



# Endocarditis in PWID

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# Disclosures

- Disclosures- Speaking Fee for
- AVIR Pharma
- Gilead
- ViiV
- Merck

# Cohort study of First Episode

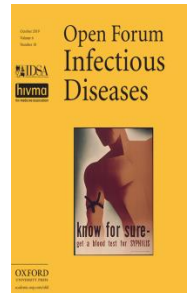
## Endocarditis Patients Roger et al JAMA OPEN 2018

- Chart Review by 2 ID Physicians and only modified Duke criteria Definite Cases included
- Of 370 total first episode cases, 202 were in PWIDs (202/370, 54.6%) (Defined by patient self report).
- Among PWIDs, the median age was 34, gender distribution was equal, and patients were predominantly HCV positive (69.8%, 141/202).

- All cause mortality rate was 33.7% (68/202).
- Adjusting for age and sex, survival analysis demonstrated that referral to addiction treatment associated with lower mortality (HR 0.29, 95% CI 0.12-0.73; p=0.008).
- Higher mortality was associated with left-sided infection (HR 3.26, 95% CI 1.82-5.84, p<0.001) and bilateral involvement (HR 4.51, 95% CI 2.01-10.1; p<0.001).
- models suggest that population-level mortality attributable to IDaIE among PWID approaches 20%, and between 2020 and 2030 approximately 257,800 people are expected to die from IDaIE in the United States (Barocas et al. CID 2020)

# Recurrent IE in PWID

Rodger et al OFID Oct 2019



- 68/212 (32%) PWID had a second episode
- 22/68 (32%) with a third recurrence and 5/22 (23%) with a fourth recurrence.
- Second episode IE was more common in PWID (11/178 [6.2%] vs 68/212 [32.1%];  $p < 0.001$ )

## Microbial Etiology of First and Second Infective Endocarditis Episodes in PWID

		First Episode (n = 212)	Second Episode (n = 68)
Organism	<i>Staphylococcus aureus</i>	165 (77.83)	43 (63.24)
	MSSA	119 (56.13)	28 (41.18)
	MRSA	46 (21.70)	15 (22.06)
	Coagulase-negative staphylococci	1 (0.47)	1 (1.47)
	Non-viridans group streptococci	1 (0.47)	1 (1.47)
	Viridans group streptococci	10 (4.72)	11 (16.18)
	Enterococci	11 (5.19)	3 (4.41)
	<i>Enterobacteriaceae</i>	1 (0.47)	1 (1.47)
	HACEK	0	1 (1.47)
	<i>Pseudomonas</i> or <i>Actinobacter</i>	3 (1.42)	0
	<i>Candida</i>	1 (0.47)	5 (7.35) <b>p=0.004</b>
	Polymicrobial <sup>a</sup>	13 (6.13)	2 (2.94)
	Culture negative <sup>b</sup>	5 (2.36)	0
	Other	1 (0.47)	0

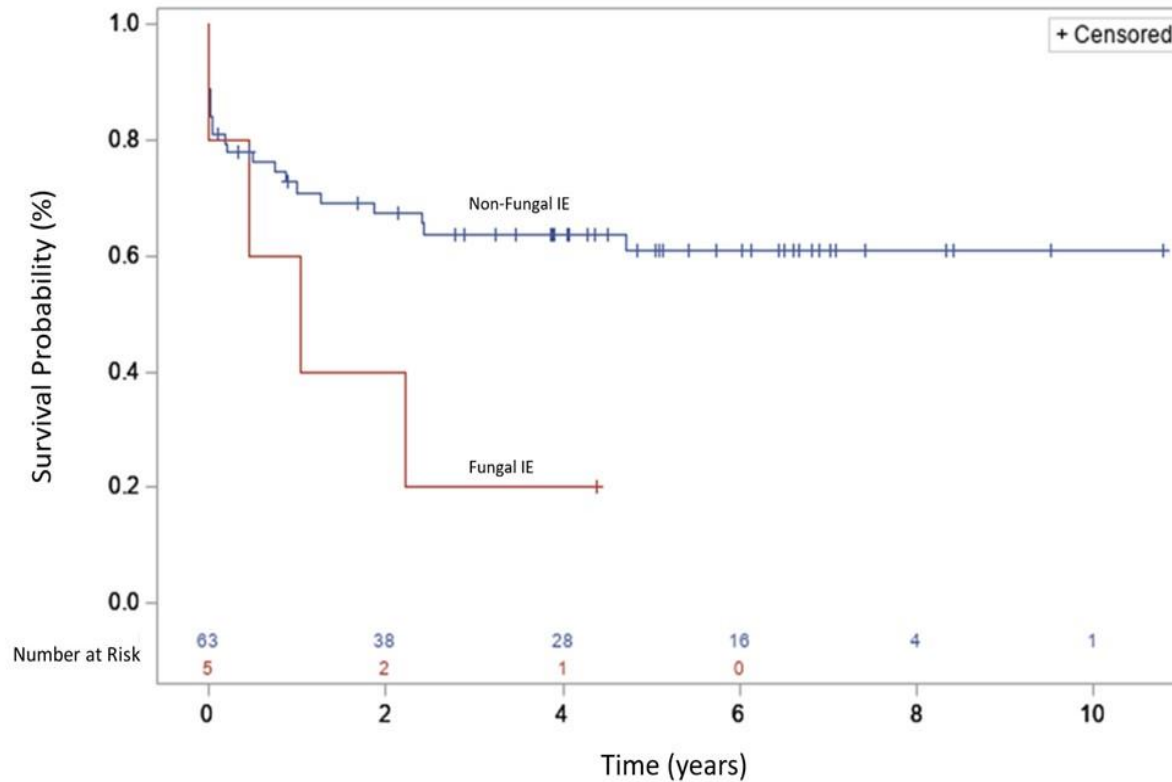
# Fungal endocarditis

- Fungi more common when assess all recurrent episodes when compared with first episodes (7/95, 7.4% vs 1/212, 0.5%;  $p=0.0005$ ).
- All fungi *Candida* species
- All isolates were fluconazole sensitive other than a single case with *C. glabrata* and a single case of *C. albicans* which occurred after 3 previous courses of fluconazole for *C. albicans* azole sensitive IE.

- mortality rate for second episode endocarditis was 38.2% with 26 deaths (n=68). The most common cause of endocarditis related mortality was sepsis (21/26, 81%).
- Multivariable analyses showed that the odds of long-term mortality (measured at 3-years) were 16.49 (95%CI 1.12, 243.17, p=.041) times greater for PWID with a fungal infection, relative to other microorganisms,



