Title

Enhancing Compassion to Self and Others Through the Use of a Compassion Training Program in End-of-Life Research Professionals

Journal

Journal of Palliative Medicine, 29(5)

ISSN

1096-6218

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Publication Date

2026-05-01

DOI

10.1177/10966218251414277

Received: 20 January 2026 | Revised: 2 March 2026 | Accepted: 9 March 2026

DOI: 10.1002/bcp.70535

ORIGINAL ARTICLE

Mapping opioid exposure through prescription data and postmortem analysis of opioid drugs in multiple tissues

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Funding information
We gratefully acknowledge support received from P01 AI169609 (Smith – Leaving, Coming

Background and Purpose: Although opioids are central to end of life (EoL) care, tissue-level opioid exposure remains poorly understood. The objective of this study was to characterize the relationship between prescription-derived morphine equivalent daily dose (MEDD) and measured morphine concentrations across multiple organs.

Experimental Approach: We analysed data from the *Last Gift* cohort, a community-centred HIV research rapid autopsy programme. Cumulative MEDD for the final 7 and 30 days before death (MEDD-7, MEDD-30) was calculated using prescription data. Postmortem samples from multiple organs were analysed using ultra-high-performance liquid chromatography with tandem mass spectrometry to quantify opioids. Mixed-effects regression models and Pearson correlations evaluated relationships between MEDD and tissue morphine concentrations.

Key Results: Among 261 samples from 27 participants (median age 65 years), 96% had ≥1 detectable opioid. Morphine was most frequently prescribed (78%), followed by fentanyl (41%), hydromorphone (37%), and oxycodone (33%). Median MEDD-7 and MEDD-30 were 940 (IQR 158–3481) and 3430 (IQR 563–9972), respectively. Morphine concentrations were highest in the ascending colon, kidney, duodenum, and liver, and lowest in adipose tissue and cerebrospinal fluid. Tissue morphine concentrations correlated with both MEDD-7 and MEDD-30 (e.g., medulla $r = .80$; spinal cord $r = .77$; parietal cortex $r = .72$; all $p < .01$). In adjusted mixed-effects models, each 10-fold increase in MEDD-7/-30 predicted a 3.7- to 3.8-fold increase in tissue morphine concentration.

Antoine Chaillon and Sara Gianella contributed equally to this work and are joint senior authors.

and Staying HIV Obligate Microenvironments [HOME]), R01 DA055491, and DA062278. This research was supported by the Center for AIDS Research, University of California, San Diego, a National Institutes of Health-funded program (P30 AI036214), which is supported by the following NIH Institutes and Centers: NIAID, NCI, NHLBI, NIA, NICHD, NIDA, NIDCR, NIDDK, NIMH, NIMHD, NINR, FIC, and OAR. This also supported by The James B. Pendleton Charitable Trust.

Conclusion and Implications: Prescription-based morphine exposure was strongly associated with morphine tissue concentrations across multiple organs, providing a quantitative framework for integrating pharmacologic data into EoL research.

KEYWORDS
drug distribution, end-of-life research, HIV, morphine, opioid analgesics, pharmacokinetics, translational pharmacology

1 | INTRODUCTION

Opioids are used for managing chronic pain and remain a cornerstone of palliative and end-of-life (EoL) care. They are among the most effective agents for alleviating severe pain in individuals with advanced illness.[1,2] Beyond analgesia, opioids are widely used in EoL settings to manage distressing symptoms such as dyspnea, agitation, and anxiety,[2] consistent with the principles of palliative care, to prioritize symptom relief, preserve dignity and improve quality of life.[3]

Chronic pain is more prevalent among people with HIV (PWH) relative to the general population,[4] with estimates ranging from 39% to 85%.[5] This disparity reflects a complex interplay of HIV-related complications, comorbidities, aging, and psychosocial factors.[6] The burden of chronic pain is often compounded by depression and anxiety, further increasing reliance on opioids.[7] As a result, PWH are at an elevated risk for opioid-related complications, including misuse, dependency, and overdose.[6,8]

Despite the widespread use of opioids in clinical and EoL care, systematic methods for characterizing opioid exposure in PWH, particularly in the context of HIV pathogenesis and cure research, remain underdeveloped and are frequently subject to confounding by comorbidities, polypharmacy, and variability in clinical documentation.[9] Existing studies rely on prescription records, converted to oral morphine equivalent daily dose (MEDD), to estimate cumulative exposure.[10,11] While informative, this approach overlooks individual pharmacokinetic variability and fails to capture opioid distribution across tissues, including sanctuary sites such as the central nervous system. Emerging evidence suggests that opioids shape immune responses and viral persistence,[12–22] underscoring the importance of examining their effects at the tissue level in PWH. Measuring opioid concentrations in solid tissues remains an underexplored approach that could illuminate opioid pharmacology, tissue-level variability, and exposure patterns in real-world EoL settings. To our knowledge, no prior studies have directly compared prescription-based MEDD estimates with pharmacologic measurements in postmortem tissues. Establishing this link may also inform studies of other EoL medications and their interactions with HIV reservoirs or host immunity.

The *Last Gift* is a unique, community-centred research cohort of altruistic PWH diagnosed with life-limiting illnesses who elect to contribute to HIV cure research through rapid autopsy.[23] This programme provides a rare and valuable opportunity to examine the relationship between prescribed opioid exposure and actual tissue concentrations in a well-characterized, EoL population.

