Research Paper

Effect of incarceration and opioid agonist treatment transitions on risk of hospitalisation with injection drug use-associated bacterial infections: A self-controlled case series in New South Wales, Australia

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ABSTRACT

Background: Transitional times in opioid use, such as release from prison and discontinuation of opioid agonist treatment (OAT), are associated with health harms due to changing drug consumption practices and limited access to health and social supports. Using a self-controlled (within-person) study design, we aimed to understand if these transitions increase risks of injection drug use-associated bacterial infections.

Methods: We performed a self-controlled case series among a cohort of people with opioid use disorder (who had all previously accessed OAT) in New South Wales, Australia, 2001-2018. The outcome was hospitalisation with injecting-related bacterial infections. We divided participants' observed days into time windows related to incarceration and OAT receipt. We compared hospitalization rates during focal (exposure) windows and referent (control) windows (i.e., 5-52 weeks continuously not incarcerated or continuously receiving OAT). We estimated adjusted incidence rate ratios (aIRR) using conditional logistic regression, adjusted for time-varying confounders.

Results: There were 7590 participants who experienced hospitalisation with injecting-related bacterial infections (35% female; median age 38 years; 78% hospitalised with skin and soft-tissue infections). Risk for injecting-related bacterial infections was elevated for two weeks following release from prison (aIRR 1.45; 95%CI 1.22–1.72). Risk was increased during two weeks before (aIRR 1.89; 95%CI 1.59–2.25) and after (aIRR 1.91; 95%CI 1.54–2.36) discontinuation of OAT, and during two weeks before (aIRR 3.63; 95%CI 3.13–4.22) and after (aIRR 2.52; 95%CI 2.09–3.04) OAT initiation.

Conclusion: Risk of injecting-related bacterial infections varies greatly within-individuals over time. Risk is raised immediately after prison release, and around initiation and discontinuation of OAT. Social contextual factors likely contribute to excess risks at transitions in incarceration and OAT exposure.

Introduction

Injecting-related bacterial infections (e.g., skin and soft-tissue infections, endocarditis, osteomyelitis, etc.) are common among people who inject drugs, causing pain, disablement, and death (Larney et al., 2017; Robertson et al., 2021; See et al., 2020). The incidence of severe injecting-related bacterial infections is rising in the United Kingdom (Lewer et al., 2019, 2023), Australia (Colledge-Frisby et al., 2022), Canada (Gomes et al., 2022; Mosseler et al., 2020), and the United States (Schranz et al., 2019; See et al., 2020; Serota et al., 2021). Individual injecting practices (e.g. skin sterilization, intramuscular/subcutaneous injecting, reusing contaminated equipment, etc.) are known risk factors
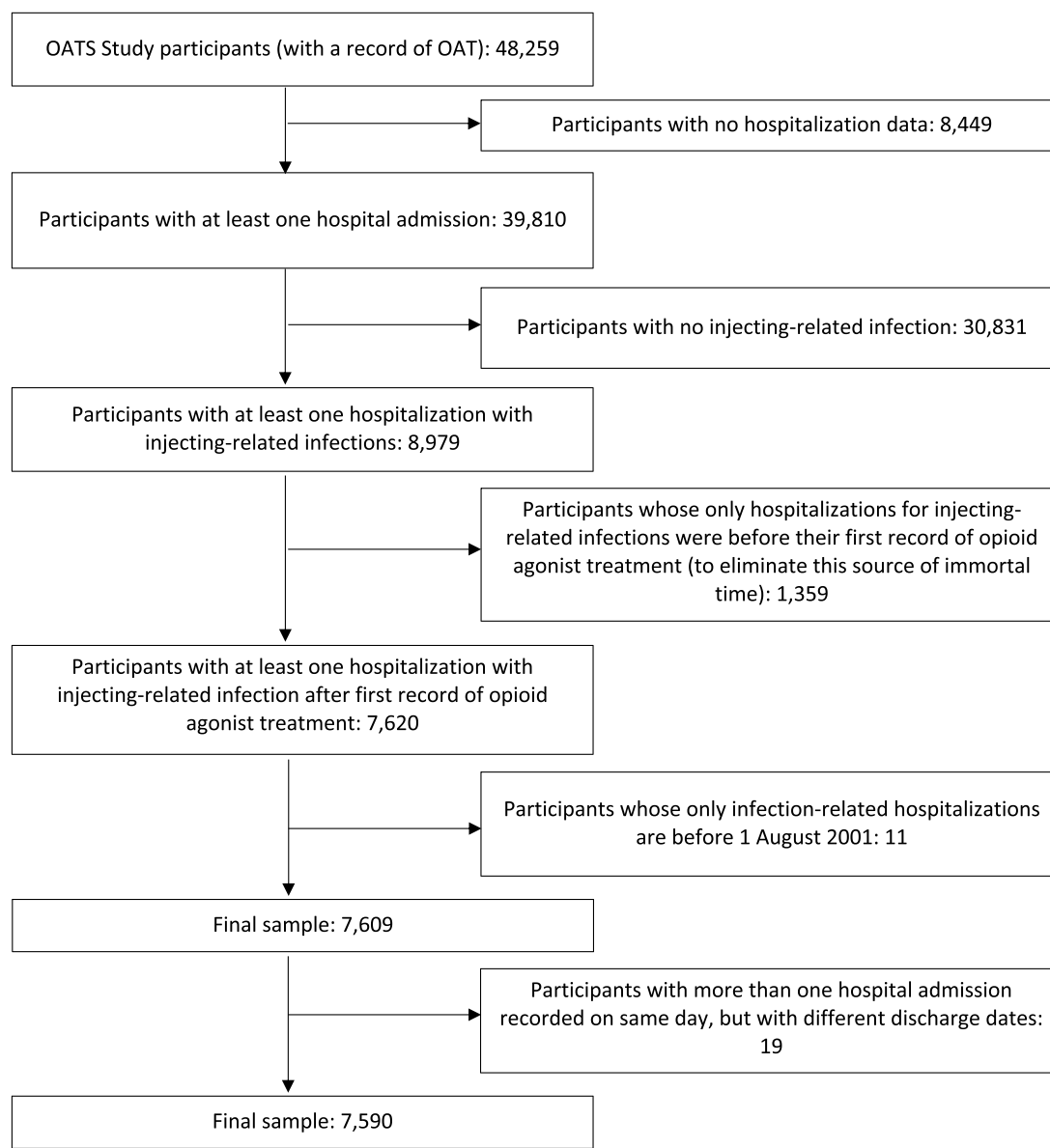

Fig. 1. Flow diagram for participants' inclusion in self-controlled case series of hospital admissions for injecting-related infections. OATS Study: opioid agonist treatment safety study.

