIR IS ASSOCIATED WITH MORE DEPRESSIVE SYMPTOMS IN OLDER PEOPLE WITH HIV

Roy, U et al. DOLUTEGRAVIR IS ASSOCIATED WITH MORE DEPRESSIVE SYMPTOMS IN OLDER PEOPLE WITH HIV. CROI 2023 Feb 20-23.

Objective

Determine the relationships between integrase strand transfer inhibitors (InSTIs), aging, antidepressant use, and depressive symptoms in people with HIV (PWH).

Background

- InSTIs such as dolutegravir (DTG) are first-line therapy in the U.S. and other countries.
- DTG has been linked to neuropsychiatric adverse events (e.g., depression) in PWH. However, standardized assessments of depression among PWH taking DTG was not well characterized.
- The present study has investigated the concomitant influence of age and antidepressant use on depression among DTG users in CHARTER cohort.

Methods

- 280 participants were comprehensively assessed in the CHARTER Aging project. All were were taking ART and had plasma HIV RNA ≤ 200 copies/mL.
- Beck Depression Inventory (BDI)-II and four subscales were compared to demographic characteristics, use of InSTIs and antidepressants, and clinical biomarkers in a cross-sectional design
- Data were analyzed using linear regression, including multivariable linear regression with backward selection by Akaike Information Criterion.

Funding support: The National Institute of Mental Health (R01 MH107345, R01 MH095621, K23 MH095679, K24 MH097673, R25 MH108389), the National Institute on Drug Abuse (K23 DA037793), the National Institute of Neurological Disorders and Stroke (R15 NS108815), and the National Institute of Allergy and Infectious Diseases (R01 AI147731).

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Results

Table 1. Demographic, Disease, and Treatment Characteristics of the Cohort Stratified by Use of DTG, Other InSTIs, or Other ART.

Characteristic	Total Cohort	DTG Users	Other InSTI Users	Non-InSTI Users	P value
Group Size	280	95	94	91	
Age (years)	56.2 (8.0)	56.8 (7.7)	55.9 (7.9)	55.8 (8.5)	0.631
Age ≥ 60 years	81 (28.9%)	31 (32.6%)	24 (25.5%)	26 (28.6%)	0.558
Gender (Female)	52 (18.6%)	23 (24.2%)	16 (17.0%)	13 (14.3%)	0.202
Race (Black)	109 (38.9%)	37 (38.9%)	40 (42.6%)	32 (35.2%)	0.589
Ethnicity (Hispanic)	32 (11.4%)	6 (6.3%)	10 (10.6%)	16 (17.6%)	0.052
Body Mass Index	26.4 (8.7)	27.8 (8.7)	26.5 (8.2)	24.7 (9.0)	0.047
HCV Seropositive	94 (33.6%)	36 (37.9%)	27 (28.7%)	31 (34.1%)	0.405
Diabetes Mellitus	58 (20.7%)	26 (27.4%)	17 (18.1%)	15 (16.5%)	0.146
Hypertension	151 (53.9%)	55 (57.9%)	58 (61.7%)	38 (41.8%)	0.016
Dyslipidemia	117 (41.8%)	44 (46.3%)	44 (46.8%)	29 (31.9%)	0.062
Chronic Pulmonary Disease	61 (21.8%)	21 (22.1%)	24 (25.5%)	16 (17.6%)	0.418
Antidepressant Use	93 (33.2%)	27 (28.4%)	34 (36.2%)	32 (35.2%)	0.465
Lifetime Major Depressive Disorder	179 (63.9%)	64 (67.4%)	62 (66.0%)	53 (58.2%)	0.384
Current Major Depressive Disorder	20 (7.7%)	9 (9.8%)	7 (8.0%)	4 (4.9%)	0.469
Duration of HIV infection (years)	22.3 (6.6)	22.8 (6.4)	22.5 (6.6)	21.8 (6.8)	0.598
AIDS Diagnosis	203 (72.5%)	77 (81.0%)	65 (69.1%)	61 (67.0%)	0.061
Tenofovir Alafenamide Use	128 (45.7%)	25 (26.3%)	74 (78.7%)	29 (31.9%)	<0.001
Abacavir Use	69 (24.6%)	50 (52.6%)	4 (4.3%)	15 (16.5%)	<0.001
Total duration of all ART (years)	15.6 (6.0)	15.3 (5.8)	15.7 (6.4)	15.8 (5.8)	0.843
Duration of current regimen (mths)	38.0 (44.8)	25.9 (26.2)	22.2 (25.2)	66.5 (59.7)	<0.001
Plasma HIV RNA (≤ 200 cp/mL)	280 (100%)	95 (100%)	94 (100%)	91 (100%)	*
Nadir CD4+ T-Cell Count	156.1 (152.6)	134.4 (142.1)	164.6 (165.0)	170.0 (148.8)	0.227
CD4+ T-Cell Count	622.8 (315.8)	581.9 (296.9)	639.0 (348.0)	649.4 (299.1)	0.291

Results

Figure 1. DTG was associated with higher BDI-II values (A) in people who were at least 60 years old, (B) people whose race was not Black, and (C) people who did not use an antidepressant drug (AD)

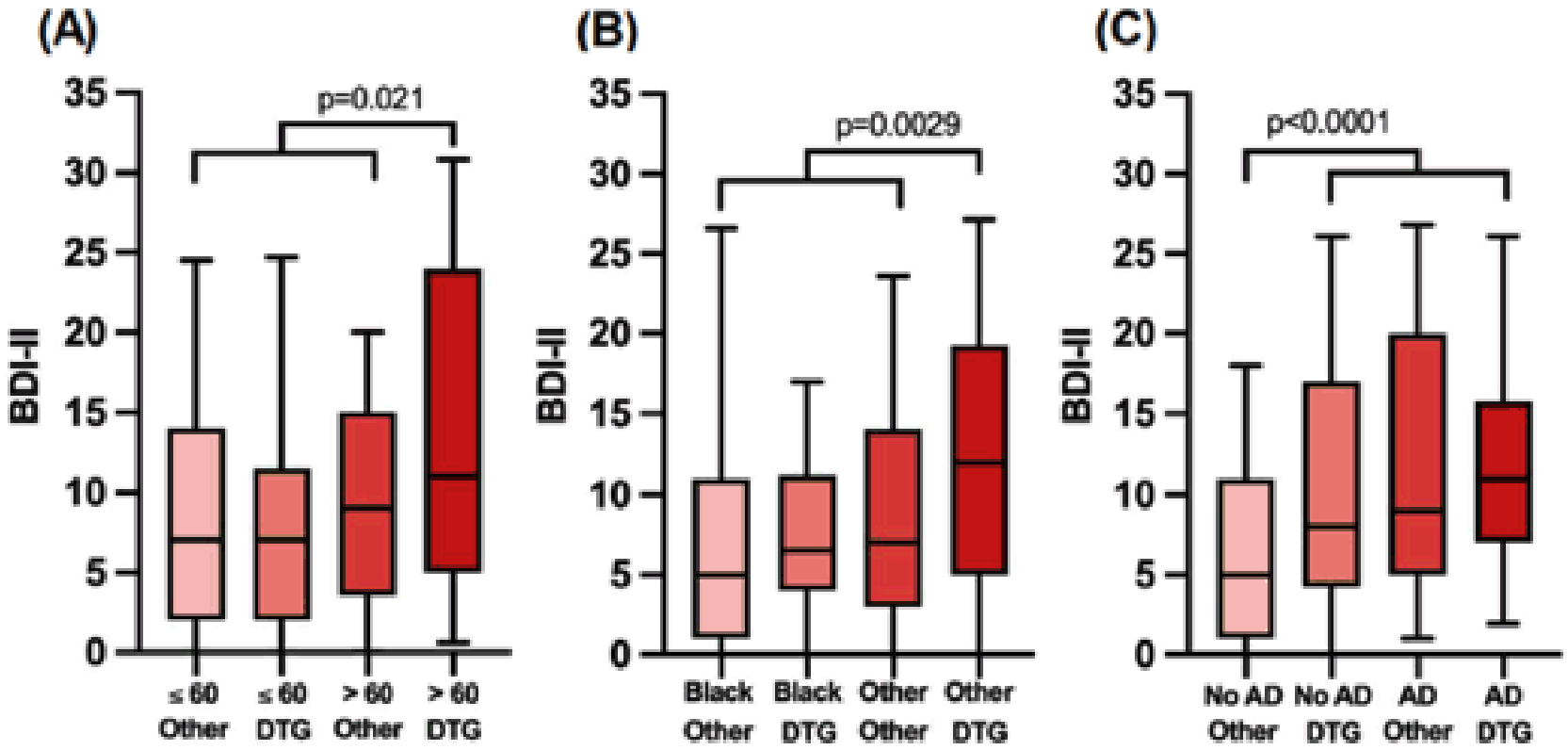

Table 2. Regression analysis of dependent variable used in this study

Independent Variable	Standard β	P Value	Standard β	P Value
Antidepressant Use	0.164	**0.002**	0.124	**0.049**
Race	0.211	**<0.001**	0.216	**<0.001**
Gender	0.122	**0.042**	0.160	**0.008**
Dolutegravir Use	0.130	**0.029**	0.189	**0.009**
Age ≤ or > 60 years	0.114	**0.056**	0.111	**0.063**
Dolutegravir x Age ≤ or > 60 years	-	-	0.123	**0.059**
Dolutegravir x Race	-	-	0.116	**0.060**
Dolutegravir x Antidepressant Use	-	-	0.128	**0.083**
Abacavir Use	0.077	0.199		
Duration of current regimen	-0.065	0.290		
AIDS Diagnosis	-0.052	0.383		
Body Mass Index	0.037	0.536		
Dyslipidemia	0.032	0.571		
Tenofovir Alafenamide Use	0.032	0.597		
Ethnicity (Hispanic)	0.017	0.774		
Other InSTI Use	0.012	0.863		
Age (years)	0.007	0.905		

