

LE IST OGGI

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KEY FACTS

- **Global Incidence:** over 1 million STIs daily worldwide.
- **Asymptomatic Nature:** Majority of STIs are asymptomatic.
- **Transmission:** 30+ pathogens transmitted through vaginal, anal, and oral sex.
- **Mother-to-child:** pregnancy, childbirth, breastfeeding.
- **High-Incidence Pathogens:** Syphilis, Gonorrhea, Chlamydia, Trichomonas, HBV, HSV, HIV, HPV.
- **Emerging Outbreaks:** Mpox, Shigella, Neisseria meningitidis, Ebola, Zika and Dermatomyces.
- **Major Threats:** Drug Resistance and Lack of Vaccines.

EPIDEMIOLOGY

Incident cases of four curable STIs among adults (15–49 years old), by WHO region, 2020

Syphilis (*Treponema pallidum*), gonorrhoea (*Neisseria gonorrhoeae*), chlamydia (*Chlamydia trachomatis*) and trichomoniasis (*Trichomonas vaginalis*)

GLOBAL
374 million
[286 million–481 million]

REGION OF THE AMERICAS
74 million
[53 million–104 million]

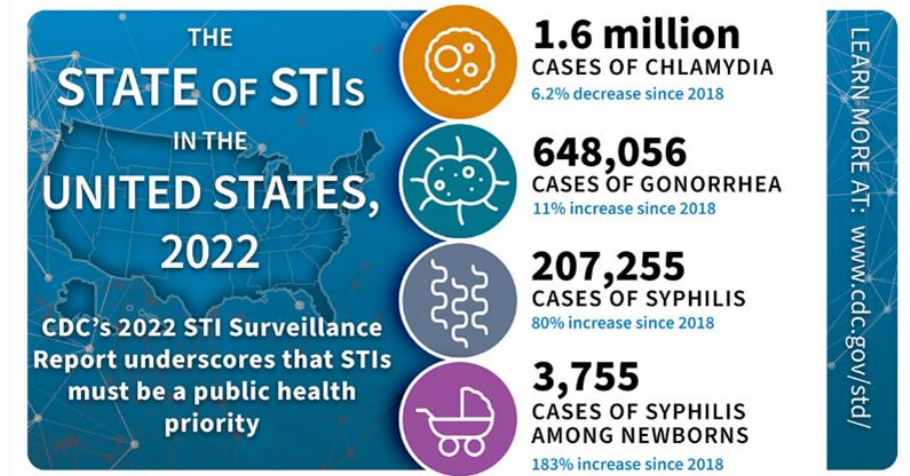
EUROPEAN REGION
23 million
[16 million–31 million]

WESTERN PACIFIC REGION
86 million
[61 million–117 million]

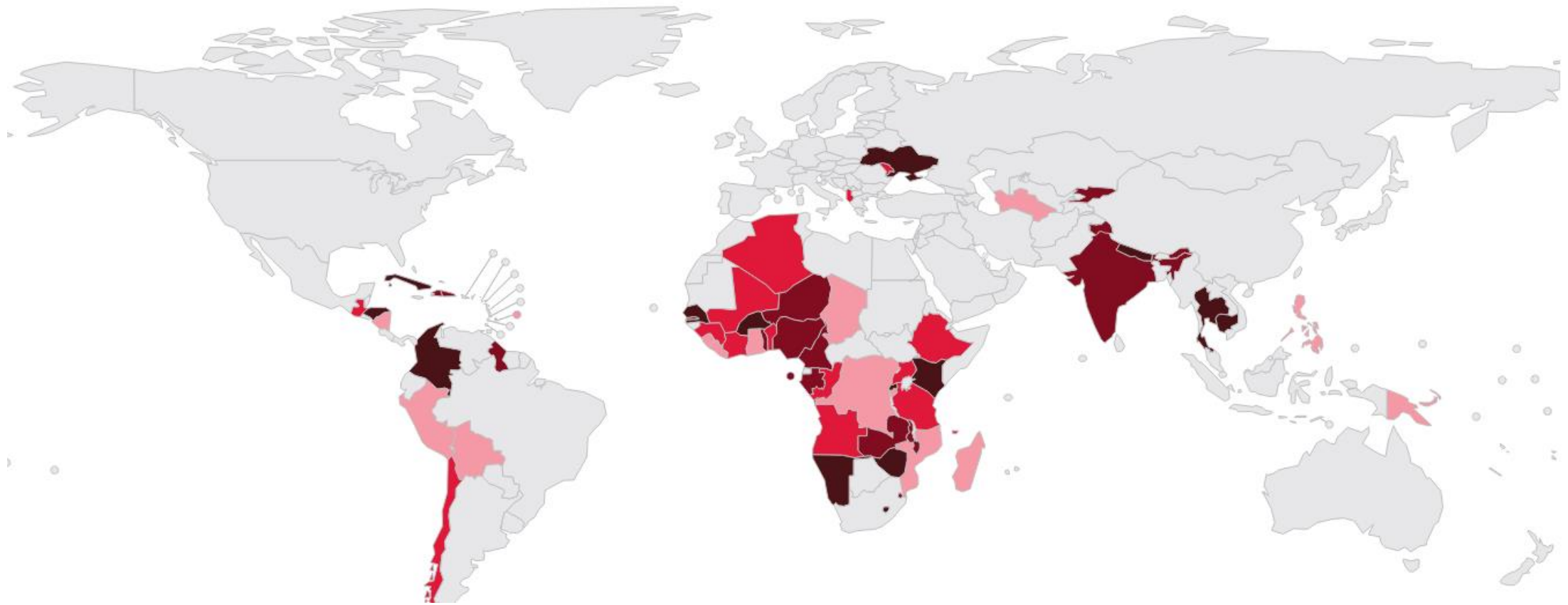


Source: WHO, 2021.

