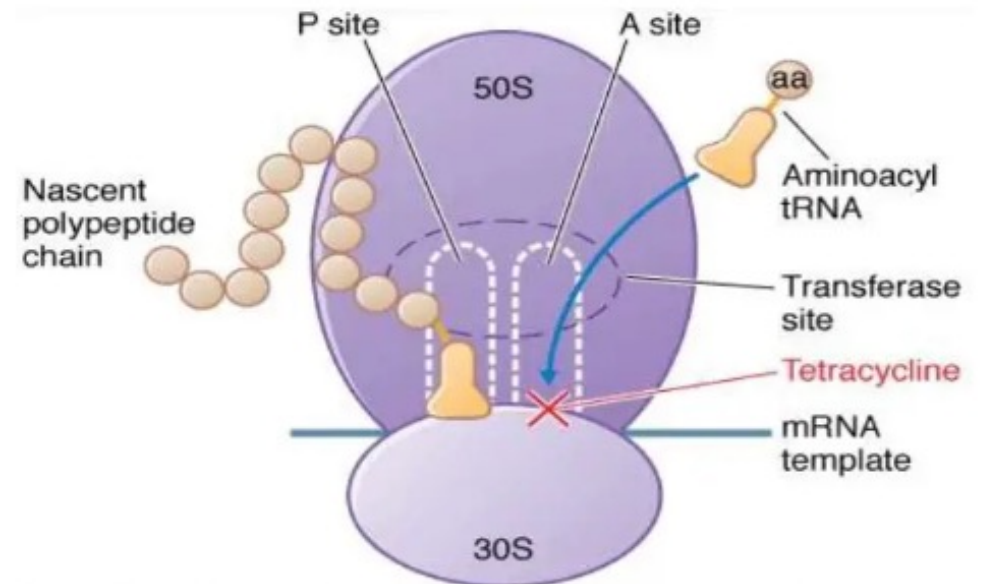
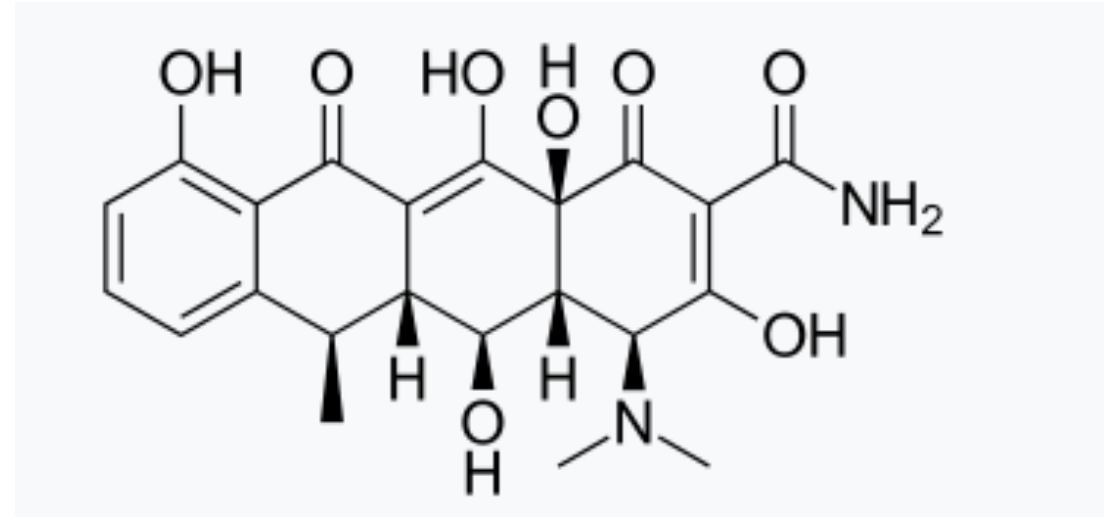


# Doxy PEP Pro - Con debate

BREACH 30-11-2023

# An 'ode' to doxycyclin

- ▶ First tetracycline reported in 1948, natural products from actinomycetes
- ▶ Doxy: commercialised in 1967
- ▶ Broad spectrum, bacteriostatic
- ▶ Binding 30S ribosomal subunit → prevents binding new amino acids → interfere with peptide growth
- ▶ Anti-inflammatory effect
  - ▶ Acne
  - ▶ Rosacea
- ▶ Not in children <8 or pregnant women
- ▶ WHO List of essential medicine



