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The Introduction of Abuse-Deterrent Opioids and Rates of Viral Infection

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Abstract: Along with the many deaths that have been attributed to opioid overdose and the substantial economic impact of the epidemic, the increasing prevalence of opioid use disorder has been associated with new viral infections. Powell et al. (2019) find that states with higher prevalence of OxyContin misuse prior to the introduction of abuse-deterrent OxyContin experienced substantially higher growth in the hepatitis C infection rate since 2010. In this study, I find that increases in hepatitis C infections have coincided with increases in hepatitis B infections in states with higher rates of OxyContin misuse prior to the introduction of abuse-deterrent OxyContin in 2010. I apply this analytical framework to HIV infections but face data limitations.

1. Introduction

The opioid epidemic has elicited responses from pharmaceutical companies, the Food and Drug Administration (FDA) and from federal, state and local governments. Many responses to the opioid epidemic have focused on the supply of prescription opioids. The FDA is encouraging pharmaceutical companies to develop abuse-deterrent versions of opioid analgesics (FDA, 2018a). Recent studies (Alpert et al., 2018; Evans et al., 2019; Powell et al., 2019) have documented how the introduction of abuse-deterrent OxyContin led to substitution among opioid users from prescription opioids to illicit heroin. Beyond the immediate risk of overdose, misuse of opioids may be contributing to increases in rates of viral infection through injection drug use (IDU). I build on these recent studies by exploring other unintended consequences of the reformation of prescription opioids. The creation of abuse-deterrent prescription opioids may increase the likelihood that those with opioid use disorder engage in IDU through substitution (for example illicit heroin) or through IDU of abuse-deterrent prescription opioids. In this study, I find that states that had higher prevalence of OxyContin misuse prior to the introduction of abuse-deterrent OxyContin have experienced increases in the rate of acute hepatitis B virus (HBV) infection. These states may also be experiencing higher rates of HIV infection though this analysis faces data limitations.

2. Background

From 1997-2017, there were almost 400,000 overdose deaths involving opioids (CDC, 2018d). The Council of Economic Advisors estimated that the economic cost of the opioid epidemic in 2015 was $504 billion (The Council of Economic Advisors, 2017). These measures may be missing the extent to which the opioid epidemic is impacting rates of viral infection including hepatitis and HIV. In 2015, almost 20,000 deaths were attributed to the hepatitis C

virus (HCV) (Powell et al., 2019). In 2016, there were almost 16,000 deaths among those diagnosed with HIV (though these deaths may be due to any cause and may not be attributed to HIV) (CDC, 2019). About 1,700 deaths were attributed to HBV in 2016 though this is an underestimate of the true number (CDC, 2018a). The treatment cost over a lifetime associated with one additional HIV infection is about $380,000 (CDC, 2017) and $205,000 associated with one additional case of chronic HCV (Razavi et al., 2013). Given these facts, it is important to understand how the epidemic of drug use in the U.S. has impacted new viral infections. This understanding could inform policy and prevention efforts going forward.

2.1 Viral Hepatitis

Both HBV and HCV can become chronic infections which remain significant public health problems throughout the U.S. HCV is responsible for more deaths in the U.S. than any other infectious disease (Powell et al., 2019). Approximately 75-85% of those infected with HCV develop chronic HCV while HBV is much more likely to develop into a chronic infection among infants and children (CDC, 2016). About 5% of infected adults will develop chronic HBV, 30-50% of children will develop chronic HBV and 90% of infants who receive HBV from their mother will develop chronic HBV (CDC, 2016). An estimated 850,000 Americans have chronic HBV (CDC, 2018a). Chronic HBV can lead to liver damage, liver cancer and death. From 1999-2005, rates of HCV and HBV infections decreased significantly (figure 1). Rates of HCV infection began to increase in 2005 while rates of HBV infection began to level off around 2008-2009.

HBV is a viral infection which can be contracted when infected blood, semen, or other bodily fluid enters the body (CDC, 2018a). Rates of acute HBV declined steadily throughout the 1990's with the introduction and dissemination of the hepatitis B vaccine (CDC, 2019). As of

2016, about 71% of newborns in the U.S. received the hepatitis B vaccine within the first 3 days of birth (CDC, 2018c). In the same year, the hepatitis B vaccine covered about 1 out of 4 adults (CDC, 2018e). The Centers for Disease Control and Prevention (CDC) estimates that there were 20,900 new cases of HBV in 2016 (CDC, 2016). Many people infected with HBV are not aware that they are infected with the virus (CDC, 2018a).

The population in the U.S. with an opioid use disorder (OUD) is estimated to be to 2.1 million (HHS, 2019). About 886,000 of those are heroin users (HHS, 2019). The increasing prevalence of OUD has increased the size of the population engaging in IDU. Among the many risks facing those who engage in IDU is the contraction of a viral disease. The CDC estimates that from 2003 to 2010 there were approximately 3.5 million new cases of HCV (CDC, 2016). From 2010-2016, there was a 3.5-fold increase in cases of HCV reported to the CDC (most cases go unreported) (CDC, 2016). About 60% of new HCV cases are related to IDU (NASTAD, 2018). Many opioid users whose first opioid use came in the form of a prescription pill go on to use opioids via injection. An estimated 10-20% who misuse prescription opioids will go on to use prescription opioids or heroin via injection (Van Handel et al., 2016).

The opioid epidemic has been linked to new cases of viral hepatitis. Most new cases of HBV and HCV have occurred among people who engage in IDU (CDC, 2018d). Zibbell et al. (2017) examine the Substance Abuse and Mental Health Services Administration's Treatment Episode Data Set. The authors find that between 2004 and 2014, admission to treatment for substance use disorder (SUD) attributed to IDU increased by 76% (Zibbell et al., 2017). Suryaprasad et al. (2014) examine follow up interviews conducted with young persons recently infected with HCV in 2011 and 2012. Among those interviewed, 84% reported ever using drugs and/or alcohol recreationally (Suryaprasad et al., 2014). Among that subgroup, 74% reported

using OxyContin or oxycodone and 61% reported using heroin (Suryaprasad et al., 2014). Of those who reported using both heroin and prescription opioids, heroin use started about 2 and a half years after the first use of prescription opioids (Suryaprasad et al., 2014). Zibbell et al. (2017) find that the increasing incidence of HCV from 2004 to 2014 mirrored increases in admission to SUD treatment attributed to injection use of heroin and prescription opioid analgesics.

Public policy intended to curb the opioid epidemic has often targeted the supply of opioids. The literature examining these supply side policies has increasingly shown the unintended consequences including causing those with OUD to seek substitutes for prescription opioid analgesics. Cicero et al. (2014) analyze survey data of patients entering substance abuse treatment for heroin dependence and found that 94% of respondents indicated that they used heroin because prescription opioid analgesics were becoming too difficult or too expensive to obtain. Further, about half of respondents indicated that if there were no limiting factors, they would prefer prescription opioid analgesics over heroin (Cicero et al., 2014).

Among the efforts focused on the supply of prescription opioids is the development of abuse-deterrent formulations of prescription opioids which has been encouraged by the FDA (FDA, 2018a). Abuse-deterrent formulations generally seek to target known forms of abuse like crushing and snorting or dissolving and injecting (FDA, 2018a). OxyContin has been one of the most widely misused prescription opioids (Cicero et al., 2005). OxyContin sales exceeded $3 billion in 2010 (Alpert et al., 2018). The introduction of abuse-deterrent OxyContin in 2010 led to a decrease in the distribution of OxyContin and a decrease in the misuse of OxyContin (Alpert et al., 2018).