The State of STIs — CDC Reports an Alarming Rise in Syphilis



CONDOM USE AT LAST HIGH-RISK SEX



Most recent data as of **2023**

■ 67.9+ % ■ 51.3 - 67.9 % ■ 37.2 - 51.3 %
■ < 37.2 % ■ No data

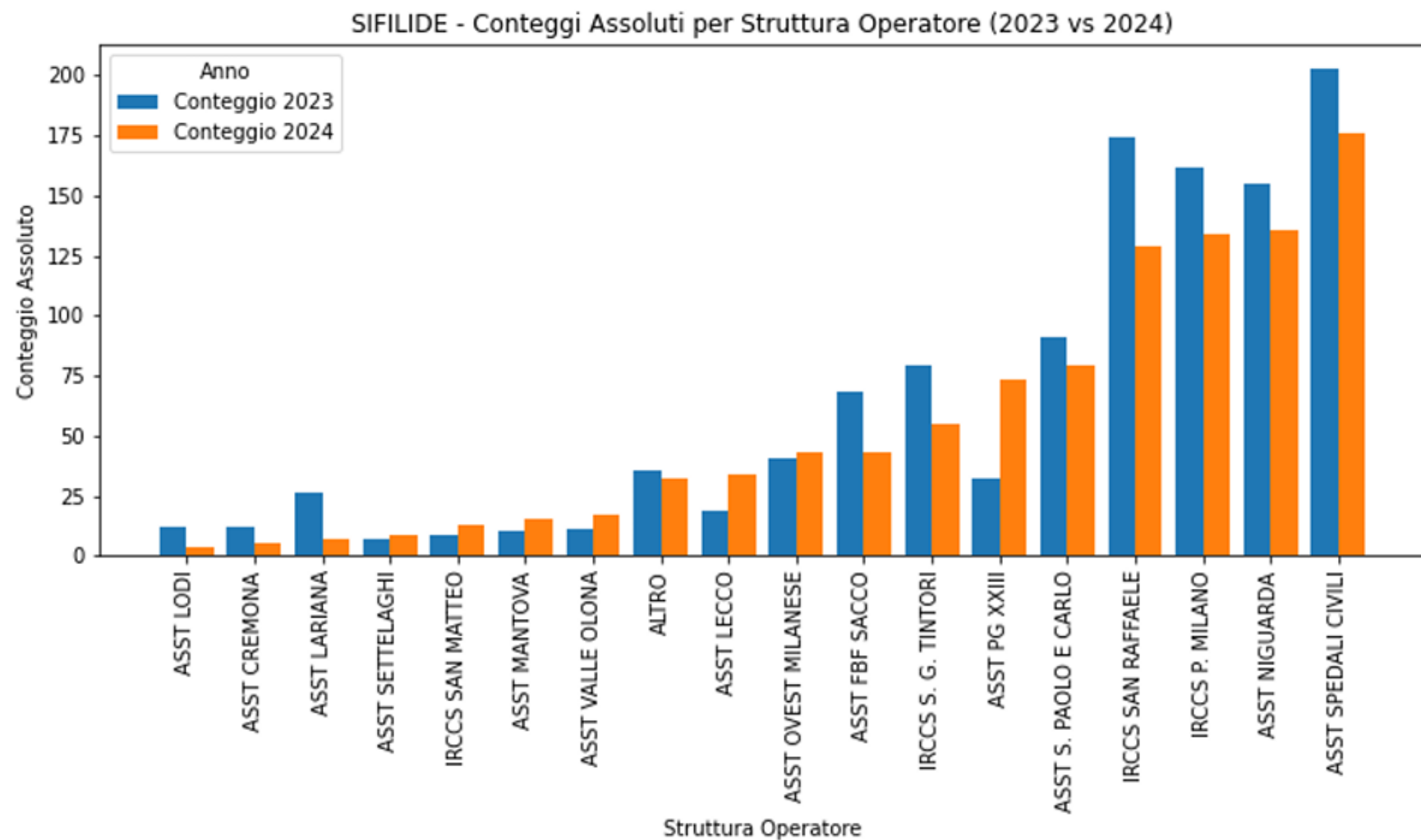
WHO STRATEGY

Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030

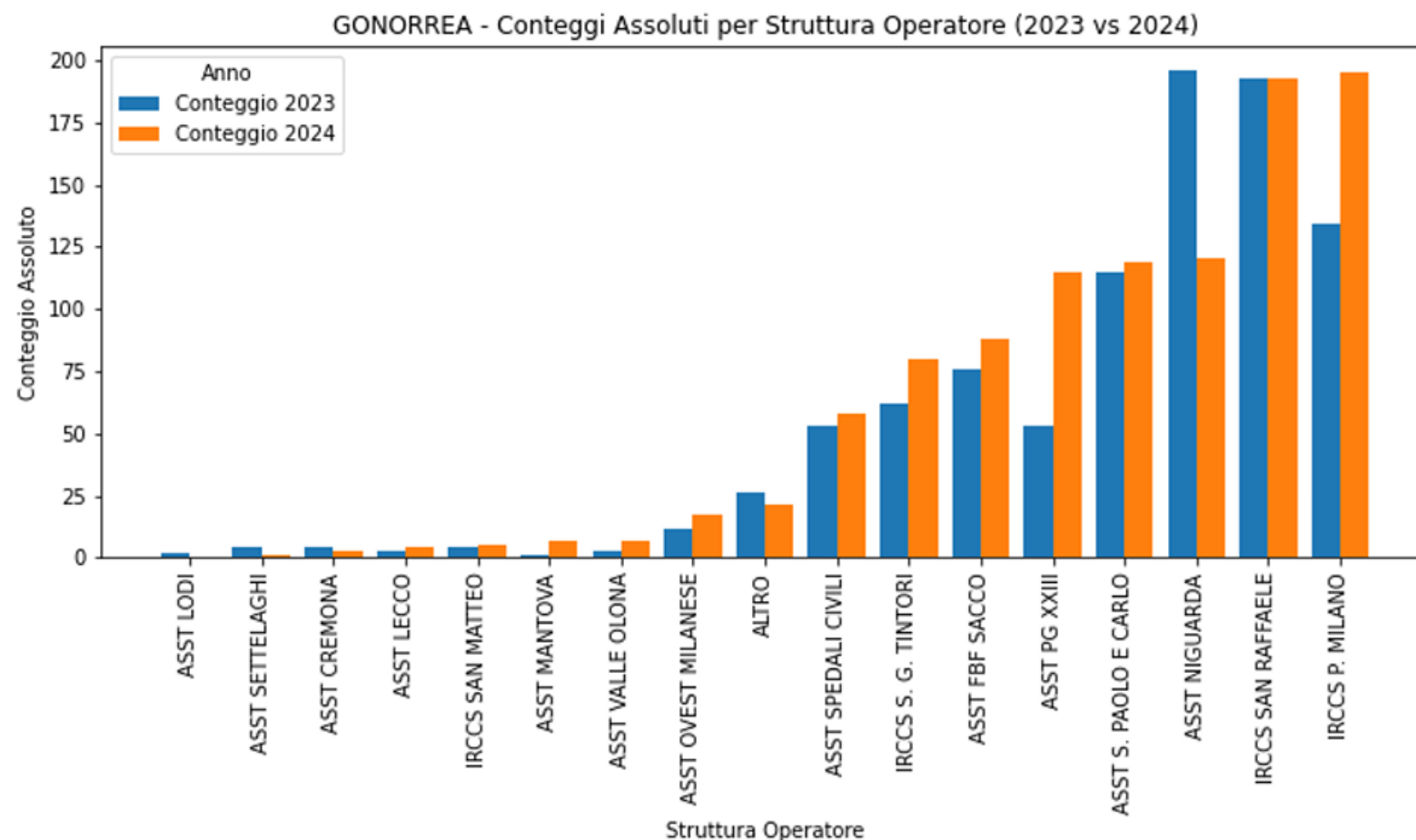
Disease area	Impact indicator	Baseline 2020 ^b	2025 target	2030 target
Sexually transmitted infections	Number of new cases of syphilis among people 15–49 years old per year	7.1 million	5.7 million	0.71 million
	Number of new cases of gonorrhoea among people 15–49 years old per year	82.3 million	65.8 million	8.23 million
	Number of congenital syphilis cases per 100 000 live births per year	425	<200	<50
	Percentage of girls fully vaccinated with human papillomavirus vaccine by 15 years of age	14%	50%	90%



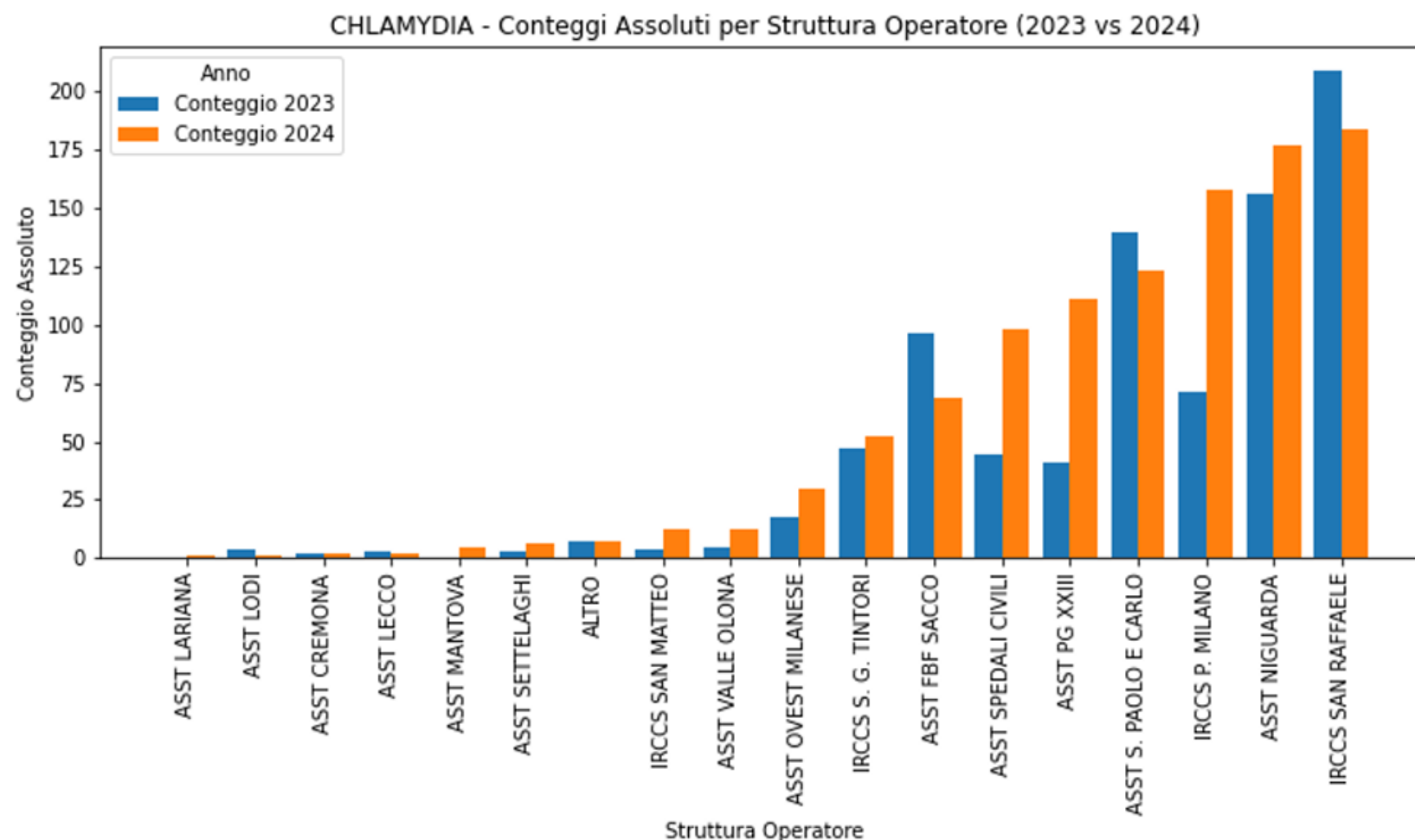
Report IST - Sifilide



Report IST - Gonorrea



Report IST - Chlamydia



Syphilis: treatment options

Figure 1. Why is there a global penicillin shortage?

Penicillin — a revolutionary antibiotic discovered 80 years ago — is now in scarce supply. 39 countries have reported benzathine penicillin G (BPG) shortages* — putting millions of lives at risk. BPG is the first-line therapy for syphilis and rheumatic heart disease. Worryingly, many countries with BPG shortages are experiencing syphilis outbreaks in parallel.

What is causing this BPG shortage?