What is already known about this subject

- Opioids are central to end-of-life care, yet the relationship between prescribed opioid dose and tissue-level drug exposure in humans is poorly understood.
- Morphine equivalent daily dose (MEDD) is widely used to standardize opioid prescribing but has not been directly linked to multi-organ tissue concentrations.
- Existing data on opioid tissue distribution largely derive from forensic overdose studies and may not reflect therapeutic end-of-life use.

What this study adds

- In a rapid research autopsy cohort, prescription-derived MEDD was strongly associated with measured morphine concentrations across multiple organs.
- The relationship between MEDD and tissue morphine concentration was sublinear, with each 10-fold increase in MEDD predicting a ~3.7-fold increase in tissue levels.
- These findings provide a quantitative framework linking standardized prescribing metrics to tissue-level opioid exposure in advanced illness.

In this study, we quantified opioid exposure in *Last Gift* participants during the final weeks of life using both standardized MEDD data derived from medical records and pharmacokinetic analyses of postmortem tissues. Our primary aim was to characterize the relationship between prescription-based MEDD and measured morphine concentrations across multiple organs—a relationship that we believe has not been systematically evaluated in people with life-limiting illnesses. Alongside these analyses, we report postmortem concentrations of several clinically relevant opioids across multiple organs and brain regions, offering descriptive pharmacokinetic data that, to our knowledge, have not been previously characterized in this context. By establishing the feasibility of integrating clinical dosing histories with tissue pharmacology, this work provides foundational data to support future investigations using the *Last Gift* platform to examine opioid pharmacology, immune effects, and HIV persistence at the EoL.

2 | METHODS

2.1 | *Last Gift* cohort

The *Last Gift* rapid autopsy programme enrols altruistic individuals aged 18 and older with HIV and who have been diagnosed with a life-limiting illness. A comparison group of people without HIV (PWoH) and advanced illness is also enrolled. All participants provided written informed consent prior to enrolment in San Diego, California. Diagnoses include malignancies, end-stage organ diseases, opportunistic infections, and neurodegenerative conditions.

Variables used in these analyses were derived from participant intake interviews and electronic medical records (EMR), including demographics, medical histories, and medication histories. All study data were entered into the secure UC San Diego *Last Gift* REDCap database (Vanderbilt University, TN). The study was approved by the UC San Diego Institutional Review Board (IRB #160563) and the use of secondary stored tissue samples was covered under the parent consent.

2.2 | Prescription data

A detailed EMR review was conducted to extract opioid exposure data, including drug name, dosage, frequency, route of administration, quantity, and dates of initiation/discontinuation. Sources included inpatient and outpatient prescriptions, hospice documentation, progress notes, and internal chart notes. Extracted data were entered into a dedicated opioid exposure database.

All opioid dosages were converted into MEDD using a custom conversion table developed by the *Last Gift* team based on consensus guidelines and literature.[24] The opioid dose and frequency were used to calculate the total daily dose, which was then converted into MEDD using a conversion factor. For example, oxycodone 10 mg once daily corresponds to a MEDD of 15. Cumulative opioid exposure was calculated by multiplying the MEDD by the number of days between stop and start dates of a prescription. In the absence of medication administration records, it was assumed that doses were administered according to the prescription. For outpatient prescriptions, information on the quantity dispensed informed the dates of initiation/discontinuation. Total MEDD exposure was calculated for the final 7 (MEDD-7) and 30 days (MEDD-30) before death.

2.3 | Quantification of opioids with UHPLC-MS/MS

Postmortem tissue samples were collected during rapid research autopsies (within 6 h of death) and analysed via ultra-high-performance liquid chromatography combined with tandem mass spectrometry (UHPLC-MS/MS) for the presence of seven commonly used opioids: methadone, morphine, oxycodone, hydrocodone, oxymorphone, hydromorphone, and fentanyl.[25] Given morphine's widespread clinical use, analyses focused on morphine concentrations. Anatomical sites analysed included, but were not limited to, liver, kidney, brain (multiple regions), lung, abdominal adipose tissue, and cerebrospinal fluid (Table S1). All tissue analyses were conducted at the Laboratory of Clinical Pharmacology and Pharmacogenetics, Department of Medical Sciences, University of Turin.

The UHPLC-MS/MS method was previously fully validated as described in our methods paper.[25] Validation included assessment of accuracy, precision, recovery, matrix effects, and stability across analysed matrices. Matrix effects were evaluated in all tissue types using post-extraction addition experiments and the Matuszewski approach (comparison of calibration curve slopes across matrices). Although matrix-dependent variability was observed, stable isotope–labelled internal standards compensated for these effects, with coefficients of variation within accepted validation criteria.

Following demonstration of matrix interchangeability with acceptable accuracy and precision across tissues, calibration curves were prepared in plasma for routine quantification. Plasma-based calibration was adopted only after validation confirmed analytical equivalence between plasma and solid tissue matrices.

Analyte stability was evaluated for up to 4 months under frozen storage conditions, with no evidence of degradation. Liver tissue was selected as the reference matrix for stability testing due to its biochemical complexity and theoretical susceptibility to instability; stability was also confirmed in plasma for comparison (see Supplementary Materials[25]).

Biological specimens were transported from San Diego (USA) to Torino (Italy) under validated IATA-compliant cold-chain conditions. Samples were verified as fully frozen (−80°C) prior to shipment, packaged with calculated quantities of dry ice, and inspected upon arrival with confirmation of residual dry ice before immediate transfer to −80°C storage.