However, the introduction of abuse-deterrent OxyContin also led to substitution across opioid types among opioid users. This substitution was particularly problematic in states with higher rates of OxyContin misuse prior to reformulation. Powell et al. (2019) show that the introduction of abuse-deterrent OxyContin had the additional consequence of increasing rates of HCV. States with rates of OxyContin misuse above the median experienced 222% growth in rates of HCV while states below the median experienced 75% growth in rates of HCV (Powell et al., 2019). In states that received oxycodone (the active ingredient in OxyContin) shipments per capita above the median, the monthly heroin related death rate per 100,000 increased from about 0.1 to 0.4 by 2014 (Evans et al., 2019). In states below the median, the monthly heroin related death rate also increased but did not exceed 0.25 by 2014 (Evans et al., 2019). Alpert et al. (2018) find that a one percentage point increase in OxyContin misuse prior to reformulation led to an increase of 2.5 additional heroin deaths per 100,000. Prior to reformulation, OxyContin was typically misused by crushing the pills which enabled chewing, snorting or injecting them (Alpert et al. 2018). To the extent that the reformulation of OxyContin led users to substitution across opioid types, the reformulation of OxyContin may have led to more IDU.

2.2 HIV

While new HIV diagnoses have declined nationally, new cases have been linked to IDU. According to the CDC: "About 1 in 10 new HIV diagnoses in the United States are attributed to injection drug use or male-to-male sexual contact *and* injection drug use" (CDC, 2018b). 2015 was the first year in over two decades in which the number of HIV diagnoses attributed to IDU increased (Dawson and Kates, 2018). Among those who engage in IDU, comorbidity rates between HIV and HCV are high. Of those with HIV who engage in IDU, about 80% also have HCV (NASTAD, 2018). Chronic pain is more prominent among those infected with HIV

(Cunningham, 2018). Estimates suggest that about 21% to 53% of individuals with HIV are prescribed opioids and that patients with HIV are prescribed opioids in higher doses (Cunningham, 2018). Compared to the general population, those infected with HIV are more likely to have a SUD (Cunningham, 2018).

Opana ER was a high strength prescription opioid produced by Endo Pharmaceuticals. Similar to OxyContin, Endo Pharmaceuticals replaced Opana ER with an abuse-deterrent formula in 2012. Here is a description of the properties of the abuse-deterrent product from the FDA: "The product, currently marketed by Endo Pharmaceuticals, is a reformulation of the original product, designed with physicochemical properties intended to make the drug resistant to physical and chemical manipulation for abuse by snorting and injecting" (FDA, 2018b). Peters et al. (2016) identified 181 diagnosed cases of HIV infection in Indiana from 2014-2015. About 88 percent of these patients reported IDU of extended release Oxymorphone (Opana ER) (Peters et al., 2016). In June of 2017, the FDA requested Endo Pharmaceuticals remove Opana ER from the marketplace (FDA, 2017).

Figure 9 shows the HIV diagnoses rate in the state of Indiana. In the years following the release of abuse-deterrent Opana, Indiana experienced a massive spike in HIV diagnoses. Interviews conducted in Austin, IN, the town at the center of the HIV outbreak, revealed how the reformulation of Opana ER may have played a role. Prior to reformulation, Opana was misused by crushing pills and then snorting, bypassing the prescription's time release (Herald, 2016). When the abuse-deterrent version was introduced, these users switched from crushing and snorting Opana to cooking the prescription for injection use (Herald, 2016). These interviews suggest that the release of abuse-deterrent Opana had the unintended consequence of leading to increased IDU which increased the potential spread of viral disease. While the release of abuse-

deterrent OxyContin had nationwide repercussions, misuse of Opana was much less widespread prior to reformulation. Oxycodone is the active ingratiate in OxyContin while oxymorphone is the active ingredient in Opana. In 2008, about 250 grams of oxymorphone were distributed in the U.S. per 100,000 people compared to about 12,450 grams of oxycodone per 100,000 people (DEA ARCOS, 2008).

3. Data

Data regarding rates of HIV and viral hepatitis infection come from the Centers for Disease Control and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP). The NCHHSTP data contain the infection rate per 100,000 at the state year level including: HIV, HBV and HCV. The explanatory variable of interest measures the amount of nonmedical use of OxyContin by state prior to the reformulation of OxyContin. These data were obtained from Alpert et al., (2018). The authors constructed the measure using data from the National Survey on Drug Use and Health. As a secondary measure, misuse of OxyContin is measured using shipments of prescription opioid analgesics. These data come from the Drug Enforcement Agency (DEA) Automation of Reports and Consolidated Orders System (ARCOS) Retail Drug Summary Reports.

A set of control variables used in the study include demographic data, economic data and data regarding changes in state policy. Population and demographic data come from the National Center for Health Statistics (NCHS) Bridged-Race Population Estimates. The demographic controls include the share of the state population that are ages 0-15, ages 16-35, ages 36-64, female, white and black. Data regarding the unemployment rate comes from the Bureau of Labor Statistics (BLS) Local Area Unemployment Statistics (LAUS). The implementation dates of Prescription Drug Monitoring Programs (PDMP) were obtained from Kilby (2015) and the

National Alliance for Model State Drug Laws (2018). Effective dates of PDMPs with physician mandates come from Buchmueller and Carey (2018). Effective dates of state Pain Clinic Laws were obtained from Meinhofer and Witman (2018).

4. Identification Strategy

The identification strategy used in this study was developed by Alpert et al. (2018). This model exploits variation in the prevalence of OxyContin misuse at the state level prior to the reformulation of OxyContin. First, the following event study model is estimated:

$$Y_{s,t} = \alpha + \beta * \rho_T * OxyRate_s^{Pre} + X'_{s,t}\,\gamma + \delta_S + \lambda_T + \epsilon_{s,t} \qquad (1)$$

Where $Y_{s,t}$ is the rate of viral infection per 100,000 in state *s* in year *t*. $OxyRate_s^{Pre}$ is the rate of OxyContin misuse in state *s* prior to the reformulation of OxyContin. This measure is interacted with a set of year dummies. $X'_{s,t}$ is a vector of control variables including state level demographic information, the state unemployment rate and changes in state law relating to the opioid epidemic. δ_S represents the state fixed effects and λ_T represents the year fixed effects.

Next, I estimate the following trend break model following Alpert et al. (2018):

$$Y_{s,t} = \alpha + \beta_1[Post_t * OxyRate_s^{Pre}] + \beta_2[t * OxyRate_s^{Pre}] + \beta_3[Post_t * (t - 2011) * OxyRate_s^{Pre}] + X'_{s,t}\,\gamma + \delta_S + \epsilon_{s,t} \qquad (2)$$

$Post_t$ is an indicator variable equal to 1 in the year 2011 and subsequent years and equal to zero otherwise, capturing the impact of the reformulation of OxyContin. t represents a linear time trend. With respect to estimation of both equations 1 and 2, standard errors are adjusted for clustering at the state level. Estimates are weighted by state population.

5. Results

Figure 2 is a replication of Exhibit 2 from Powell et al. (2019). This evidence in Powell et al. (2019) shows that higher rates of OxyContin misuse prior to reformulation were associated with higher rates of HCV infection in the years following reformulation. In figure 3, I apply the same empirical strategy and find similar trends with respect to HBV infection rates. There does not appear to be any relationship between OxyContin misuse and rates of HBV or HCV infection prior to reformulation. However, following reformulation in 2010, states with higher levels of OxyContin misuse in the pre-reform period experienced significantly higher growth in the HBV infection rate. In figure 4, I consider the HIV infection rate. Unfortunately, the CDC NCHHSTP data of HIV diagnoses does not contain records prior to 2008. The 2009 event study coefficient estimate is normalized to zero leaving only one year of pre-reform data. In the post reformulation years, confidence intervals are large and coefficient estimates are positive. There is insufficient evidence in the event study to suggest that states with higher levels of OxyContin misuse prior to reformulation experienced higher rates of HIV infection.