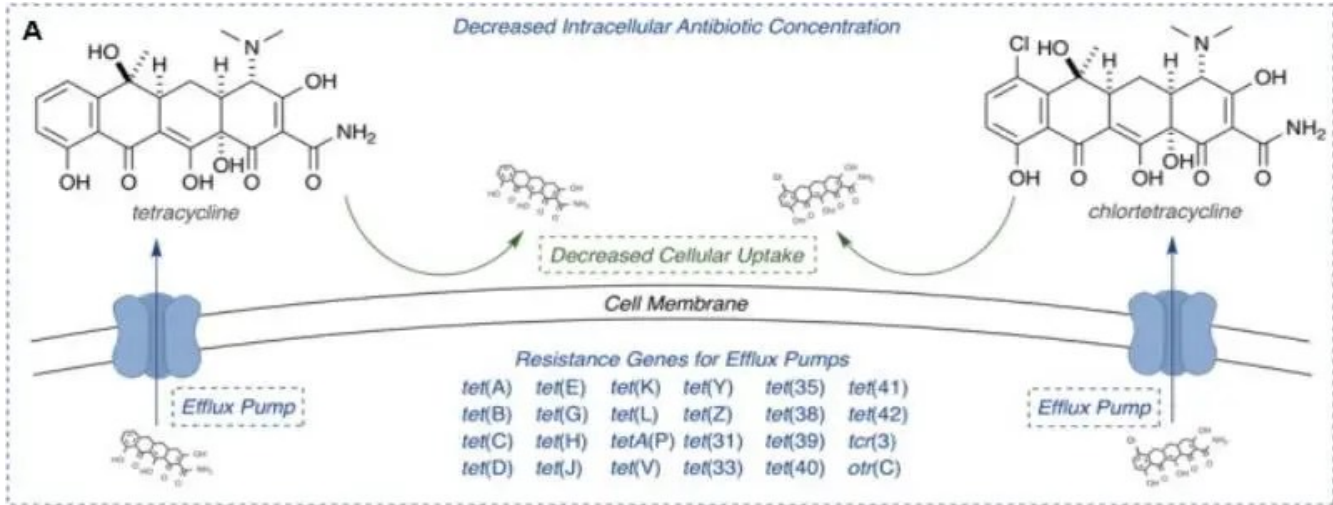
## Coverage doxycycline

Gram (+)	<i>Staphylococci spp</i> ( <i>S aureus</i> , including <i>MRSA</i> en <i>CNS</i> ) <i>Streptococci spp</i>
Gram (+) bacilli	<i>Bacillus anthracis</i>
Gram (-)	<i>Brucella species</i> <i>Vibrio cholerae</i> <i>Yersinia pestis</i> <i>Bartonella spp</i> <i>Coxiella burnetii</i> <i>Francisella tularensis</i> <i>Neisseria spp</i> <i>Chlamydia spp</i> <i>Legionella</i> <i>Mycoplasma</i>
Anaerobic	<i>Clostridium perfringens</i> <i>Clostridium tetani</i>
Spirochetes	<i>Borrelia burgdorferi</i> <i>Leptospira interrogans</i> <i>Treponema pallidum</i> <i>Anaplasma</i>
Other	<i>Rickettsia spp</i> <i>Ehrlichia</i> <i>Actinomyces</i> <i>Malaria</i>

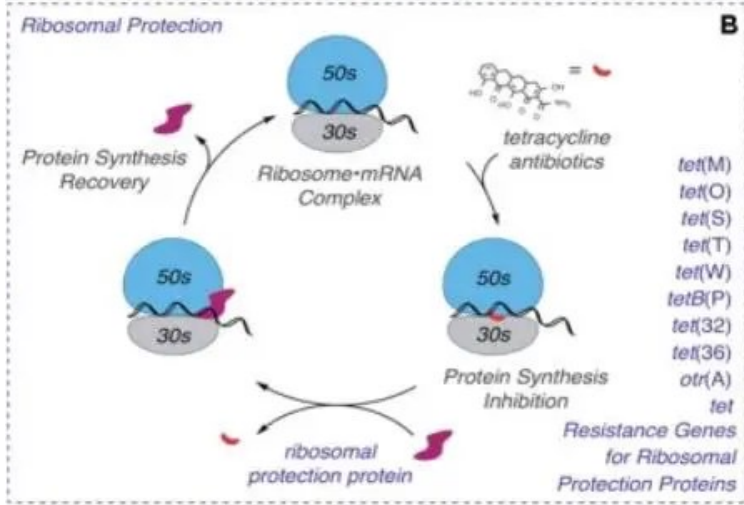
# Possible side effects

- ▶ Headache
  - ▶ Gastro-intestinal disturbances
  - ▶ Fotosensitivity
  - ▶ Esofageal ulcera (intake upright position and not before sleeping)
  - ▶ Black coloration of tongue
- 
- ▶ Gastric/intestinal perforation