Doxycycline PEP

AIDS 2022
29 July – 2 August

TITLE

Doxycycline post-exposure prophylaxis for STI prevention among MSM and transgender women on HIV PrEP or living with HIV: high efficacy to reduce incident STI's in a randomized trial

PRESENTER

Annie Luetkemeyer

AUTHORS

A. Luetkemeyer * (1), J. Dombrowski (2,3), S. Cohen (4,5), D. Donnell (2), C. Grabow (2), C. Brown (2), C. Malinski (2,3), R. Perkins (2), M. Nasser (4), C. Lopez (6), S. Buchbinder (4), H. Scott (4), E. Charlebois (5), D. Havlir (6), O. Soge (2), C. Celum (2)

INSTITUTIONS

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Methods

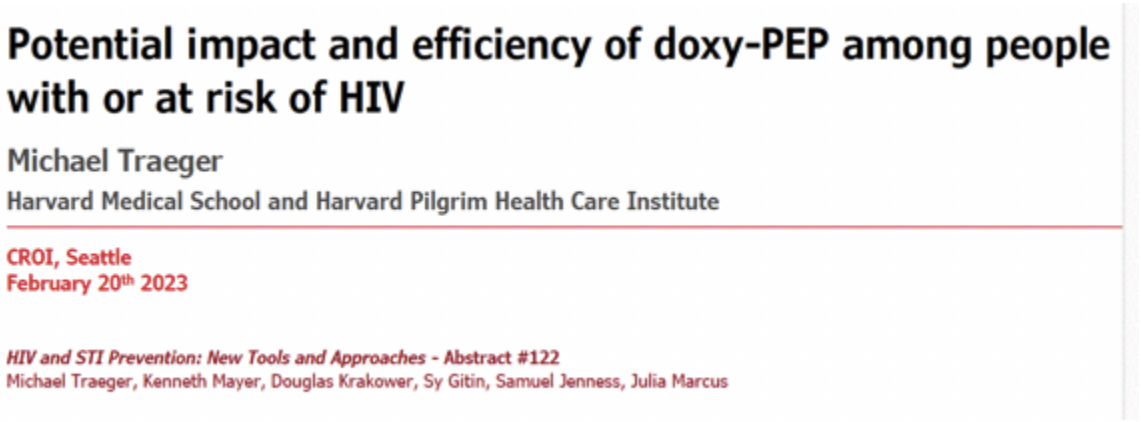
- Randomized, open-label trial among Seattle and San Francisco MSM/TGW living with HIV or on PrEP who had N. gonorrhea, C. trachomatis, or early syphilis in the past year.
- Subjects were randomized 2:1 to 200 mg doxycycline within 72 hours of condomless sex or no doxycycline with STI testing at enrollment, quarterly, and when symptomatic.
- Trial had >80% power to detect a 50% reduction in STI incidence, assuming a 10% quarterly STI incidence

Table: Quarterly STI incidence by HIV status and by randomization to doxyPEP & control arms

	HIV uninfected MSM/TGW on PrEP		MSM/TGW living with HIV		Total	
	Doxy arm N=240	Control arm N=120	Doxy arm N=134	Control arm N=60	Doxy Arm N=374	Control arm N=180
Follow up quarters	491	220	266	108	757	328
Participants with an incident STI (GC, CT or syphilis)	41	42	24	18	65	60
Primary STI endpoints	47 (9.6%)	65 (29.5%)	31 (11.7%)	30 (27.8%)	78 (10.3%)	95 (29.0%)
Gonorrhea	40 (8.1%)	45 (20.5%)	21 (7.9%)	20 (18.5%)	61 (8.1%)	65 (19.8%)
Chlamydia	7 (1.4%)	23 (10.5%)	12 (4.5%)	16 (14.8%)	19 (2.5%)	39 (11.9%)
Syphillis	1 (0.2%)	5 (2.3%)	3 (1.1%)	2 (1.9%)	4 (0.5%)	7 (2.1%)

CONCLUSIONS: Doxycycline 200 mg taken within 72 hours after condomless sex significantly reduced STIs in MSM/TGW. Effects on antimicrobial resistance, gut microbiome, and sexual behavior are being assessed as important considerations for this STI prevention strategy.

Potential impact and efficiency of doxy-PEP among people with or at risk of HIV



Potential impact and efficiency of doxy-PEP among people with or at risk of HIV

Michael Traeger

Harvard Medical School and Harvard Pilgrim Health Care Institute

CROI, Seattle
February 20th 2023

HIV and STI Prevention: New Tools and Approaches - Abstract #122
Michael Traeger, Kenneth Mayer, Douglas Krakower, Sy Gitin, Samuel Jenness, Julia Marcus

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Introduction

Doxy-PEP is highly efficacious

- Multiple studies show reduction in bacterial STIs in PrEP users and people with HIV
- Potential concerns around antimicrobial resistance and long-term use

Prescribing guidelines

- Guidelines will need to balance potential benefits and harms
- Prescribing strategies to maximize efficiency
- Recommendations easily implemented by providers

Aims

- Estimate how many STIs could be averted using different doxy-PEP prescribing strategies
- Identify prescribing strategies that minimize doxy-PEP use and maximize impact on STIs

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Methods *Data source & study cohort*

Fenway Health

- Federally qualified health center in Boston, Massachusetts
- Largest PrEP provider in New England, specializing in LGBTQ+ health & STI care

EHR-based cohort

- Gay and bisexual men, transgender women, and non-binary people assigned male sex at birth
- ≥2 STI test events for chlamydia, gonorrhoea or syphilis during 2015-2020
- People with HIV, PrEP users and non-PrEP users

Observation

- Person-time began at first STI test after January 1, 2015
- Censored at last STI test or December 31, 2020

Methods *Potential doxy-PEP prescribing strategies*

- Explored 10 potential doxy-PEP prescribing strategies

Prescribe doxy-PEP to patient groups

1. All patients accessing care
2. People with HIV & PrEP users
3. PrEP users only

Prescribe doxy-PEP for 12m after STI* diagnosis

4. Any STI diagnosis
5. Rectal STI diagnosis
6. STI at current visit + STI in past 12 months
7. STI at current visit + STI in past 6 months
8. Concurrent (2+) STIs at same visit
9. Syphilis diagnosis
10. Gonorrhea diagnosis

*STI = chlamydia, gonorrhea, syphilis

Methods *Counterfactual doxy-PEP scenarios*

Doxy-PEP use

- Assumed doxy-PEP would have been prescribed to and used by patients who met criteria
- Could be prescribed multiple times per patient
- Calculated proportion of people who would be prescribed doxy-PEP using each strategy

