PrEP IST : Quelle position?

Alain Makinson

Réunion commission CeGIDD

Commande de ENIPSE

- Questions de personnes qui appellent : quelle position vis-à-vis de la PEP doxycycline

Doxycycline –données pharmacologiques et bactériologiques

- Tétracycline de deuxième génération
- Bactériostatique, inhibition de la protéine ribosomale
- Spectre bactérien :
  - Pathogènes intracellulaires, certains germes aérobies positifs et gram négatifs
  - Pour les IST contre *Chlamydia trachomatis*, *Treponema pallidum*, *Neisseria gonorhoeae* et *Mycoplasma genitalium*

(1) unari SM,. J Chromatogr B 2013; 939: 17–22; (2)

Doxycycline- données pharmacologiques

- Biodisponibilité per os : 95% et non affecté par la prise alimentaire, lait
- Demi-vie de 20H permettant une pise QD ou bid
- Fort excrétion hépatique, rénale (30-40%) et gastro-intestinale
- Diffusion dans le SNC, et 4 h après administration C de 0,6 mg/L (CMI Treponma pallidum de 0,2 mg/L) et après 7 doses de doxycycline (200 mg pour 21 jours), 5,8 mg/L n moyenne, 1,3 mg/L dans le LCR, ration plasma/CSF de 26%
- C de doxycycline dans liquide séminal : 0.89+- 0.07 mg/L et 0.45+-0.26 mg/L 6 h et 12 h après administration 1 dose 100 mg (1)
- Peu de données sur les C rectales (2) : étude randomisée en double aveugle d'un dose de 200 mg en prophylaxie dans la chirugie du colon objectivait une C > CMI du Chlamydia en post-dose
- Pas de modification de la demi-vie ni de la clairance en cas d'insuffisance rénale (ratio protéine liée ou non), ni cumul

Interactions médicamenteuses

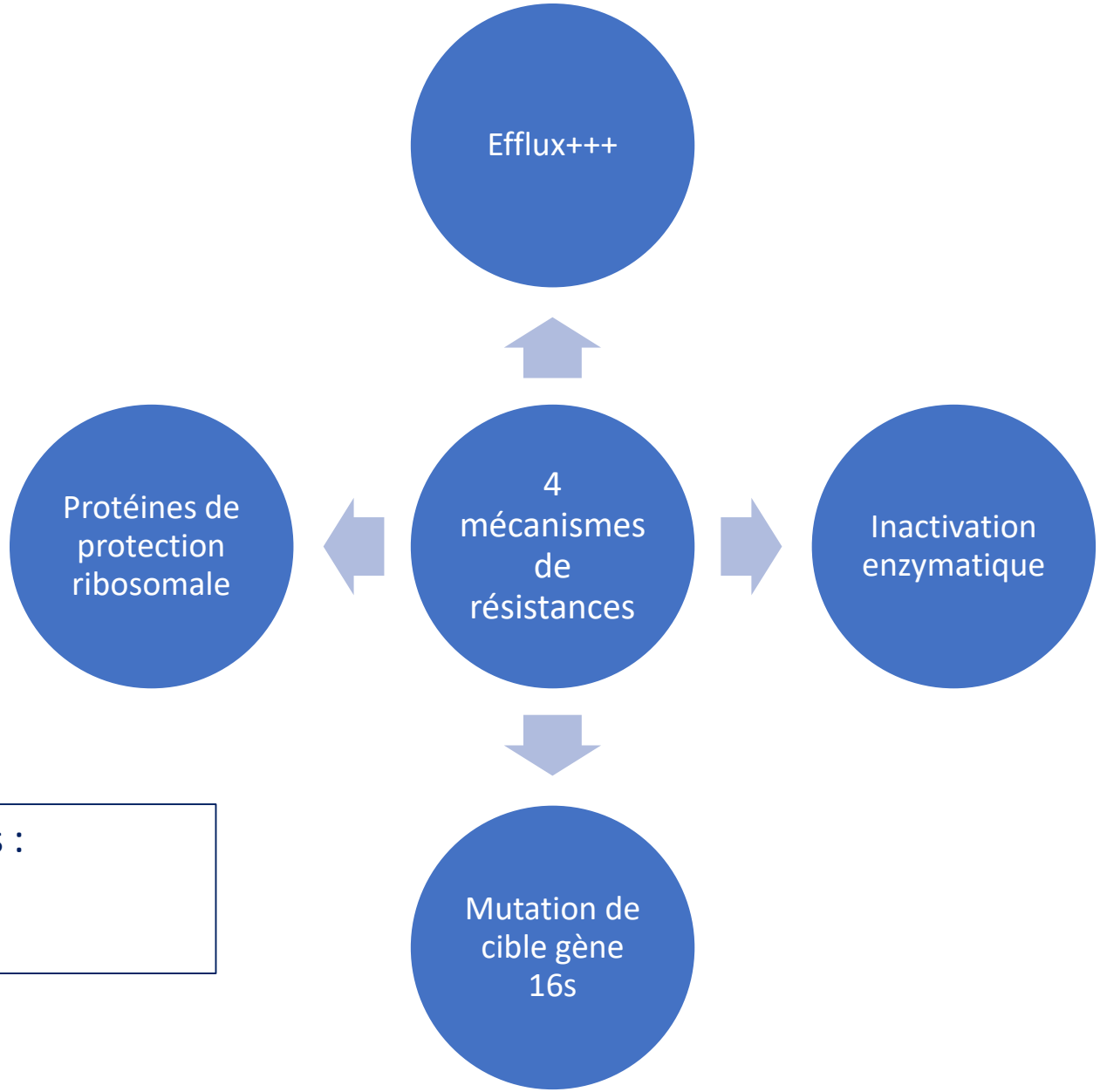
- Diminution de l'absorption par le sulfate de fer, bismuth, et anti-acides avc aluminium, calcium et magnésium (doxyxycline à donner 2h avant ou 3 h après supplémentation en ions)
- Diminution du TP (attention aux anticoagulants)
- Induction enzymatique possible par inducteurs enzymatiques
- Demi-vie diminuée par prise d'alcool au long cours
- Contre-indication femme enceinte après 5^{ieme} semaine de grossesse, même si par rapport à la tétracycline, données plutôt rassurantes