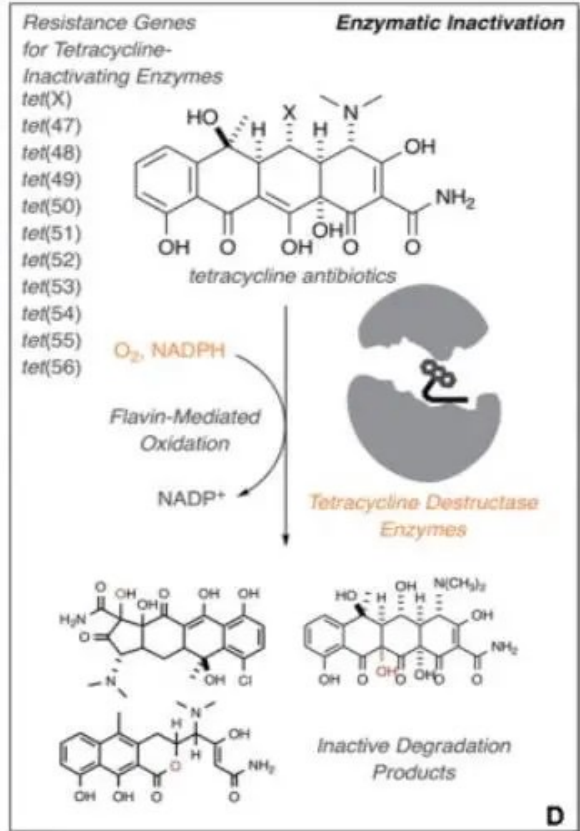
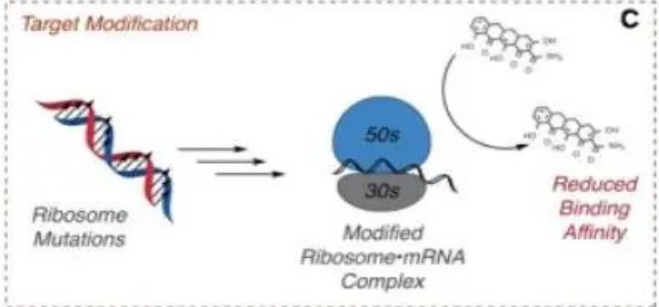
**EFFLUX**



**Ribosome protection**



**Ribosome modification**



**Enzymatic inactivation**

# Mostly asymptomatic infections!

Study	Country	Study details	Study population	Findings							
				Any STI		NG		CT		Syphilis	
				HR <sup>†</sup> or RR <sup>‡</sup>	95% CI	HR <sup>†</sup> or RR <sup>‡</sup>	95% CI	HR <sup>†</sup> or RR <sup>‡</sup>	95% CI	HR <sup>†</sup> or RR <sup>‡</sup>	95% CI
Sub-study of ANRS IPERGAY Molina et al. (2018)	France	<b>Design:</b> Open-label RCT of doxyPEP versus standard of care (1:1) <b>Primary endpoint:</b> occurrence of first STI during 10 months follow-up	232 Men who have condomless sex with men and are using HIV PrEP	0.53 <sup>†</sup>	0.33–0.85	0.83 <sup>†</sup>	0.47–1.47	0.30 <sup>†</sup>	0.13–0.70	0.27 <sup>†</sup>	0.07–0.98
ANRS 174 DOXYVAC Molina et al. (2023)	France	<b>Design:</b> 2 × 2 RCT of doxyPEP vs. standard of care (2:1) and 4CMenB vaccine vs. no vaccine (1:1) <b>Primary endpoint:</b> time to first episode of CT or syphilis and time to first NG episode	502 asymptomatic MSM on HIV PrEP > 6 months, enrolled in ANRS Prevenir, and with bacterial STI in prior 12 months	0.16 <sup>†</sup>	0.08–0.30 <sup>§</sup>	0.49 <sup>†</sup>	0.32–0.76	0.11 <sup>†</sup>	0.04–0.40	0.21 <sup>†</sup>	0.09–0.47
DoxyPEP Luetkemeyer et al. (2023)	US	<b>Design:</b> Open-label RCT of doxyPEP vs. standard of care (2:1) <b>Primary endpoint:</b> incidence of at least one STI per follow-up quarter	432 MSM or TGW taking HIV PrEP who had had an STI <sup>†</sup> in the past year	0.34 <sup>‡</sup>	0.24–0.46	0.45 <sup>‡</sup>	0.32–0.65	0.12 <sup>‡</sup>	0.05–0.25	0.13 <sup>‡</sup>	0.03–0.59
		<b>Design:</b> RCT of doxyPEP vs. standard of care (2:1) <b>Primary endpoint:</b> incidence of at least one STI per follow-up quarter	209 MSM or TGW living with HIV who had had an STI <sup>†</sup> in the past year	0.38 <sup>‡</sup>	0.24–0.60	0.43 <sup>‡</sup>	0.26–0.71	0.26 <sup>‡</sup>	0.12–0.57	0.23 <sup>‡</sup>	0.04–1.29
dPEP Kenya Stewart et al. (2023)	Kenya	<b>Design:</b> RCT of doxyPEP vs. standard of care (1:1) <b>Primary endpoint:</b> any incident STI measured quarterly for one year	449 cisgender women (18–30 years) taking HIV PrEP	0.88 <sup>‡</sup>	0.60–1.29	1.64 <sup>‡</sup>	0.78–3.47	0.73 <sup>‡</sup>	0.47–1.13	-	-