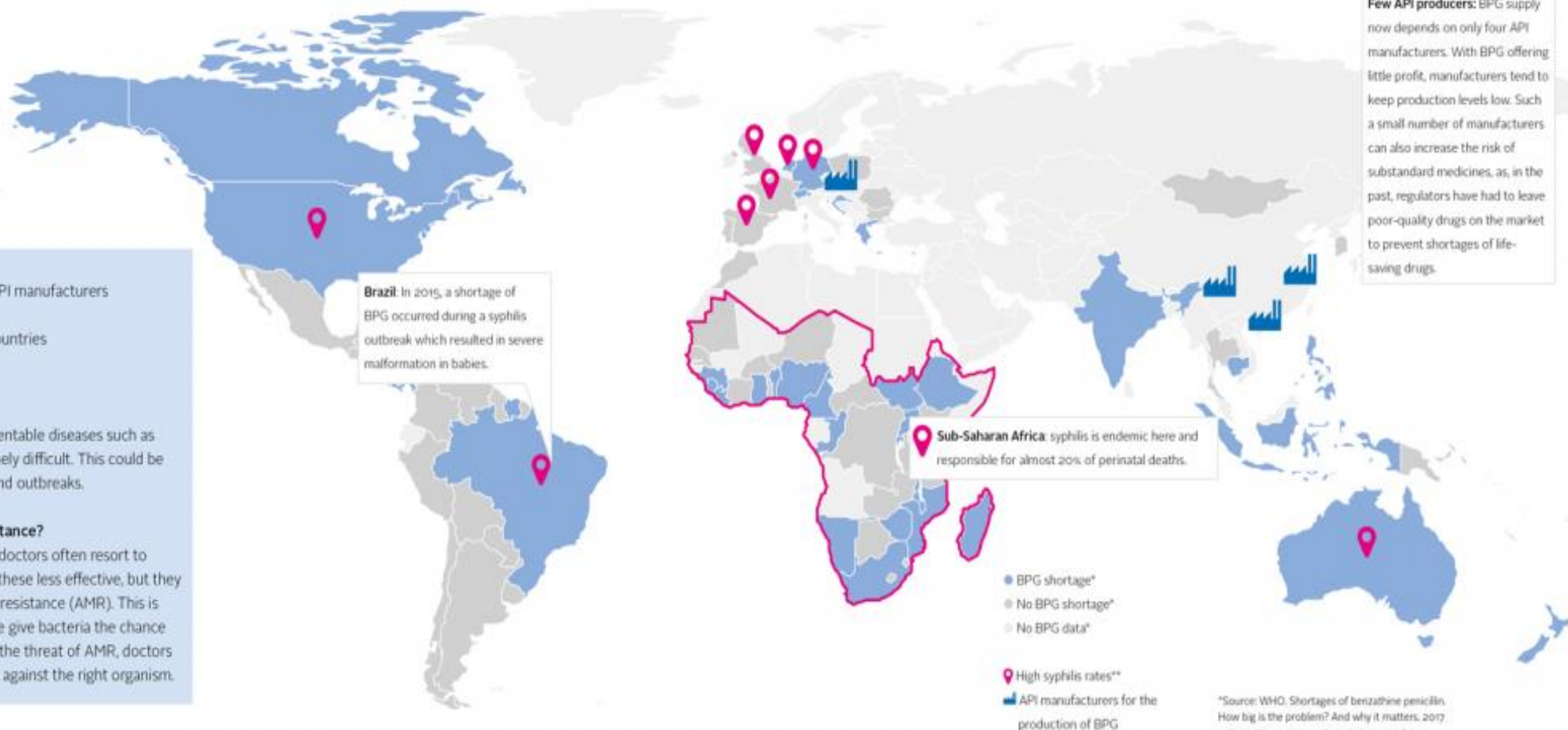
- Fragile supply chain, reliant on only four API manufacturers
- BPG offers little profit
- Demand is high but largely from poorer countries
- Production levels kept low

What is the effect of this BPG shortage?

Shortages of BPG make treatment for preventable diseases such as syphilis and rheumatic heart disease extremely difficult. This could be contributing to increased rates of disease and outbreaks.

How do shortages fuel antimicrobial resistance?

When demand spikes and shortages occur, doctors often resort to using less optimal treatments. Not only are these less effective, but they also bring an increased risk of antimicrobial resistance (AMR). This is because, every time we use an antibiotic, we give bacteria the chance to adapt and develop resistance. To reduce the threat of AMR, doctors must ensure that the right antibiotic is used against the right organism.



Few API producers: BPG supply now depends on only four API manufacturers. With BPG offering little profit, manufacturers tend to keep production levels low. Such a small number of manufacturers can also increase the risk of substandard medicines, as, in the past, regulators have had to leave poor-quality drugs on the market to prevent shortages of life-saving drugs.

*Source: WHO. Shortages of benzathine penicillin. How big is the problem? And why it matters. 2017.

**Syphilis endemic: Sub-Saharan Africa
Syphilis outbreaks declared: Brazil, Australia
Syphilis on the rise: USA, Germany, UK, Netherlands, Spain and France

DOXYPEP

Intervention: Open label doxycycline 200mg taken as PEP within 72 hours after condomless sexual contact
Maximum of 200 mg every 24 hours

Inclusion criteria:

- Male sex at birth
- Living with HIV or on PrEP
- ≥ 1 STI in past 12 months
- Condomless sex with ≥ 1 male partner in past 12 months

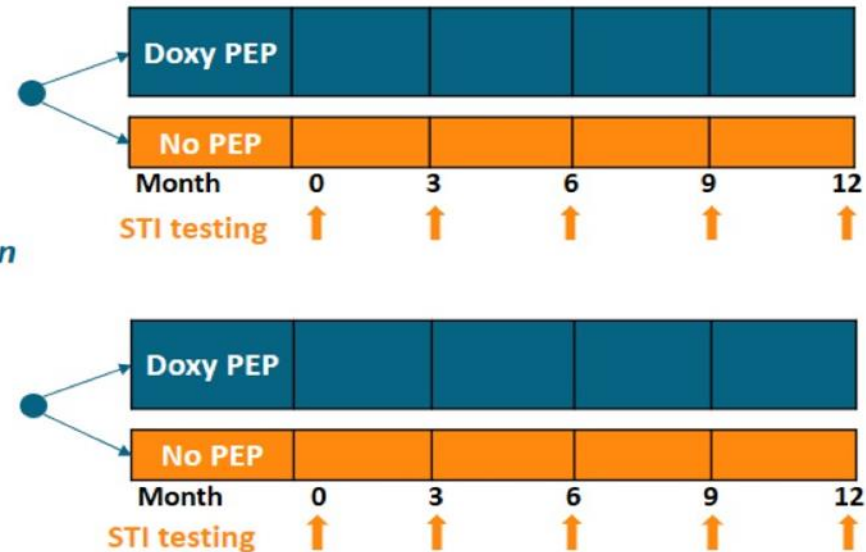
STI Testing: Quarterly 3 site GC/CT testing + RPR, GC culture before treatment

Sites: San Francisco & Seattle HIV & STI clinics

**MSM & TGW
living with HIV**
(planned n = 390)

2:1 randomization

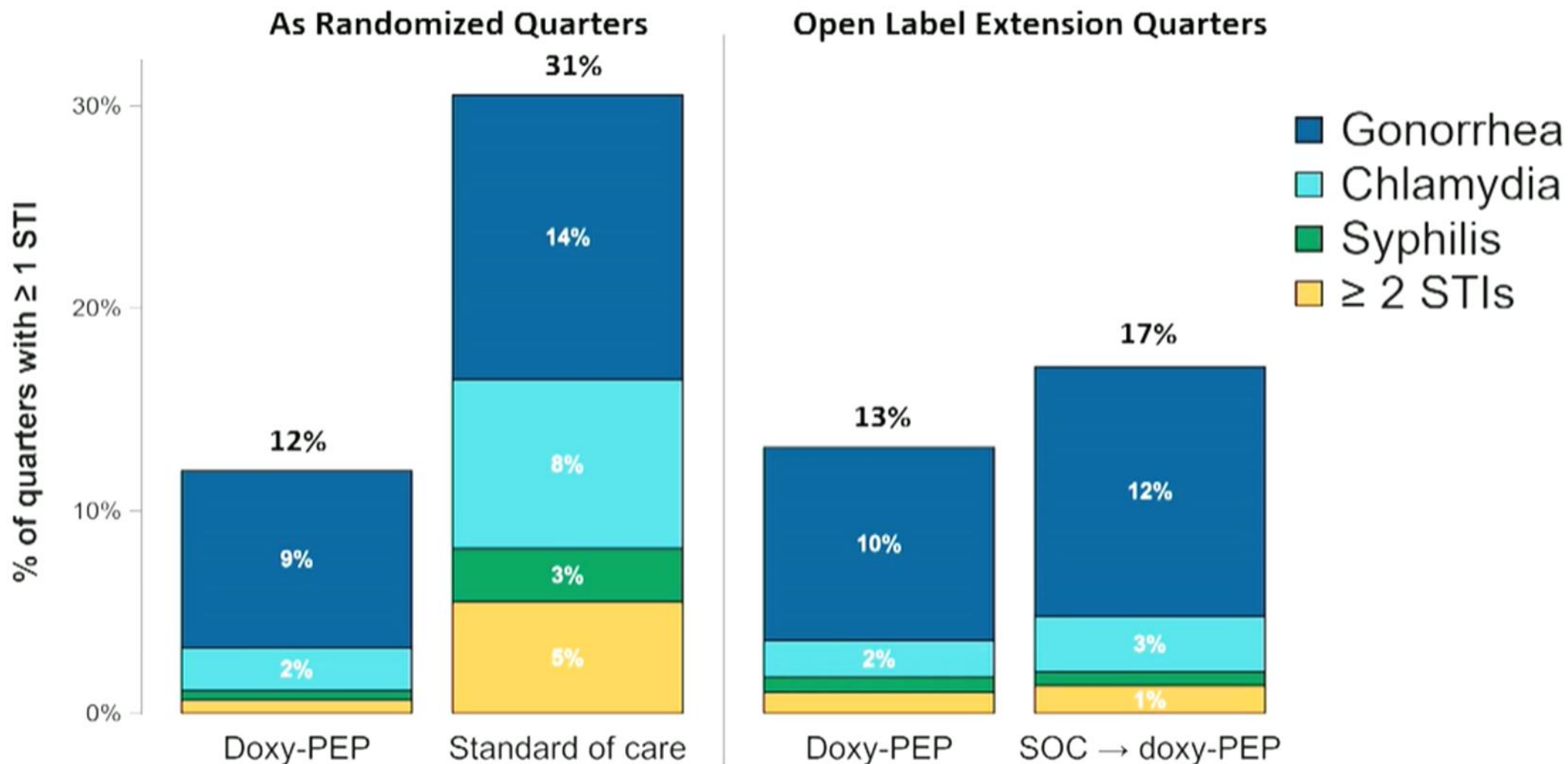
**MSM & TGW
on HIV PrEP**
(planned n = 390)