Effets indésirables chez l'adulte

- Œsophagite (55%) et photosensibilité (36%) dans une revue systématique
- Etudes clinique :
  - effets gastro-intestinaux (0,54% des effets indésirables de 1653 patients avec la doxycycline 100-200 mg/jr 4-20 jrs à 51% chez 120 patients pour 10-20 jrs pour une maladie de Lyme précoce)
  - Rash cutané 0,42% (1653 patients) à 30,5% (6 mois de traitement pour un anévrysmes mycotique)
    - érythrodermie, photosensibilité et rash (6-42%)
- réactions allergiques : urticaire, rash, prurit, angiodeme, réaction anaphylactique, purpura rhumatoïde, péricardite, lupus
- Hypertension intracrânienne (surtout tetracycline) : rare cependant

Smith K, Clin Ther 2005; 27: 1329–42.

Mécanismes de résistance à la doxycycline



Transmission horizontale des mutations :
plasmides, transposons ou insertions
Pas de procédure standardisée

Des spectres thérapeutiques à préserver

- Alternative en cas d'allergie ou de CI à la penicilline et contre-indication à la désensibilisation pour la syphilis
- Des résistances sont décrites contre doxycycline avec *C. trachomatis*
- Prévalence de résistance du gonocoque aux tetracyclines entre 12-100%, souvent co-résistance