2.4 | Data analysis

Descriptive statistics summarized demographic and clinical characteristics. Individuals without a documented opioid exposure during the last 30 days before death were excluded. Samples were excluded when an individual had no documentation of a specific opioid prescription *and* the tissue samples were undetectable for the corresponding opioid. For example, if a participant had no documentation of a morphine prescription and morphine was undetectable in all their tissue samples, it was assumed that this participant did not receive morphine, and their samples were excluded from the analysis. For brain tissue and lymph node tissue, arithmetic means across sampled regions were calculated as the composite brain concentration and composite lymph concentration.

Values below the lower limit of quantification (LLOQ) were imputed assuming a log-normal distribution estimated by maximum likelihood from left-censored data. Imputations were performed at the replicate level, and all replicates were included in the analyses. MEDD and tissue concentrations were $\log_{10}$-transformed. Multiple

TABLE 1 Demographic and clinical characteristics.

Characteristic	Overall $N = 27$[a]	Morphine unexposed $N = 8$[a]	Morphine exposed $N = 19$[a]
Age at enrolment	65 (58, 72)	64 (62, 68)	66 (52, 72)
Sex at birth			
Male	23 (85%)	7 (88%)	16 (84%)
Female	4 (15%)	1 (13%)	3 (16%)
Race			
White	22 (81%)	5 (63%)	17 (89%)
Black/African American	3 (11%)	2 (25%)	1 (5.3%)
Declines to State	1 (3.7%)	1 (13%)	0 (0%)
Other or Multiracial	1 (3.7%)	0 (0%)	1 (5.3%)
Ethnicity			
Hispanic/Latino(a)	3 (11%)	1 (13%)	2 (11%)
Not Hispanic/Latino(a)	24 (89%)	7 (88%)	17 (89%)
Life-limiting illness			
Neurological disease			
No	24 (89%)	8 (100%)	16 (84%)
Yes	3 (11%)	0 (0%)	3 (16%)
Hematologic malignancy			
No	23 (85%)	8 (100%)	15 (79%)
Yes	4 (15%)	0 (0%)	4 (21%)
Solid tumour malignancy			
No	15 (56%)	3 (38%)	12 (63%)
Yes	12 (44%)	5 (63%)	7 (37%)
Renal disease			
No	22 (81%)	5 (63%)	17 (89%)
Yes	5 (19%)	3 (38%)	2 (11%)
Pulmonary disease			
No	25 (93%)	8 (100%)	17 (89%)
Yes	2 (7.4%)	0 (0%)	2 (11%)
Infectious disease			
No	26 (96%)	8 (100%)	18 (95%)
Yes	1 (3.7%)	0 (0%)	1 (5.3%)
Hepatic disease			
No	25 (93%)	6 (75%)	19 (100%)
Yes	2 (7.4%)	2 (25%)	0 (0%)
HIV status			
HIV+	25 (93%)	8 (100%)	17 (89%)
HIV−	2 (7.4%)	0 (0%)	2 (11%)
Last HIV RNA suppressed			
No	2 (8.0%)	1 (13%)	1 (5.9%)
Yes	23 (92%)	7 (88%)	16 (94%)
Unknown	2	0	2
Last CD4 T-cell count	212 (100, 397)	187 (129, 309)	237 (87, 467)
Nadir CD4 count	91 (41, 212)	153 (74, 204)	74 (29, 287)
Postmortem interval (h)	5.99 (5.50, 6.52)	7.62 (5.87, 8.72)	5.92 (5.45, 6.07)
Unknown	1	1	0
Duration of HIV infection (year)	23 (20, 32)	28 (20, 36)	23 (20, 32)

TABLE 1 (Continued)

Characteristic	Overall $N = 27$[a]	Morphine unexposed $N = 8$[a]	Morphine exposed $N = 19$[a]
Unknown	2	0	2
Opioid use in last 30 days of life			
No	1 (3.7%)	1 (13%)	0 (0%)
Yes	26 (96%)	7 (88%)	19 (100%)
30-day MEDD (total, all opioid RX)	3430 (563, 9972)	1340 (323, 5761)	5228 (773, 13 141)
7-day MEDD (total, all opioid RX)	940 (158, 3481)	362 (68, 1988)	1410 (263, 3600)
30-day MEDD (total, all morphine RX)	288 (0, 3720)	0 (0, 0)	1395 (240, 6000)
7-day MEDD (total, all morphine RX)	240 (0, 1280)	0 (0, 0)	615 (120, 3249)
Fentanyl			
IV	7 (26%)	3 (38%)	4 (21%)
TD	4 (15%)	1 (13%)	3 (16%)
Hydrocodone			
PO	1 (3.7%)	0 (0%)	1 (5.3%)
Hydromorphone			
IV	8 (30%)	5 (63%)	3 (16%)
PO	2 (7.4%)	0 (0%)	2 (11%)
Meperidine			
IV	1 (3.7%)	0 (0%)	1 (5.3%)
Methadone			
IV	1 (3.7%)	0 (0%)	1 (5.3%)
PO	4 (15%)	0 (0%)	4 (21%)
Morphine			
IV	7 (26%)	0 (0%)	7 (37%)
PO	14 (52%)	0 (0%)	14 (74%)
Opium			
PO	1 (3.7%)	0 (0%)	1 (5.3%)
Oxycodone			
PO	8 (30%)	5 (63%)	3 (16%)
Sufentanil			
IV	1 (3.7%)	0 (0%)	1 (5.3%)
Tramadol			
PO	4 (15%)	2 (25%)	2 (11%)

[a]Median (Q1, Q3); *n* (%).