(Larney et al., 2017; Robertson et al., 2021) and individual-level educational interventions have been developed to promote safer injecting techniques (Phillips et al., 2021; Roux et al., 2021; Stein et al., 2021). However, educational interventions show inconsistent efficacy and have not reduced population incidence (Kesten et al., 2023; Phillips et al., 2021; Roux et al., 2021; Stein et al., 2021). This is likely because health behaviours and risk for infections are shaped and constrained by multiple social and structural factors beyond individuals' control, including the quality of the unregulated drug supply, homelessness, and insufficient access to harm reduction programs (Brothers et al., 2023; Lewer et al., 2023). Better understanding of social and clinical factors influencing risk is needed to inform new prevention approaches (Brothers et al., 2021, 2023; Khan et al., 2021; Lewer et al., 2023).

Incarceration and opioid agonist treatment (OAT; e.g., methadone, buprenorphine) are social and clinical exposures, respectively, that may modify risks for injecting-related bacterial infections. People in prison could face increased risks because they often need to hide drug use and reuse contaminated equipment, due to prohibitive drug use policies and inadequate access to harm reduction supplies (e.g., sterile needles)

(Altice et al., 2016; Cunningham et al., 2018; Treloar et al., 2021). Risk could alternatively be reduced in some prisons, because of decreased access to drugs (Cunningham et al., 2018). Time periods immediately following release from prison are associated with increased risks of other drug-related harms, including HIV (Choopanya et al., 2002; Lucas et al., 2015; Martin et al., 2014; Stone et al., 2018), hepatitis C virus (Iversen et al., 2013; Sacks-Davis et al., 2016; Stone et al., 2018; Tsui et al., 2014), and overdose (Binswanger et al., 2007, 2012; Bird & Hutchinson, 2003; Farrell & Marsden, 2008; Joudrey et al., 2019; Keen et al., 2021; Merrall et al., 2010; Seaman et al., 1998). This time period may be risky for many reasons, including loss of opioid tolerance while in prison, return to injection use, poor access to health and social supports, and material deprivation (poverty and homelessness) (Binswanger et al., 2012; Harney et al., 2022; Joudrey et al., 2019; Treloar et al., 2021). Some of these factors could also increase risks of bacterial infections after release (Brothers et al., 2021, 2023). Several prior studies assessed whether people who were recently incarcerated (e.g., past year) were more likely to experience injecting-related infections than people who had not been incarcerated. Some found increased risk (Colledge-Frisby
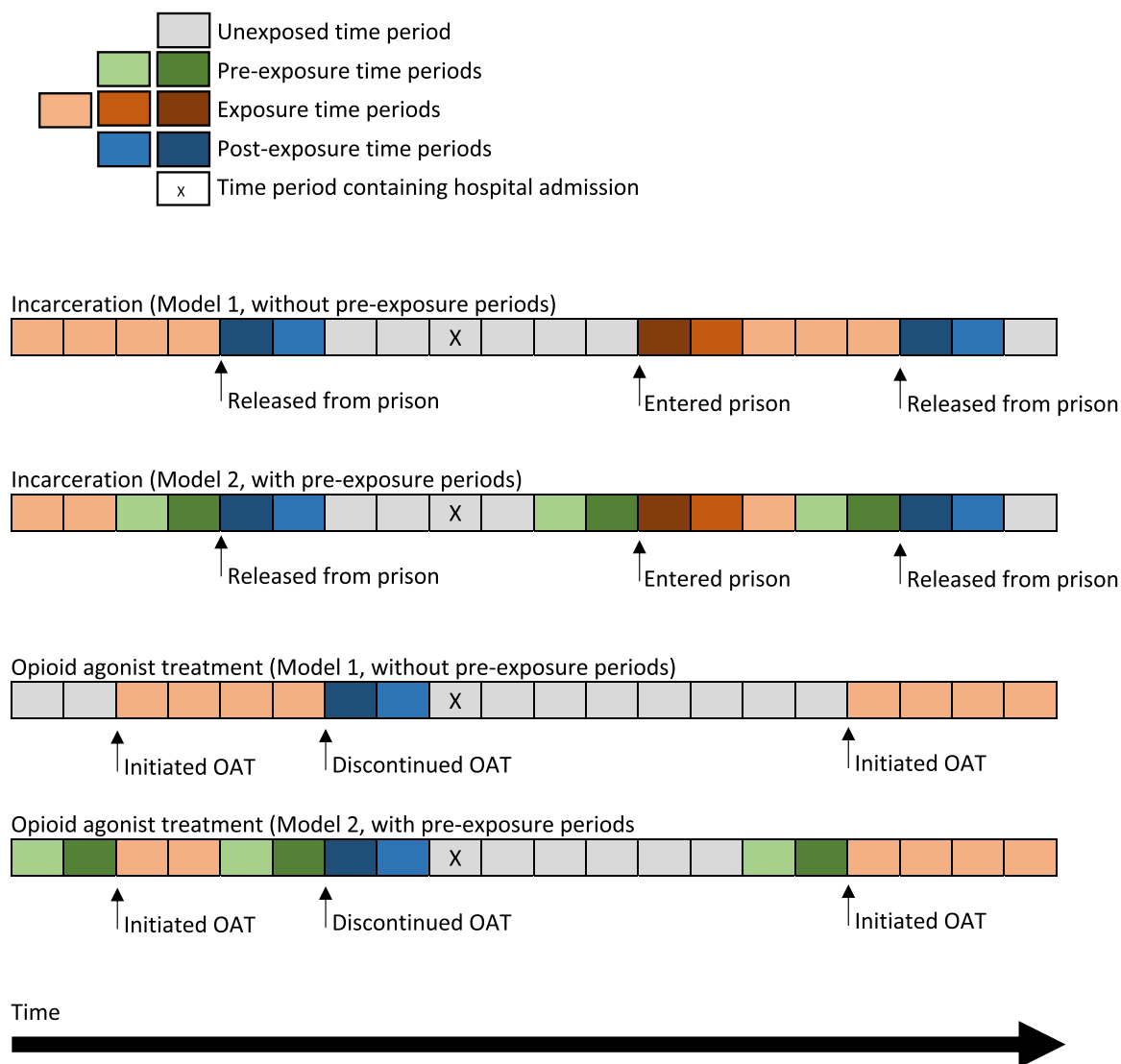
Fig. 2. Time periods of potentially altered risk for injection drug use-associated bacterial infections in the self-controlled case series. Each horizontal bar represents the same single study participant, with each shaded block representing a different time window. The top two horizontal bars represent exposure changes over time related to incarceration, in models without pre-exposure time periods (first row) and with pre-exposure periods (second row). The bottom two horizontal bars represent exposure changes over time related to opioid agonist treatment receipt, in models without pre-exposure time periods (third row) and with pre-exposure periods (fourth row).