In figures 5-8, I utilize a secondary measure of OxyContin misuse in the pre-reform period. Following Evans et al. (2019), I categorize states that received oxycodone shipments per 100,000 residents above the median and below the median in 2008 based on DEA ARCOS data. In figure 5, it appears that states above and below the median were following similar trends with respect to HCV infection rates. Both states above and below the median experience increases in HCV infection rates immediately following reformulation. However, states above the median continue to experience growth in HCV infection rates from 2013-2016 while the infection rate remains relatively flat in states below the median. In figure 6, it appears that states above and below the median were following nearly identical trends in terms of HBV infection rates prior to

reformulation. While states below the median continued to experience decreasing HBV infection rates after the reformulation of OxyContin, states above the median begin experiencing increasing HBV infection rates. Using the same classification of states, I plot the population weighted mean number of HIV diagnoses. In figure 7, HIV diagnoses from transmission type IDU are plotted and in figure 8, HIV diagnoses from transmission type male to male sexual contact and IDU are plotted. In both cases, states with oxycodone shipments per 100,000 below the median in 2008 have higher mean HIV diagnoses. Following the introduction of abuse-deterrent OxyContin, the mean number of HIV diagnoses declines more rapidly in states below the median than in states above the median.

In table 2, I estimate the impact of misuse of OxyContin prior to reformulation on rates of HBV and HIV. Following Alpert et al. (2018), table 2 reports estimates of $\beta_1 + 2\,\beta_3$ from equation 2 above. In column 3, the estimates suggest that one additional percentage point of OxyContin misuse prior to reformulation would lead to 0.376 additional cases of HBV per 100,000 and 3.27 additional cases of HIV per 100,000. In both cases, the OLS results are not precise and the coefficient of interest is not statistically significant. Table 3 presents the results of Poisson regression estimation. In the Poisson models, the dependent variable is the number of cases of viral infection at the state year level. Results in column 3 suggest that a one percentage point increase in OxyContin misuse prior to reform would result in approximately 2 additional HBV infections and 1.6 additional HIV infections. For the HBV cases outcome, the coefficient of interest is statistically significant at the 1% level in the baseline model but is no longer significant with the inclusion of a full set of controls. For the HIV cases outcome, the results are significant at the 1% level in all specifications.

Finally, I examine the heterogeneity of the effect by transmission type, age, gender and race. In table 4, I test each type of HIV transmission. The largest estimated effect size of OxyContin misuse prior to reformulation is on HIV diagnoses relating to IDU. The coefficient of interest is also statistically significant with respect to HIV diagnoses relating to heterosexual and male-to-male sexual contact. In tables 5 and 6, the impact of OxyContin reformulation is largest with respect to HIV infections occurring among people between the ages of 25-34, people between the ages of 45-54, males and blacks.

6. Conclusion

In this study, I build on recent work that has shed light on the large scale, unintended consequences of the introduction of abuse-deterrent opioids. These papers (Alpert et al., 2018; Evans et al., 2019; Powell et al., 2019) have shown that the reformulation of OxyContin led to increases in the heroin related death rate and the HCV infection rate. This study shows that the increase in the HCV infection rate in states with higher levels of OxyContin misuse coincided with increases in the HBV infection rate. I test the impact of the reformulation of OxyContin on rates of HIV infection as well. While these results may be indicative of higher rates of HIV infection in states with higher rates OxyContin misuse, the results cannot be validated because of insufficient data in the pre-reform period. Results presented in the paper suggest that many measures underestimate the true cost of the opioid epidemic. Additional resources many be needed to prevent further spread of viral disease related to intravenous use of opioids.

7. References

Alpert, Abby, David Powell, and Rosalie Liccardo Pacula. (2018). "Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids: Dataset." *American Economic Journal: Economic Policy*, 10(4): 1–35

Buchmueller, Thomas C. and Carey, Colleen. (2018). "The Effect of Prescription Drug Monitoring Programs on Opioid Utilization in Medicare." *American Economic Journal: Economic Policy*, 10, (1): 77-112

Bureau of Labor Statistics. Local Area Unemployment Statistics

Centers for Disease Control and Prevention National Center for Health Statistics

Centers for Disease Control and Prevention. "Hepatitis B Questions and Answers for the Public." May 22, 2018. https://www.cdc.gov/hepatitis/hbv/bfaq.htm

Centers for Disease Control and Prevention. "HIV Cost-effectiveness." March 8, 2017. https://www.cdc.gov/hiv/programresources/guidance/costeffectiveness/index.html

Centers for Disease Control and Prevention. "HIV in the United States and Dependent Areas." January 29, 2019. https://www.cdc.gov/hiv/statistics/overview/ataglance.html

Centers for Disease Control and Prevention. "Injection Drug Use and HIV Risk." November 9, 2018. https://www.cdc.gov/hiv/risk/idu.html

Centers for Disease Control and Prevention. "National Progress Report 2020 Goal: Increase the percentage of infants who receive hepatitis B vaccine within 3 days of birth to 85.0%". October 18, 2018.
https://www.cdc.gov/hepatitis/policy/NationalProgressReport-HepB-IncreaseVacinations.htm

Centers for Disease Control and Prevention. "Understanding the Epidemic." December 19, 2018. https://www.cdc.gov/drugoverdose/epidemic/index.html

Centers for Disease Control and Prevention. "Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2016". February 8, 2018.
https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/NHIS-2016.html

Centers for Disease Control and Prevention. "Viral Hepatitis and Young Persons Who Inject Drugs." March 29, 2018. https://www.cdc.gov/hepatitis/populations/youngpwid.htm

Centers for Disease Control and Prevention. "Viral Hepatitis Surveillance United States, 2016"
https://www.cdc.gov/hepatitis/statistics/2016surveillance/pdfs/2016HepSurveillanceRpt.pdf

Centers for Disease Control and Prevention National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention *(*NCHHSTP) AtlasPlus https://www.cdc.gov/nchhstp/atlas/index.htm

Cicero, T., Ellis, M., Surratt, H., & Kurtz, S. (2014). "The changing face of heroin use in the United States: A retrospective analysis of the past 50 years." *JAMA Psychiatry*, 71(7), 821-6.

Cicero, Inciardi, & Muñoz. (2005). "Trends in Abuse of OxyContin® and Other Opioid Analgesics in the United States: 2002-2004." *Journal of Pain,6*(10): 662-672.

Cunningham, C. (2018). "Opioids and HIV Infection: From Pain Management to Addiction Treatment." *Topics in Antiviral Medicine, 25*(4): 143-146.

Dawson, Lindsey and Jennifer Kates. "HIV and the Opioid Epidemic: 5 Key Points." The Keiser Family Foundation. March 27, 2018 https://www.kff.org/hivaids/issue-brief/hiv-and-the-opioid-epidemic-5-key-points/

Drug Enforcement Agency (DEA) Automation of Reports and Consolidated Orders System (ARCOS) Retail Drug Summary Reports. Report 4: Cumulative Distribution in Grams per 100K Population

Evans, William, Ethan Lieber, and Patrick Power. (2019) "How the Reformulation of OxyContin Ignited the Heroin Epidemic." *Review of Economics and Statistics, 101*(1): 1-15.

Herald, Seth. (2016). "Inside A Small Brick House At The Heart Of Indiana's Opioid Crisis." Shots Health News from NPR. March 31, 2016 https://www.npr.org/sections/health-shots/2016/03/31/469525114/inside-a-small-brick-house-at-the-heart-of-indianas-opioid-crisis

Kilby, Angela E. (2015). "Opioids for the masses: Welfare tradeoffs in the regulation of narcotic pain medications". Unpublished.

Meinhofer, Angélica and Witman, Allison E. (2018). "The role of health insurance on treatment for opioid use disorders: Evidence from the Affordable Care Act Medicaid expansion." *Journal of Health Economics*, 60: 177-197.

National Alliance for Model State Drug Laws. (2018). PDMP Dates of Operation. Retrieved from: http://www.namsdl.org/prescription-drug-monitoring-programs-maps.cfm

National Alliance of State and Territorial AIDS Directors. (2018). "The Intersection of Hepatitis, HIV, and the Opioid Crisis: The Need for a Comprehensive Response." https://www.nastad.org/sites/default/files/Uploads/2018/issue-brief-hep-hiv-opioid.pdf

Peters, Pontones, Pamela Pontones, Karen W. Hoover, Monita R. Patel, Romeo R. Galang, Jessica Shields, Sara J. Blosser, Michael W. Spiller, Brittany Combs, William M. Switzer, Caitlin Conrad, Jessica Gentry, Yury Khudyakov, Dorothy Waterhouse, Michele Owen, Erika Chapman, Jeremy C. Roseberry, Veronica McCants, Paul J. Weidle, Pharm.D., Dita Broz, Taraz

Samandari, Jonathan Mermin, Jennifer Walthall, John T. Brooks and Joan M. Duwve. (2016). "HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014–2015." *The New England Journal of Medicine*,*375*(3): 229-239.