Abbreviations: IV, intravenous; PO, oral; RX, prescription; TD, transdermal.

imputation (m = 10) was applied and results were pooled using Rubin's rule.[26] The LLOQ for each drug is provided in the Supporting Information (Table S2). Mixed-effects regression models were fitted with $\log_{10}$-transformed morphine tissue concentration as the outcome and $\log_{10}$-transformed MEDD as the predictor with statistical significance set at $p < .05$ (see groups in Table S1). Tissue group was included as a fixed effect with random intercepts for individuals to account for clustering of multiple tissue samples within participants. Likelihood-ratio tests assessed random slopes. Replicate-level results were incorporated. Pearson correlation coefficients between tissue concentrations and MEDD were calculated for descriptive purposes (averaged across replicates) with statistical significance set at $p < .05$. Analyses were performed in R v4.4.1.

3 | RESULTS

Demographic and clinical characteristics of the cohort are presented in Table 1. Among 27 participants contributing postmortem tissue samples included in this analysis ($N = 261$), 26 had detectable concentrations of at least one opioid. Twenty-five participants were PWH and two were PWoH. Age ranged from 30 to 89 years. Participants

were predominantly male (85%, $n = 23$), non-Hispanic (89%, $n = 24$) and White (81%, $n = 22$). The most common life-limiting illnesses included solid tumour malignancy (44%, $n = 12$), kidney disease (19%, $n = 5$), hematologic malignancy (15%, $n = 4$), and neurological disease (11%, $n = 3$). The median (IQR) time from death to autopsy conclusion was 6 h (5.5–6.5).

3.1 | Opioid use

Opioid consumption during the final month of life is summarized in Table 1. The most used (non-mutually exclusive) opioids were morphine (78%), fentanyl (41%), hydromorphone (37%), and oxycodone (33%). Three participants independently elected to use medical aid-in-dying (MAID) protocols outside the context of the research study, each of which included 15 g of morphine. The median MEDD-7 and MEDD-30 exposure prior to death were 940 (IQR: 158–3481) and 3430 (IQR: 563–9972), respectively.

We reviewed antiretroviral therapy (ART) regimens at the time of death to assess for potential opioid–ART drug–drug interactions. Of 27 participants, 19 received concomitant ART and opioids; among these, three were prescribed boosted protease inhibitor—or cobicistat-containing regimens with theoretical interaction potential. Only one participant receiving such a regimen also received morphine, and exposure was limited.

3.2 | Body site distribution of opioid concentrations

The median (min, max) concentrations of all opioids across anatomical sites are presented in Table S3. Figure 1 illustrates morphine concentrations across body tissues. Highest median concentrations were observed in the ascending colon (2246 ng/g), kidney (948 ng/g), duodenum (755 ng/g), and liver (687 ng/g), with lowest levels in abdominal adipose (29 ng/g), cerebrospinal fluid (CSF; 44 ng/g), and pericardial adipose (65 ng/g). A heatmap depicting morphine concentrations for each participant across anatomical regions is presented in Figure S1.

3.3 | Relationship between MEDD and morphine concentrations

Morphine concentrations were strongly correlated with both MEDD-7 and MEDD-30 across several tissues (Table 2). The strongest correlations for MEDD-7 were observed in the medulla ($r = .80$), spinal cord ($r = .77$), ascending colon ($r = .71$) and parietal cortex ($r = .72$); similar results were seen for MEDD-30. In mixed-effects models adjusting for individual variability and tissue compartment, both MEDD-7 and MEDD-30 remained significant predictors of morphine concentration (Table 3). A 10-fold increase in morphine dose over the final 7 days was associated with a 3.7-fold increase in tissue concentration ($\beta = 0.566$; 95% CI 0.101–1.031), and a 3.8-fold increase over 30 days ($\beta = 0.582$; 95% CI 0.249–0.914).

Significant mean differences between tissue groups were also observed; for the 30-day model, compared with adipose tissue (reference), estimated effects were central nervous system tissues $\beta = 0.300$ (95% CI: 0.127–0.474; ≈2.00-fold higher), gastrointestinal tract $\beta = 0.951$ (0.766–1.136; ≈8.93-fold higher), genitourinary tract $\beta = 0.848$ (0.657–1.038; ≈7.05-fold higher), liver $\beta = 0.866$ (0.612–1.119; ≈7.35-fold higher), lung $\beta = 1.021$ (0.761–1.282; ≈10.50-fold higher), pancreas $\beta = 0.735$ (0.465–1.005; ≈5.43-fold higher), spleen $\beta = 0.841$(0.558–1.125; ≈6.93 fold higher), and heart $\beta = 0.837$ (0.570–1.104; ≈6.87-fold higher). These results indicate significantly higher morphine concentrations across nearly all tissue compartments relative to adipose tissue, with the largest differences observed in lung, gastrointestinal tract, liver, spleen, and heart. Similar results were observed in the 7-day model.

4 | DISCUSSION AND CONCLUSIONS

Opioid therapy is central to symptom management for people with advanced illness, yet little is known about how prescribed opioid doses relate to actual tissue-level drug exposure, particularly at the EoL. Postmortem studies that integrate prescription data with multiorgan drug measurements are rare but essential for understanding opioid pharmacokinetics in real-world clinical contexts. In this study, we empirically quantified morphine concentrations across multiple tissues in PWH at the EoL and examined how these levels related to morphine exposure derived from standardized prescription measures (MEDD). This approach provides a unique window into in vivo opioid distribution during the final stages of life.