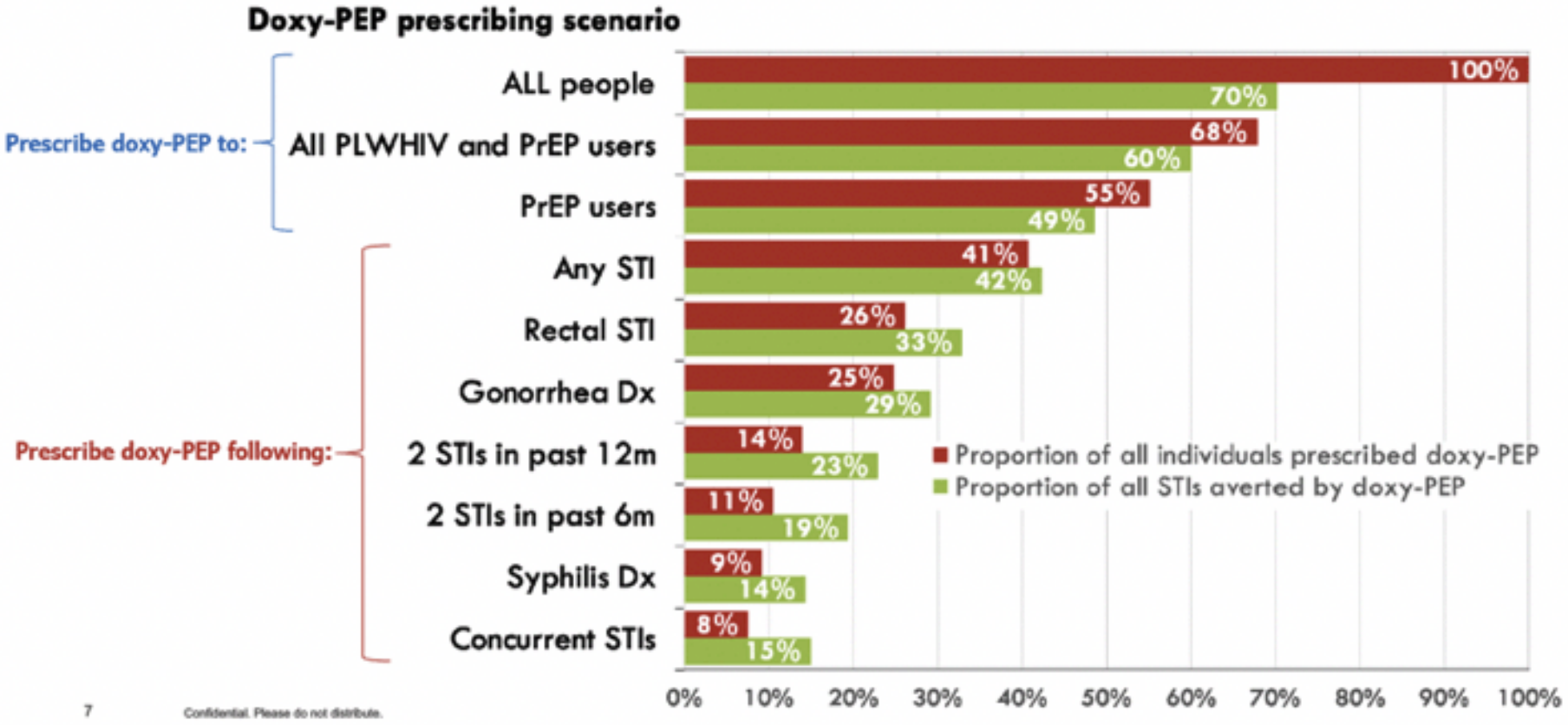
STIs averted

- Assume STI incidence would have been reduced by clinical trial disease-specific efficacy estimates[1]
- Calculated proportion of STIs that would have been averted by doxy-PEP

Number needed-to-treat (NNT)

- Calculated NNT for 1 year to avert 1 STI (person-years of doxy-PEP use / number of STIs averted)

Results *Doxy-PEP use vs STIs averted*



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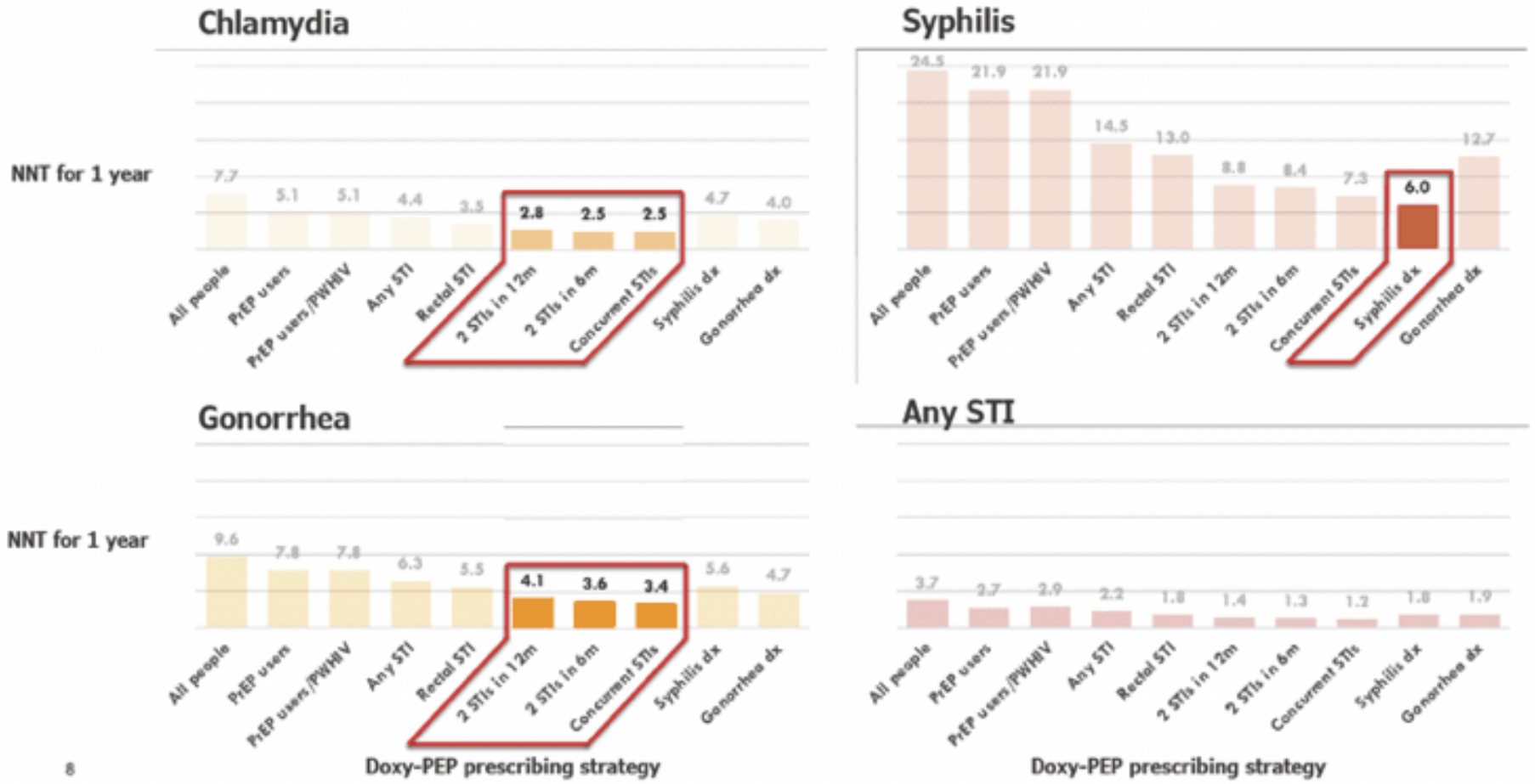
Results *Efficiency of doxy-PEP strategies for each STI*



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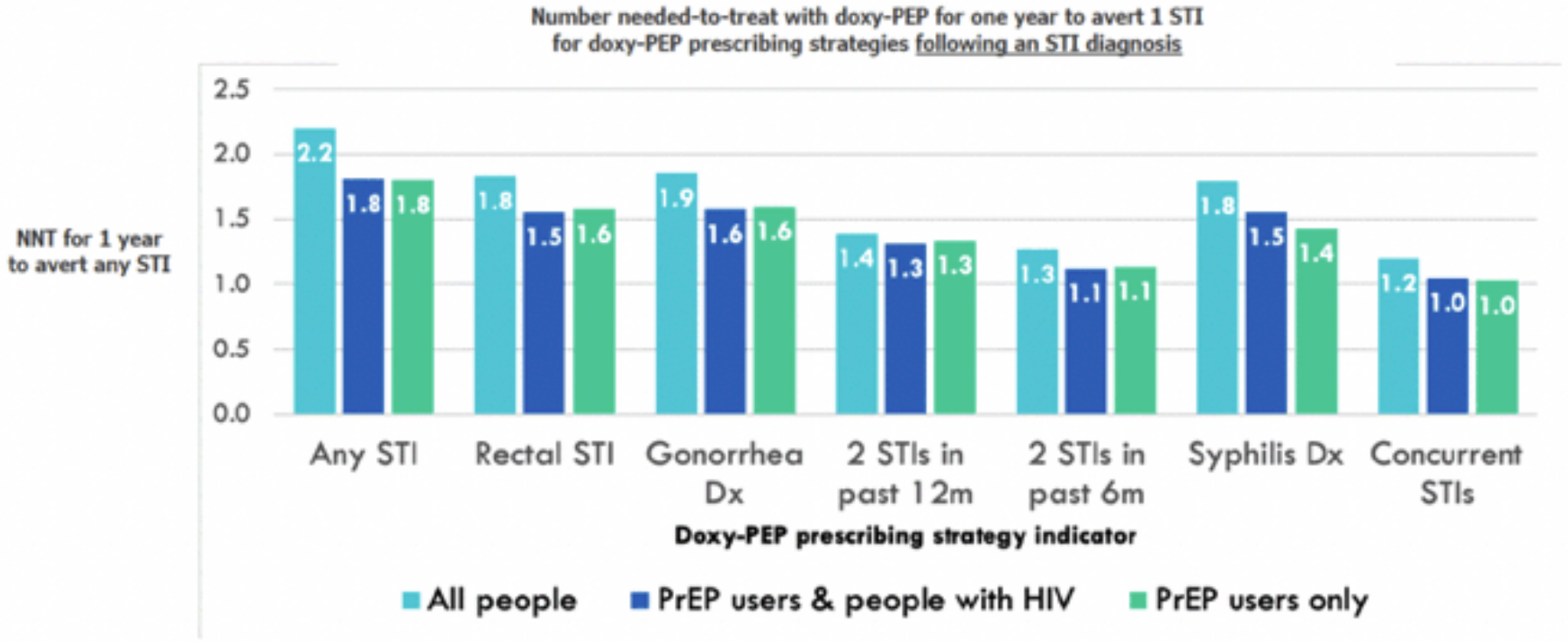
Southeast