DOXYPEP

DOXYPEP: USA

Sustained reduction in STIs during OLE



DOXYPEP USAGE

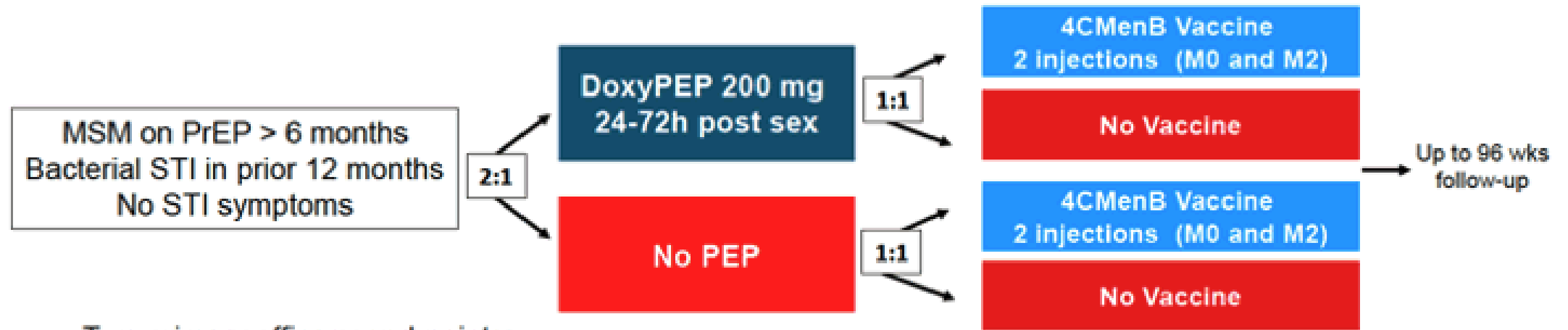
Average doxy-PEP usage

	As-randomized		AR→OLE	
	doxy-PEP <i>median (IQR)</i> N quarters = 1077	SOC N quarters = 455	doxy-PEP N quarters = 388	SOC → doxy-PEP N quarters = 146
Doxy doses/quarter	15 (4-30)	—	17 (7-32)	17 (5-30)
Doxy doses/month	5	—	6	6

- **Reported number of doxy-PEP doses:** Modest ↑ during the OLE period in both doxy-PEP OLE & SOC → doxy-PEP groups
- Wide range of dosing frequency reported

DOXYPEP: FRANCE

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



- Two primary efficacy end-points:
 - Impact of **DoxyPEP** on time to a first episode of syphilis or chlamydia
 - Impact of the 4CMenB vaccine on time to a first episode of *N. gonorrhoeae* infection.

DOXYPEP: FRANCE

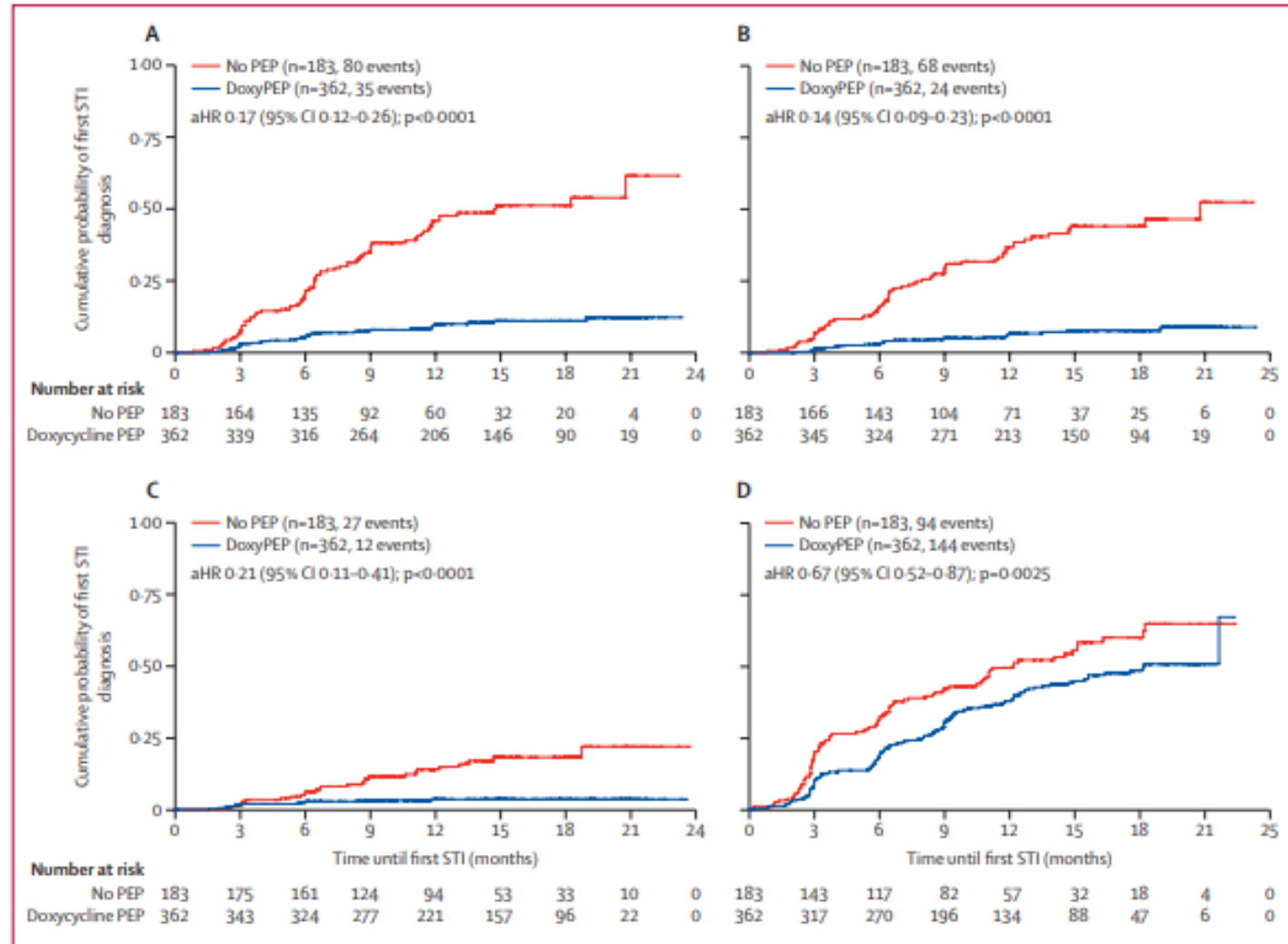
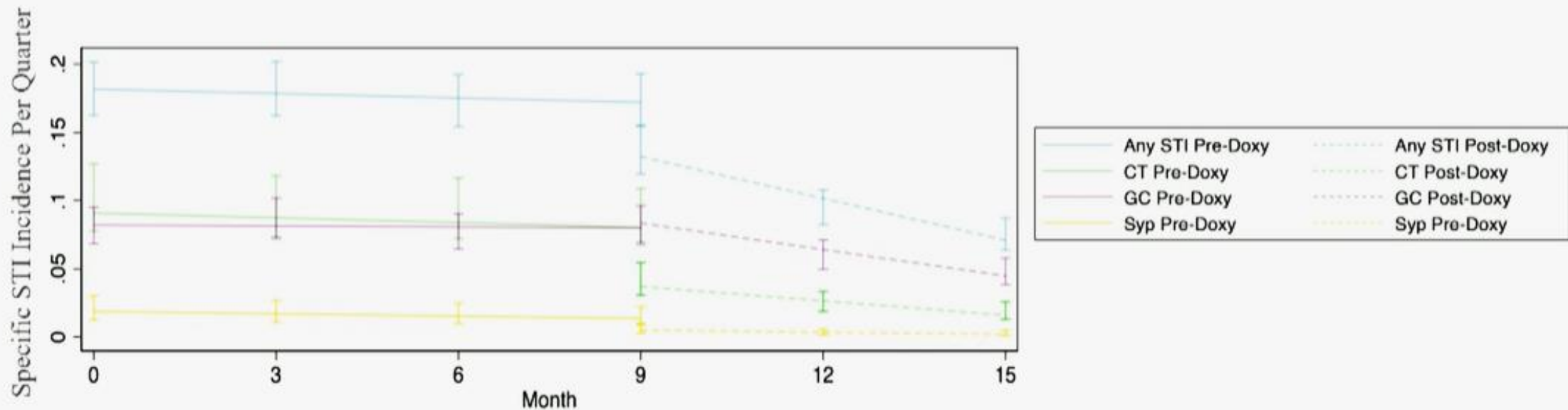


Figure 2: Kaplan-Meier analysis of the probability of the first episode of chlamydia, syphilis, and gonorrhoea in the modified intention-to-treat population. Estimates of the probability of the first episode of chlamydia or syphilis (A); chlamydia (B); syphilis (C); and gonorrhoea (D). aHR=adjusted hazard ratio. PEP=post-exposure prophylaxis. STI=sexually transmitted infection.

DOXYPEP: REAL LIFE

Interrupted Time Series: STI Incidence Pre- Post-DoxyPEP



ITS: Any STI: $p=0.032$; Chlamydia: $p=0.021$; Gonorrhea: $p=0.003$; Syphilis: $p=0.360$

DOXYPEP REAL LIFE: OSR

Retrospective study on gay men and other men who have sex with men in care for HIV or HIV PrEP at the Infectious Diseases Unit of San Raffaele Hospital, Milan, Italy.

People received DoxyPEP counselling and prescription between August 2022 (first DoxyPEP prescription, baseline-BL) and July 2024 (freeze date).

DoxyPEP counselling and prescription was offered to people with an STI history or who reported condomless sex with ≥ 1 casual partner.

DoxyPEP with doxycycline 200mg within 72h from potential exposure was suggested for intense sexual activity (>5 partners).