We found that morphine concentrations were highest in the colon and kidney, with substantial heterogeneity across tissue groups. According to our mixed-effects model, concentrations in gastrointestinal tissues and lung exceeded those of adipose tissue by nearly an order of magnitude. This pattern aligns with morphine's hydrophilicity[27] and the influence of tissue perfusion and water content on drug distribution. Morphine consumption (MEDD) during both the last 7 and 30 days before death strongly predicted morphine concentrations in multiple tissues, including brain regions implicated in pain processing, emotional regulation, and reward. Together, these results offer a foundation for understanding how prescribed morphine doses map onto actual tissue exposure in PWH at the EoL.

A major observation was the sublinear relationship between standardized MEDD and tissue morphine concentrations. Increases in MEDD were associated with smaller-than-proportional increases in tissue morphine levels. Several pharmacokinetic mechanisms could explain this pattern, including limited or compartment-specific tissue diffusion, saturation of tissue binding sites, reduced clearance or redistribution in advanced illness, or slow equilibration or accumulation in specific anatomic sites—especially in the three participants who ingested MAID regimens and may not have reached full tissue distribution before death. The similarity in effect sizes between

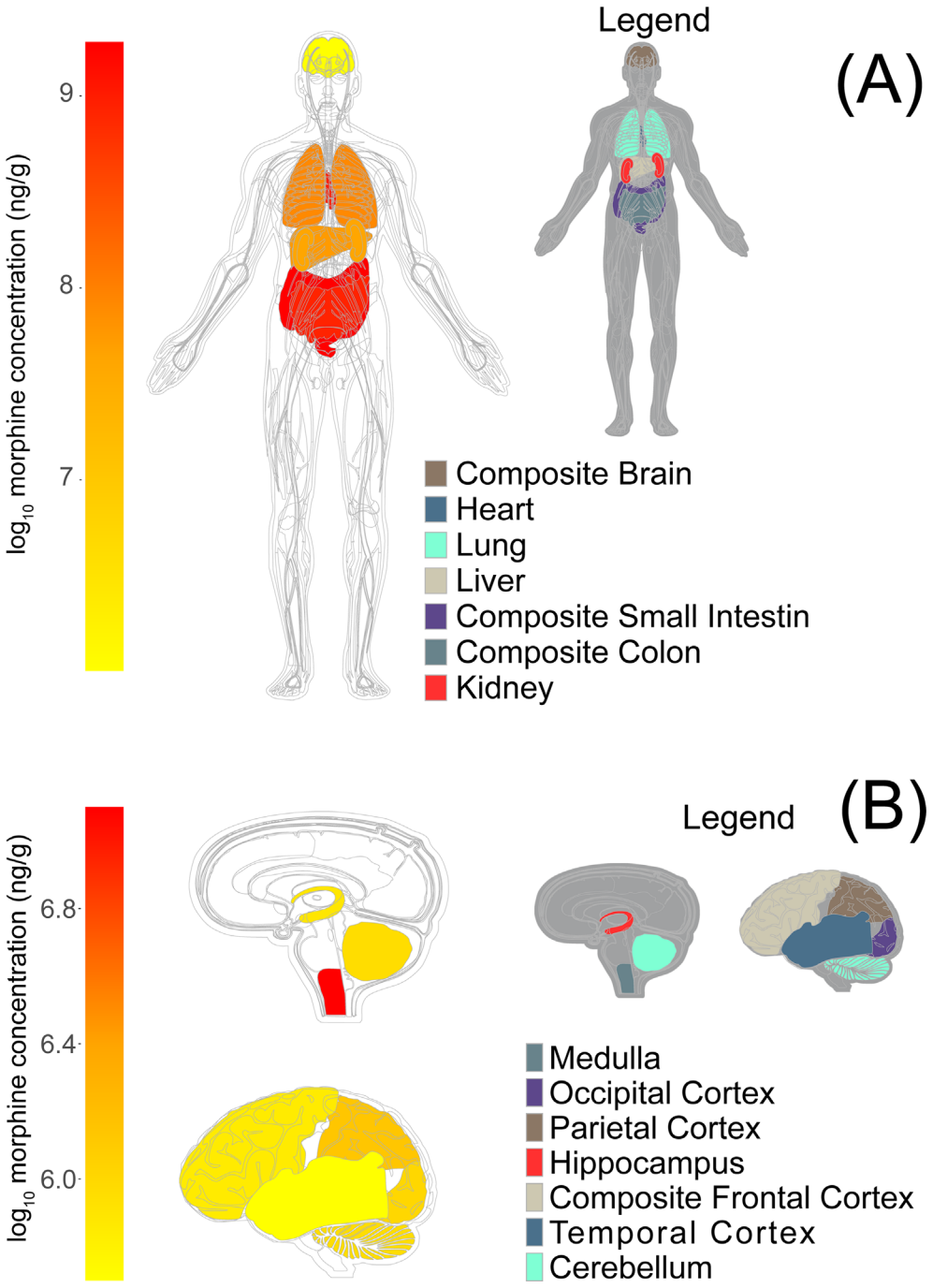

FIGURE 1 Heat map: log_{10} transformed mean morphine concentration across all individuals within each systemic tissue (a) and central nervous system (b). Descending and acending colon averaged to create large intestine. Duodenum, ileum, jejunum averaged to create small intestine. Colour key. The colour scale indicates the level of log_{10} transformed tissue morphine concentrations. A high positive log_{10}-fold change (red) signifies higher concentrations, while a low log_{10}-value (yellow) indicates lower concentrations.