Results *Restricting doxy-PEP to PrEP users & people with HIV*



STI-based prescribing strategies had a similar NNT across subgroups

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Implications

Guidelines should incorporate recent STI diagnosis as an indication for doxy-PEP

- Prescribing for 12 months after STI diagnosis could avert ~42% of STIs
- More efficient than prescribing to all people with HIV or PrEP users
- Prescribing after multiple STIs reduces impact but improves efficiency

Consider people not on PrEP with an STI for doxy-PEP

- Following STI diagnosis, doxy-PEP has similar efficiency for people with HIV, PrEP users and non-PrEP users
- Restricting doxy-PEP to subgroups of people with STIs (e.g., PrEP users) may not be warranted

Local epidemiology to target specific STIs

- Prescribing after syphilis diagnosis could avert 25% of syphilis infections, with only 9% of people on doxy-PEP
- Background tetracycline resistance in gonorrhea ~25% in US (60-80% in Europe & Australia)

Limitations

Generalizability

- Study population may not represent all people at risk of STIs

Loss-to-follow-up

- Only captured STIs for returning patients (may have over / underestimated impact on STIs)

Impact on onwards transmission

- Not able to estimate impact on onwards transmission (likely underestimated impact)

Real-world assumptions

- Assumed same uptake, adherence, and sexual activity as in trials; real world may differ

Stewart *et al. Trials* (2022) 23:495
https://doi.org/10.1186/s13063-022-06458-8

Trials

STUDY PROTOCOL Open Access

Doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections among Kenyan women using HIV pre-exposure prophylaxis: study protocol for an open-label randomized trial

Jenell Stewart[1,2*], Elizabeth Bukusi[1,3], Fredericka A. Sesay[1,4], Kevin Oware[3], Deborah Donnell[1,5], Olusegun O. Soge[1,2,6], Connie Celum[1,2,4], Josephine Odoyo[3], Zachary A. Kwena[3], Caitlin W. Scoville[1], Lauren R. Violette[2,4], Susan Morrison[1], Jane Simoni[7], R. Scott McClelland[1,2,4], Ruanne Barnabas[1,2,4], Monica Gandhi[8] and Jared M. Baeten[1,2,4]

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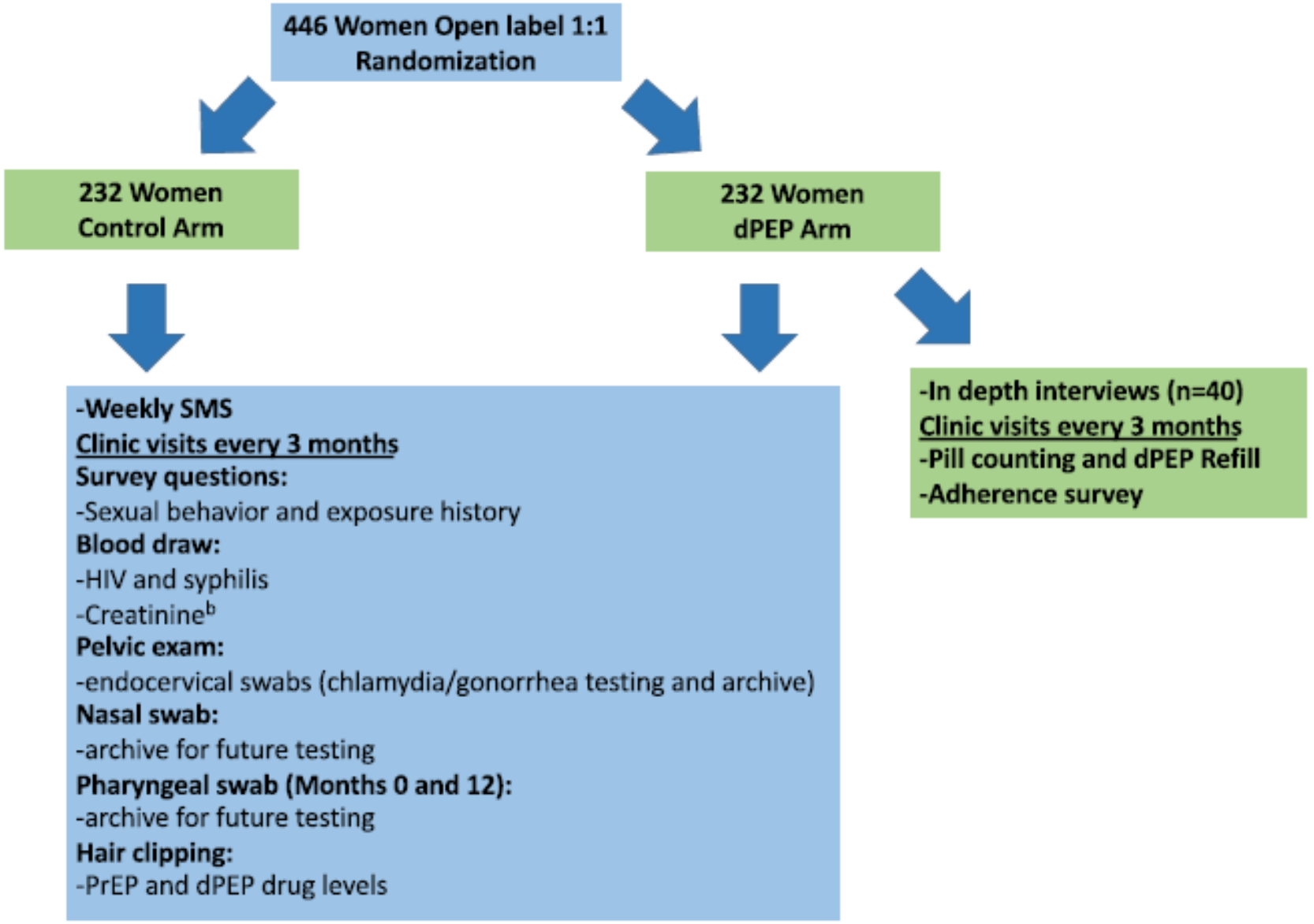
Methods

- 1:1 Open labeled, randomized, superiority trial to determine the effectiveness benefit of dPEP to reduce STI incidence among women taking PrEP for HIV prevention
- Kisumu, Kenya
- Cisgendered women 18 – 30 years of age.
- Had current prescription PrEP according to Kenyan national guidelines

Methods - Intervention

- Doxycycline 200 mg within 24 hrs and up to 72 hrs after each vaginal receptive sex act as daily as if indicated
- Routine pregnancy counseling was performed and provided
- 1:1 adherence counseling for PrEP was provided


446 Women Open label 1:1 Randomization
232 Women Control Arm
232 Women dPEP Arm
-Weekly SMS
Clinic visits every 3 months
Survey questions:
-Sexual behavior and exposure history
Blood draw:
-HIV and syphilis
-Creatinine[b]
Pelvic exam:
-endocervical swabs (chlamydia/gonorrhea testing and archive)
Nasal swab:
-archive for future testing
Pharyngeal swab (Months 0 and 12):
-archive for future testing
Hair clipping:
-PrEP and dPEP drug levels
-In depth interviews (n=40)
Clinic visits every 3 months
-Pill counting and dPEP Refill
-Adherence survey

Results

- Enrolled 449 cisgender women on PrEP
- 18% had an STI at the time they entered the study
- 109 new STIs were diagnosed, 50 among those using doxycycline PEP compared to 59 among those randomized to no doxycycline and standard of care
- 78% of the new STIs were chlamydia, only 1 new case of syphilis

HIV Breakthrough On Time LA Prep

Howard Brown Health

Breakthrough HIV-1 Infection in Setting of Cabotegravir for PrEP

0981

Aniruddha Hazra[1,2], Connor Quinby[1], Catherine Creticos[1]
[1]Howard Brown Health, Chicago, IL, USA, [2]University of Chicago Medicine, Chicago, IL, USA