Results

DoxyPEP counselling and prescription

754 gay men and other men who have sex with men (197 living with HIV, 531 PrEP users)

DoxyPEP uptake

222 (29.4%) gay men and other men who have sex with men (69 living with HIV, 153 PrEP users)

Median months of follow-up (DoxyPEP users)

Before prescription 15.8 (IQR=12.1-19.2) months

After prescription: 10.8 (IQR=6.88-13.1) months

Characteristics of individuals who received DoxyPEP counselling according to DoxyPEP uptake

	Overall n=754	Non-users n=532	DoxyPEP users n=222	p-value
Age (years, IQR)	38.3 [33.5;45.0]	38.1 [33.2;45.0]	38.9 [34.1;44.9]	0.323
Living with HIV	197 (26.1%)	128 (24.1%)	69 (31.1%)	0.056
HCVAb ⁺	35 (5.12%)	16 (3.32%)	19 (9.41%)	0.002
HbsAg ⁺	7 (1.81%)	6 (2.10%)	1 (1.00%)	0.682
PrEP user	531 (70.4%)	378 (71.1%)	153 (68.9%)	0.619
Previous AIDS event	14 (1.86%)	8 (1.50%)	6 (2.70%)	0.373
Years from HIV diagnosis	11.8 [7.82;17.3]	12.2 [8.29;18.6]	10.5 [7.30;15.9]	0.046
Years of ART	10.3 [7.15;14.2]	10.8 [7.32;15.6]	9.11 [6.07;12.7]	0.030
HIV-RNA (<50 copies/mL)*	189 (97.9%)	122 (98.4%)	67 (97.1%)	0.618
Nadir CD4 ⁺ (cells/microL)	462 [284;669]	410 [258;622]	547 [375;695]	0.005
CD4 ⁺ (cells/microL)*	866 [727;1134]	859 [689;1103]	889 [758;1173]	0.475
CD4 ⁺ /CD8 ⁺⁺	0.95 [0.73;1.28]	0.97 [0.70;1.28]	0.94 [0.78;1.18]	0.944
4CMenB vaccination	169 (22.4%)	99 (18.6%)	70 (31.5%)	<0.001

* at DoxyPEP counselling

Results

Previous and concurrent STIs according to DoxyPEP uptake at time of DoxyPEP counselling

	Overall n=754	Non-users n=532	DoxyPEP users n=222	p-value
At least 1 concomitant STI*	157 (20.8%)	100 (18.8%)	57 (25.7%)	0.043
Concomitant chlamydia*	69 (9.15%)	44 (8.27%)	25 (11.3%)	0.246
Concomitant gonorrhea*	67 (8.89%)	33 (6.20%)	34 (15.3%)	<0.001
Concomitant syphilis*	53 (7.03%)	39 (7.33%)	14 (6.31%)	0.730
Concomitant mpox*	1 (0.13%)	1 (0.19%)	0 (0.00%)	1.000
Concomitant Mgen*	4 (0.53%)	3 (0.56%)	1 (0.45%)	1.000
At least 1 previous STI	417 (55.3%)	252 (47.4%)	165 (74.3%)	<0.001
Previous chlamydia	216 (28.6%)	132 (24.8%)	84 (37.8%)	<0.001
Previous gonorrhea	267 (35.4%)	159 (29.9%)	108 (48.6%)	<0.001
Previous syphilis	119 (15.8%)	65 (12.2%)	54 (24.3%)	<0.001
Previous mpox	72 (9.55%)	32 (6.02%)	40 (18.0%)	<0.001
Previous Mgen	34 (4.51%)	21 (3.95%)	13 (5.86%)	0.338

* at DoxyPEP counselling

bSTIs among DoxyPEP users

Before prescription: 401 bSTIs (Tp 70, Ct 139, Ng 192)
 After prescription: 146 bSTIs (Tp 26, Ct 32, Ng 88)

Regression models among users showed a significant reduction of -80% (IRR=0.20, 95%CI=0.17-0.25, p<0.001) in the IR of all bSTIs after DoxyPEP prescription compared to before.

Doxycycline consumption

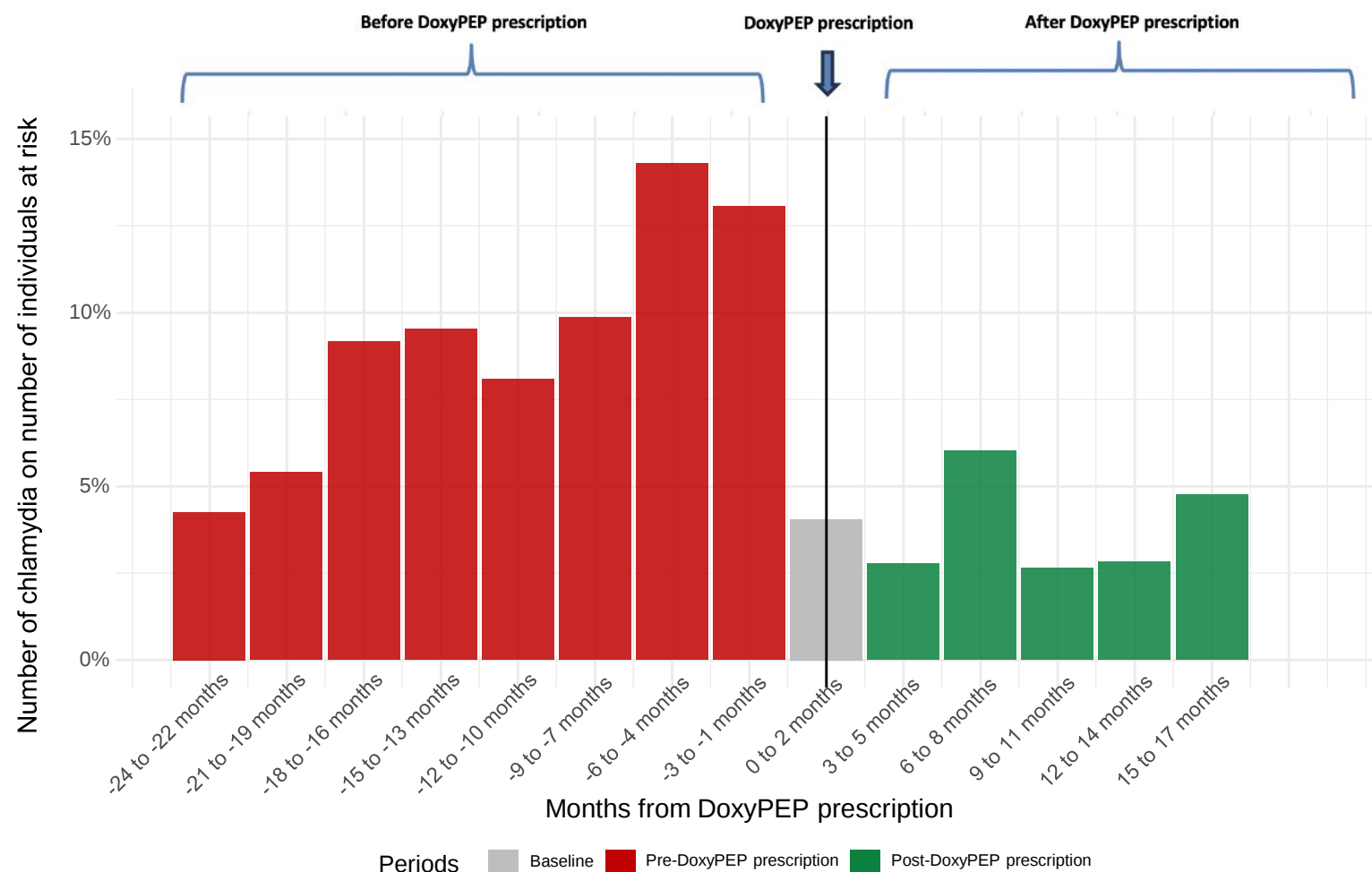
The overall DOT per 1000-PD was 7.00 (median DOT=5.53) among users.

Chlamydia



HIVR4P 2024

Chlamydia Proportions Before and After DoxyPEP Prescription (3-month intervals)



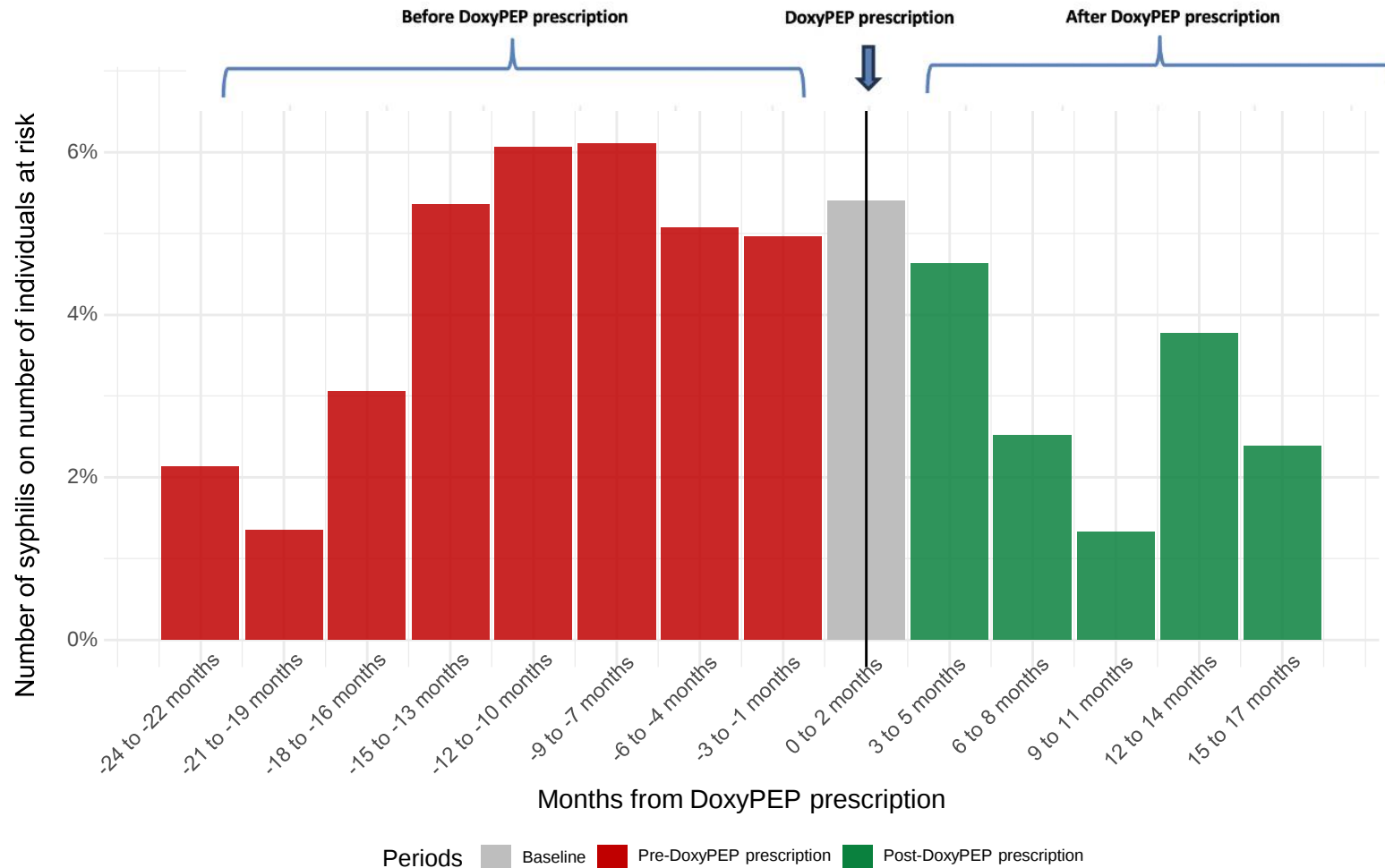
Ct: -87%
(IRR=0.13, 95%CI=0.09-0.19, p<0.001)