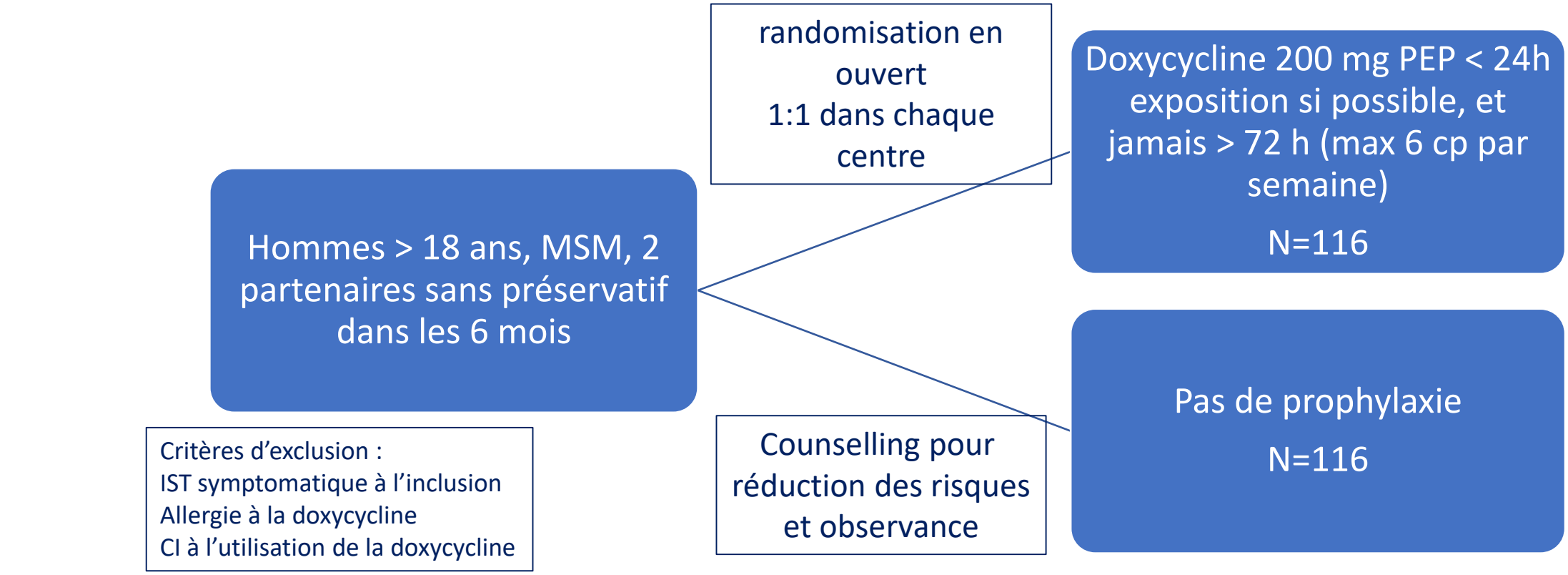
Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial

*Jean-Michel Molina, Isabelle Charreau, Christian Chidiac, Gilles Pialoux, Eric Cua, Constance Delaugerre, Catherine Capitant, Daniela Rojas-Castro, Julien Fonsart, Béatrice Bercot, Cécile Bébéar, Laurent Cotte, Olivier Robineau, François Raffi, Pierre Charbonneau, Alexandre Aslan, Julie Chas, Laurence Niedbalski, Bruno Spire, Luis Sagaon-Teyssier, Diane Carette, Soizic Le Mestre, Veronique Doré, Laurence Meyer, for the ANRS IPERGAY Study Group**