et al., 2022; Lloyd-Smith et al., 2005; Milloy et al., 2010; Wheeler et al., 2022) and some found similar risks (Hope et al., 2014, 2015; Pollini et al., 2010).

OAT may reduce risks of injecting-related bacterial infections. OAT enables some people to decrease or stop injection opioid use, and facilitates access to primary care where superficial infections may be treated before they progress (Brothers et al., 2021, 2023; Brothers, Lewer, Jones, et al., 2022; Colledge-Frisby et al., 2022; Curtis et al., 2023; Frank, 2018). However, many people receiving OAT continue injecting and infections continue to occur (Brothers, Lewer, Jones, et al., 2022; Colledge-Frisby et al., 2022). Prior studies found reduced risks of bacterial infections among people receiving OAT (Brothers, Lewer, Jones, et al., 2022; Colledge-Frisby et al., 2022; Dunleavy et al., 2017; Hope et al., 2008) but several others identified no effect (Milloy et al., 2010; Roux et al., 2021; Wheeler et al., 2022). Relationships between OAT receipt and infection risk may also change over time; for example, Colledge-Frisby and colleagues (2022) observed increased rates of hospitalization with injecting-related bacterial infections during the first four weeks of an OAT episode compared to time not receiving OAT. They

hypothesized this was due to OAT clinicians recognizing pre-existing infections and referring people to hospital. In a post-hoc analysis, they found the rate of infections was even higher during two weeks preceding OAT initiation, which may reflect increased motivation to start OAT after developing infections (Brothers et al., 2023; Colledge-Frisby et al., 2022). The time period immediately following OAT discontinuation is associated with excess risks of overdose and all-cause mortality; this is thought to be reflective of loss of opioid tolerance, return to drug use, and life stressors that may contribute to both treatment discontinuation and riskier drug use (Cousins et al., 2011; Pearce et al., 2020). This time period might also be associated with excess risk for injecting-related bacterial infections for similar reasons, but to our knowledge this has not been studied.

A limitation of these prior studies is that people who are incarcerated or receive OAT differ from people who never experience these exposures, in important ways that are difficult to measure (Keen et al., 2021; Lewer et al., 2021, 2022; Petersen et al., 2016; Whitaker et al., 2006; Whitaker & Ghebremichael-Weldeselassie, 2019). Self-controlled study designs make within-person comparisons in the probability of an event

Table 1

Descriptive characteristics of sample in self-controlled case series of hospital admissions for injection drug use-associated bacterial infections.

Variable	Level	Value
Sample size	N (%)	7590 (100%)
Age at study entry, years	Median (IQR)	38 (32 – 46)
Age at first hospital admission for injecting-related infection, years	Median (IQR)	40 (33 – 47)
Sex	Female, N (%)	2655 (35%)
Aboriginal or Torres Strait Islander identity	Yes, N (%)	970 (13%)
Ever incarcerated during observation period	Yes, N(%)	3748 (49%)
Ever on OAT during observation period	Yes, N(%)	7590 (100%)
Infection type in first hospital admission for injecting-related infection	N (%)[a]	
	Skin and soft-tissue infections	5895 (78%)
	Sepsis/bacteraemia	1048 (14%)
	Endocarditis	406 (5%)
	Osteomyelitis	347 (5%)
	Septic arthritis	290 (4%)
	Central nervous system	63 (1%)

IQR: Interquartile range. OAT: Opioid agonist treatment.

[a] Values sum to greater than 100% because each hospital admission can have more than one infection diagnosis.

occurring during different time periods in a person's life, and therefore control unmeasured confounding factors that do not vary over time (because people serve as their own control). Self-controlled studies can also identify time periods of excess risk to inform time-specific health and social care responses (i.e., "critical time interventions") (Lewer et al., 2021; Pho et al., 2021; Treloar et al., 2021). This has been investigated for overdose risk reduction after prison release (Joudrey et al., 2019; Pho et al., 2021), but to our knowledge has not been explored for injecting-related infections.

Using a self-controlled study design, we aimed to assess the relative incidence of injecting-related bacterial infections before, during, and after incarceration and receipt of OAT, among a large sample of people with opioid use disorder.

Methods

This was a self-controlled case series. This method includes only cases (i.e., people who experienced a hospital admission with injecting-related infections) and focuses on the timing of outcomes in relation to exposure status (Cadarette et al., 2021; Petersen et al., 2016; Whitaker et al., 2006; Whitaker & Ghebremichael-Weldeselassie, 2019). We published a study protocol before beginning analyses (Brothers, Lewer, Colledge-Frisby, et al., 2022). This manuscript follows Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (von Elm et al., 2007).

Setting and data sources

Data came from the Opioid Agonist Treatment Safety study (Brothers, Lewer, Jones, et al., 2022; Colledge-Frisby et al., 2022; Jones et al., 2020; Larney et al., 2018, 2021). This administrative data cohort includes everyone in New South Wales, Australia, who accessed OAT (methadone or buprenorphine) for opioid use disorder from 2001 to 2018, linked to health services and criminal-legal administrative databases.

Sample

We included those who experienced at least one outcome (i.e., hospitalization with injecting-related infection). Observation began at the latter of a participant's first recorded use of OAT (making them eligible for inclusion in the parent study) or 1 August 2001 (the start of linkage to hospital data). Observation ended at the earlier of death or 29 June 2018. Participants' observed time was not censored during nor after hospitalization. See Fig. 1 for a participant flow diagram.