BACKGROUND

- Long-acting cabotegravir (CAB-LA) is highly effective as HIV PrEP and superior to daily oral F/TDF in sexually active adults
- Despite its superior efficacy, PrEP failures associated with CAB-LA have been described in clinical trials
- We report a 28-year-old gender diverse patient assigned male at birth whose HIV-1 infection was detected 91 days after transitioning from F/TAF to CAB-LA despite on-time dosing

METHODS

- Electronic medical records were reviewed to assess patient history and CAB-LA administration
- Plasma 4th generation HIV-1/2 Ag/Ab combination immunoassay and HIV-1 RNA quantitative PCR were performed at each injection visit
- Plasma CAB concentration was performed by a research laboratory

CASE DESCRIPTION

- Patient on daily F/TAF for PrEP the past 10 months, reporting one missed dose per week
- History of controlled hypothyroidism and self-reported hypogonadism with unsupervised use of testosterone (IM) and significantly elevated total testosterone levels
- Sexually active with cisgender men
  - condomless oral and anal sex
  - primary partner & 20-30 unique partners monthly
  - recently engaging in anal fisting intercourse
  - diagnosed with syphilis and mpox in past 6 months
- Primary partner was living with HIV resistant to NRTIs (65R, 118I) and INSTIs (92G) with undetectable HIV-1 RNA for over 24 months on DRV/c + DTG
- Uncomplicated administration of 600mg of CAB-LA into left gluteal medius on day 0, 27, and 91
- Flu-like illness with + SARS-COV-2 PCR on day 76; completed course of nirmatrelvir-ritonavir (NMV/r)

RESULTS

- HIV 1/2 Ag/Ab non-reactive and HIV-1 RNA PCR not detected on Day 0 and 27 injections
- At 3rd injection on Day 91
  - HIV 1/2 Ag/Ab non-reactive
  - HIV-1 RNA PCR test detected at 1.48 log10 c/mL
- Repeat testing on day 100
  - HIV 1/2 Ag/Ab reactive
  - HIV-1 Ab detected on differentiation assay
  - HIV-1 RNA PCR detected at 1.30 log10 c/mL
  - unable to perform standard HIV-1 sequencing
- HIV-1 DNA qualitative PCR below LLOQ and HIV-1 proviral DNA resistance unable to be performed
- Plasma CAB concentration on Day 128 (Day 37 from most recent injection) 1180 ng/mL
- Fully suppressive ART regimen (DRV/c + DTG) chosen based on primary partner's historical regimens and genotypes

CONCLUSIONS

- Patient's history and testing suggests HIV infection despite on-time and appropriate CAB-LA injections and detectable CAB concentration
- To our knowledge, this is the first case of CAB-LA PrEP failure outside the setting of a clinical trial
- Highlights diagnostic and management challenges that may occur with CAB-LA PrEP failures
- Reinforces need to better understand HIV-1 reservoirs in such breakthrough infections (ACTG A5321)

ACKNOWLEDGMENTS

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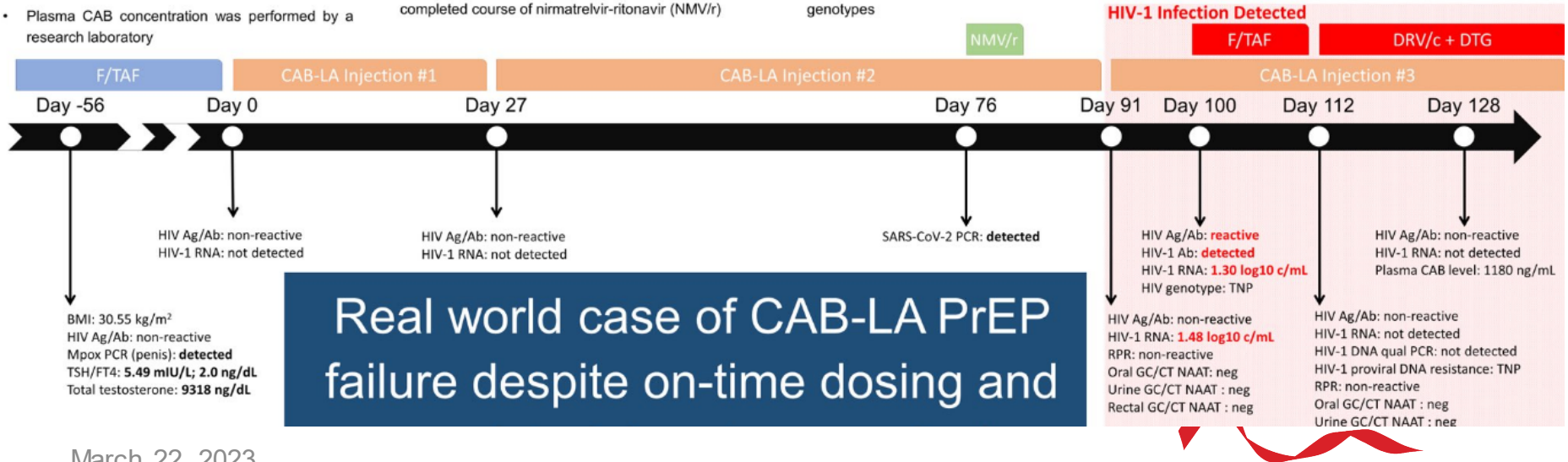
- Toyin Nwafor, MD, Heidi Swygard, MD, MPH, Sonia Patel, PharmD; ViiV Healthcare



Breakthrough HIV-1 Infection in Setting of Cabotegravir for PrEP

Aniruddha Hazra[1,2], Connor Quinby[1], Catherine Creticos[1]
[1]Howard Brown Health, Chicago, IL, USA, [2]University of Chicago Medicine, Chicago, IL, USA

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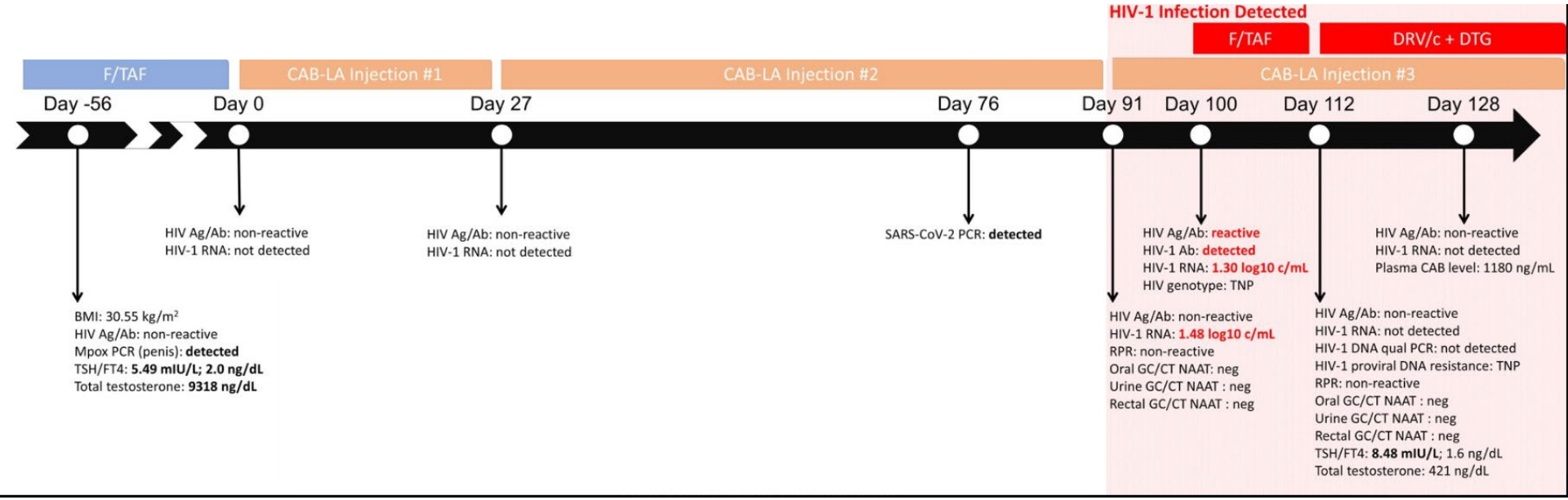

Thank you!