# Kaplan Meier Survival Analysis of PWID with Second Episode Infective Endocarditis



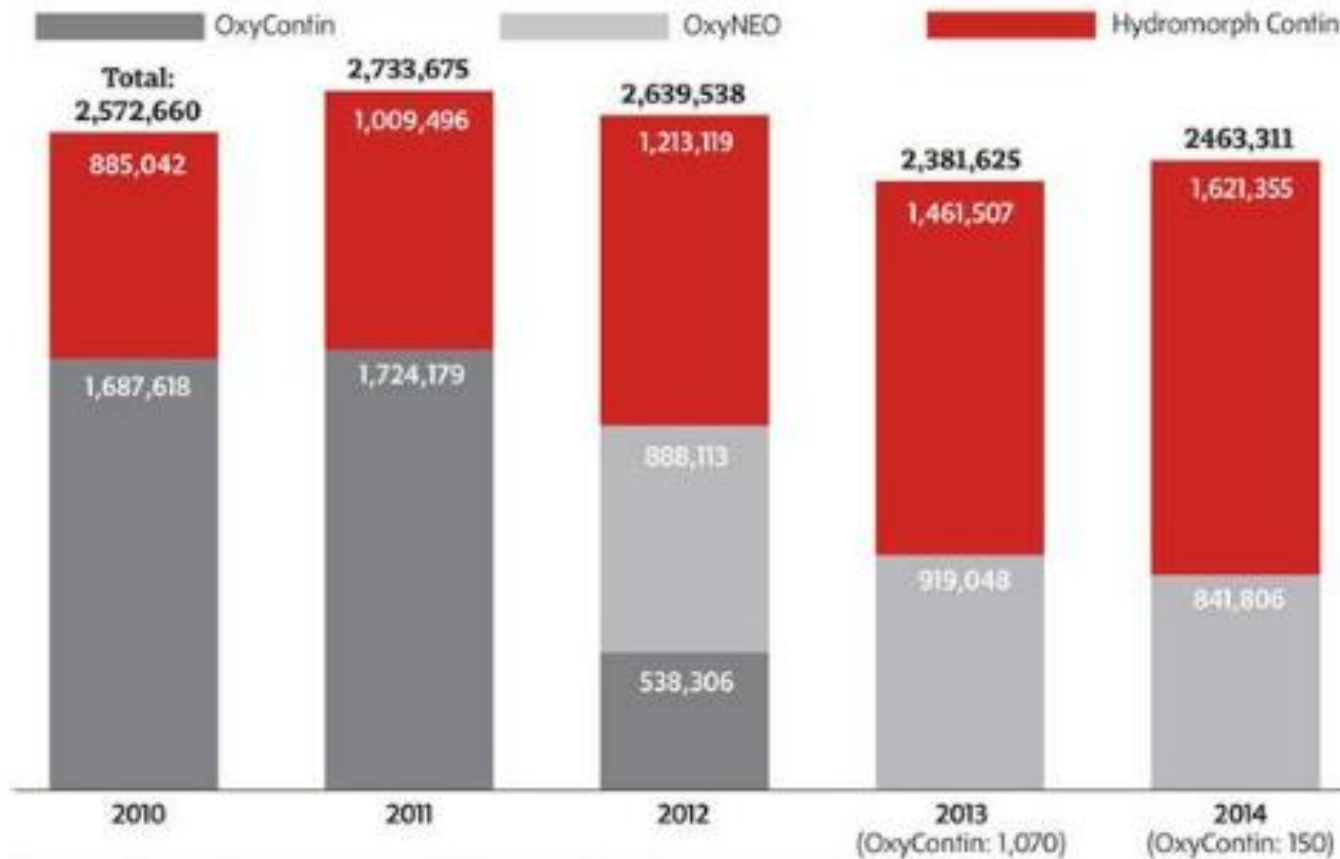
- all cases of Candida endocarditis which occurred in a recurrent episode, occurred on a valve also involved in a previous episode-supporting hypothesis

- lemon juice as the solvent for heroin preparation can acquire *Candida* species fungemia and endocarditis (Antionori Mycopathologia. 2014)
- Very little heroin in London, and only white (not brown) in community, which does not need acidifier (ITRACK 2018). Also Vitamin C widely distributed so unlikely to need Lemon Juice

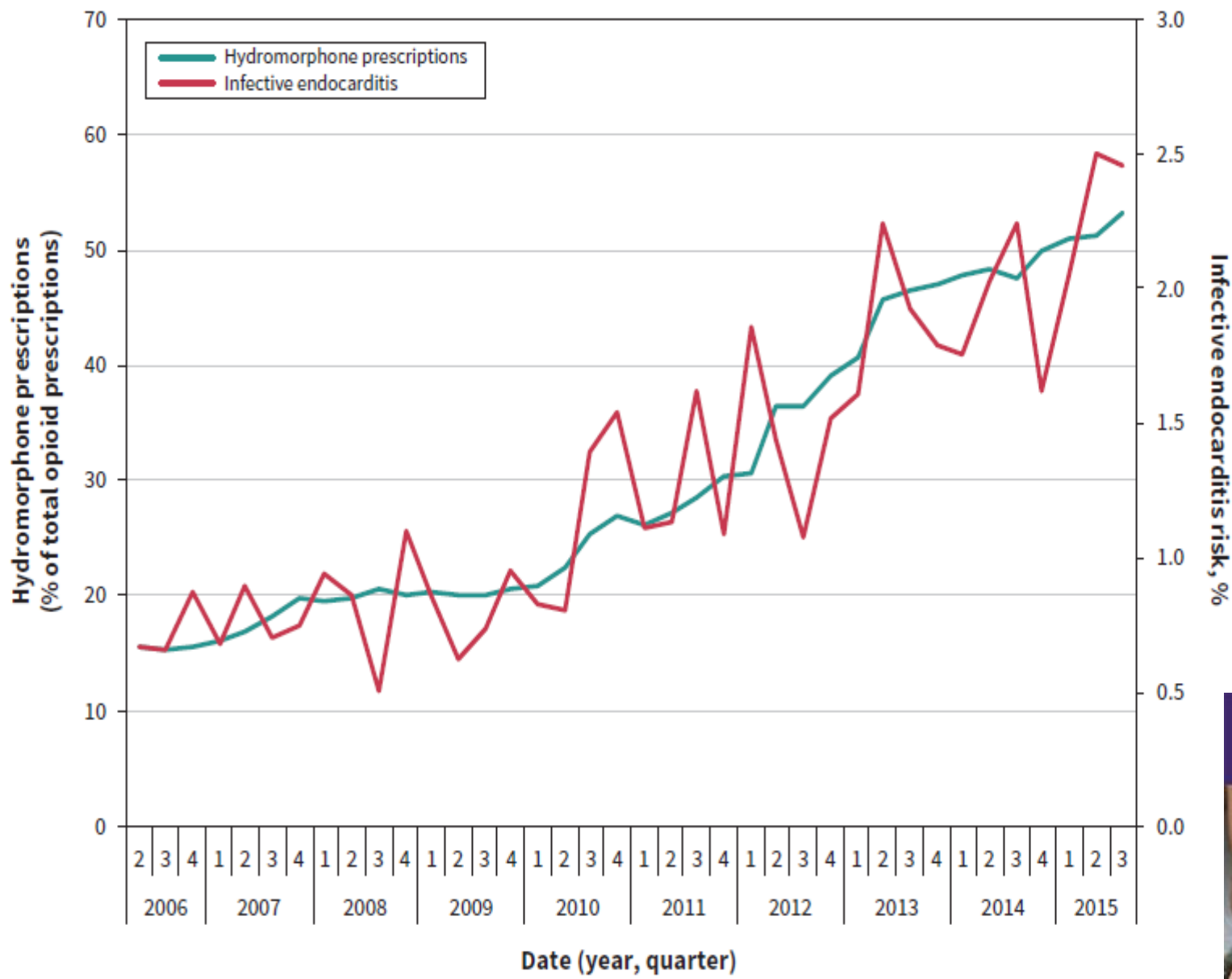
# How can we improve survival in fungal endocarditis

- Fungal infective endocarditis is a “stand-alone indication” for a surgical valve replacement
- Surgery is controversial in PWID and especially in recurrent IE as 32% will have a third or more (Straw et al CID 2019 in England).
- Lifelong azoles problematic in PWID due to raising fentanyl levels via CYP3A4 inhibition (and thus risk for overdose), QT prolongation which can complicate methadone therapy, (but not buprenorphine) and difficulties with long term adherence to therapy.
- In recurrent episode of endocarditis in a person who injects drugs empiric antifungal treatment should be considered and referral to Addictions services