Syphilis



HIVR4P 2024

Syphilis Proportions Before and After DoxyPEP Prescription (3-month intervals)



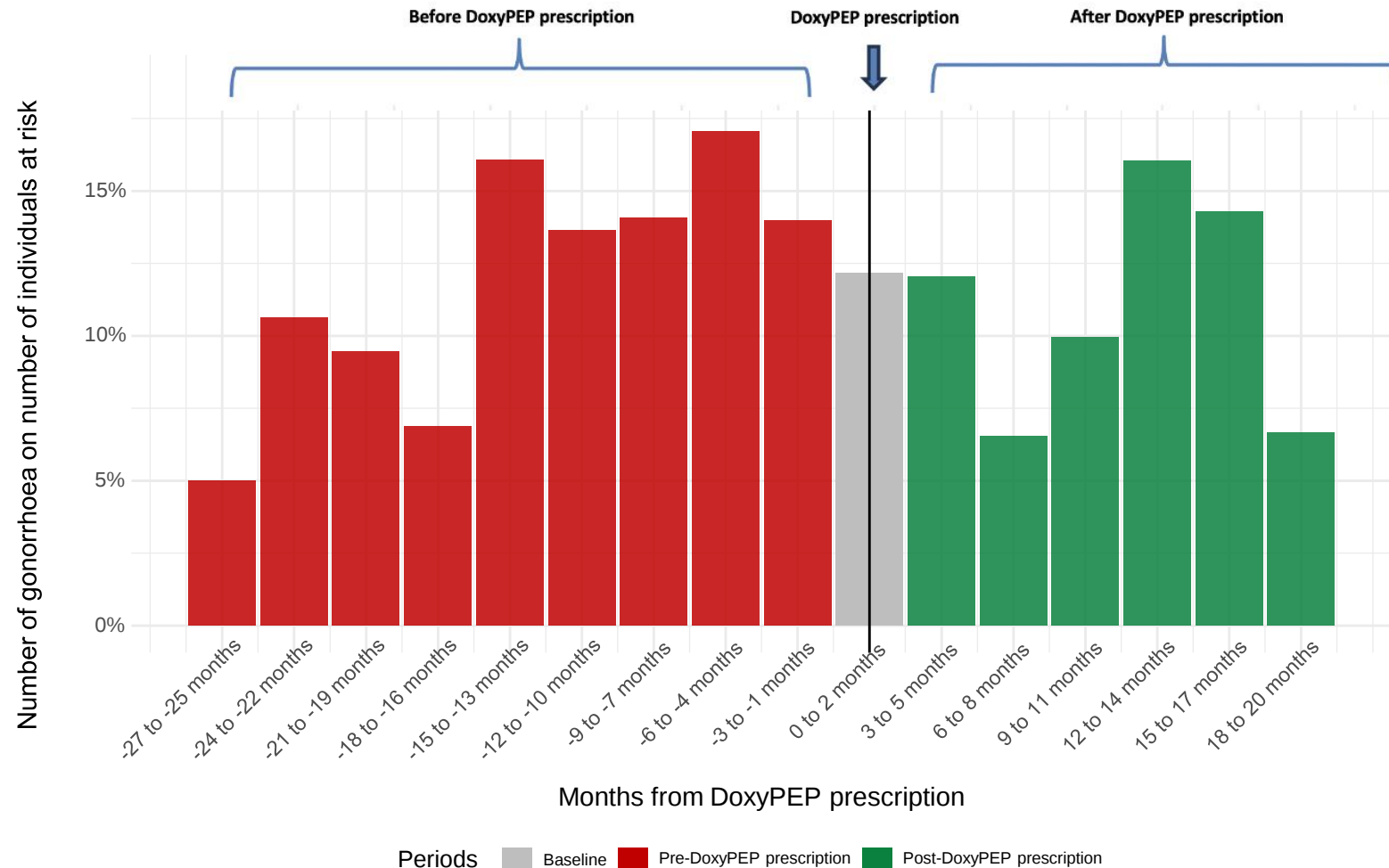
Tp: -80%
(IRR=0.20, 95%CI=0.13-0.32, p<0.001)

Gonorrhoea



HIVR4P 2024

Gonorrhea Proportions Before and After DoxyPEP Prescription (3-month intervals)



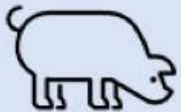
Ng: -74%
(IRR=0.26, 95%CI=0.20-0.33, p<0.001)

4CMenB: 70 (31.5%)

Potential doxy-PEP impact on other STIS

Chlamydia

- Doxy is now 1st line treatment for CT
- No clinical resistance to TCN class reported
- TCN resistance has been seen in *C.suis* (pig chlamydia) – could this be transferred to humans or acquired de novo?



Syphilis

- Doxy is an alternative therapy
- No clinical resistance to TCN class reported
- TCN resistance has been with single point mutation in other spirochetes
- Potential impact on syphilis serologies- delayed diagnosis or false negative?



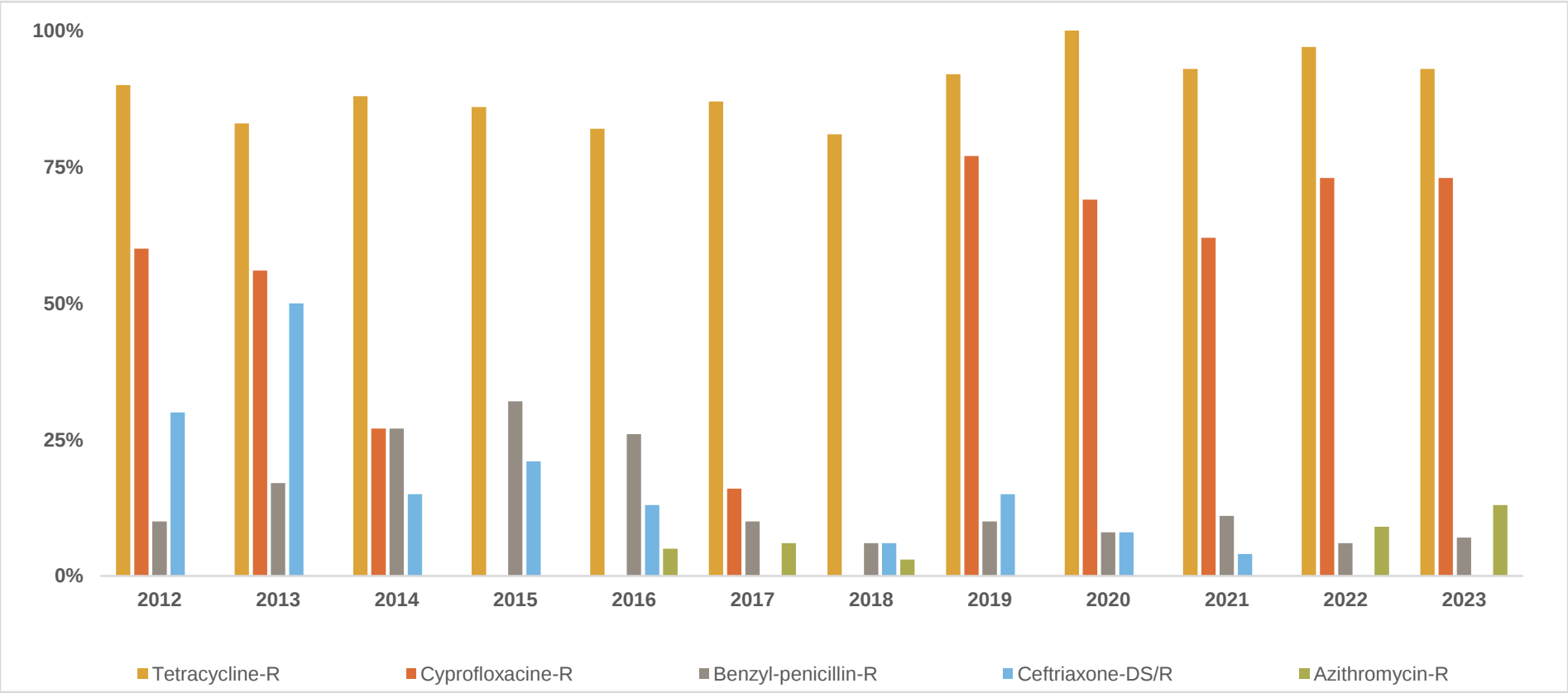
M.genitalium

- Doxy not very effective - poor cure rate as monotherapy, but part of two-step therapy for *M. gen*
- Substantial resistance to macrolides & fluoroquinolones
- Clinical *M. gen* resistance not yet described



Percentage of isolates showing TET-R, CIP-R, PenG-R, CRO-DS/R and AZM-R over years

Cochran-Armitage test to assess linear trend over time of proportions of resistant strains
TET: $p=0.001$; CIP: $p < 0.0001$; PenG: $p < 0.0001$; CRO: $p < 0.0001$; AZM: $p=0.007$



Report IST

Percentuali asintomatici per malattia

Malattia	2023	2024
CHLAMYDIA	67.88%	75.62%
GONORREA	54.30%	57.99%
SIFILIDE	56.67%	64.94%

Percentuale nati all'estero per malattia

Malattia	2023	2024
CHLAMYDIA	15.29%	15.33%
GONORREA	17.75%	15.59%
SIFILIDE	21.53%	20.62%

- Raccagni AR et al., Lancet Infect Dis. 2024 Oct;24(10):e614-e615
- Vanbaelen T et al., Lancet HIV. 2024;11(4): e233-e244.
- Van Praet JT et al., Acta Clin Belg. 2024;79(2): 121-129.
- Kenyon C et al., Lancet Reg Health Eur. 2023; 34:100743.