Powell, David, Abby Alpert and Rosalie Liccardo Pacula. (2019). "A Transitioning Epidemic: How The Opioid Crisis Is Driving The Rise In Hepatitis C". *Health Affairs* 38, (2): 287–294

Razavi, H., ElKhoury, A., Elbasha, E., Estes, C., Pasini, K., Poynard, T., & Kumar, R. (2013). "Chronic hepatitis C virus (HCV) disease burden and cost in the United States." *Hepatology*, 57(6): 2164-2170.

Suryaprasad, A., White, J., Xu, F., Eichler, B., Hamilton, J., Patel, A., . . . Holmberg, S. (2014). "Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006-2012." *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 59*(10): 1411-9.

The Council of Economic Advisors. (2017). "The Underestimated Cost of the Opioid Epidemic." https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf

United States Department of Health and Human Services. (2019). "The Opioid Epidemic by The Numbers." https://www.hhs.gov/opioids/sites/default/files/2019-01/opioids-infographic_1.pdf

United States Food & Drug Administration. "Abuse-Deterrent Opioid Analgesics." April 23, 2018 https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm600788.htm

United States Food & Drug Administration. "FDA requests removal of Opana ER for risks related to abuse." News release, June 8. 2017 https://www.fda.gov/news-events/press-announcements/fda-requests-removal-opana-er-risks-related-abuse

United States Food & Drug Administration. "Oxymorphone (marketed as Opana ER) Information." February 6, 2018 https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm562339.htm

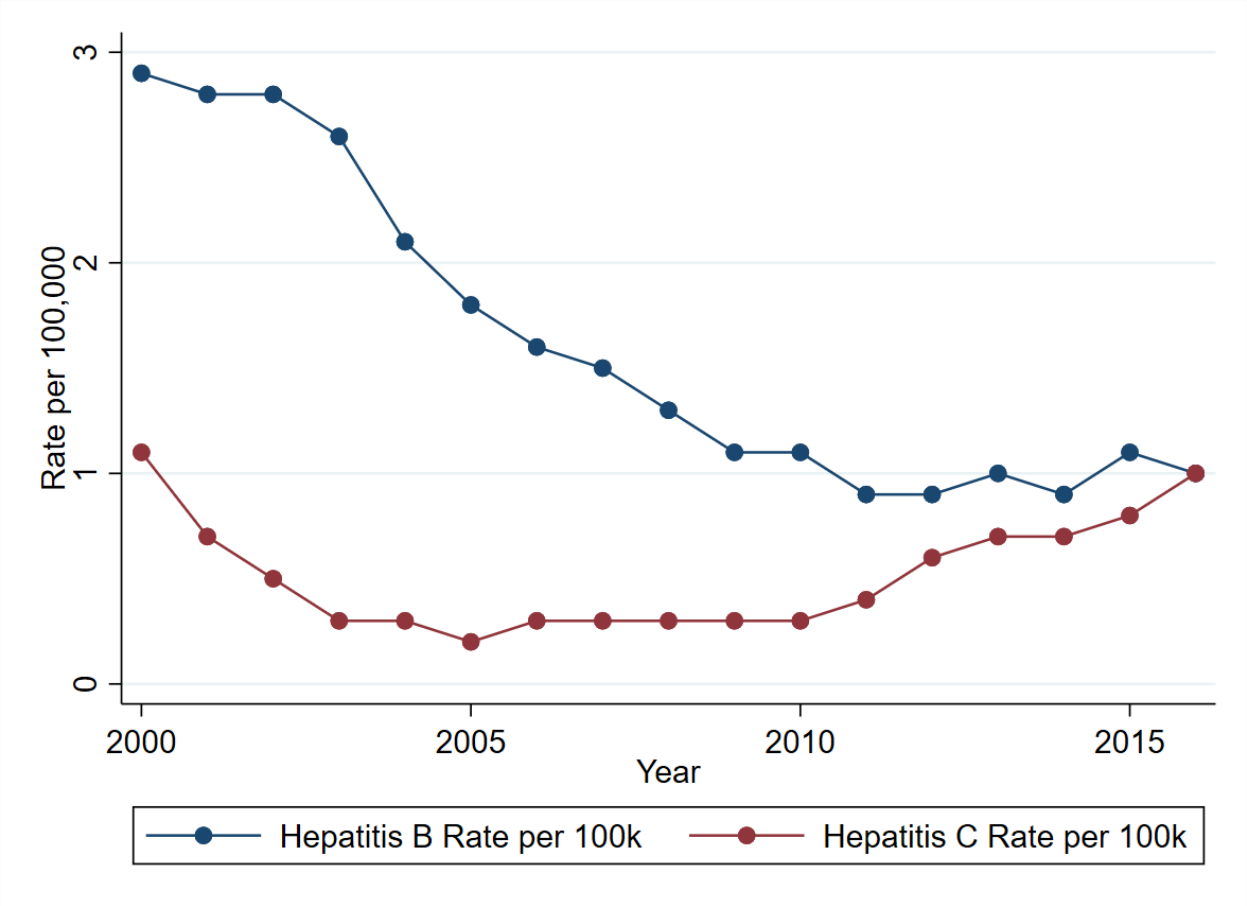
Van Handel, Rose, Hallisey, Kolling, Zibbell, Lewis, . . . Brooks. (2016). "County-Level Vulnerability Assessment for Rapid Dissemination of HIV or HCV Infections Among Persons Who Inject Drugs, United States." *JAIDS Journal of Acquired Immune Deficiency Syndromes, 73*(3): 323-331.

Zibbell, J., Asher, A., Patel, R., Kupronis, B., Iqbal, K., Ward, J., & Holtzman, D. (2017). "Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and

Associated Injection Drug Use, United States, 2004 to 2014.” *American Journal of Public Health,108*(2): E1-e7.