Etude ancillaire PreP en continue ou à la demande ANRS IPERGAY

Lancet Infect Dis 2017

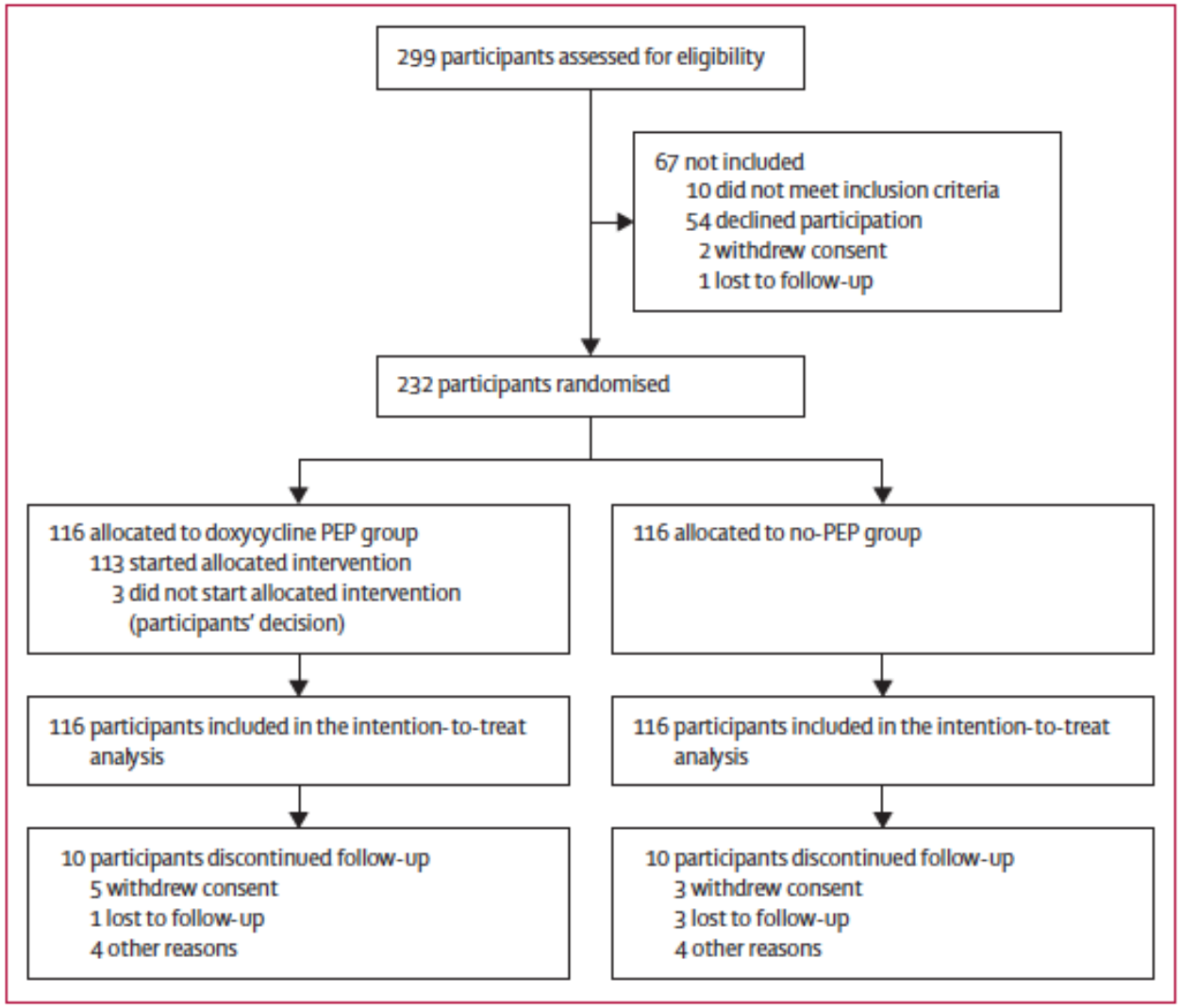
Méthodologie



Suivi médian de 8,7 mois IQ 7,8-9,7)
Suivi des IST : à J0 puis tous les 2 mois (sérologie syphilis, PCR Chlamydia, gonocoque anal, gorge, 1er jet urinaire)

Endpoint :
IST (gonorrhée, chlamydia ou syphilis) (ITT)

Flow shart et adhésion au suivi



	Doxycycline PEP	No PEP
2 months	111/116 (96%)	107/114 (94%)
4 months	112/116 (97%)	109/114 (96%)
6 months	106/114 (93%)	105/111 (95%)
8 months	99/101 (98%)	91/97 (94%)
10 months	45/46 (98%)	42/42 (100%)

PEP=post-exposure prophylaxis.