MEDD-7 and MEDD-30, suggests that tissue morphine concentrations may integrate cumulative exposure, rather than reflecting only recent dosing. This supports the idea of a possible saturation or 'ceiling effect', where tissues reach stable concentration ranges despite escalating opioid doses. These observations underscore the need for further research to clarify how both short- and long-term morphine exposure shape tissue pharmacokinetics in people with advanced illness.

Although pharmacokinetic interactions between certain ART regimens and opioids are biologically plausible—particularly for CYP3A4 substrates[28]—only one participant receiving morphine was exposed to a boosted regimen. In addition, morphine primarily undergoes glucuronidation[29] rather than CYP3A4 metabolism, making a clinically meaningful interaction unlikely to have substantially influenced our morphine tissue findings.

We observed striking differences between adipose tissue sites, with pericardial adipose tissue showing higher morphine concentrations and stronger correlations with prescription-based MEDD compared with abdominal adipose tissue. This may reflect proximity of pericardial fat to the central blood compartments, or potential post-mortem redistribution (PMR) from the heart to adjacent lipid-rich, vascularized tissue.[30] It is possible that pericardial adipose tissue may have a higher water content than peripheral adipose tissue, which

TABLE 2 Pooled Pearson correlation of $\log_{10}$ (morphine tissue concentration) and $\log_{10}$(MEDD) over 7-day and 30-day windows.

		7-day MEDD		30-day MEDD	
Anatomical site	***N***	***ρ* (95% CI)**	***p* value**	***ρ* (95% CI)**	***p* value**
Adipose (abdominal)	15	0.06 (−0.37, 0.46)	.797	0.00 (−0.41, 0.41)	.996
Adipose (pericardial)	14	0.60 (0.18, 0.83)	.008**	0.51 (0.05, 0.79)	.031*
Basal ganglia	19	0.49 (0.13, 0.74)	.010*	0.41 (0.02, 0.69)	.041*
Frontal cortex (motor)	18	0.51 (0.14, 0.75)	.009**	0.44 (0.05, 0.71)	.029*
Frontal cortex (pre-motor)	15	0.42 (−0.00, 0.72)	.051	0.32 (−0.11, 0.66)	.144
Hippocampus	18	0.44 (0.04, 0.72)	.031*	0.35 (−0.06, 0.66)	.096
Occipital cortex	18	0.48 (0.09, 0.74)	.018*	0.40 (−0.01, 0.69)	.057
Parietal cortex	16	0.72 (0.45, 0.87)	<.001***	0.67 (0.36, 0.84)	<.001***
Spinal cord (thoracic)	15	0.77 (0.55, 0.89)	<.001***	0.75 (0.52, 0.88)	<.001***
Pons	15	0.56 (0.17, 0.80)	.008**	0.50 (0.09, 0.77)	.020*
Cerebellum	16	0.45 (0.04, 0.73)	.033*	0.35 (−0.08, 0.67)	.110
Medulla	12	0.80 (0.52, 0.92)	<.001***	0.76 (0.46, 0.91)	<.001***
Cerebrospinal fluid	10	0.55 (−0.00, 0.84)	.052	0.46 (−0.13, 0.81)	.118
Temporal cortex	11	0.69 (0.31, 0.88)	.002**	0.68 (0.29, 0.87)	.002**
Composite brain	19	0.51 (0.16, 0.75)	.006**	0.42 (0.05, 0.69)	.028*
Colon (descending)	14	0.65 (0.29, 0.85)	.001**	0.59 (0.20, 0.82)	.005**
Colon (ascending)	13	0.71 (0.41, 0.88)	<.001***	0.67 (0.34, 0.86)	<.001***
Duodenum	17	0.49 (0.09, 0.75)	.018*	0.36 (−0.06, 0.67)	.087
Ileum	15	0.46 (0.05, 0.73)	.028*	0.35 (−0.08, 0.67)	.105
Rectum	15	0.46 (0.06, 0.74)	.025*	0.35 (−0.07, 0.67)	.099
Jejunum	18	0.56 (0.18, 0.79)	.006**	0.45 (0.05, 0.73)	.030*
Kidney	19	0.14 (−0.27, 0.51)	.503	0.19 (−0.22, 0.55)	.357
Prostate	15	0.66 (0.33, 0.85)	<.001***	0.55 (0.17, 0.79)	.007**
Testes	14	0.68 (0.37, 0.85)	<.001***	0.60 (0.25, 0.81)	.002**
Epididymis	12	0.70 (0.34, 0.88)	.001**	0.57 (0.12, 0.82)	.016*
Liver	19	0.47 (0.10, 0.73)	.015*	0.39 (−0.00, 0.68)	.050
Lung	19	0.47 (0.10, 0.73)	.015*	0.40 (0.00, 0.68)	.047*
Pancreas	18	0.44 (0.04, 0.72)	.032*	0.32 (−0.10, 0.64)	.129
Spleen	19	0.41 (0.02, 0.69)	.038*	0.31 (−0.09, 0.62)	.123
Heart	17	0.47 (0.10, 0.73)	.016*	0.37 (−0.02, 0.67)	.065
Composite lymph node	14	0.02 (−0.41, 0.44)	.942	0.10 (−0.34, 0.50)	.677

could facilitate a greater accumulation of morphine, due to its hydrophilicity.[27] Abdominal adipose tissue could be less perfused and have more heterogeneity among participants, reducing its use as a proxy for recent systemic morphine exposure.