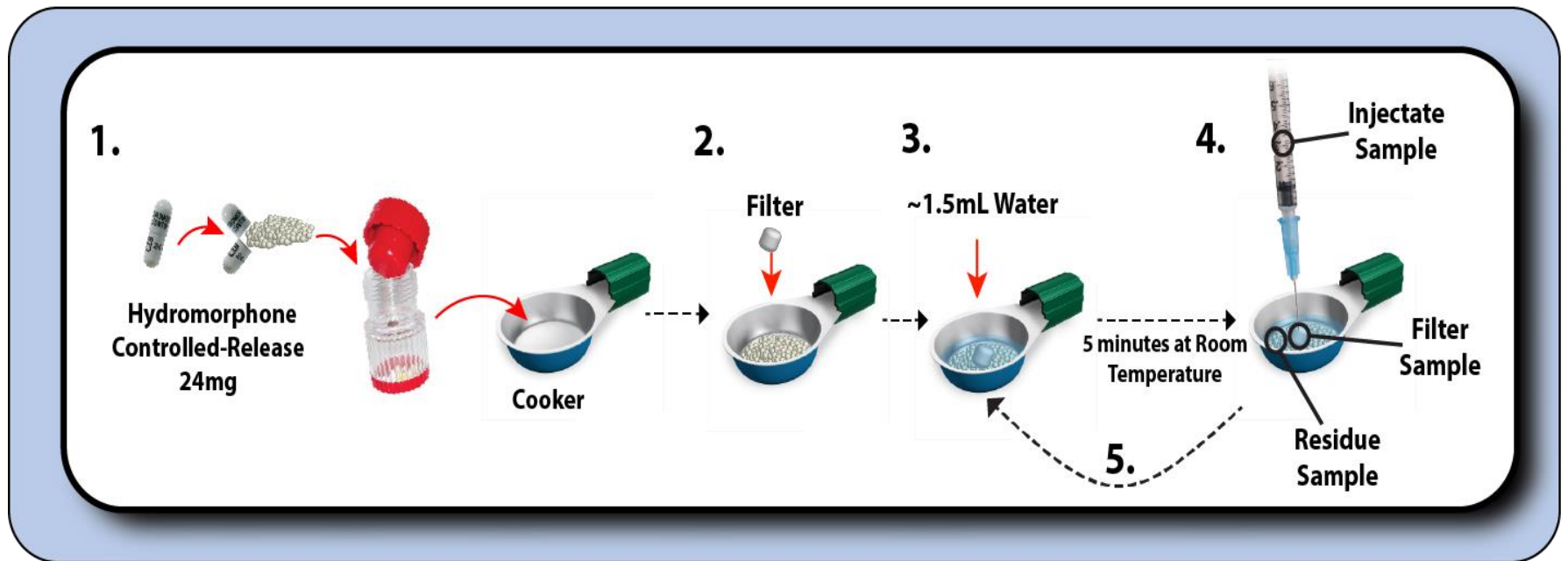
### Total Ontario prescriptions dispensed for:



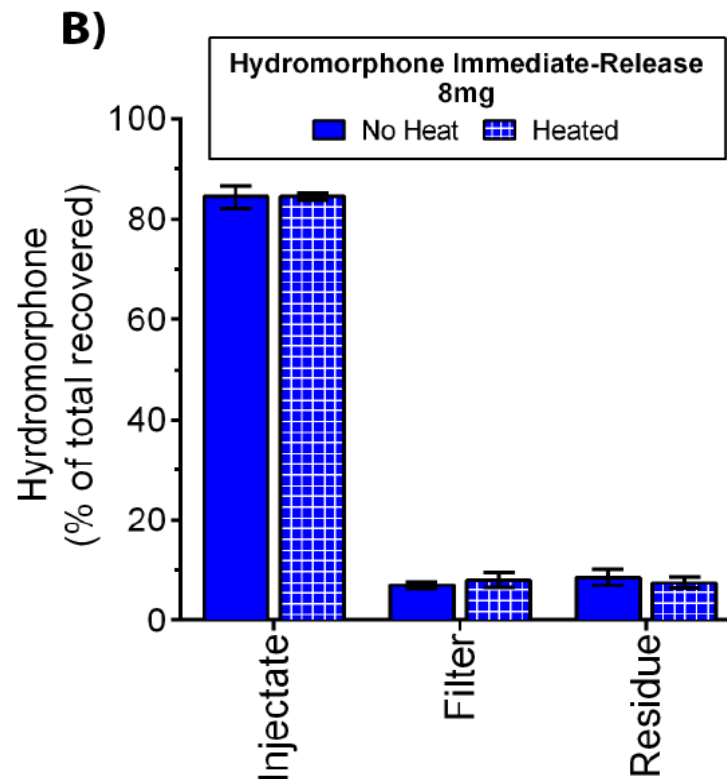
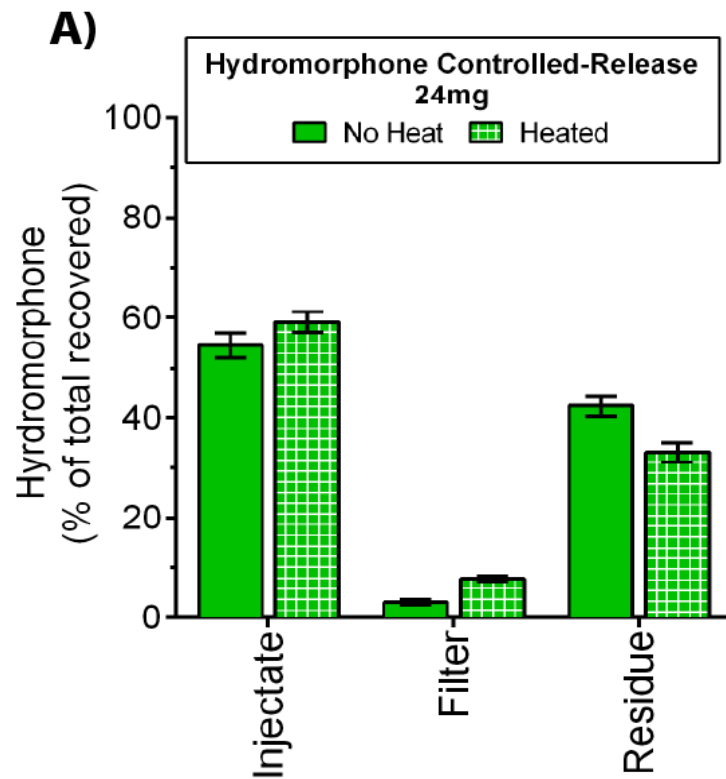
TRISH McALASTER / THE GLOBE AND MAIL | SOURCE: PAIN PHYSICIAN/JOURNAL.COM, IMS BROGAN



# How do you inject HMC?



# How much drug remains after a first wash? (JAIDS Ball et al 2019)





Colloidal silicon dioxide, dibutyl sebacate, ethyl cellulose, gelatin, hydroxypropyl methylcellulose, microcrystalline cellulose and titanium dioxide. 18 mg and greater- Iron Oxide

Hydromorphone controlled release has carbohydrate and protein and iron in binder- Is this a wet culture medium (preservative)?