ANAL CANCER: RISK FACTORS

- Age
- Multiple sex partners
- History of genital warts
- Immune suppression due to chemotherapy, organ transplant, CD4 idiopathic lymphopenia
- Sexually transmitted diseases
- Chronic inflamed areas, such as anal fistulas or open wounds
- Prior pelvic radiation therapy for rectal, prostate, bladder, or cervical cancer

Variable	Risk
Female gender	2–4×
Anal intercourse	RR = 1.8–2.4; OR = 6.9
HIV-positive	RR = 3.2
Abnormal cervical cytology	RR = 1.8–4.13
Smoking	RR = 7.7
Anal condyloma	SIR = 8.5
High-risk HPV	Detected in 95% of HSILs and 88% of invasive squamous cell carcinomas

Role of CD4 count

Risk factors for anal cancer in the multivariable model.

Variable		N	Adjusted IRR	p-value
Age (time updated), years	<30	4171	Reference	
	30-44	10188	5.08 (1.03, 91.86)	0.116
	45-59	6836	21.59 (4.74, 382.30)	0.002
	>=60	1736	27.55 (5.67, 496.39)	0.001
Transmission group	Women	4603	Reference	
	MSM	10561	3.48 (1.99, 6.40)	<0.001
	Non-MSM men	7767	0.56 (0.29, 1.09)	0.081
Nadir CD4+ cell count	>350	6533	Reference	
	200-350	6723	3.78 (1.74, 159.76)	0.037
	<200	9675	9.05 (6.35, 515.15)	<0.001
Calendar period of HIV diagnosis	>=2015	4445	Reference	
	2009-2014	5612	2.90 (0.75, 19.04)	0.173
	2004-2008	4964	4.28 (1.20, 27.20)	0.054
	1998-2003	5323	3.00 (0.81, 19.39)	0.151
	<1998	2587	32.99 (10.04, 203.52)	<0.001

aHSIL and Nadir CD4s Below 200 Boost Invasive Anal Cancer Risk

107 AC events among 14,238 PWH

Only cytological aHSIL and nadir CD4≤ 200 predicted risk of IAC

Hazard Ratio (HR) using Inverse Probability Weighted (IPW) Cox Models for Incident IAC

Cytology/CD4	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
aHSIL (baseline)	3.86 (1.79–8.34)*	
aHSIL (time-updated)	5.08 (2.43–10.61)*	4.54 (2.19–9.43)*
Nadir CD4 ≤ 200	3.32 (1.48–7.45)**	2.99 (1.35–6.62)**

*P < 0.001, ** P < 0.0001

Having aHSIL cytology & nadir CD4 ≤ 200 increased IAC risk 13-fold

IPW Cox Models for Anal Cancer: Joint Effects of Initial and Time-updated cytological aHSIL and CD4 Nadir

Covariate	Baseline HSIL ^a HR (95% CI)	P	Time-updated HSIL ^a HR (95% CI)	P
Never cytology aHSIL, Nadir CD4 >200	1.00		1.00	
Cytology aHSIL, Nadir CD4 >200	1.83 (0.38–8.93)	0.45	2.35 (0.48–11.54)	0.29
Never cytology HSIL, Nadir CD4 ≤200	2.54 (0.99–6.51)	0.05	2.38 (0.92–6.18)	0.07
Cytology aHSIL, Nadir CD4 ≤200	9.05 (3.23–25.40)	0.00	13.03 (4.78–35.38)	0.00

^aEstimates of RERI, the attributable proportion due to interaction, and the synergy index from both joint effect models met criteria for super-additive interaction

Cachay E et al., CROI 2024.

Martin-Iguacel et al., CROI 2024.

Role of HIV

A 12-year retrospective evaluation of anal pre-cancerous lesions and cancer in people living with HIV-1 infection in the Southeastern U.S

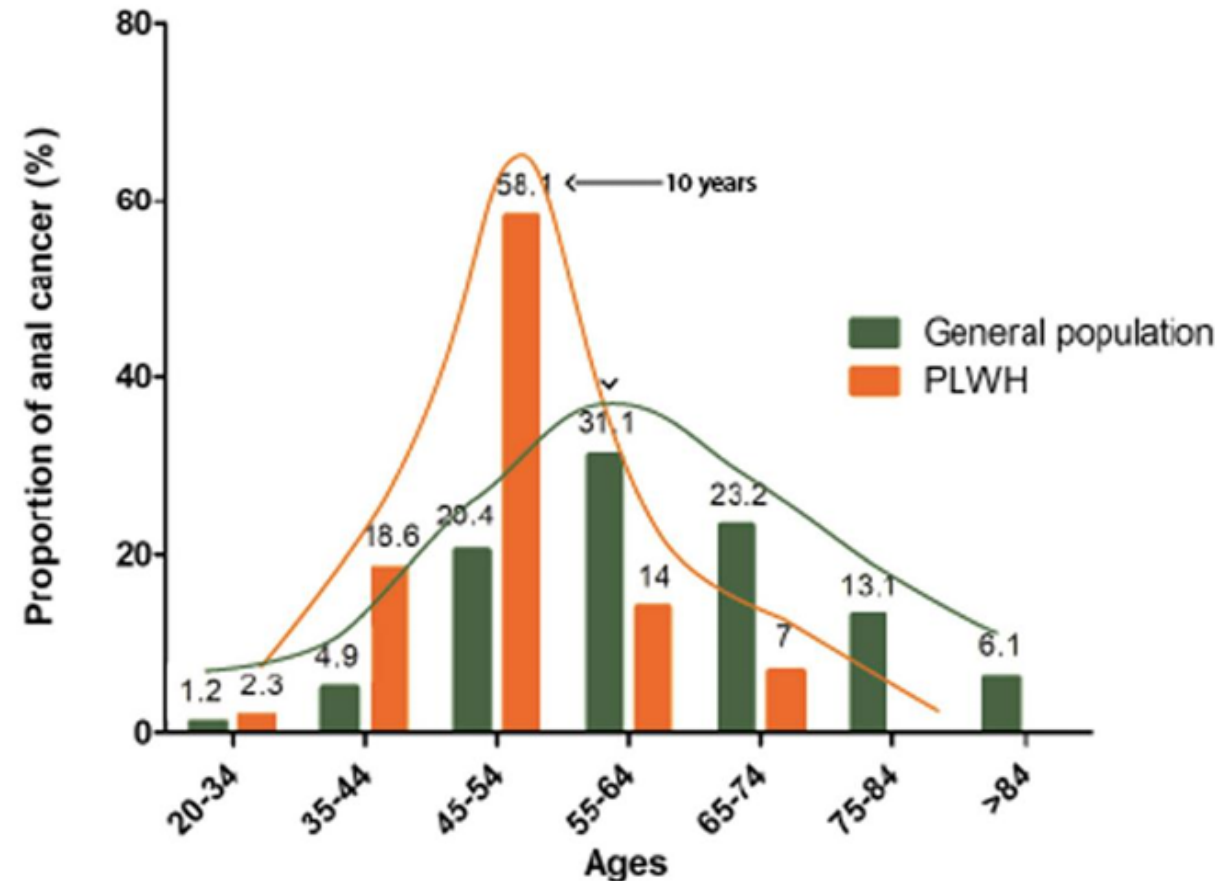


Fig. 1 Ages at anal cancer diagnosis among PLWH compared to the general US population from the SEER. Percentage of each age group is given

Role of STI

The Journal of Infectious Diseases

Risk Factors for Anal HPV Infection and Anal Precancer in HIV-Infected Men Who Have Sex With Men

Lauren M. Schwartz,¹ Philip E. Castle,² Stephen Follansbee,³ Sylvia Borgonovo,³ Barbara Fetterman,⁴ Diane Tokugawa,⁴ Thomas S. Lorey,⁴ Vikrant V. Sahasrabudhe,¹ Patricia Luhn,¹ Julia C. Gage,¹ Teresa M. Darragh,⁵ and Nicolas Wentzensen¹

Lu et al. *BMC Infectious Diseases* (2024) 24:229
<https://doi.org/10.1186/s12879-024-09094-6>

BMC Infectious Diseases

RESEARCH

Open Access

Chlamydia trachomatis enhances HPV persistence through immune modulation

Yingying Lu^{1*}, Qi Wu², Li Wang² and Lingting Ji²



Microbial Pathogenesis

Volume 175, February 2023, 105971



The association of *Chlamydia trachomatis* and human papillomavirus co-infection with abnormal cervical cytology among women in south of Morocco

Laila Ferrera^a , Hanane Rogua^a, Nezha El Mansouri^a, Farid Kassidi^a, Mohamed Aksim^b, Abdallah El Farouqi^c, Said Chouham^a, Mohamed Nejmeddine^a



Chlamydia trachomatis and Human Papillomavirus Infection in Women From Southern Hunan Province in China: A Large Observational Study

Hongliang Chen^{1,2}, Lipai Luo^{2,4}, Yating Wen¹, Bei He¹, Hua Ling^{2,4}, Jinwei Shui⁵, Ping He², Xiaoli Hou², Shixing Tang^{2,5*} and Zhongyu Li^{1*}