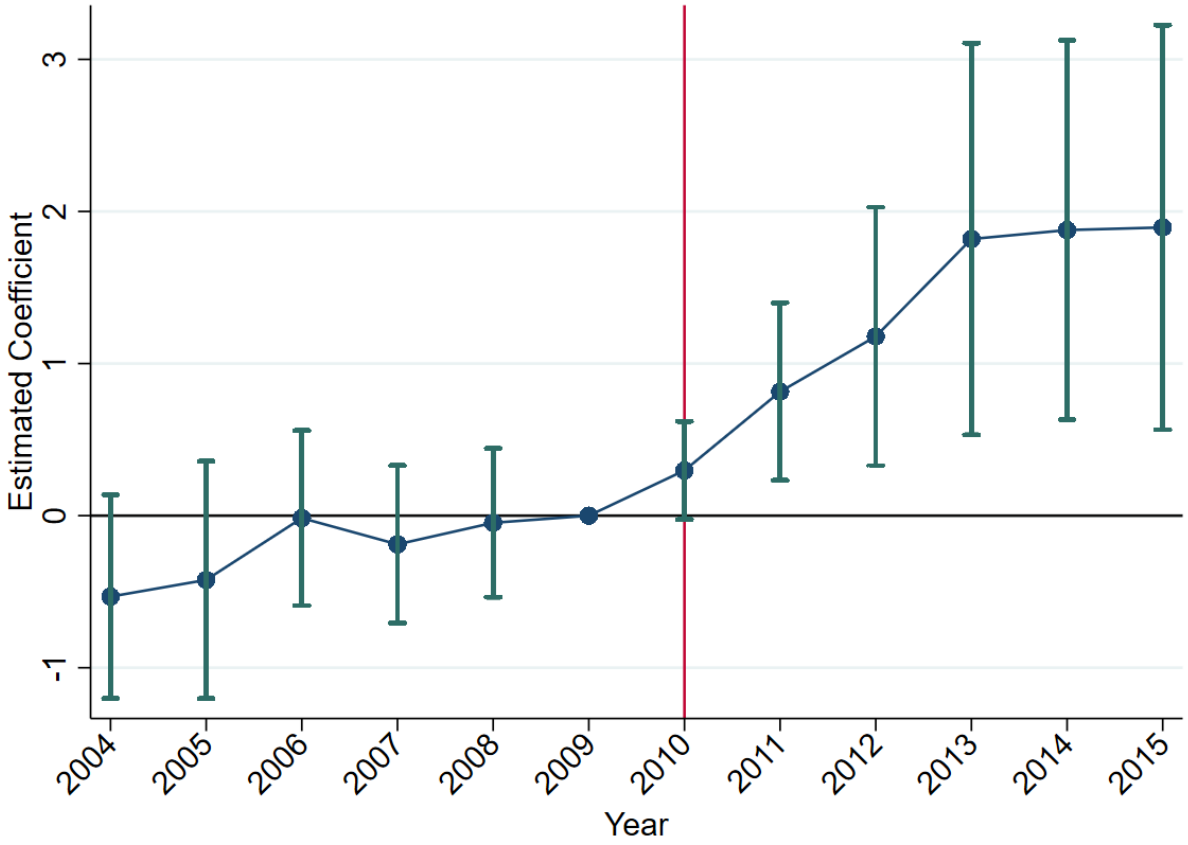
8. Tables and Figures

Figure 1: Rates of Hepatitis



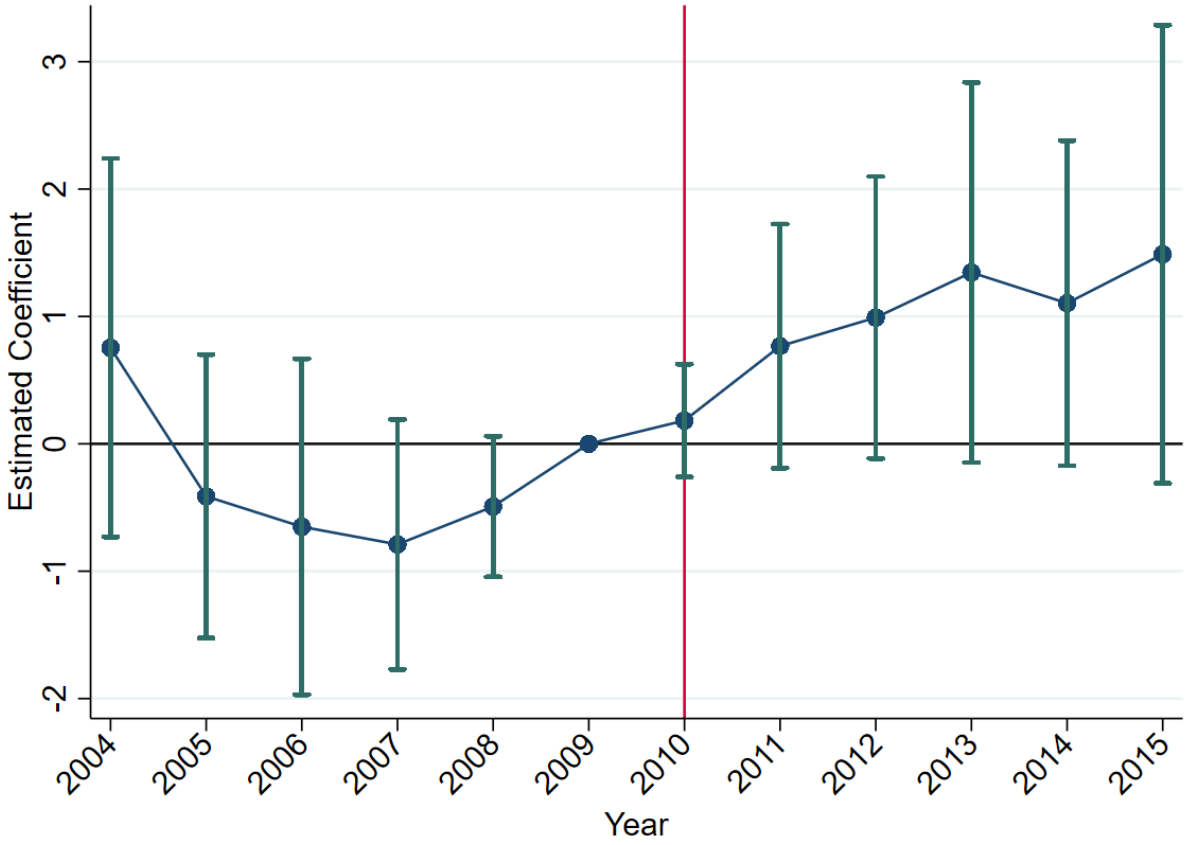
Source: Centers for Disease Control and Prevention National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention *(*NCHHSTP*)*

Figure 2: Hepatitis C Rate Event Study



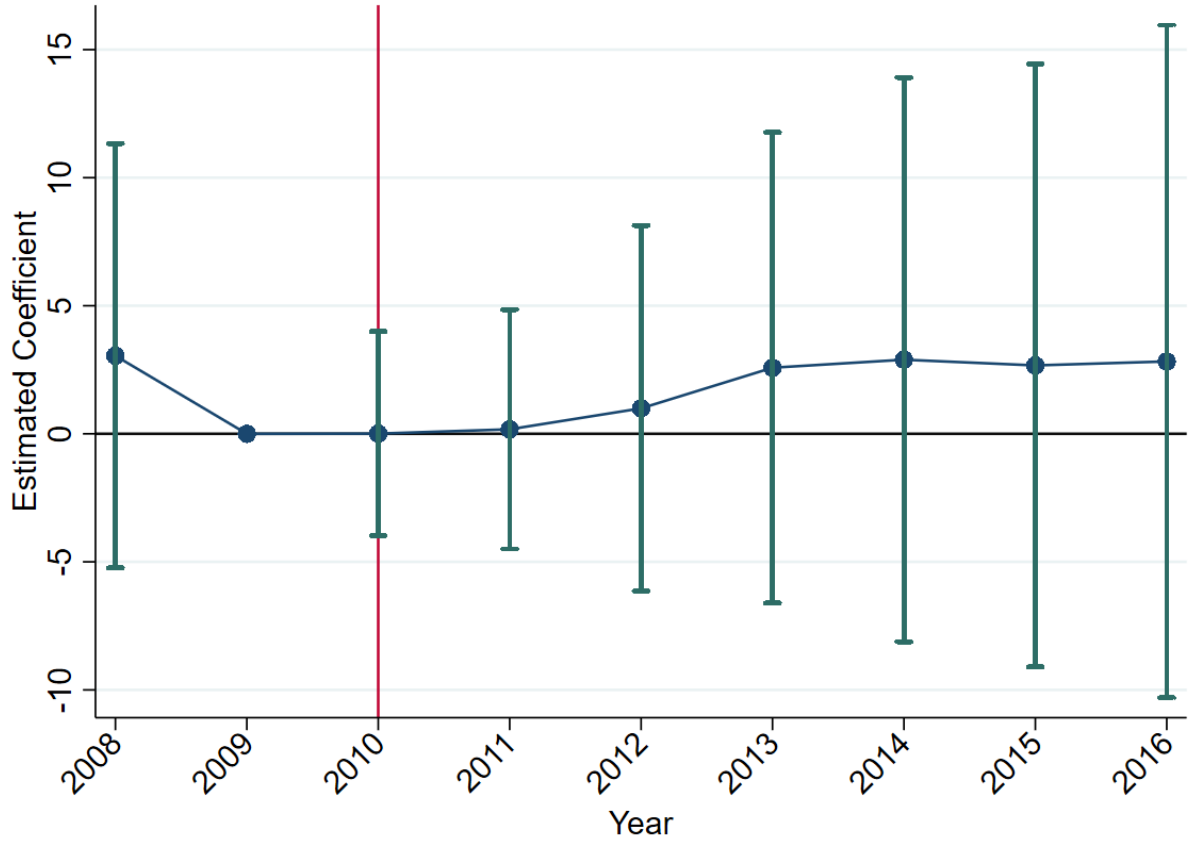
Notes: Replication of Powell et al., (2019) Exhibit 4. The outcome variable is the rate of hepatitis C infections per 100,000 at the state year level. Model includes year fixed effects and state fixed effects. Controls include age and demographic controls and the unemployment rate and Prescription Drug Monitoring Programs, PDMPs with a must access clause, and Pain Clinic Laws. Estimates are weighted by the state population. Standard errors are adjusted for clustering at the state level.