Outcomes

The primary outcome was emergency (i.e., nonelective) hospital admissions with principal or contributing diagnoses of injecting-related bacterial infections (i.e., skin and soft-tissue infection, sepsis or bacteraemia, endocarditis, osteomyelitis, septic arthritis, or central nervous system infections [brain or spine abscess]), defined using ICD-10 code groupings consistent with prior studies (Brothers, Lewer, Jones, et al., 2022; Colledge-Frisby et al., 2022). See Supplementary Appendix 1 for ICD codes. Consistent with previous studies, continuous episodes of care (including inter-departmental or inter-hospital transfers) were aggregated and considered as a single hospital admission (Jones et al., 2020).

In our preregistered protocol, the primary outcome included only hospitalizations with skin and soft-tissue infections (rather than multiple types of bacterial infections); we have included results using this approach in Supplementary Appendix 2. We chose to include all injecting-related infections in the main analysis given the shared pathophysiology and risk factors among multiple types of injecting-related infections, and because of the larger sample size.

Self-controlled case-series require recurrent outcome events to be independent, where experiencing one event does not increase the likelihood of subsequent events (i.e., the method assumes that events do not cluster). However, developing one injecting-related infection may increase risk of subsequent infections due to damage to skin, vascular, and lymphatics, and/or repeat hospitalisations for treatment of the same infection. We therefore limited the main analysis to participants' first hospitalization with injecting-related infections during the study period (Whitaker et al., 2006; Whitaker & Ghebremichael-Weldeselassie, 2019). We conducted a sensitivity analysis including all hospital admissions with injecting-related infections.

Exposures

Timing of focal windows and referent windows

In separate models, we examined pre-specified time periods, known as "focal windows" (Cadarette et al., 2021). Focal windows for the two main time-varying exposures (incarceration and OAT episodes) were defined as: (a) first two weeks of an exposed/unexposed episode; (b) weeks three and four of an exposed/unexposed episode; (c) weeks five to 52 of an exposed/unexposed episode; and (d) remaining time during an exposed/unexposed episode, beyond 52 weeks. See Fig. 2 for an illustrative schematic.

We also assessed two, two-week time windows immediately before a transition in exposure status (i.e., incarceration admission/release and OAT initiation/discontinuation). If we observed increasing risk of injecting-related infections in time windows preceding a transition (e.g., discontinuation of OAT), it may point to a third factor (e.g., life stressors) contributing to both the outcome and transition in exposure status. If risk of injecting-related infections is elevated immediately following the beginning of incarceration or OAT episodes, this could reflect a process of recognizing pre-existing infections in these settings and facilitating treatment. A potential bias is introduced when including pre-exposure windows, as these rely on "immortal time" (i.e., we can only identify pre-exposure time retrospectively). Also, as we recode these days to be negative, this changes how some exposure episodes (e.g., periods of less than 28 days) are handled in regression models. We

Table 2

Risk of first hospitalization for injecting-related bacterial infections according to time period in relation to incarceration (results of self-controlled case series).

Exposure	Levels	Model 1 (Not including pre-exposure periods)				Model 2 (Including pre-exposure periods)			
		Person-years in this time window (% of total person-years observed)[a]	Events	Incidence rate (per person-year)	aIRR (95% CI)[b]	Person-years in this time window (% of total person-years observed)[a]	Events	Incidence rate (per person-year)	aIRR (95% CI)[b]
Incarceration	4 to 3 weeks before incarceration	-	-	-	-	932 (1.79%)	122	0.13	1.28 (1.06 - 1.54)
	2 weeks before incarceration	-	-	-	-	1026 (1.97%)	125	0.12	1.18 (0.98 - 1.43)
	Incarcerated, first 2 weeks	571 (1.10%)	67	0.12	1.10 (0.85 - 1.40)	414 (0.79%)	49	0.12	1.10 (0.83 - 1.47)
	Incarcerated, weeks 3 and 4	487 (0.93%)	12	0.02	0.23 (0.13 - 0.40)	411 (0.79%)	11	0.03	0.25 (0.14 - 0.45)
	Incarcerated, weeks 5 to 52	4745 (9.11%)	121	0.03	0.23 (0.19 - 0.27)	4067 (7.80%)	99	0.02	0.22 (0.18 - 0.27)
	Incarcerated, beyond 52 weeks	2030 (3.90%)	43	0.02	0.15 (0.11 - 0.21)	1896 (3.63%)	40	0.02	0.16 (0.11 - 0.22)
	4 to 3 weeks before release from incarceration	-	-	-	-	464 (0.89%)	14	0.03	0.29 (0.17 - 0.49)
	2 weeks before release from incarceration	-	-	-	-	581 (1.12%)	30	0.05	0.50 (0.35 - 0.72)
	Community (after release), first 2 weeks	957 (1.84%)	145	0.15	1.45 (1.22 - 1.72)	796 (1.53%)	112	0.14	1.39 (1.14 - 1.69)
	Community, weeks 3 and 4	924 (1.77%)	117	0.13	1.21 (1.00 - 1.47)	786 (1.51%)	100	0.13	1.26 (1.02 - 1.55)
	Community, weeks 5 to 52	11357 (21.8%)	1158	0.1	Reference (1.00)	10427 (20.02%)	1030	0.1	Reference (1.00)
	Community, beyond 52 weeks	31023 (59.6%)	2085	0.07	0.75 (0.69 - 0.82)	30296 (58.2%)	2016	0.07	0.77 (0.70 - 0.83)
Opioid agonist treatment	1 day intervals	-	-	-	0.79 (0.72 - 0.86)	-	-	-	0.79 (0.73 - 0.86)
Age	10 year intervals	-	-	-	0.95 (0.85 - 1.07)	-	-	-	0.95 (0.85 - 1.07)
Calendar year	1 year intervals	-	-	-	1.01 (0.99 - 1.03)	-	-	-	1.01 (0.99 - 1.02)
Time since first opioid agonist treatment	1 year intervals	-	-	-	1 (0.98 - 1.02)	-	-	-	1.00 (0.98 - 1.02)

[a] In this analysis, 3842 participants, associated with 48,950 years of observation time, are excluded because these participants were never incarcerated (so their time under observation could not be categorized in relation to incarceration).