Forensic toxicology studies of fatal morphine overdose consistently demonstrate substantial PMR, with marked accumulation of morphine in highly perfused organs such as liver and lung and central-to-peripheral concentration gradients that evolve over time.[31] Interpretation of such data are inherently confounded by PMR, variable survival intervals, route of administration, decomposition, and acute overdose scenarios, limiting inference regarding true antemortem tissue distribution.[32] In contrast, the present study employed rapid research autopsy (within 6 h of death) in a medically supervised population with predominantly therapeutic opioid exposure, thereby substantially reducing PMR-related artefacts (which become increasingly significant over the first 24 h postmortem[33]) and preserving tissue concentrations closer to antemortem steady-state conditions. A small subset of participants ($n = 3$) received MAID regimens resulting in supratherapeutic morphine exposure; these cases represent a distinct exposure context but were collected under the same rapid autopsy protocol. Overall, our findings provide complementary data to forensic studies by characterizing tissue-level morphine distribution in clinically managed EoL care rather than in uncontrolled overdose settings. Observed differences from forensic reports likely reflect both methodological advantages (reduced PMR) and population characteristics (therapeutic or medically supervised exposure versus acute opioid toxicity).

TABLE 3 Pooled mixed-effects model results: morphine MEDD and plasma concentration over 7-day and 30-day windows.

	7-day MEDD					30-day MEDD				
Term	Estimate	Std. error	*t* value	95% CI	*p* value	Estimate	Std. error	*t* value	95% CI	*p* value
(Intercept)	0.129	0.692	0.186	−1.229 to 1.487	.852	0.017	0.414	0.041	−0.8 to 0.835	.967
MEDD	0.566	0.237	2.387	0.101–1.031	.017*	0.582	0.169	3.447	0.249–0.914	<.001***
Anatomical Compartment										
Adipose (reference)										
CNS	0.300	0.088	3.398	0.127–0.474	<.001***	0.300	0.088	3.402	0.127–0.474	<.001***
Gastrointestinal tract	0.951	0.094	10.078	0.765–1.136	<.001***	0.951	0.094	10.087	0.766–1.136	<.001***
Genitourinary tract	0.848	0.097	8.737	0.657–1.038	<.001***	0.848	0.097	8.742	0.657–1.038	<.001***
Liver	0.865	0.129	6.692	0.611–1.119	<.001***	0.866	0.129	6.697	0.612–1.119	<.001***
Lung	1.021	0.133	7.699	0.76–1.281	<.001***	1.021	0.133	7.704	0.761–1.282	<.001***
Lymph node	0.299	0.154	1.940	−0.004 to 0.603	.053	0.299	0.154	1.939	−0.005 to 0.603	.054
Pancreas	0.734	0.137	5.342	0.464–1.005	<.001***	0.735	0.137	5.346	0.465–1.005	<.001***
Spleen	0.841	0.144	5.857	0.558–1.125	<.001***	0.841	0.144	5.863	0.558–1.125	<.001***
Heart	0.836	0.136	6.152	0.569–1.103	<.001***	0.837	0.136	6.158	0.57–1.104	<.001***

Note: Models include random intercepts for participant ID. Tissue type is also included as a fixed effect.

Understanding the relationship between MEDD and tissue morphine concentrations has important implications for pain and symptom management and improving quality of life. Mu-opioid receptors are densely expressed across brain regions involved in nociception (periaqueductal grey, thalamus, cingulate cortex, and insula),[34] emotional regulation (amygdala) and reward (ventral tegmental area and nucleus accumbens).[34] If validated prospectively, MEDD could serve as a non-invasive proxy for estimating morphine exposure in these otherwise inaccessible central nervous system tissues, informing efforts to optimize analgesia while minimizing toxicity or under-treatment.

This study highlights the power of the *Last Gift* cohort to expand research beyond symptom management. Opioids influence immune function, inflammation, and viral persistence,[12–22] yet their effect at the tissue level is largely unexplored. Quantifying opioid levels across multiple organs creates new opportunities to examine how opioid exposure interacts with inflammatory signalling pathways, HIV reservoirs, and tissue-specific immune responses, insights that may ultimately inform personalized therapeutic strategies for PWH.

This study has several limitations. First, the sample size was small, especially for the group of PWoH, which is typical for pharmacokinetic studies and those involving persons at EoL. Despite the limited sample size, we identified moderate-to-strong correlations between MEDD and morphine concentrations in tissues. Moreover, interindividual variability in opioid metabolism and comorbidities (e.g., age, weight, renal, and hepatic function) might affect the precision of the point estimates but not the observed associations. It is also worth noting although prescription records used to estimate MEDD were collected and reviewed meticulously, we were unable to confirm administration accuracy in a minority of cases. In addition, although morphine tissue concentrations were quantified, we did not measure morphine-3-glucuronide (M3G) or morphine-6-glucuronide (M6G), the primary metabolites formed via UGT2B7-mediated glucuronidation.[35] M6G possesses analgesic activity and may contribute substantially to central nervous system effects,[35,36] while M3G has been associated with neuroexcitatory properties.[27,35,37] The absence of metabolite quantification limits our ability to fully characterize total active opioid burden or assess tissue-specific parent-to-metabolite ratios. However, as the primary objective of this study was to describe morphine distribution across tissues rather than to evaluate pharmacodynamic effects, the central findings regarding relative morphine partitioning remain interpretable. Finally, as a postmortem study, tissue concentrations could have been affected by differences in the time interval from death to autopsy and may also differ from tissue concentrations in a living cohort.