Prevalence and Risk Factors of Anal HPV Infection in MSM Living With HIV: Identifying the Target Groups to Prioritize for Immunization

Bruzzesi, Elena MD^a; Galli, Laura MSc^b; Poli, Andrea MSc^b; Bossolasco, Simona MD^b; Cernuschi, Massimo MD^b; Spagnuolo, Vincenzo MD^{a,b}; Tamburini, Andrea Marco MD^c; Canetti, Diana MD^b; Messina, Emanuela MD^b; Gianotti, Nicola MD^b; Raccagni, Angelo Roberto MD^a; Castagna, Antonella MD^{a,b}; Nozza, Silvia MD^b

[Author Information](#)

JAIDS Journal of Acquired Immune Deficiency Syndromes 91(2):p 226-231, October 1, 2022. | DOI:

International Anal Neoplasia Society's consensus guidelines for anal cancer screening

Population—Risk category	When	Anal cancer incidence ^{2,5} per 100,000 person-years
Risk Category A (incidence $\geq$ 10-fold compared to the general population)		
MSM and TW with HIV	Age 35	>70/100,000 age 30–44 >100/100,000 age 45+
Women with HIV	Age 45	>25/100,000 age 45+
MSW with HIV	Age 45	>40/100,000 age 45+
MSM and TW not with HIV	Age 45	>18/100,000 age 45–59 >34/100,000 age 60+
History of vulvar HSIL or cancer	Within 1 year of diagnosis	>40/100,000
Solid organ transplant recipient	10 years post-transplant	>25/100,000

Cytology/hrHPV co-testing

TEST RESULTS	MANAGEMENT
NILM/hrHPV negative	Repeat screening 12–24 months
ASC-US/hrHPV negative	Repeat screening 12 months
NILM/hrHPV positive (non HPV16)	Repeat screening 12 months/HRA
LSIL/hrHPV negative	Repeat screening 12 months/HRA
ASC-US or LSIL/ hrHPV positive	HRA
HSIL, ASC-H (regardless of HPV)	HRA
HPV16 POS (regardless of cytology)	HRA

NILM: negative for intraepithelial lesion or malignancy.

ASC-US: atypical squamous cells of undetermined significance.

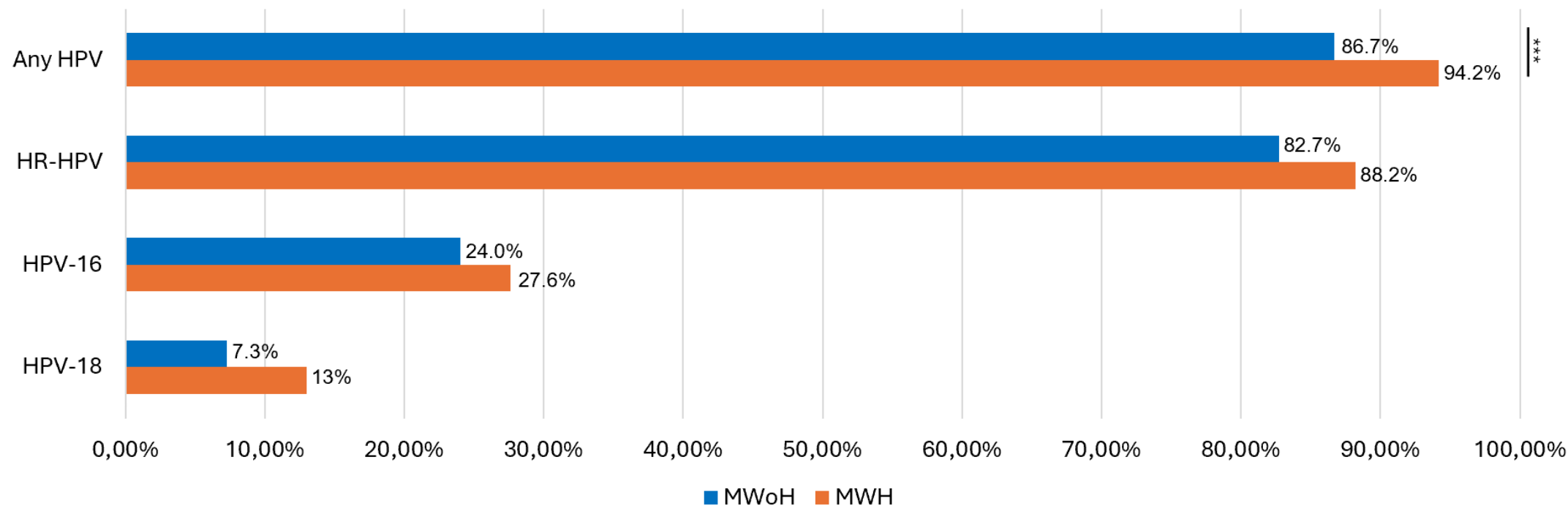
LSIL: low grade squamous intraepithelial lesion.

HSIL: high grade squamous intraepithelial lesion.

ASC-H: atypical squamous cells cannot exclude high grade.

PREVALENCE OF HPV GENOTYPES

Among **1577** people, **1427** (90%) were MWH and **150** (10%) MWoH

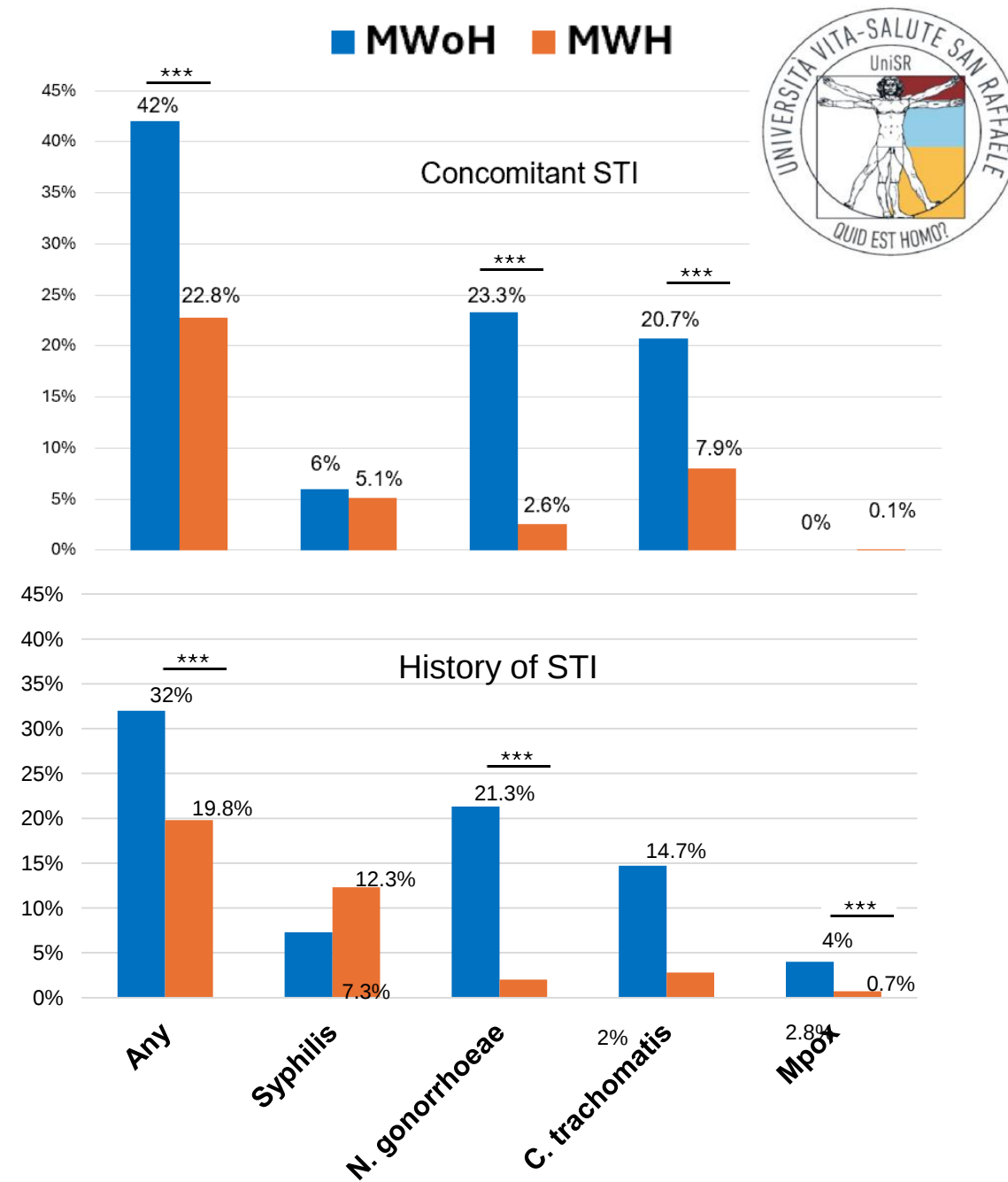


* indicates significance at $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p \leq 0.001$

Bruzzesi E et al., submitted

ASSESSMENT OF RISK FACTORS

	TOT	MWoH	MWH	P.overall
	N = 1577	N = 150	N = 1427	
Age	43.8 [35.2;52.1]	39.7 [33.3;47.8]	44.5 [35.5;52.4]	<0.001
Vaccination status with Gardasil-9	432 (27.4%)	39 (26.0%)	393 (27.5%)	0.759
Smokers	512 (43.3%)	9 (26.5%)	503 (43.8%)	0.058
History of HBV	71 (5.5%)	0 (0.00%)	71 (5.7%)	0.171
History of HCV	132 (8.8%)	2 (1.83%)	130 (9.3%)	0.013
HIV-RNA below 40 cp/mL	-	-	1158 (89.8%)	
Nadir CD4+	-	-	355 [231;543]	
CD4+ (cells/microL)	-	-	737 [554;940]	



DISCUSSION

- Global incidence of STI: is the 2030 target reliable?
- Asymptomatic infections in MSM: is time to stop screening?
- DOXYPEP works, but local guidelines are needed.
- HPV testing and anal cancer screening: is it our job (again) ?