# dPEP Stewart et al (2023)

- ▶ Kenya
- ▶ RCT of doxyPrEP vs SOC (1:1)
- ▶ Primary endpoint: any incident STI measured quarterly for 1 year
- ▶ 449 cisgender women (18-30 years) taking HIV PrEP
  
- ▶ RR
  - ▶ any STI: 0.88 (95% CI 0.60-1.29)
  - ▶ NG: 1.64 (95% CI 0.78-3.47)
  - ▶ CT 0.73 (95% CI 0.47-1.13)
  - ▶ Syf: no data
  
- ▶ **Issue of non-compliance?**

# Doxycycline and antimicrobial resistance (AMR)

- ▶ IPERGAY and DoxyPEP
  - ▶ Gono: median FU 9 months, small sample sizes: no significant increase in doxy R
- ▶ Little evidence of AMR in Chlam/Treponema
  - ▶ Theoretically R through single-point mutations or gene transfer
- ▶ *Mycoplasma genitalium*
  - ▶ Potential to rapid acquirement of tetracyclin R mutations



# Doxycycline and antimicrobial resistance (AMR)

- ▶ 'Bystander' pathogens
  - ▶ Limited number of prospective studies
  - ▶ Suggestion of increased resistance in bacterial flora after 2-18 weeks treatment
  - ▶ Effects may be modest and transient
  
- ▶ <https://www.cdc.gov/std/treatment/doxypep-amr-toe-mmwr.htm>
  - ▶ Studies on doxy use for different indications (Acne, STIs, travelers diarrhea, *S. aureus*) and impact on resistance on different species
  - ▶ Quality of evidence mostly low (mostly low numbers)

N=501

Nasal/  
oropharyngeal  
swabs

Conclusion:

Modest changes in *S. aureus* and *Neisseria spp* doxyR are unlikely to have clinical significance (??)

Surveillance for the impact of TCN-R GC on doxy-PEP efficacy and GC resistance is needed

Standard of care	34	25.0% (2/8)	78	12.5% (2/16)
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[Front Microbiol.](#) 2023; 14: 1208014.

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PMCID: PMC10498386

PMID: [37711686](https://pubmed.ncbi.nlm.nih.gov/37711686/)

## Doxycycline PEP can induce doxycycline resistance in *Klebsiella pneumoniae* in a *Galleria mellonella* model of PEP

[Chris Kenyon](#),<sup>✉1, 2, \*</sup> [Zina Gestels](#),<sup>1</sup> [Thibaut Vanbaelen](#),<sup>1</sup> [Said Abdellati](#),<sup>3</sup> [Dorien Van Den Bossche](#),<sup>3</sup> [Irith De Baetselier](#),<sup>3</sup> [Basil Britto Xavier](#),<sup>1, 4, †</sup> and [Sheeba Santhini Manoharan-Basil](#)<sup>1, †</sup>

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- ▶ Under doxycycline in *G. mellonella* model: increased MIC's *K. pneumoniae* for doxycycline, ceftriaxon and ciprofloxacin unde



# Policies in other countries

- ▶ USA: few criticism on dPEP
  - ▶ Recommendation for dPEP by MSM with recent history of STI
  - ▶ CDC bit cautious
  
- ▶ Australasia
  - ▶ Risk-benefit calculation most favourable for prevention of syphilis so dPEP should be considered primarily (only) to prevent syphilis
  
- ▶ UK: Public Health England and BASHH
  - ▶ Do not endorse the use of dPEP for STI because of potential benefits will be outweighed by the considerable potential for AMR to develop in STI and other bacteria

# Conclusion

- ▶ Personal opinion:
  - ▶ No room for doxy PEP (and PrEP)
  - ▶ In population that is already advised to screen 2 or 4 times a year
  - ▶ With potential increase of doxy resistance in bystanders
  - ▶ Impact on microbiome unknown

# But....

- ▶ Are we already 'too late'?
  - ▶ Large campaigns around doxy PEP/PrEP, also from medical community
  - ▶ USA: very little criticisms
  - ▶ Current viewpoints: if it is available and effective; why not provide it?
  - ▶ 'black' market, people can get doxy without prescription
- ▶ regulation
  - ▶ Only provision for syphilis prophylaxis (since only disease with serious morbidity and possible mortality)



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