Extensive handling to crush and dissolve

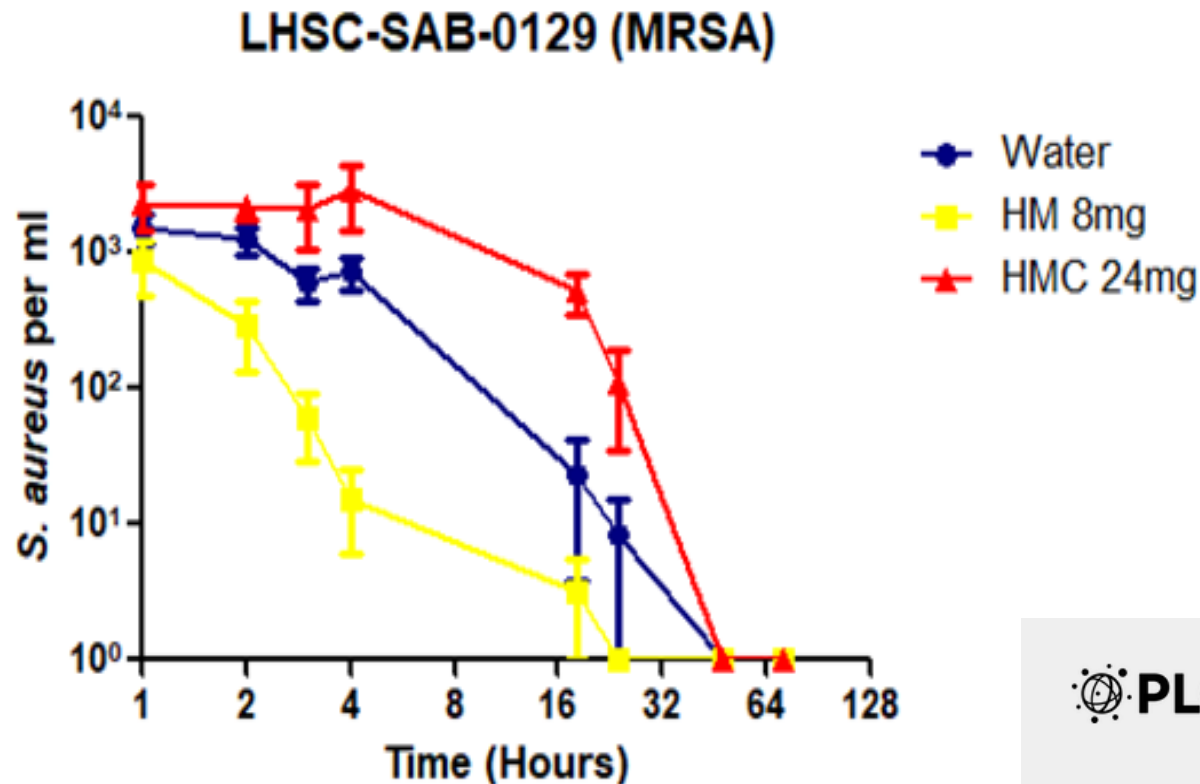
# Kadian

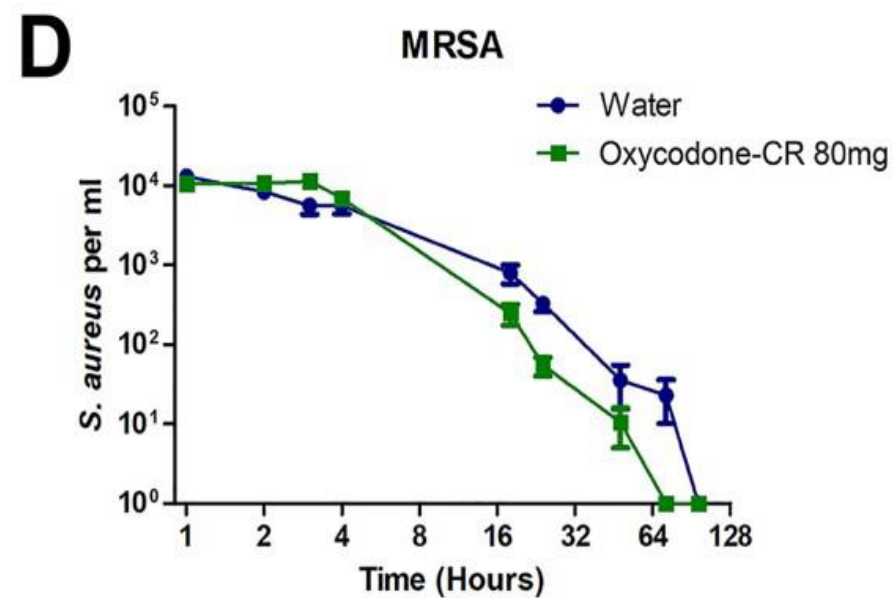
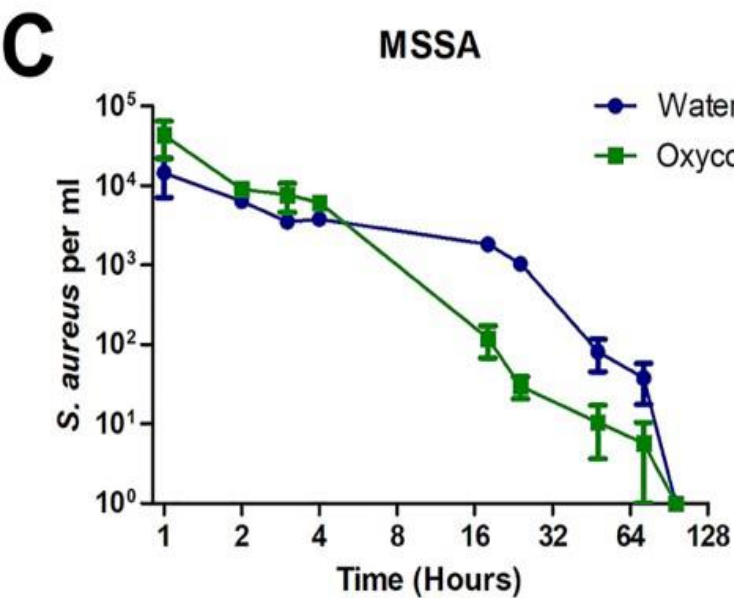
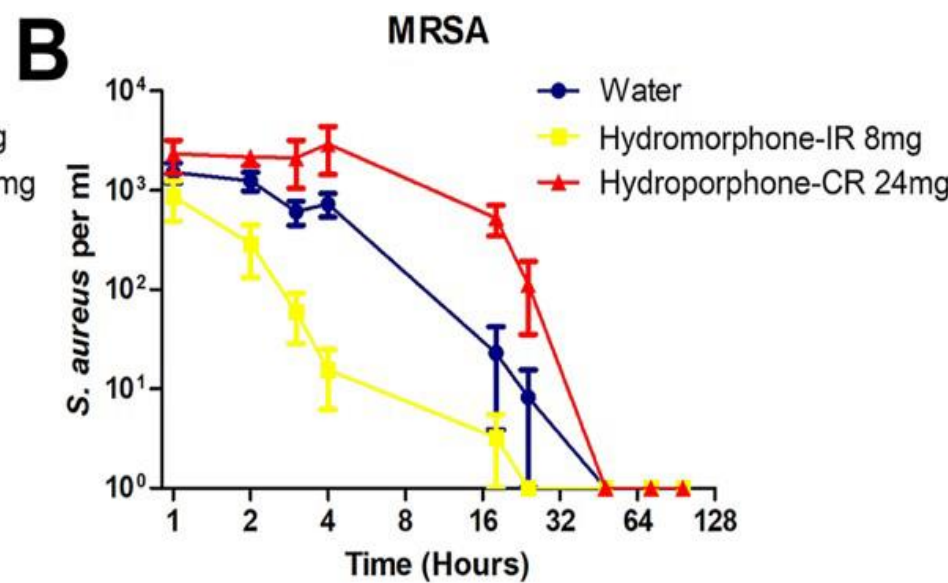
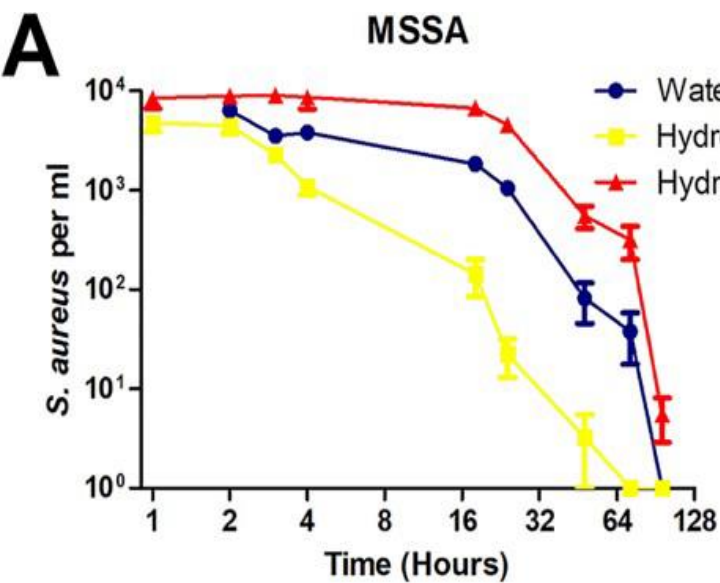
- HYPROMELLOSE
- ETHYLCELLULOSE
- POLYETHYLENE GLYCOL
- DIETHYL PHTHALATE
- TALC
- STARCH, CORN
- SUCROSE
- GELATIN
- SILICON DIOXIDE
- SODIUM LAURYL SULFATE
- TITANIUM DIOXIDE