Figure 3: Hepatitis B Rate Event Study



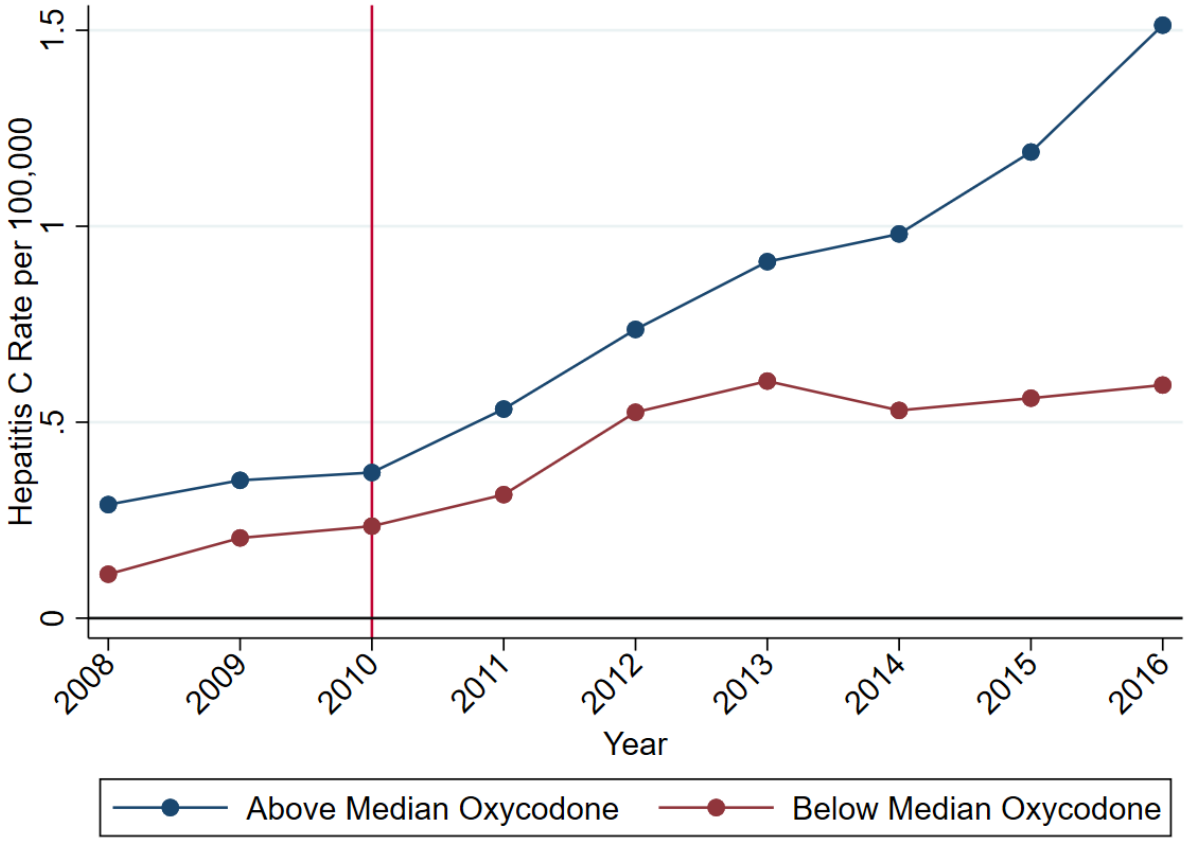
Notes: The outcome variable is the rate of hepatitis B infections per 100,000 at the state year level. Model includes year fixed effects and state fixed effects. Controls include age and demographic controls and the unemployment rate and Prescription Drug Monitoring Programs, PDMPs with a must access clause, and Pain Clinic Laws. Estimates are weighted by the state population. Standard errors are adjusted for clustering at the state level.

Figure 4: HIV Diagnoses Rate Event Study



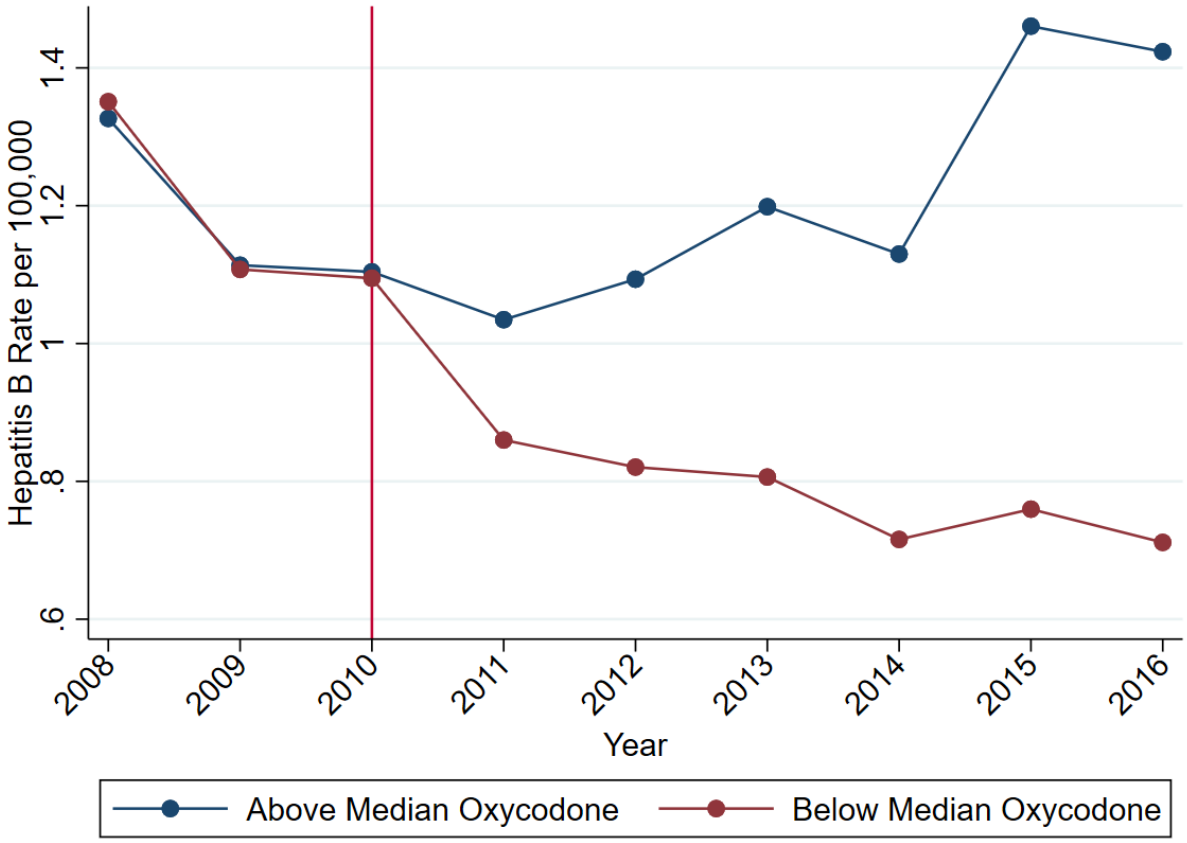
Notes: The outcome variable is the rate of HIV diagnoses per 100,000 at the state year level. Model includes year fixed effects and state fixed effects. Controls include age and demographic controls and the unemployment rate and Prescription Drug Monitoring Programs, PDMPs with a must access clause, and Pain Clinic Laws. Estimates are weighted by the state population. Standard errors are adjusted for clustering at the state level.