Table 1: **Bi-monthly visit attendance in both groups**

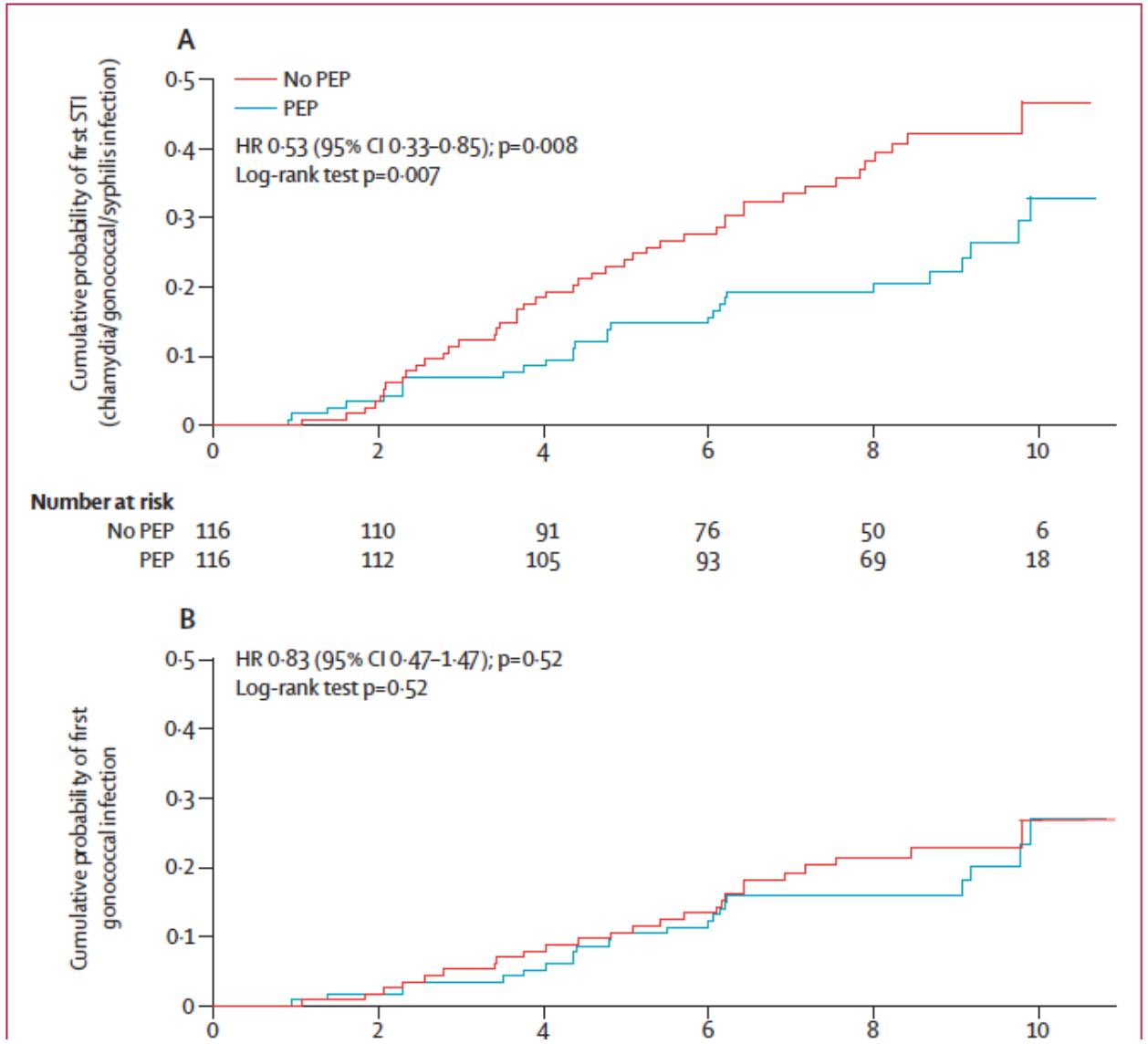
Caractéristiques des patients

	PEP* (n=116)	No PEP (n=116)
Age		
Median age (years)	38 (33–48)	39 (32–44)
18–24	0 (0%)	5 (4%)
25–29	12 (10%)	11 (10%)
30–39	47 (41%)	41 (35%)
40–49	31 (27%)	44 (38%)
>49	26 (22%)	15 (13%)
Ethnic origin		
White	110 (95%)	110 (95%)
Other	6 (5%)	6 (5%)
Employed	102 (88%)	98 (84%)
Not in a relationship	82 (71%)	81 (70%)
Post-secondary education	109 (94%)	103 (89%)
Use of recreational drugs†	49 (42%)	49 (42%)
Site of enrolment		
Paris, France	64 (55%)	72 (62%)
Lyon, France	25 (22%)	21 (18%)
Nice, France	9 (8%)	13 (11%)
Tourcoing, France	6 (5%)	8 (7%)
Nantes, France	12 (10%)	2 (2%)
Sexual risk factors at screening		
Number of partners in past 2 months	10 (5–15)	10 (5–20)
Number of sexual intercourse acts in past 4 weeks	10 (5–15)	10 (4–20)
Number circumcised (%)	28 (24%)	21 (18%)
STIs diagnosed at screening ‡	22 (19%)	16 (14%)

Data are n (%) and median (IQR). PEP=post-exposure prophylaxis. *PEP with doxycycline. †Recreational drugs in past 12 months included ecstasy, crack, cocaine, crystal meth (methamphetamine), speed (amphetamine), gamma butyrolactone (GHB), and gamma hydroxybutyrate (GBL). ‡Sexually transmitted infection (STI) screening included serological testing for syphilis by means of rapid plasma reagin confirmed with the use of a treponema-specific assay. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were detected by PCR on urine samples and throat and anal swabs.