[b] Adjusted incidence rate ratio. Estimated from conditional logistic regression model incorporating all covariates listed in the table.

therefore present regression models both with and without pre-exposure time periods.

For incarceration, referent windows included time periods from week five through week 52 of a continuous episode of community living (i.e., not incarcerated). For OAT, referent windows included time periods from week five through 52 of a continuous OAT episode.

Consistent with prior studies, we defined a new OAT episode as one starting more than six days after the end of a previous episode (Brothers, Lewer, Jones, et al., 2022; Colledge-Frisby et al., 2022; Degenhardt et al., 2009). The same definition was used for defining the end of OAT episodes, interpreting the six days following the final day as exposed to OAT. This was originally based on consultation with clinicians and pharmacologists (Degenhardt et al., 2009) and similar approaches (e.g., three to six days) have been used by other investigators (Cousins et al., 2011; Pearce et al., 2020). In a sensitivity analysis we limited OAT exposure to two days after the final date of the OAT treatment episode, as done in prior studies (Brothers, Lewer, Jones, et al., 2022).

Covariates

Time-invariant confounders (e.g., sex) are eliminated by the self-controlled study design. Time-varying potential confounders were restricted to among those available in this administrative data source. We incorporated into multivariable regression models: calendar year; age; time since first OAT episode; and OAT or incarceration (i.e., time on

OAT treated as covariate in the regression models for incarceration, and vice-versa).

Analyses

We reported characteristics of cases, including age, sex, and Aboriginal or Torres Strait Islander identity. We calculated adjusted incidence rate ratios (aIRRs) using conditional logistic regression, adjusted for time-varying covariates. These compared the incidence of hospitalizations with injecting-related bacterial infections during focal time windows and referent windows. In the sensitivity analysis incorporating all of participants' hospitalizations for injecting-related bacterial infections, we used conditional Poisson regression to calculate aIRRs. All analyses were conducted with R version 4.0.4.

Results

The study included 7590 participants who experienced at least one hospitalization with injection drug use-associated bacterial infections. The median age was 38 years and 35% were female (Table 1). Most hospital admissions included diagnoses of skin and soft tissue infections (5895; 78%). The next most common diagnoses were sepsis/bacteraemia (1048; 14%), endocarditis (406; 5%), and osteomyelitis (347; 5%).

Forty-nine percent of participants experienced incarceration during

Table 3

Risk of first hospitalization for an injecting-related bacterial infection according to time period in relation to opioid agonist treatment (results of self-controlled case series).

Exposure	Levels	Model 1 (Not including pre-exposure periods)				Model 2 (Including pre-exposure periods)			
		Person-years in this time window (% of total person-years)	Events	Incidence rate (per person-year)	aIRR (95% CI)[a]	Person-years in this time window (% of total person-years)	Events	Incidence rate (per person-year)	aIRR (95% CI)[a]
Opioid agonist treatment	4 to 3 weeks before starting OAT	-	-	-	–	738 (0.73%)	145	0.20	2.51 (2.10 - 3.01)
	2 weeks before starting OAT	-	-	-	–	825 (0.82%)	232	0.28	3.63 (3.13 - 4.22)
	On OAT, first 2 weeks	830 (0.82%)	174	0.21	2.49 (2.12 - 2.94)	628 (0.62%)	129	0.21	2.52 (2.09 - 3.04)
	On OAT, weeks 3 and 4	732 (0.72%)	97	0.13	1.58 (1.28 - 1.95)	634 (0.63%)	84	0.13	1.63 (1.30 - 2.04)
	On OAT, weeks 5 to 52	10785 (10.7%)	881	0.08	Reference (1.00)	10186 (10.1%)	802	0.08	Reference (1.00)
	On OAT, beyond 52 weeks	48999 (48.5%)	3234	0.07	0.86 (0.79 - 0.94)	48161 (47.7%)	3119	0.06	0.87 (0.80 - 0.95)
	4 to 3 weeks before stopping OAT	-	-	-	–	795 (0.79%)	101	0.13	1.50 (1.22 - 1.84)
	2 weeks before stopping OAT	-	-	-	–	942 (0.93%)	151	0.16	1.89 (1.59 - 2.25)
	Off OAT, first 2 weeks	773 (0.76%)	119	0.15	1.85 (1.52 - 2.24)	630 (0.62%)	96	0.15	1.91 (1.54 - 2.36)
	Off OAT, weeks 3 and 4	735 (0.73%)	79	0.11	1.30 (1.03 - 1.64)	629 (0.62%)	55	0.09	1.10 (0.84 - 1.45)
	Off OAT, weeks 5 to 52	9804 (9.70%)	992	0.10	1.27 (1.15 - 1.40)	9124 (9.03%)	828	0.09	1.17 (1.06 - 1.30)
	Off OAT, beyond 52 weeks	28386 (28.1%)	2014	0.07	0.98 (0.90 - 1.08)	27752 (27.5%)	1848	0.07	0.92 (0.83 - 1.01)
Incarcerated	1 day intervals	-	-	-	0.28 (0.24 - 0.32)	-	-	-	0.30 (0.26 - 0.35)
Age	10 year intervals	-	-	-	0.98 (0.90 - 1.06)	-	-	-	0.98 (0.90 - 1.06)
Calendar year	1 year intervals	-	-	-	1.02 (1.01 - 1.03)	-	-	-	1.02 (1.01 - 1.03)
Time since first OAT	1 year intervals	-	-	-	0.97 (0.96 - 0.99)	-	-	-	0.98 (0.97 - 0.99)

[a] Adjusted incidence rate ratio. Estimated from conditional logistic regression model incorporating all covariates listed in the table.

follow-up, and the entire sample received OAT at least once (as OAT records were used as the sampling frame). Among the 3748 participants who were in prison at some point, the median number of incarceration episodes was four (interquartile range [IQR] 2-9). Incarceration episodes were a median of 16 (IQR 1-135) days long. Participants had a median of two (IQR 1-4) OAT episodes during the observation period, and the median OAT episode duration was 223 (IQR 33-937) days. See Tables 2 and 3 for the distribution of events and observed time categorized within each window.