# MSSA and MRSA survival enhanced by HMC (Hydromorph contin) but inhibited by HM (Immediate release)

(Kasper PLOS ONE 2019)





# *S. aureus* in PWID associated IE

- Collection of used IPE with Hydromorphone controlled release 12/87 (14%) grew *S.aureus* (50% MRSA) (Kasper PLOS ONE 2019)

# Oxycontin

- ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin.
- No gelatin or Iron. Not a capsule

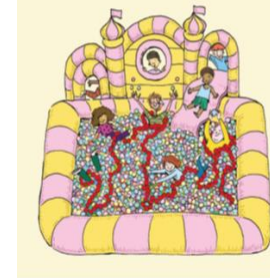
# Immediate release

## Morphine sulfate

- Lactose Anhydrous
- Hydroxyethylcellulose
- Purified Water
- Cetostearyl Alcohol
- Magnesium Stearate
- Purified Talc

## Hydromorphone (Dilaudid)

- Lactose anhydrous, magnesium stearate, D&C Yellow No. 10 Lake and FD&C Blue No. 1 Lake (for 1 mg), D&C Red No. 30 Lake and D&C Yellow No. 10 Lake (for 2 mg) and D&C Yellow No. 10 Lake (for 4 mg)



Silverman et al. *Lancet ID* in Jan 20, 2020

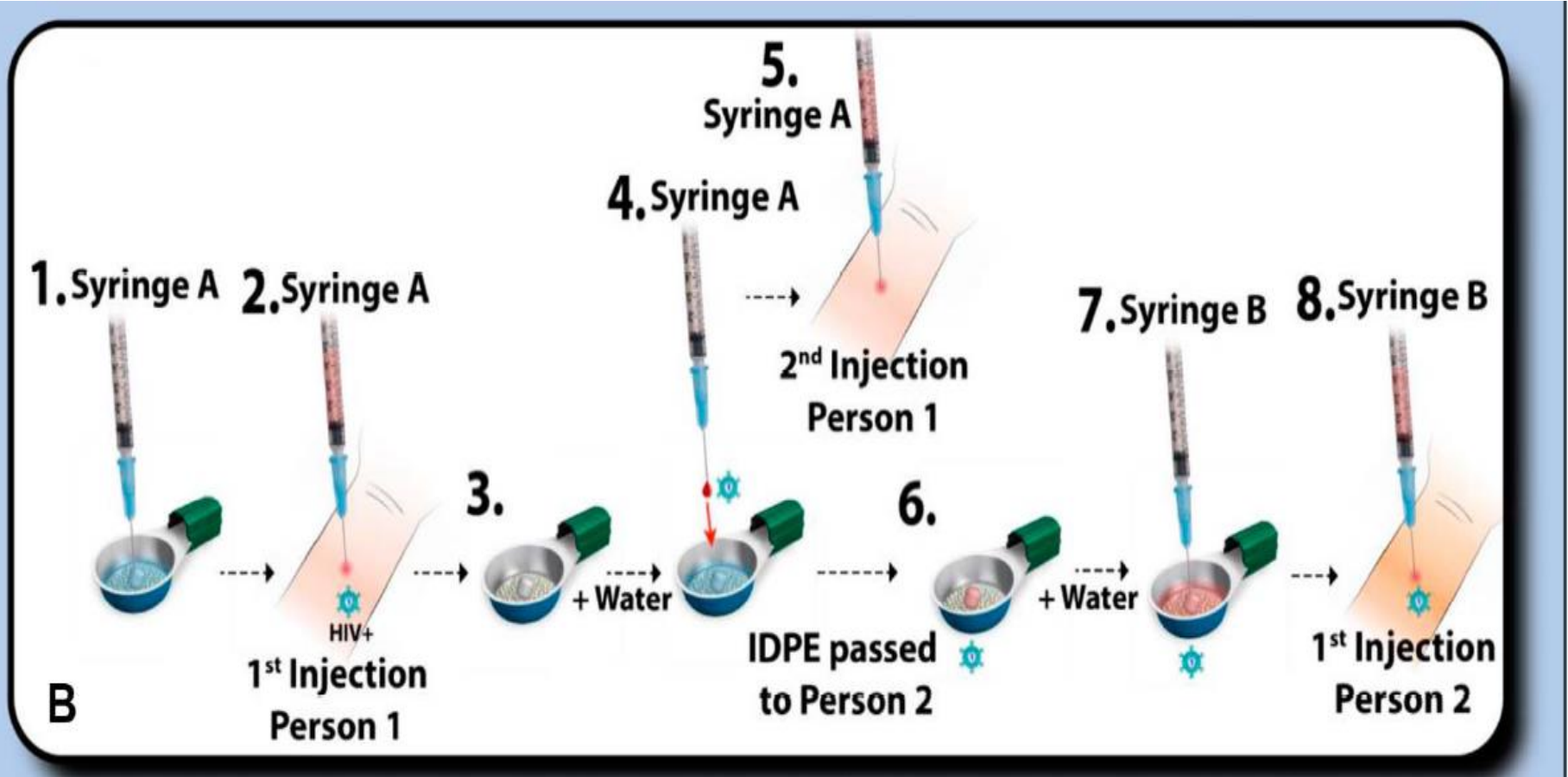
- Over a 10-year period, 60,529 patients had evidence of injection drug use and 733 (1.2%) had infective endocarditis.
- Identified regions with high HMC use (25% or more of the total opioid prescriptions) and those with low hydromorphone prescription rates (15% or less of total opioid prescriptions)
- regional analysis of 32,576 patients, we identified 254 (1.5%) admissions with infective endocarditis in regions with high hydromorphone use and 113 (0.7%) admissions in regions with low use (odds ratio 2.2, 95% confidence ratio [CI] 1.8 to 2.8,  $P < 0.001$ ).