Table 2: **Baseline characteristics of the study participants according to study group**

Résultats

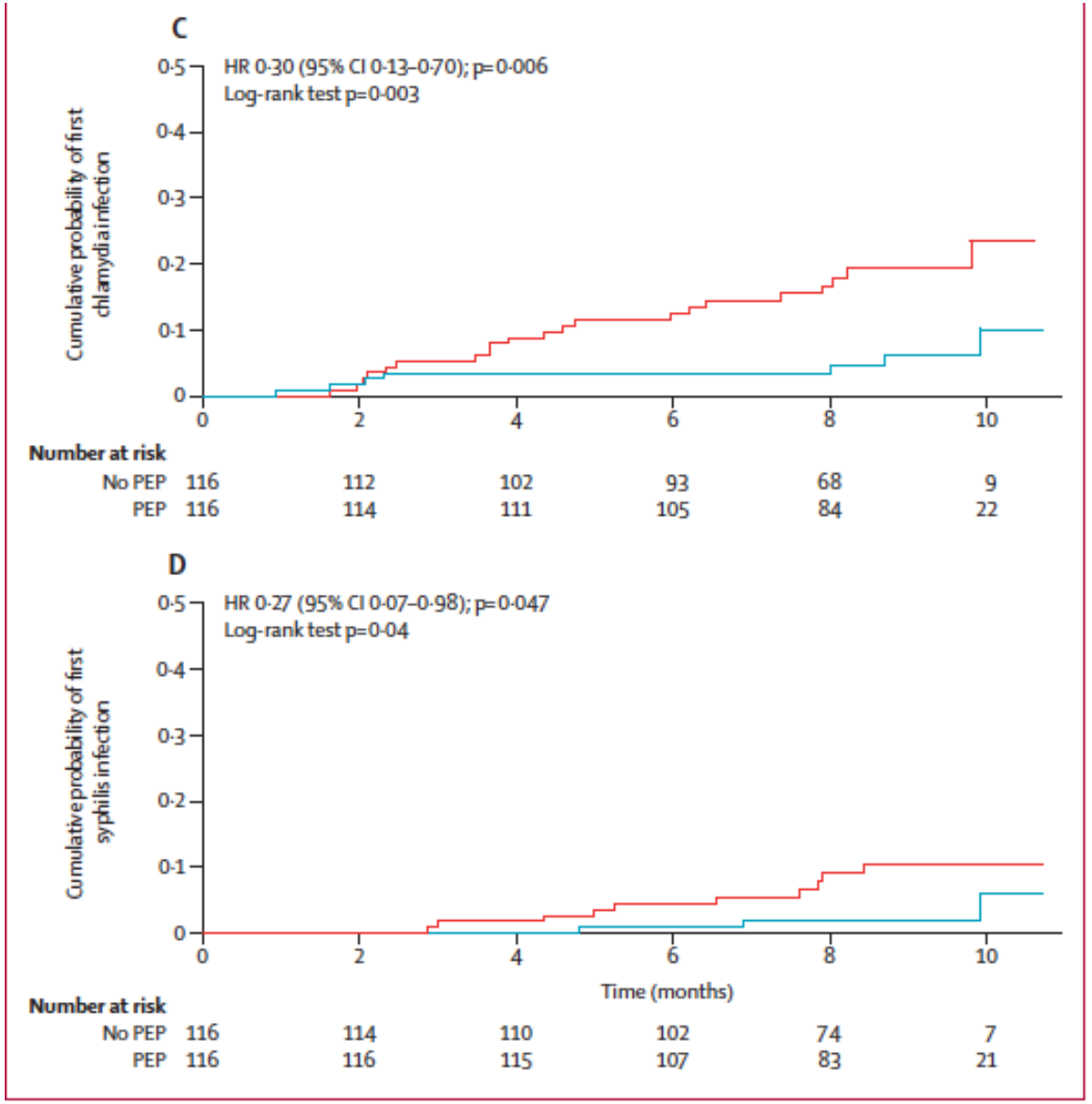


9/28 culture gonocoque positive (8 sujets)

- Résistance à la tétracycline dans 4
- Intermédiaire dans 3 sujets

Résultats

Chlamydia 5/22 prélèvements pas de résistance
83% des prises de doxycycline < 24h
29 (26%) ont arrêté la PEP en cours de suivi