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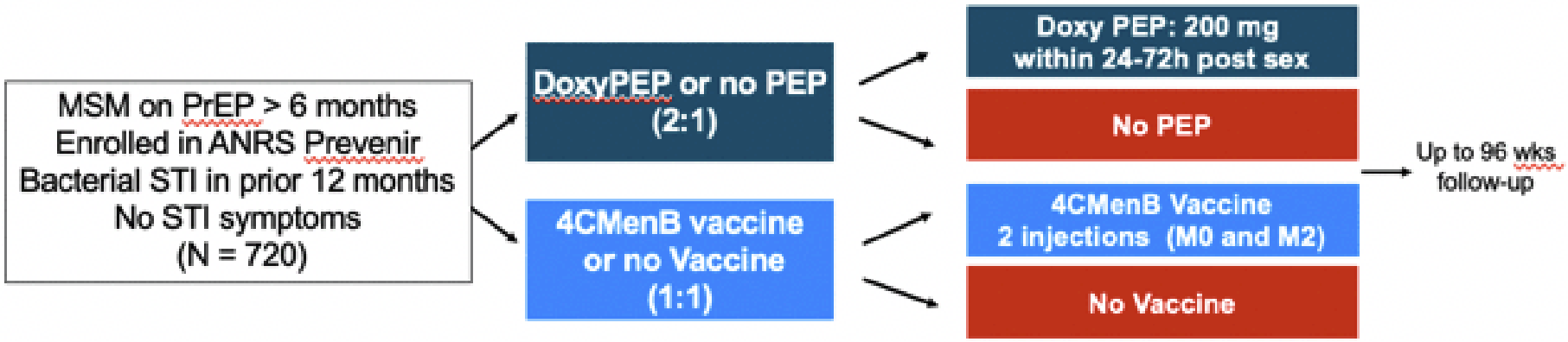
DoxyPEP and Meningococcal Vax Keep Protecting MSM PrEP Users From STIs

Study Design

- Multicenter, 2 x 2 factorial randomized, open-label, superiority, phase III trial (NCT04597424)

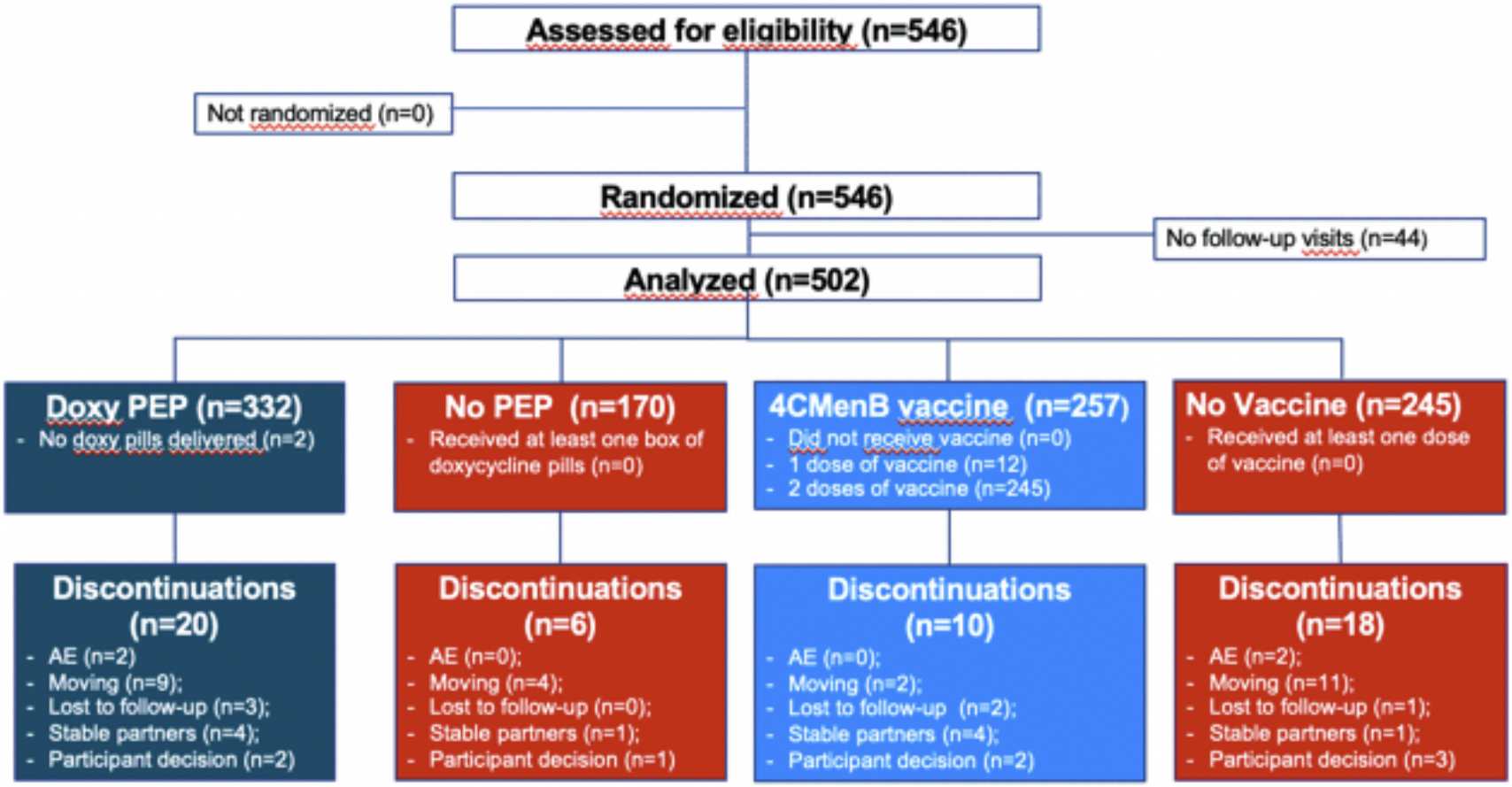


- Primary efficacy end-points: impact of DoxyPEP on time to a first episode of syphilis or chlamydia and impact of the 4CMenB vaccine on time to a first episode of *N. gonorrhoae* infection.
- Sample size: based on vaccine effectiveness assuming no impact of Doxy PEP on GC: 720 subjects needed for an HR: 0.70 (Estimated probability of a first GC episode over 18 months: 52%, 18% lost to FU).
- Quaterly visits with PCR tests (Roche dual target Cobas°) for GC/CT/MG (3 sites) and serology for TP
- Doxycycline monohydrate purchased from Arrow and 4CMenB vaccine purchased from GSK

ANRS 174 DOXYVAC Premature Study Discontinuation

- August 2022 DOXYPEP results: 65% reduction in STIs incidence (CT and syphilis ~ 80%; GC ~ 55%)
- September 2, 2022: DOXYVAC DSMB requested unblinded analysis on participants enrolled from 01/19/2021 to 07/15/2022
- Significant effectiveness of both interventions and DSMB recommended to:
  - stop enrollment of new participants
  - offer Doxy PEP and 4CMenB vaccine to all
- Recommendations endorsed by the scientific committee and ANRS

Study Flow-Chart (July 2022)



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Participants Baseline Characteristics

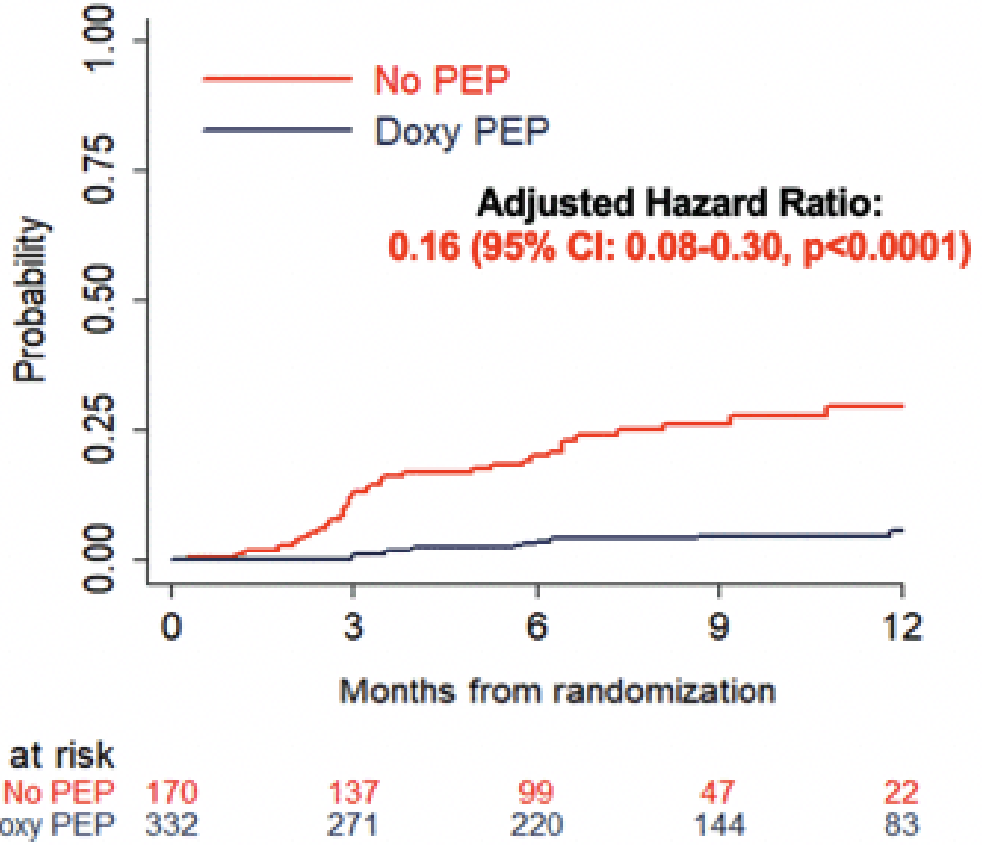
Median (IQR) or %	Doxy PEP (n = 332)	No PEP (n = 170)	4CMenB vaccine (n = 257)	No Vaccine (n = 245)	Total (n=502)
Age, years	40 (33-48)	39 (33-47)	40 (33-47)	39 (33-48)	39 (33-47)
White	79.2	82.9	75.9	85.3	80.5
Born in France	84.8	81.7	82.7	84.8	83.8
Secondary education	89.1	88.4	90.7	87.0	88.9
Employed	87.0	87.5	89.6	84.6	87.2
PrEP use, months	42 (32-55)	43 (35-55)	43 (32-55)	42 (33-54)	42 (32-55)
No. STIs in prior 12 months	2 (1-2)	2 (1-2)	2 (1-3)	2 (1-2)	2 (1-2)
Gonorrheae	67.3	70.1	67.5	69.0	68.2
Chlamydiae	50.3	47.9	52.5	46.3	49.5
Syphilis	21.5	17.4	20.4	19.8	20.1
M. genitalium	3.9	4.2	3.5	4.5	4.0
Condomless sex (4 weeks) no.	5 (3-10)	5 (2-10)	5 (2-10)	5 (3-10)	5 (2-10)
Partners (last 3 months) no.	10 (5-20)	10 (5-20)	10 (5-20)	10 (5-20)	10 (5-20)
Chemsex at last sex act	11.8	10.6	12.5	10.2	11.4