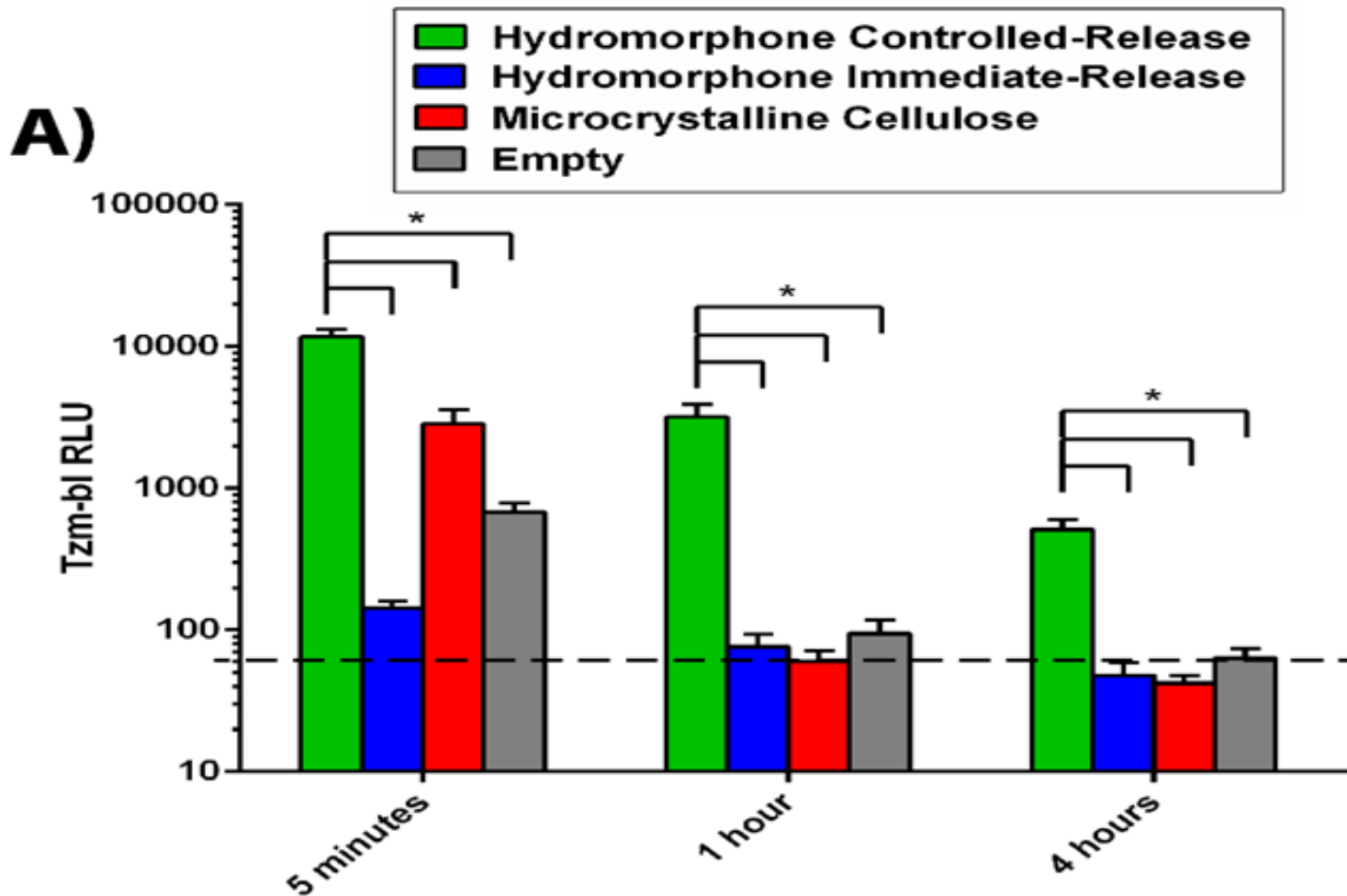


- individual level analysis of 7,768 patients
- compared those who filled prescriptions for controlled-release hydromorphone vs any other opioid within 120 days
- If HM-CR; had a three-fold higher risk of infective endocarditis compared to those prescribed other opioids (3.9% versus 1.1%, adjusted odds ratio of 3.3 [95% CI 2.1 to 5.6,  $P < 0.0001$ ]).
- This increased risk was not observed with immediate-release hydromorphone.

# Could this lead to HIV transmission?



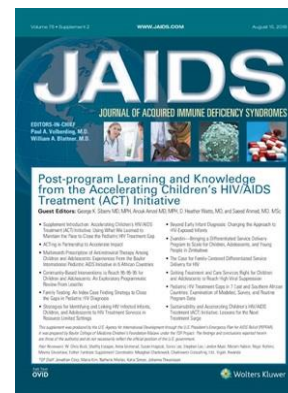
# Infectivity of wash after “spiking” then wash placed on Tzm-bl cells