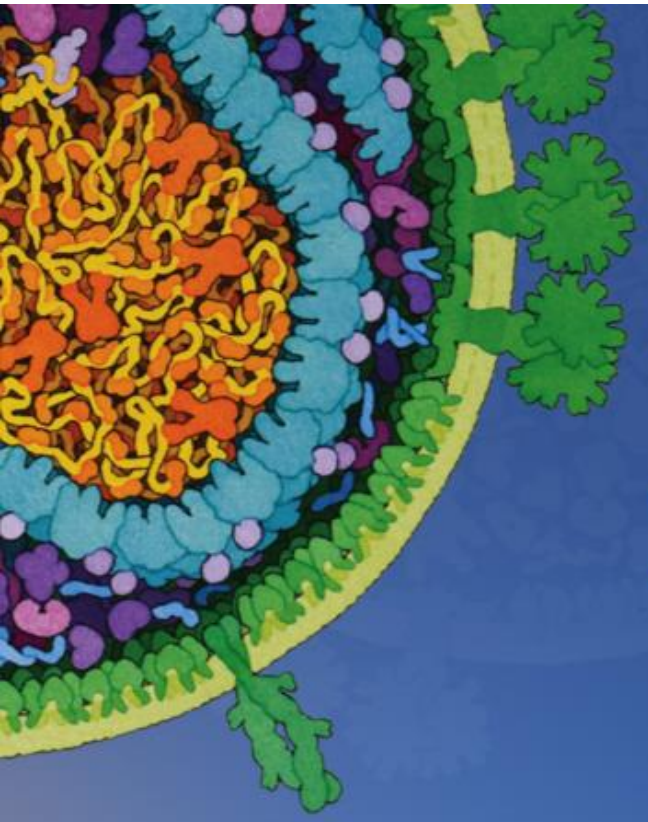
Effets indésirables

	PEP (n=116)	No PEP (n=116)	p value
Any adverse events	106 (91%)	104 (90%)	0·65
Any serious adverse events	5 (4%)	10 (9%)	0·18
Any grade 3 or 4 events	4 (3%)	8 (9%)	0·24
Treatment discontinuation because of adverse events	8 (7%)	NA	..
Gastrointestinal adverse events	62 (53%)	47 (41%)	0·05
Drug-related gastrointestinal adverse events	29 (25%)	16 (14%)	0·03
Nausea or vomiting	10 (9%)	3 (3%)	..
Abdominal pain	14 (12%)	5 (4%)	..
Diarrhoea	6 (5%)	9 (8%)	..
Other gastrointestinal disorders	5 (4%)	1 (1%)	..
Confirmed laboratory events			
Elevated plasma creatinine			
All grades	15 (13%)	15 (13%)	1·00
Grade 2	3 (3%)	0 (0%)	..
Proteinuria grade 2 or worse	4 (3%)	5 (4%)	0·73
Glycosuria grade 2 or worse	1 (<1%)	1 (<1%)	1·00
Elevated ALT concentrations			
All grades	14 (12%)	20 (17%)	0·27
Grade 4	1 (<1%)	2 (2%)	1·00

Data are n (%). Only the first occurrence of adverse events per patient was reported. ALT=alanine aminotransferase. PEP=post-exposure prophylaxis (with doxycycline).

Table 3: **Adverse events according to study group**

SCIENCE SPOTLIGHT



Daily Doxycycline in MSM on PrEP for Prevention of Sexually Transmitted Infections

The DuDHS Study

Troy Grennan, MD MSc FRCPC

British Columbia Centre for Disease Control and the University of British Columbia
Vancouver, BC, Canada

Disclosure: This study was partially supported by funds given directly to the Principal Investigator's institution (UBC).

CROI 2021

METHODS

- Randomized, controlled pilot trial (n=52)
  - HIV-neg MSM or transgender women (TW) with prior syphilis

- Participants randomized 1:1 to 48 weeks of HIV PrEP with tenofovir/emtricitabine (TDF/FTC) in one of the following arms:
  1. Immediate doxycycline (IMM): doxycycline 100mg daily x 48w
  2. Deferred doxycycline (DEF): doxycycline 100mg daily starting at w24

- Followed every 3 months:
  - STI and HIV screening; tolerability and acceptability; tetracycline resistance (nares for *S. aureus* culture via disc diffusion); adherence (pill counts, doxycycline drug levels); questionnaires on sexual behaviour; rectal microbiome.

- 52 participants recruited: 51 MSM, 1 TW; median age 34 (IQR 29-43)
- No participants on doxycycline developed syphilis or chlamydia
  - Receipt of doxycycline associated with *reduced likelihood of any STI*
    - Odds ratio 0.18 (95% CI: 0.05-0.68; p=0.011)
  - Chlamydia: 10 cases in DEF (81.83 per 100PY) vs. none in IMM in first 24w (p=0.001). Nil thereafter.
  - Syphilis: 1 case in DEF (8.16 per 100PY) vs. none in IMM in first 24w (p=0.98). Nil thereafter.
  - Gonorrhea: 8 cases in DEF (57.14 per 100PY) vs. 4 cases in IMM (31.37 per 100PY) in first 24w (p=0.505). 1 case in IMM post-24w.
- Tetracycline resistance in *S. aureus* in 1/3 and 3/6 samples at w24 and w48, respectively, in IMM arm; 1/2 in DEF arm at w48.
- Self-reported adherence (≥95%): 89.5% and 72.2% in IMM and DEF arm, respectively, at 48w.