Doxycycline PEP
Time to First CT or Syphilis Infection

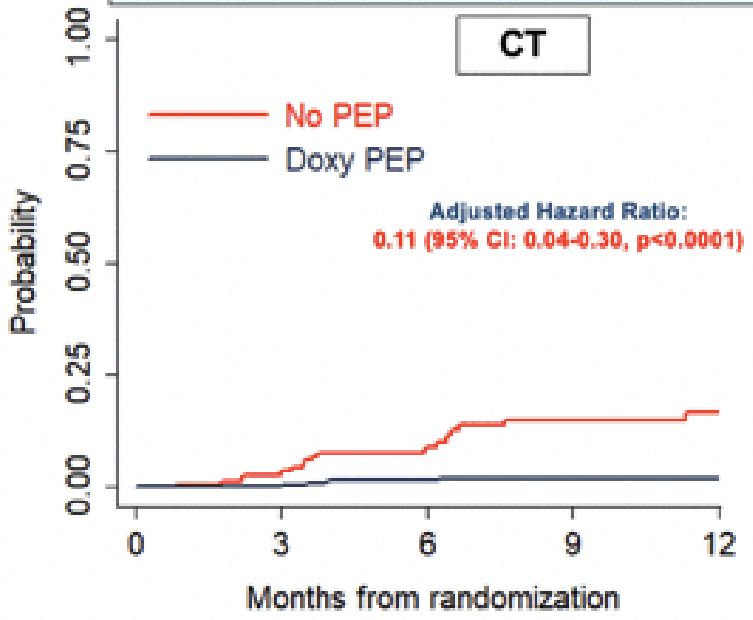
No interaction between Doxy PEP and 4CMenB vaccine (p=0.99)

Median follow-up: **9 months**
(IQR: 6 to 12)

49 subjects infected
36 in No PEP arm
(incidence: 35.4/100 PY),
13 in Doxy PEP arm
(incidence: 5.6/100 PY)



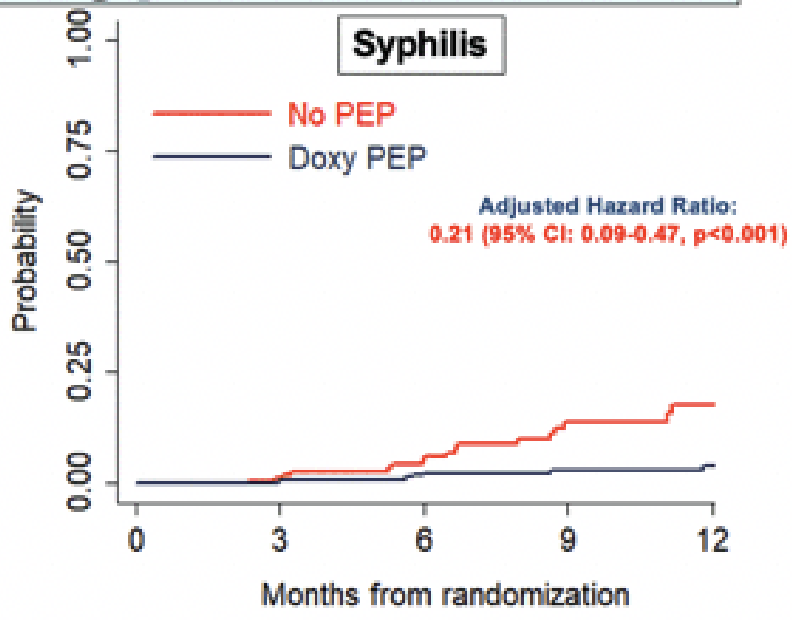
Doxycycline PEP
Time to First CT and Syphilis Infection



Number at risk

No PEP	170	139	105	58	30
Doxy PEP	332	274	223	147	86

26 subjects infected
21 in No PEP arm (incidence: 19.3/100 PY),
5 in Doxy PEP arm (incidence: 2.1/100 PY)



Number at risk

No PEP	170	142	109	56	27
Doxy PEP	332	272	224	147	85

26 subjects infected
18 in No PEP arm (incidence: 16.3/100 PY),
8 in Doxy PEP arm (incidence: 3.4/100 PY)

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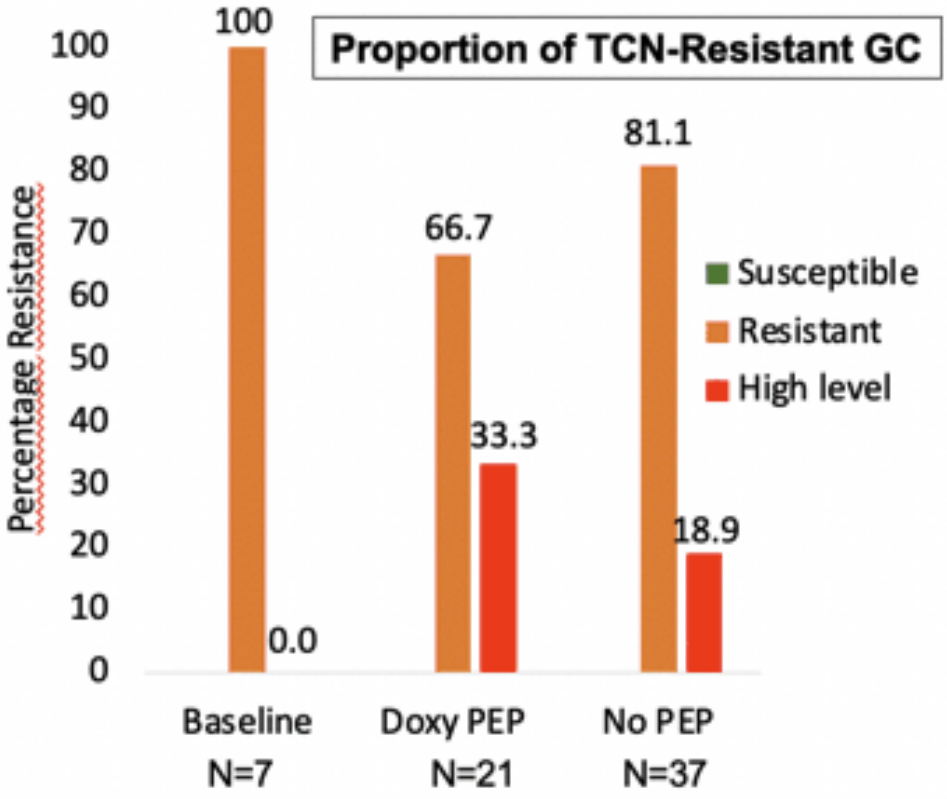
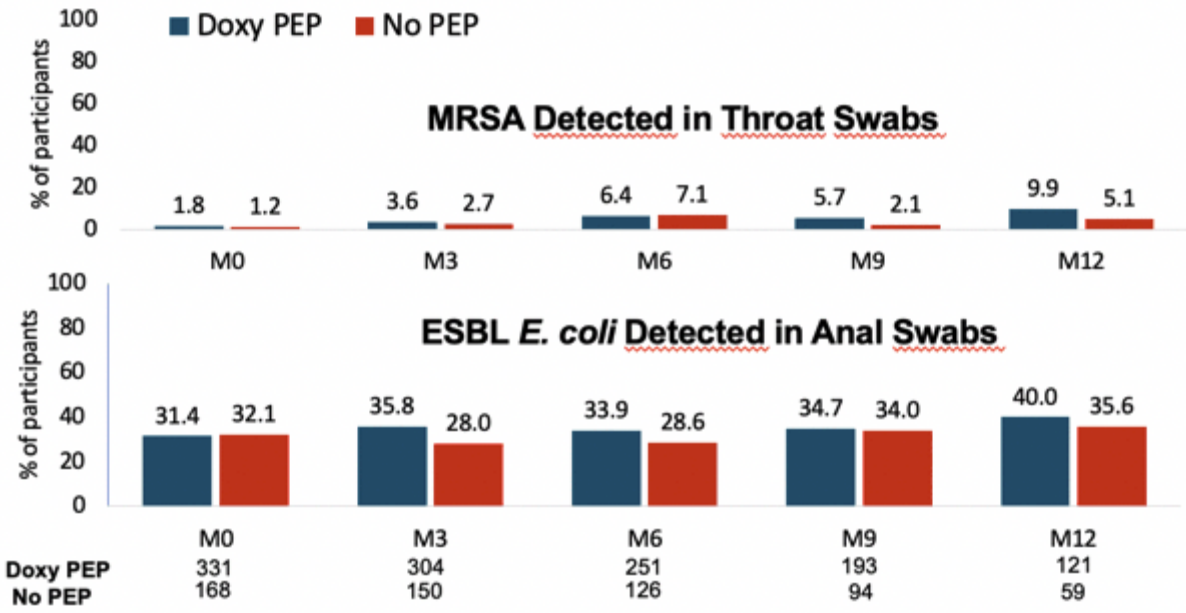
Tetracycline (TCN) Resistance for GC and CT