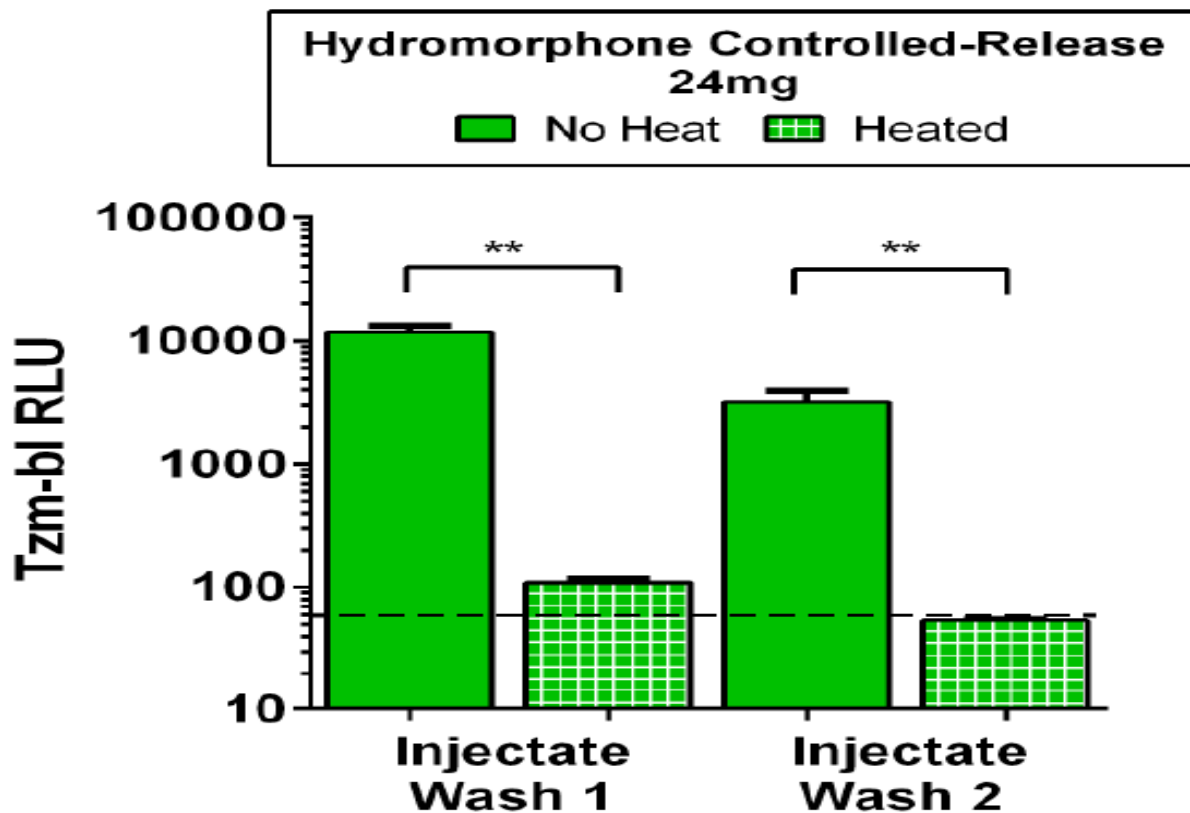
# Logistic Regression of HIV infection

## n=35 HIV+, 84 HIV-

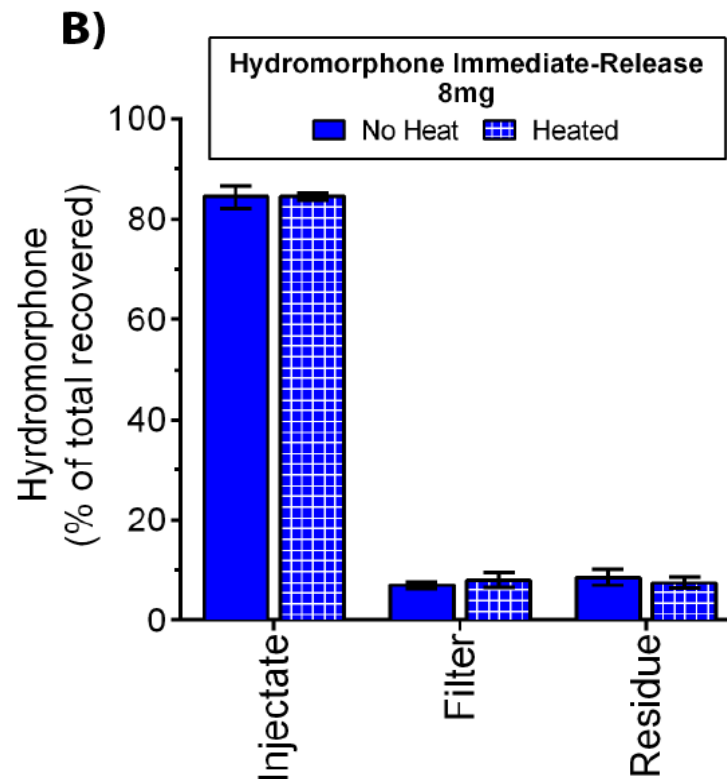
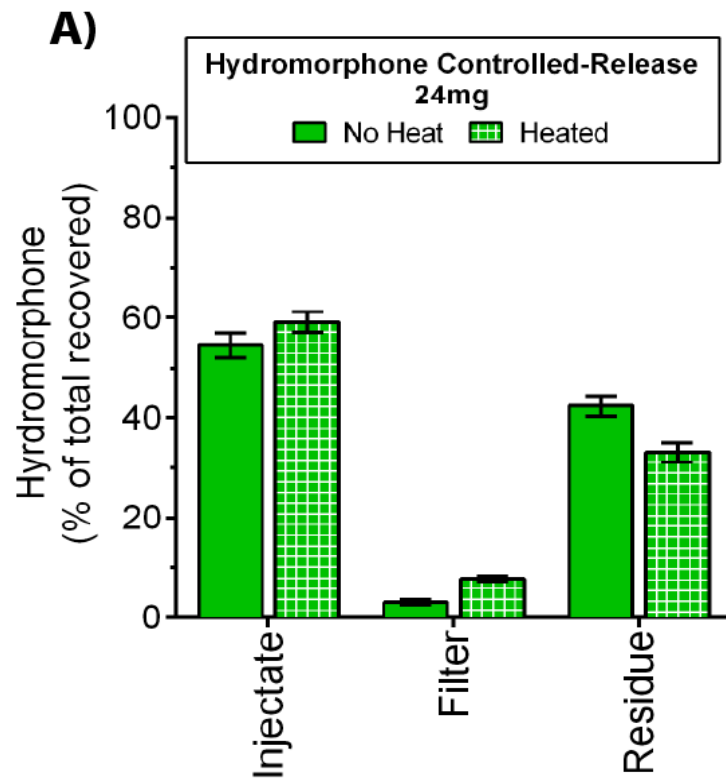
	OR (95% CI)	p value
Sharing (Ref=neither)		<.001
Both IDPE and needle/syringes	23.88 (2.36, 241.82)	.007
Only IDPE	22.12 (4.51, 108.59)	<.001
Only needle/syringes	0.91 (0.16, 5.37)	0.92
MSM	11.34 (1.79, 71.69)	0.01
Stable housing	1.83 (0.55, 6.10)	0.32



# Effect of heating either initial wash (5min) or second wash (at 1hr) until bubbling on infectivity



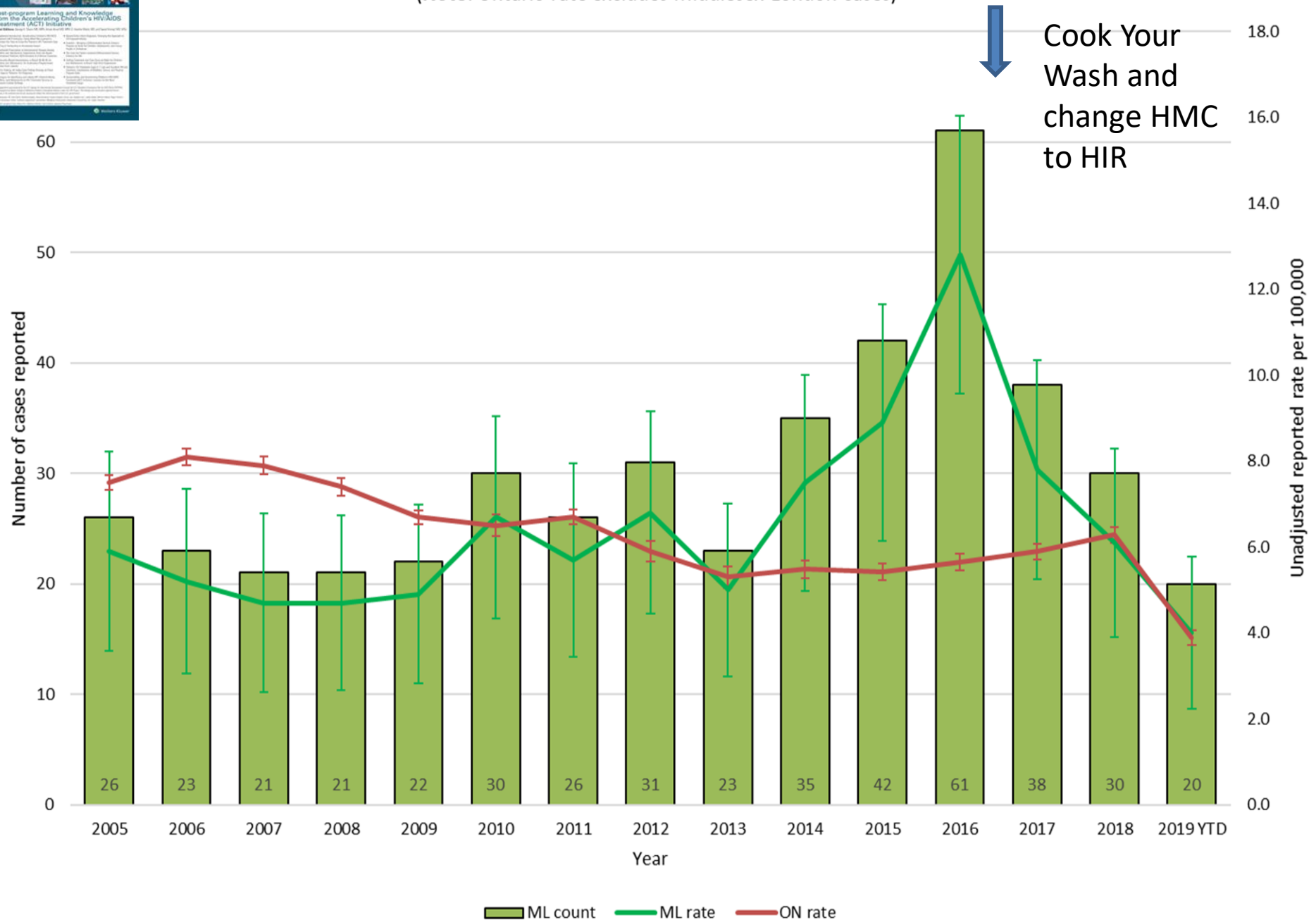
# How much drug remains after a first wash? (JAIDS Ball et al 2019)





# Count and rate of new HIV cases, Middlesex-London and Ontario, 2005-2019

(Note: Ontario rate excludes Middlesex-London cases)



# Debate about right sided predominance of IE in PWID



Does what you inject impact  
which valve is infected?