Main analysis

Incarceration

Compared to referent windows (i.e., days between five and 52 weeks continuously living in the community, not incarcerated), risk of hospitalization with injecting-related bacterial infections increased during two weeks immediately following release from prison (aIRR 1.45; 95% confidence interval [CI] 1.22-1.72). When participants were incarcerated, risk of injecting-related infections was similar during the first two weeks as in the community (aIRR 1.10; 95%CI 0.85–1.40), then reduced significantly during weeks three and four of incarceration (aIRR 0.23, 95%CI 0.13–0.40) and remained low during the remaining time in prison. See Table 2 for all effect estimates, and Fig. 3 for a visual summary.

In the model incorporating pre-exposure time windows, risk for injecting-related infections was increased during three to four weeks prior to an incarceration episode (aIRR 1.28; 95%CI 1.06–1.54) and was not significantly different in the two weeks immediately preceding incarceration (aIRR 1.18; 95%CI 0.98–1.43).

Opioid agonist treatment

Risk of hospitalization with injecting-related bacterial infections was elevated (aIRR 1.85; 95%CI 1.52–2.24) during the first two weeks after stopping OAT, compared to referent time windows (i.e., during week five to 52 of a continuous OAT episode). Risk continued to be elevated during the first year off-OAT, while time greater than one year off-OAT showed similar risk to week five to 52 of a continuous OAT episode. See Table 3 for all effect estimates, and Fig. 4 for a visual summary.

In the model incorporating pre-exposure time windows, risk for injecting-related infections increased prior to both stopping and starting OAT. The highest relative incidence was in the two weeks preceding OAT initiation (aIRR 3.63; 95%CI 3.13–4.22). Risk of injecting-related infections was similar during the two weeks prior to stopping OAT (aIRR 1.89; 95%CI 1.59–2.25) compared to two weeks after stopping OAT.

Sensitivity analyses

When we included all of participants' hospitalizations with injecting-related infections (rather than just their first hospitalization), there were
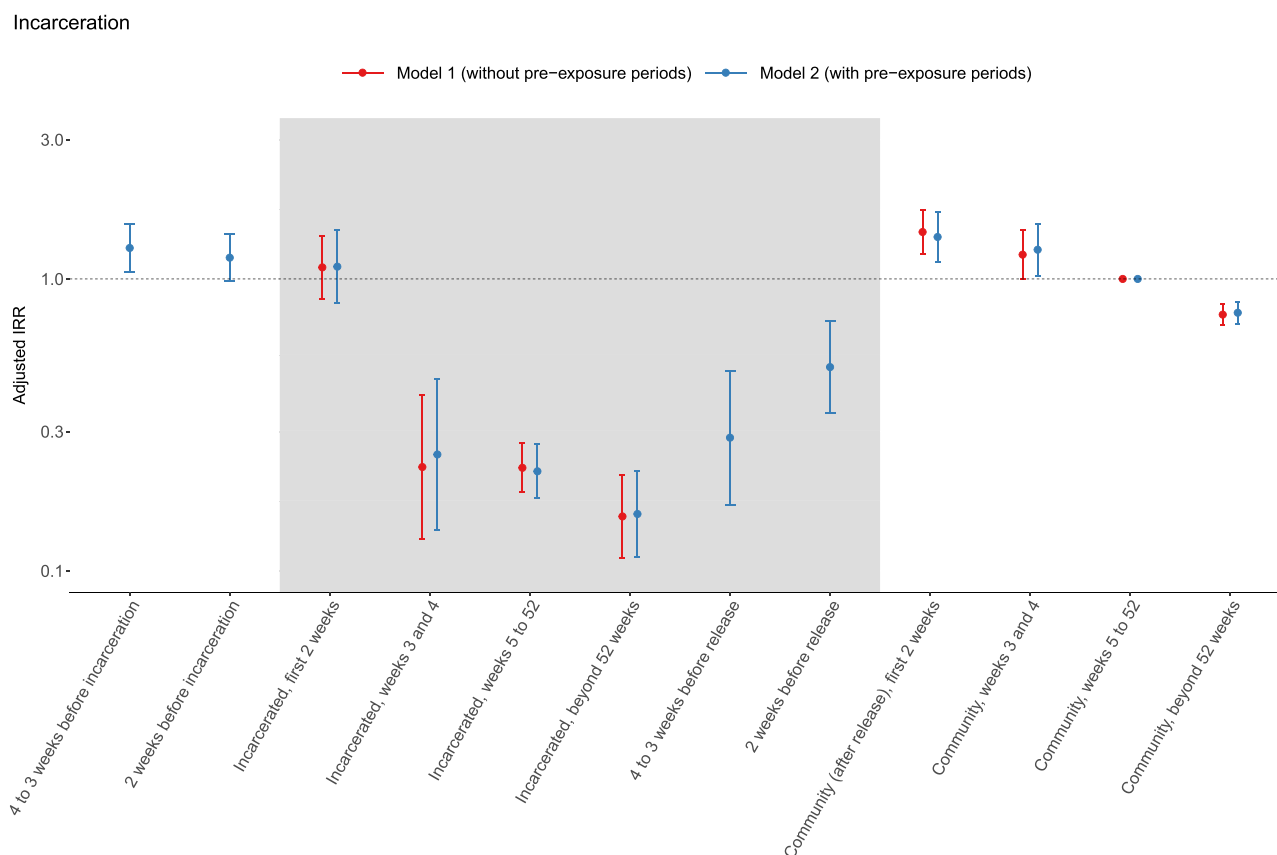
Incarceration

Fig. 3. Relative incidence of hospital admission with injecting-related infections in relation to incarceration time windows in self-controlled case series. Figure shows incident rate ratios (with 95% confidence intervals) during time windows relative to incarceration; the referent time window is time living in the community from 5 to 52 weeks after release from prison, and the grey box highlights time while in prison. IRR: incidence rate ratio.

13,958 hospitalizations; participants experienced a mean of 1.5 admissions each. Results were consistent with our main analysis (Supplementary Appendix Tables S5 and S6). When the OAT exposure definition was limited to include two days after the final date of OAT (rather than six days), results were also similar to the main analysis (Supplementary Appendix Table S7).