Figure 5: Hepatitis C Rate by 2008 Oxycodone Shipments



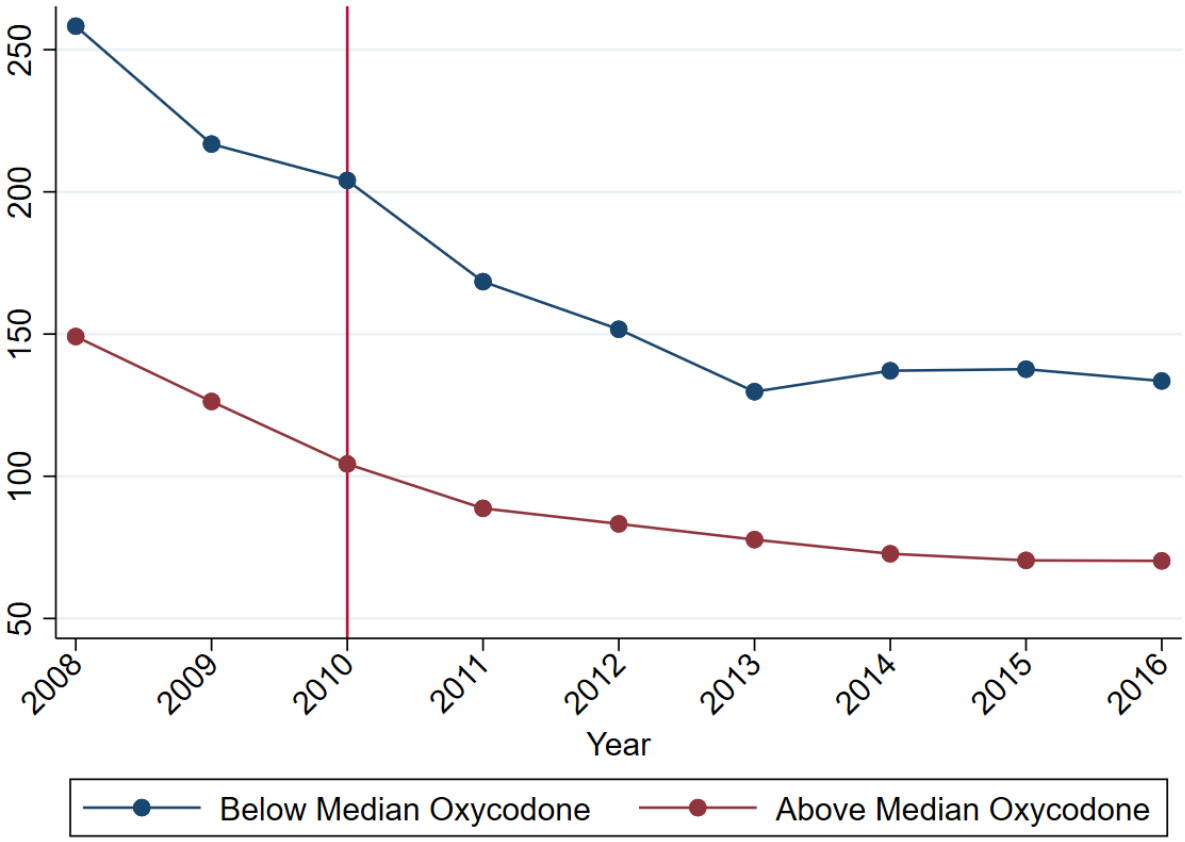
Notes: Plot of the Hepatitis C rate per 100,000 separating states by Oxycodone shipments relative to the median using data from DEA ARCOS and NCHHSTP. Vertical line indicates the year in which the abuse-deterrent formula of OxyContin was introduced.

Figure 6: Hepatitis B Rate by 2008 Oxycodone Shipments



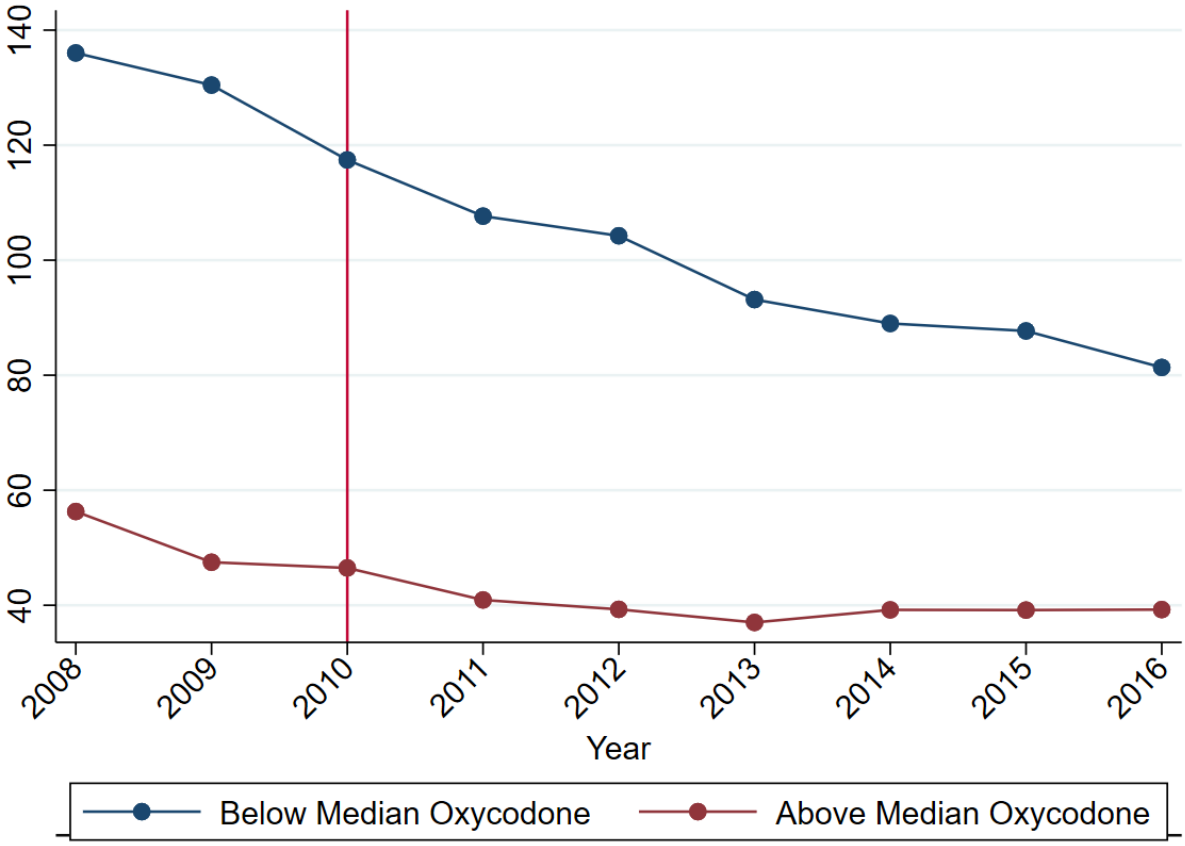
Notes: Plot of the Hepatitis B rate per 100,000 separating states by Oxycodone shipments relative to the median using data from DEA ARCOS and NCHHSTP. Vertical line indicates the year in which the abuse-deterrent formula of OxyContin was introduced.