# Why right sided predominance

- mechanical particle bombardment of the tricuspid valve endothelium
- Certain injected opioids, however, can have direct, dose related, clinically significant immunosuppressive effects (especially Morphine and Fentanyl)[Edelman et al JAMA Intern Med 2019]. (Increased incidence of pneumonia and pneumococcal bacteremias)
- first-pass action of opioids directly on cardiac endothelia, which contain mu-opioid receptors [Cadet et al Endothelium 2000]. disruption of endothelial tight junctions via toll-like receptor 2, promoting bacterial translocation (especially *S. aureus*) may then be better able to adhere to the underlying tissues[Bassero et al Lancet ID 2020].
- opioid effects, strongest at the point of least dilution, i.e. the tricuspid valve

# Why left sided

- stimulants (e.g. cocaine and methamphetamine) may predispose to left-sided IE by exacerbating the factors which predispose the left side of the heart to IE in non-PWID: Increased Cardiac output, turbulence, and systemic pressures, and predisposing the left side of the heart to ischemia with valvular compromise (Lange NEJM 2001), while exerting less impact on the pulmonary circulation (Kleerup et al Chest 1999)

	Right	Left	Bilateral
Opioid Only (n=71)	47 (69%)	17 (29%)	4 (6%)
Stimulant Only (n=24)	11 (46%)	11 (46%)	2 (8%)

Stimulant Users were 1.75 times (95%CI 1.05, 2.93) (p=0.03) more likely to have Left or Bilateral vs Opiate users and 1.88 (1.05, 3.37) (p=0.03) times more likely to have Left vs Right

Those who injected both opioids and stimulants (n=166, 56%)

- side looked like opiates (right predominant)

- Opiate effect on Tricuspid valve endothelium?
- Opiates used predominantly with stimulants used when opiates not available (MMWR Morb Mortal Wkly

Rep 2020;69:317–323)

# PWID IE Cohort Study

- 309 patients
- Ongoing inpatient IVDU was documented by a physician in 194/420 infective endocarditis episodes) (46.2% [194/420]), and 127 of these (65.5%) were confirmed by urine toxicology results.

# Blood Stream Infections [London Data] (Tan, C JAMA Open 2019)

- 82/420 episodes(19.5%) complicated by new BSIs.
- 138 independent new BSIs, of which 68(49.3%) were polymicrobial.
- Aerobic gram-negative bacilli (143/266 [53.8%]) and Candida species (75/266[28.2%]) were the most common.
- Bacteria generally ESKAPE Organisms (requiring Imipenim and Vanco) (Enterococcus, Staph (CNSS), Klebsiella, Acinetobacter, Pseudomonas, Enterobacter)

- Inpatient addiction treatment was associated with a significantly lower rate (HR 0.53; 95% CI,0.32-0.88).
- New BSIs were not significantly associated with 90-day mortality (HR,1.76; 95%CI, 0.78-4.02)



# Oral Therapy? Marks et al CID 2020

- n=293 PWID
- who received an infectious diseases consultation for an invasive bacterial or fungal infection. (multiple clinical diagnoses)
- multivariate analysis, compared with ongoing inpatient IV Rx:
- 90-day readmission risk was higher among PWID who did not receive oral antibiotic therapy on AMA discharge (adjusted hazard ratio [aHR], 2.32; 95% [CI], 1.41–3.82) and not different among PWID prescribed oral antibiotic therapy on AMA discharge (aHR, .99; 95% CI, .62–1.62).

- Surgical source control (aHR, .57; 95% CI, .37–.87) and addiction medicine consultation (aHR, .57; 95% CI, .38–.86) were both associated with reduced readmissions

Most cohort studies complicated by survival bias (only those still living can get surgery so surgery looks protective)

- Multivariable analysis with correction for survival bias re Cardiac Surgery
- n=310 patients; 74 with multiple episodes
- **Risk for recurrent IE**
- Surgical intervention non-significant (RR=1.12 p=0.77)
- PICC Line misuse RR 2.63 (1.27-5.46; p=0.009)

# Risk of Death

- Left Sided RR 1.98 (1.16-3.39,  $p=0.01$ )
- PICC Misuse 2.87 (1.37-6.02,  $p=0.005$ )
- No PICC 11.38 (5.79-22.4,  $p<0.001$ )
- ICU Admission 3.54 (2.06-6.08,  $p<0.001$ )
- **Associated with Protection**
- Referral to Addiction Services 0.37 (0.2-0.69,  $p=0.002$ )
- Oral 0.32 (0.13-0.77,  $p=0.01$ )
- Outpatient 0.41 (0.41, 0.19-0.85,  $p=0.02$ )
- Surgery 0.99 ( $p=0.99$ ) (DATA in Press)

# POET Iverson et al NEJM 2019

- In left sided IE (including those who are postoperative) in Denmark (n=400)
- Partial Oral Therapy in Endocarditis (at least 10 days IV then switch to Oral using 2 active oral drugs for G+ or at least one for G-) vs ongoing IV therapy
- oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment
- Very Few PWID (5/400)

# In PWID

- May be less likely to adhere to oral
- More likely to sign out AMA making IV therapy difficult to coordinate
- More likely to inject into PICC
- Much Less likely to complete a course of outpatient Vanco (Grattan et al JAC 2020)
- Need RCT

# Summary

- Certain controlled release opiates are associated with greater risk of PWIDaIE (and HIV/HCV [Ball et al JAIDSx2 and Meyer et al J Viral Hepatitis, CMAJ Lancet ID]).
- Cook your wash and reduction of HMC prescribing brought end to local HIV epidemic (reduction in IE to be confirmed)
- *S. aureus* makes up the vast majority of first and less so recurrent cases
- Fungal IE is more common in recurrent IE, has a very high mortality and so empiric azoles should be considered in recurrent cases

- Right Sided IE is More Common in Opiate only users but not stimulant only users
- Ongoing IDU is very common into PICC lines in inpatients (at least 46%)- associated with higher relapse and mortality
- BSIs associated with ESKAPE Organisms and Yeast – Rx with Carbapenem/Fluconazole and if not already on it- Vanco
- PICC Line misuse associated with increased risk of relapse and death
- Inpatient addiction counseling associated with reduced PICC line misuse, reduced BSIs and reduced death
- Effect of Surgery needs further prospective study



# Presently Randomizing to POET in PWID

- RCT of Oral vs IV Therapy
- Can be treated as outpatient or inpatient at clinicians discretion
- Looking for new sites
- [Michael.Silverman@sjhc.London.on.ca](mailto:Michael.Silverman@sjhc.London.on.ca)

# Thank You

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- Esfandiar Shojaee
- Charlotte Coleman
- Laura Rodger
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- Meera Shah

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- John McCormick
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- Dan Lizotte
- Jacqueline Kueper
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Sonja Burke  
Brian Lester  
Karen Burton  
Blair Henry

**All the  
PWIDs who  
trusted us  
and taught  
us about  
what they  
were doing**

# Questions

- -How does the risk/benefit balance of safer supply position itself in an endocarditis context? **Avoid long acting Opioids-** review warning signs for endocarditis **Fever, Chest pain, SOB, systemic embolic phenomena.**
- -What scientific evidence supports the refusal to re-operate patients who have had 1 valve replacement and have bacterial endocarditis again? **No data available- No evidence of higher recurrence- but selected population. If recur high death rate but only offered to those with high risk of death without Sx**
- **Refusal often done but no evidence. Single “slip patient” a major concern**
  - Principles of harm reduction during a hospital stay to treat endocarditis and concrete suggestions for joining health care teams? **Critical to see in hospital and initiate OST with linkage to outpatient care. Need addiction teams in hospital- not just a single person- burnout**

- -Suggested framework for treating endocarditis in IVDU patients in hospital and when is it ok to treat in a outpatient service? Poor data- need RCTs to clarify as data on non-PWID doesn't necessarily apply. Oral versus IV therapy RCT underway, but outpatient versus inpatient unknown. Many patients have no home or shelter and unable to follow-up, may need "hostel" as in Vancouver.