Discussion

Within a large cohort of people with opioid use disorder in New South Wales, Australia, we performed a self-controlled study to test the effect of incarceration and OAT transitions on the risk of hospitalization with injection drug use-associated bacterial infections. Compared to time between five and 52 weeks continuously living in the community, incidence of injecting-related infections increased before incarceration; was similar during the first two weeks of incarceration; and then substantially decreased among people in prison for more than three weeks. Risk was again elevated in the weeks immediately following release from prison. Compared to time between five and 52 weeks continuously receiving OAT, incidence of injecting-related infections was highest during the weeks both before and after OAT initiation and OAT discontinuation. Overall, we found that risk for injecting-related bacterial infections varies greatly within-individuals over time. Social contextual factors likely contribute to the substantially raised risks around transitions in incarceration and OAT exposure. People entering and leaving prison, and people starting and stopping OAT, may benefit from improved access to harm reduction programs and health and social services to prevent injecting-related bacterial infections. Changes in the risk of hospital admissions with injecting-related infections in and out of prison and OAT may also reflect changes in the ability to access primary

and secondary health services.

The increase in risk immediately following prison release may reflect return to injection use, poor access to health and social supports, and material deprivation (poverty and homelessness) (Binswanger et al., 2012; Joudrey et al., 2019; Treloar et al., 2021). This underscores that people leaving prison would benefit from better health, social, and economic supports, and linkages to harm reduction services and primary care. The excess risk for injecting-related infections during this time period (when compared to people injecting drugs in the community at other times, we estimate 1.45 times the risk, 95% CI 1.22-1.72) may be more modest than that seen for overdose (e.g., 2.44 times higher fatal overdose rate in a cohort study from New South Wales, Australia (Degenhardt et al., 2014); 2.76 times higher nonfatal overdose risk in a self-controlled cases series from British Columbia, Canada (Keen et al., 2021)). Incarceration often leads to loss of opioid tolerance, especially among people not receiving OAT in prison (Degenhardt et al., 2014; Joudrey et al., 2019), which likely increases overdose risk more so than infection risk. Given that the median duration of prison stay was only 16 days, excess risk of infection-related hospitalization after release may also reflect people seeking treatment outside prison for infections that initially developed before or during incarceration (Lloyd et al., 2015).

Several prior studies assessed whether people who were recently incarcerated (e.g., past year) were more likely to experience injecting-related infections than people who had not been incarcerated. Some found increased risk (Colledge-Frisby et al., 2022; Lloyd-Smith et al., 2005; Milloy et al., 2010; Wheeler et al., 2022) and some found similar risks (Hope et al., 2014, 2015; Pollini et al., 2010). Our self-controlled (within-person) study demonstrated changing risk of injecting-related infections over time among a subsample of people who all experienced incarceration at some point. Decreased incidence of severe

Opioid agonist treatment
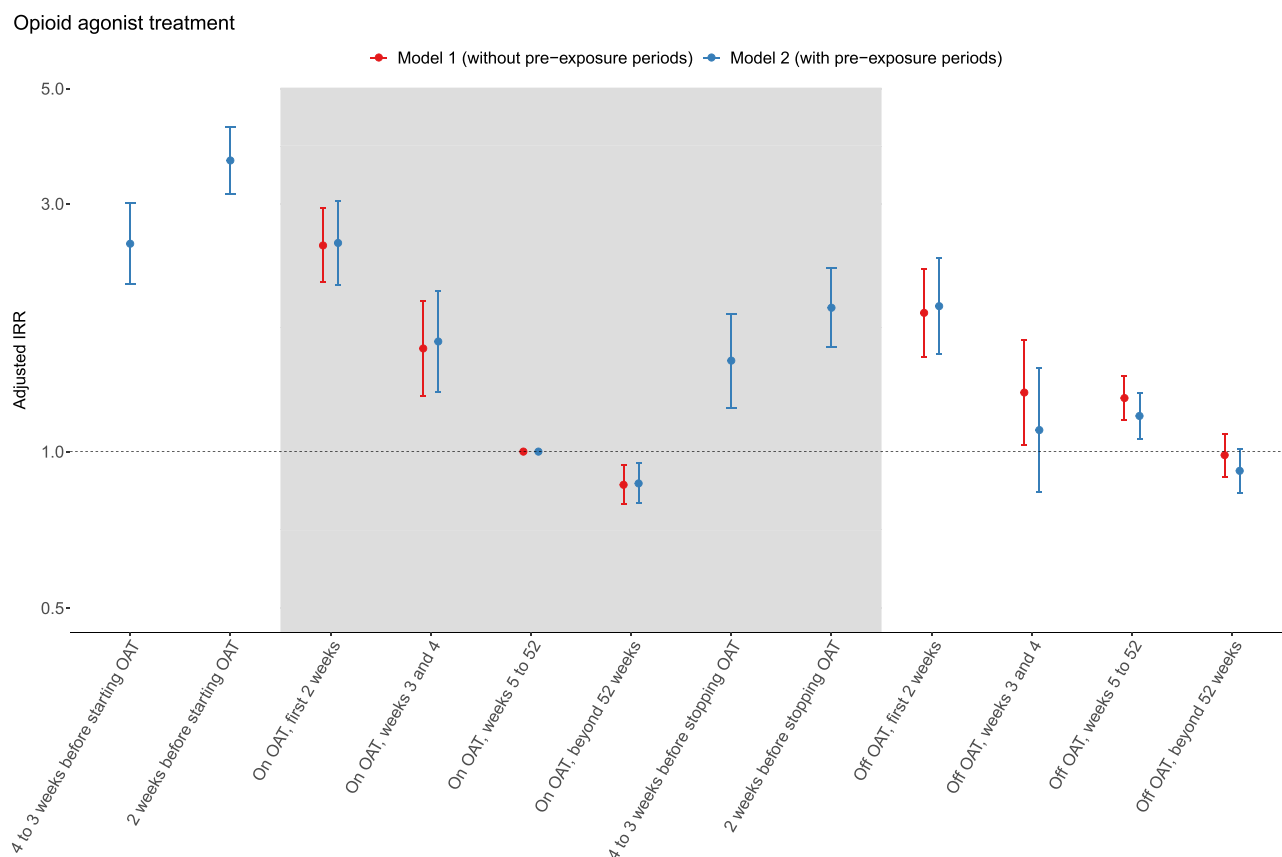
Fig. 4. Relative incidence of hospital admission with injecting-related infections in relation to opioid agonist treatment time windows in self-controlled case series. Figure shows incident rate ratios (with 95% confidence intervals) during time windows relative to opioid agonist treatment; the referent time window is time from 5 to 52 weeks continually on opioid agonist treatment, and the grey box highlights time while receiving OAT. IRR: incidence rate ratio.

injecting-related infections while in prison likely reflects decreased access to drugs and reduced frequency of injection use. A longitudinal study in New South Wales found the prevalence of self-reported injection drug use dropped by around two-thirds once people were incarcerated (Cunningham et al., 2018). Sustained reductions in risk during incarceration may also reflect differences in ability to access primary health services and/or the propensity of prison staff to transport a person in prison to an external hospital setting (Edge et al., 2020; Lloyd et al., 2015).