Figure 7: HIV Diagnosis by 2008 Oxycodone Shipments, Transmission Category IDU



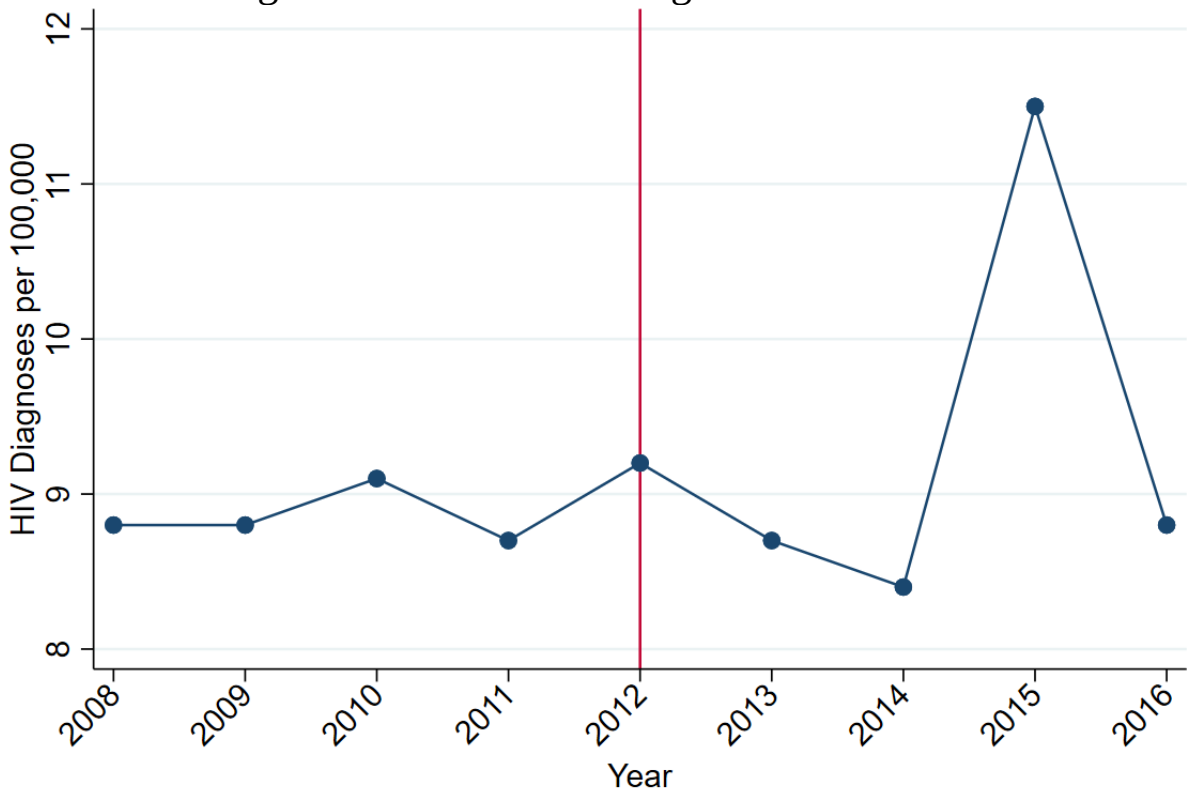
Notes: Plot of the HIV diagnosis within transmission category IDU, separating states by Oxycodone shipments relative to the median using data from DEA ARCOS and NCHHSTP. Vertical line indicates the year in which the abuse-deterrent formula of OxyContin was introduced.

Figure 8: HIV Diagnosis by 2008 Oxycodone Shipments, Transmission Category Male to Male Sexual Contact and IDU



Notes: Plot of the HIV diagnosis within transmission category male to male sexual contact and IDU, separating states by Oxycodone shipments relative to the median using data from DEA ARCOS and NCHHSTP. Vertical line indicates the year in which the abuse-deterrent formula of OxyContin was introduced.

Figure 9: Rate of HIV Diagnoses in Indiana



Notes: Plot of the HIV Diagnoses rate per 100,000 in the state of Indiana. Vertical line indicates the year in which the abuse-deterrent formula of Opana ER was introduced.

Table 1
Summary Statistics

Variable	Mean	Std. Dev
Hepatitis B Rate per 100,000	1.73	1.26
Hepatitis B Cases	219.86	235.65
Hepatitis C Rate per 100,000	0.42	0.85
Hepatitis C Cases	47.08	65.03
HIV Diagnoses Rate per 100,000	16.79	9.95
HIV Diagnoses Cases	2,120.54	1,905.46
Initial OxyContin Misuse	0.57	0.22
Fraction Ages 0-15	0.22	0.02
Fraction Ages 16-35	0.26	0.01
Fraction Ages 35-64	0.39	0.02
Fraction White	0.80	0.09
Fraction Black	0.13	0.08
Fraction Female	0.51	0.01
Prescription Drug Monitoring Programs	0.48	0.50
Must Access Prescription Drug Monitoring Programs	0.03	0.17
Pain Clinic Laws	0.07	0.26

Notes: Data - 1999-2016. Summary statistics are weighted by state population.

Table 2
Impact of OxyContin Reformulation on Viral Disease (OLS)

	(1)	(2)	(3)
Panel A: Hepatitis B			
Initial OxyContin 3-year effect	0.673	0.835	0.376
	(0.641)	(0.712)	(0.686)
Panel B: HIV			
Initial OxyContin 3-year effect	1.658	3.013	3.283
	(2.825)	(2.865)	(3.578)
Demographic and Economic Covariates	No	Yes	Yes
Controls for State Policy	No	No	Yes

Notes: Dependent Variable - infection/diagnoses rate per 100,000. Population weighted OLS regression estimates. Models include year fixed effect and state fixed effect. Standard errors in parentheses are adjusted for clustering at the state level. * p<0.10, ** p<0.05, *** p<0.01

Table 3
Impact of OxyContin Reformulation on Viral Disease (Poisson)

	(1)	(2)	(3)
Panel A: Hepatitis B			
Initial OxyContin 3-year effect	1.343***	1.143	0.717
	(0.412)	(0.386)	(0.4878)
Panel B: HIV			
Initial OxyContin 3-year effect	0.377***	0.571***	0.495***
	(0.1454)	(0.1379)	(0.143)
Log Population Control	Yes	Yes	Yes
Demographic and Economic Covariates	No	Yes	Yes
Controls for State Policy	No	No	Yes

Notes: Dependent Variable - new infections/cases of viral disease. Population weighted Poisson regression estimates. Models include year fixed effect and state fixed effect. Standard errors in parentheses are adjusted for clustering at the state level. * p<0.10, ** p<0.05, *** p<0.01

Table 4
HIV Diagnoses Heterogeneity by Transmission Type

	All HIV Diagnoses	IDU	MM Sexual Contact and IDU	MM Sexual Contact	Heterosexual Contact
Initial OxyContin 3-year effect	0.500***	0.795**	-0.088	0.450**	0.513***
	(0.141)	(0.310)	(0.263)	(0.178)	(0.177)
Log Population Control	Yes	Yes	Yes	Yes	Yes
Demographic and Economic Covariates	Yes	Yes	Yes	Yes	Yes
Policy Covariates	Yes	Yes	Yes	Yes	Yes

Notes: Dependent Variable - new infections/cases of viral disease. Population weighted Poisson regression estimates. Models include year fixed effect and state fixed effect. Standard errors in parentheses are adjusted for clustering at the state level. * p<0.10, ** p<0.05, *** p<0.01

Table 5
HIV Diagnoses Heterogeneity by Age Group

	Ages 25-34	Ages 35-44	Ages 45-54	Ages 55 plus
Initial OxyContin 3-year effect	5.867	3.967	5.260	2.614
	(3.885)	(8.344)	(6.196)	(1.688)
Demographic and Economic Covariates	Yes	Yes	Yes	Yes
Policy Covariates	Yes	Yes	Yes	Yes

Notes: Dependent Variable - infection/diagnoses rate per 100,000. Population weighted OLS regression estimates. Models include year fixed effect and state fixed effect. Standard errors in parentheses are adjusted for clustering at the state level. * p<0.10, ** p<0.05, *** p<0.01

Table 6
HIV Diagnoses Heterogeneity by Race and Gender

	Male	Female	White	Black	Hispanic
Initial OxyContin 3-year effect	5.718	1.496	1.515	31.049*	1.615
	(4.703)	(2.696)	(1.522)	(15.605)	(5.609)
Demographic and Economic Covariates	Yes	Yes	Yes	Yes	Yes
Policy Covariates	Yes	Yes	Yes	Yes	Yes

Notes: Dependent Variable - infection/diagnoses rate per 100,000. Population weighted OLS regression estimates. Models include year fixed effect and state fixed effect. Standard errors in parentheses are adjusted for clustering at the state level. * $p<0.10$, ** $p<0.05$, *** $p<0.01$