L’impact de l’antibiothérapie ne peut que se mesurer à long terme

- NG a développé des mécanismes de résistances contre tous les antibiotiques qui étaient recommandés de manière empirique
  - spectinomicine, pénicillines, tétracyclines, fluoroquinolones, macrolides ainsi que plus récemment les C3G.
  - En 2015, résistance à la tétracycline et à la ciprofloxacine était respectivement de 45 et 40 %.

Impact clinique de l'utilisation de la doxycycline sur la flore digestive

Heimdahl & Nord (1983)[56]	Sweden	Trial	N=10	Not specified	Healthy volunteers	Doxycycline 100 mg daily for 7 days	Faecal culture on selective media	Effect of doxycycline on the normal human flora and on colonisation of the oral cavity and colon	No change in abundance of *Bacteroides* spp, *Bifidobacterium* spp, *Clostridium* spp, *Eubacterium* spp, *Lactobacillus* spp or *Veillonella* spp. Fusobacteria were eliminated. A 2–3 log decrease in enterococci, streptococci and enterobacteria. Emergence of new strains *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter cloacae* in some subjects. All colonising microorganisms were resistant to doxycycline. Normalisation of aerobic bacterial abundance 9 days after antibiotic treatment.
Walker *et al* (2005)[57]	USA	RCT	N=69 adult; 55 analysed	Clinic	Periodontitis	20 mg doxycycline	Faecal samples plated on a number of selective agar and incubated for CFU counts	To determine if a 9-month regimen of suboptimal doxycycline had an effect on either the intestinal or the vaginal microflora	The only statistically significant differences between the two treatment groups occurred in the doxycycline-resistant counts at the baseline sample. No between-treatment differences were detected at 3-month or 9-month period either in the predominant bacterial taxa or in antibiotic susceptibilities

Impact clinique de l'utilisation de la doxycycline sur la flore digestive

Study ID	Country	Design	Population	Setting	Infection	Antibiotic of interest (and dosage)	Sample and analysis
Rashid *et al* (2013)[59]	Sweden	Double-blind, randomised, placebo-controlled, parallel group study	N=34, 17 treated, 17 controls	Clinical trial unit	Healthy volunteers	Doxycycline 40mg capsules orally once daily	Culture on selective media aerobic and anaerobic
Matto *et al* (2008)[58]	Finland	Not specified	N=19; 10 controls	Not specified	Not specified	Doxycycline 150mg daily for 10 days with probiotic	Faecal 16S rRNA PCR for *Bifidobacterium* sp and DGGE and culturing and sequencing

	Primary objective of this study was to assess the impact of antimicrobial treatment on the oropharyngeal and intestinal microflora during and after administration of 40mg doxycycline capsule given once daily to healthy volunteers	Doxycycline was detectable in stool up to 16 weeks. No changes in abundance (>2 log CFU/g) of *Bacteroides* spp, *Bifidobacterium* spp, *Clostridium* spp, *Candida* spp, *Lactobacillus* spp or Enterobacteriaceae anaerobic intestinal microflora. No new colonisation with *C. difficile*. At week 20, the anaerobic microflora was normal. In aerobic intestinal microflora, there were changes (2 log CFU/g) in the numbers of enterococci and *E. coli* during the 16-week treatment. Other microorganisms such as other enterobacteria, *Candida* spp and other microorganisms were not affected. The aerobic microflora was normal at week 20. Increase in doxycycline resistance in *Bifidobacterium* spp, anaerobic cocci and Gram-positive rods.
To evaluate the influence of doxycycline therapy on the composition and antibiotic susceptibility of intestinal bifidobacteria	*Bifidobacterium* diversity was markedly higher in the control group than antibiotic group; each subject had 2–3 genotypes in the control group; 0–3 in the antibiotic group. The isolated bifidobacteria represented *B. adolescentis*/ *B. ruminantium*, *B. longum*, *B. catenulatum*/ *B. pseudocatenulatum*, *B. bifidum* and *B. dentium*. Tetracycline-resistant *Bifidobacterium* isolates were more commonly detected in the antibiotic group than in the control group, thus increasing the pool of resistant commensal bacteria in the intestine.	

Place au débat