Our results also show that risk for injecting-related bacterial infections is increased immediately following discontinuation of OAT. While some excess risk may be attributable to loss of protective effects of OAT medications, we observed that risk began to increase in the weeks preceding OAT discontinuation. This suggests that underlying stressors or other contextual factors in peoples' lives may increase risks for both injecting-related bacterial infections and OAT discontinuation. Similarly, we observed increased risk for injecting-related infections during the first two weeks of OAT compared to time more stable on OAT (after one month continually on treatment), but the highest relative risks were in the two weeks preceding OAT initiation. This suggests that changes in risk of injecting-related infections seen around times of OAT transitions may reflect other contextual factors, rather than the benefits of OAT medications alone.

These within-person findings support the results of a cohort study by Colledge-Frisby and colleagues (which used the same parent study dataset) that risk for injecting-related infections was highest before starting OAT (Colledge-Frisby et al., 2022). This suggests that developing an injecting-related infection may motivate people to initiate OAT, or may reflect referrals to OAT from health care settings when people seek treatment for injecting-related infections.

Our findings that risk of injecting-related infections was modestly higher while off OAT (e.g., around 1.3 times relative incidence) compared to time receiving OAT is consistent with several recent studies (Brothers, Lewer, Jones, et al., 2022; Colledge-Frisby et al., 2022; Dunleavy et al., 2017; V. Hope et al., 2008). This suggests that OAT should be offered as part of a strategy for primary and secondary prevention injecting-related infections, but OAT alone is unlikely to prevent a large proportion of infections. Preventing injecting-related infections likely requires more broadly addressing the social determinants of health, including the social and material conditions within which people obtain drugs, prepare and inject them, and access health and social care (Bonn et al., 2020; Brothers et al., 2021, 2023; Collins et al., 2019; Rhodes et al., 2012; Touesnard et al., 2022).

Limitations

Our study has five key limitations. First, self-controlled designs do not produce estimates of absolute risk, only relative risk (Whitaker et al., 2006). However, estimates of relative risk in self-controlled studies are applicable to the wider population from which the cases were drawn (Lewer et al., 2022; Whitaker et al., 2006). Second, some time-varying exposures are not measured in the administrative data, including individual injecting behaviours, the evolving unregulated drug supply, housing, income supports, life stressors, and access to harm reduction services; these may be important contributors to infections that we could not account for. For example, we do not have information on how participants' injecting frequency changed before, during, and after incarceration. Prior research suggests that injecting frequency decreases when people are incarcerated (Cunningham et al., 2018), but people who have recently been incarcerated are less likely to stop injecting

drugs than people who have not been incarcerated (DeBeck et al., 2009). Some of these exposures, including injecting frequency, may be better characterized as mediators rather than confounders, and so would not necessarily be included in multivariable regression models. Third, onset duration of injecting-related infections might vary from days to weeks between an initial abscess and hospitalization, so timing might differ from (or overlap) our focal windows. To account for this, we pre-specified time windows to comprise at least two weeks duration. Fourth, our study excludes people who were never on OAT, but prior work suggests most people with opioid use disorder in New South Wales have accessed OAT at some point (Brothers, Lewer, Jones, et al., 2022; Colledge-Frisby et al., 2022; Larney et al., 2018). Fifth, we do not have reliable data on people's reasons for discontinuing OAT; future work accounting for motivations to discontinue OAT could help with understanding risks observed around this time (Thakrar et al., 2023).

Conclusions

Risk for severe injection drug use-associated bacterial infections varies greatly within individuals over time. Time periods leading up to, and immediately following release from, incarceration are associated with excess risk, as are time periods around initiation and discontinuation of OAT. Social contextual factors likely contribute to the substantially raised risks preceding transitions in incarceration and OAT exposure. People entering and leaving prison, and people starting and stopping OAT, may benefit from improved access to harm reduction programs and health, social, and economic services to help prevent injecting-related bacterial infections. Improved access to primary care (e.g., through outreach or embedded with harm reduction programs) could also facilitate early diagnosis and treatment of superficial infections before they progress and require hospital admission.

Ethics and approvals

Approval for the OATS Study is provided by New South Wales Population & Health Services Research Ethics Committee (2018/HRE0205), the NSW Corrective Services Ethics Committee and the Aboriginal Health and Medical Research Council Ethics Committee (1400/18).

CRediT authorship contribution statement

Thomas D. Brothers: Writing – original draft, Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Dan Lewer:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Nicola Jones:** Writing – review & editing, Resources, Project administration, Data curation, Conceptualization. **Samantha Colledge-Frisby:** Writing – review & editing, Investigation, Conceptualization. **Matthew Bonn:** Writing – review & editing, Investigation, Conceptualization. **Alice Wheeler:** Writing – review & editing, Investigation, Conceptualization. **Jason Grebely:** Writing – review & editing, Investigation, Conceptualization. **Michael Farrell:** Writing – review & editing, Investigation, Conceptualization. **Matthew Hickman:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Andrew Hayward:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Louisa Degenhardt:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MB reports personal fees from AbbVie, a pharmaceutical research and development company, and grants and personal fees from Gilead Sciences, a research-based biopharmaceutical company, outside of the submitted work. JG is a consultant/advisor and has received research grants from AbbVie, bioLytical, Camurus, Cepheid, Gilead Sciences, Hologic, and Indivior. LD and MF have received untied educational grant funding from Indivior and Seqirus. The other authors report no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2023.104218.

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