- **GC:**
  - 65 cultures available for resistance testing (15% of PCR positive samples)
  - Tetracycline MICs determined by Etest
  - Resistance using EUCAST 2023 breakpoints
    - Resistance: MIC > 0.5 mg/L
    - High level resistance: MIC > 8 mg/L
- **CT:**
  - 4/23 strains tested for TCN-R in culture: no resistance (but none from PEP arm)
  - 53/65 PCR+ swabs with16S rRNA sequenced: no TCN-R mutation (only 3 from PEP arm)



Microbiome Analysis



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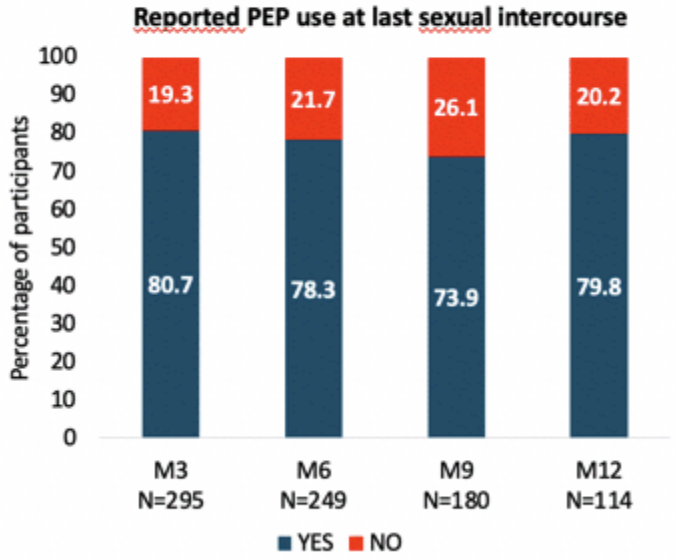
Self-Reported Adherence to Doxy PEP



- **Median (IQR) time to PEP intake: 27h** (5-33) after sex
- **Median no. of pills/month (IQR): 7 pills** (4-11)
- **3 (0.9%) discontinued PEP:** GI AEs (n=2) and fear of AEs (n= 1)

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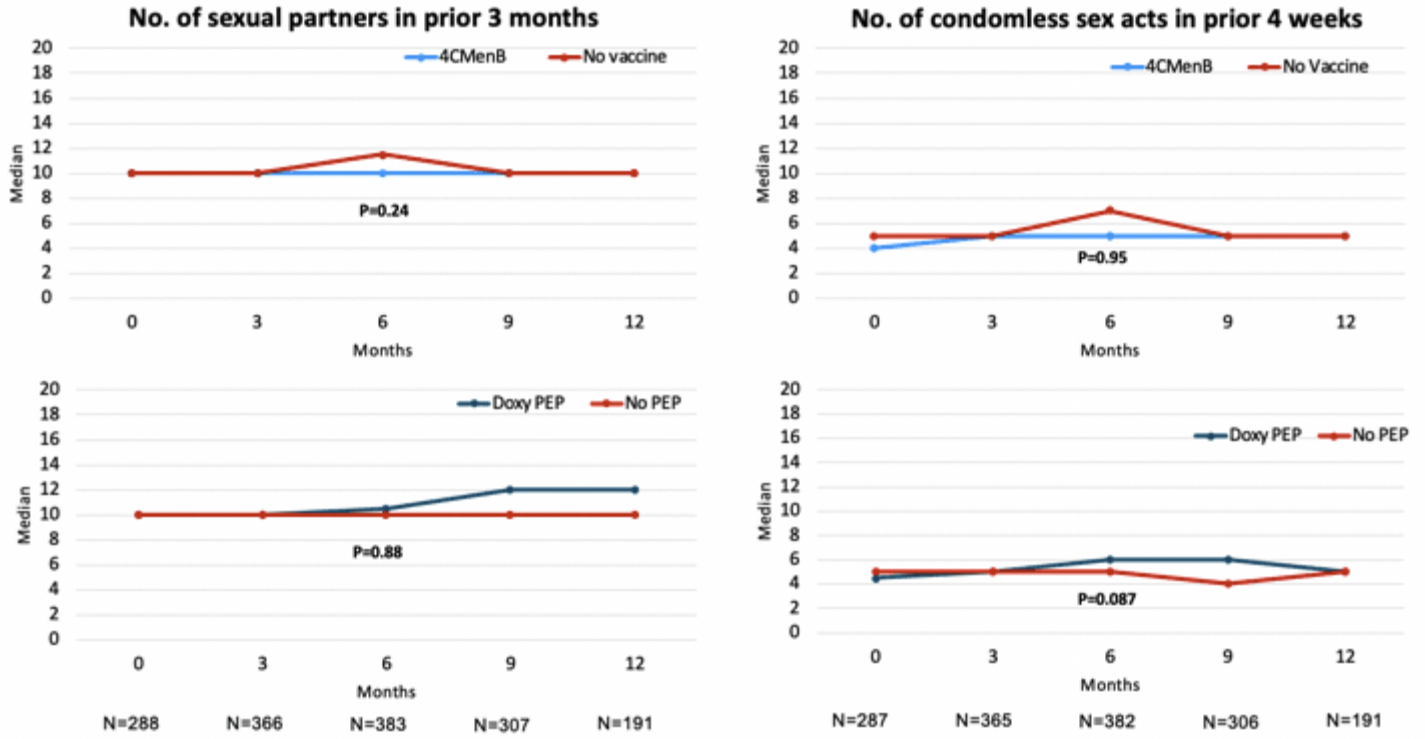
Adverse Events

Nb of Participants (%)	PEP Doxy N=332	No PEP N=170	P value	4CMenB N=257	No Vaccine N=245	P value
Any Serious AE	26 (7.8)	10 (5.9)	0.58	23 (9.0)	13 (5.3)	0.16
Any drug-related SAE	0 (0)	0 (0.0)		0 (0)	0 (0.0)	
Any Grade 3 or 4 AE	10 (3.0)	6 (3.5)	0.75	10 (3.9)	6 (2.5)	0.36
Treatment D/C due to AE	3 (0.9)			0 (0.0)		
Drug-Related AEs	19 (5.7)			89 (34.6)		
Drug-Related AEs in > 3 pts						
Nausea/vomiting	7			1		
Abdominal pain	6			1		
Diarrhea	4			0		
Asthenia	0			9		
Fever	0			5		
Headache	0			5		
Nodule	0			6		
Oedema	0			8		
Pain	0			4		
Pain at injection site	0			77		
Redness	0			12		

Changes in Sexual Behavior



Summary

- **Doxycycline PEP:**
  - 3 large studies have shown significant reductions of STIs among MSM
  - Doxycycline PEP is well tolerated with high self-reported adherence
  - Evaluation of full impact on antibiotic resistance is underway (STIs, microbiome)
- **4CMenB Vaccine:**
  - 4CMenB vaccine reduced incidence of a first episode of GC among MSM
- **There is no magic bullet:** Interest for combined approaches
- **STI research:** a scientific priority to meet 2030 WHO/UNAIDS targets to reduce incidence of HIV and STIs by 90%

Impact of vaccination on mpox incidence in the ANRS 174 DOXYVAC trial (J. Ghosn, Wednesday Feb. 22, oral abstract 208)