Despite these limitations, this study leverages a unique and valuable dataset which combines postmortem tissue concentrations of morphine with prescription-based MEDD. Our findings suggest that MEDD retains meaningful predictive value for tissue morphine exposure even under complex physiologic conditions. Future work will examine whether tissue-level opioid concentrations are associated with clinical outcomes, including pain control and quality of life, as well as virologic and immunologic measures. Establishing these links could support the use of MEDD as a surrogate for otherwise inaccessible tissue compartments and help clinicians optimize opioid therapy in advanced illness.

AUTHOR CONTRIBUTIONS

Niamh Higgins: Conceptualization (lead); data curation (lead); formal analysis (equal); methodology (lead); validation (equal); visualization (lead); writing—original draft (lead); writing—review and editing (lead).

Alan Wells: Oversight of formal data analysis including statistical modelling (lead), created all tables and figures, and writing—original draft (equal); writing—revised the manuscript for intellectual content (equal). Nimish Patel: Conceptualization (lead); validation (equal), provided methodological guidance (equal), contributed to data interpretation (equal), and critically revised the manuscript (equal). Nicole Muttera: Data curation (equal), writing—review and editing (equal). Amedeo De Nicolò: Oversaw laboratory procedures (lead), supervised quantitative opioid assays (lead), and contributed to data interpretation and manuscript revision (equal). Alessandra Manca: Quantitative opioid assays (equal), contributed to assay interpretation (equal), manuscript revision (equal). Micol Ferrara: Quantitative opioid assays (equal), contributed to assay interpretation (equal). Stefano Bonora: Quantitative opioid assays (equal), contributed to assay interpretation (equal). Alice Palermiti: Quantitative opioid assays (equal), contributed to assay interpretation (equal). Jessica Cusato: Quantitative opioid assays (equal), contributed to assay interpretation (equal). Antonio D'Avolio: Quantitative opioid assays (equal), contributed to assay interpretation (equal). Marissa Borochoff: Writing—original draft (equal). Patricia K. Riggs: Contributed to clinical data collection and reviewed the manuscript for accuracy. Elizabeth Hastie: Contributed to clinical data collection and reviewed the manuscript for accuracy. Rabia S. Atayee: Provided methodological guidance (equal), contributed to data interpretation (equal), and critically revised the manuscript (equal). Mattia Trunfio: Provided methodological guidance (equal), contributed to data interpretation (equal), writing—critically revised the manuscript (lead). Stephanie Solso: Coordinated participant care, project coordination, contributed to clinical data collection, and reviewed the manuscript for accuracy. Cheryl Dullano: Coordinated participant care, project coordination, contributed to clinical data collection, and reviewed the manuscript for accuracy. Vanessa Gomez-Moreno: Coordinated sample processing and shipping (equal). Tara Tenenbaum: Data curation (equal); writing—review and editing (equal). Robert Deiss: Provided clinical oversight, supervised participant care within the Last Gift programme, contributed to study design, writing—review and editing (equal). Davey M. Smith: Funding acquisition (lead); investigation (lead); supervision (lead); writing—review and editing (equal). Antoine Chaillon: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); supervision (lead); validation (lead); visualization (lead); writing—critically revised the manuscript (lead). Sara Gianella: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); supervision (lead); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead).

ACKNOWLEDGEMENTS

We are grateful to all members of the *Last Gift* research team who contributed to this study and who care for participants at the end of life. We are especially indebted to the *Last Gift* participants and their next-of-kin/loved ones. We also thank the UCSD AntiViral Research Center Community Advisory Board, the HIV + Aging Research Project–Palm Springs (HARP–PS), the Palm Springs Positive Life Program, the California NeuroAIDS Tissue Network.

CONFLICT OF INTEREST STATEMENT

Antonio D'Avolio:

- Grant/Research Support: CoQua Lab, Correvio
- Consultant/Advisor: Shimadzu, HDC, Gilead, Waters, CoQua Lab,
- Janssen, Infectopharm, Menarini, DiaSorin, EOS, AdvicePharma, Roche
- Sponsored Lectures: Thermofisher, Merck-Millipore, Infectopharm
- Sponsored Writing: Novartis, CoQua Lab, Angelini, DiaSorin, Menarini
- Shareholder Company: CoQua Lab

Rabia S. Atayee:

- Pharmacy Advisory Board, Vertex Pharmaceuticals, Incorporated

Davey Smith:

- Consultant for Model Medicines, Hyundai Biosciences, Gilead and Pfizer.
- Equity in Fluxergy and Model Medicines

Alessandra Manca:

- Reports a relationship with CoQua Lab srl that includes: equity or stocks.

Stefano Bonora:

- Speaker's fees, consultancies or research grants from: Abbvie, Gilead Sciences, MSD Pharmaceuticals, and ViiV

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

AI DISCLOSURE STATEMENT

During the preparation of this work, the author(s) used ChatGPT (OpenAI) to assist with language editing, grammar checking, and shortening word count. The author(s) reviewed and edited the content extensively, ensuring accuracy, originality, and scientific integrity, and take full responsibility for the final published article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Higgins N, Wells A, Patel N, et al. Mapping opioid exposure through prescription data and postmortem analysis of opioid drugs in multiple tissues. *Br J Clin Pharmacol*. 2026;1-12. doi:10.1002/bcp.70535