ESSAYS ON INNOVATION AND DIGITIZATION IN HEALTH CARE MARKETS

A Dissertation

Presented to the Faculty of the Graduate School

of Cornell University

In Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

by

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May 2020

ESSAYS ON INNOVATION AND DIGITIZATION IN HEALTH CARE MARKET

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Cornell University 2020

My dissertation consists of three essays on the causes and consequences of innovation and digitization in health care markets. The first essay sheds light on institutions affecting technological diffusion and innovation in a global setting, and the second and third essays analyze the benefit and cost of digitization in health care markets within the US context. In addition, I include a technical memo I wrote about patent classification systems.

The first essay studies the impact of the first joint licensing platform for patented drugs, the Medicines Patent Pool, on global drug diffusion and innovation. The pool allows generic firms worldwide to license drug bundles cheaply and conveniently for sales in a set of developing countries. I construct a novel dataset from licensing contracts, public procurement, clinical trials, and drug approvals. Using difference-in-differences methods, I find that the pool leads to substantial increases in the generic supply of drugs purchased. In addition, there are positive responses in R&D inputs and outputs. Finally, I estimate a simple structural model to quantify welfare gains. I find the pool balances diffusion and innovation cost-effectively.

The second essay investigates digital solutions to the opioid crisis. In response to the opioid crisis, each US state has implemented a prescription drug monitoring program (PDMP) to collect data on controlled substances prescribed and dispensed in the state. I study whether health information technology (HIT) complements PDMPs to reduce opioid-related mortality and morbidity. I collect data on state policies that integrate PDMP with HIT and facilitate interstate data sharing. Using difference-in-differences models, I find that PDMP-HIT integration policies reduce opioid-related mortality and morbidity. The reductions in inpatient morbidity are substantial in states that established integration without ever mandating PDMP access. The impacts are strongest for the most vulnerable groups—middle-age, low- to middle-income patients, and publicly insured. I find suggestive evidence that interstate data sharing further

complements integration. The total benefits of integration far exceed the costs.

The third essay (co-authored with Jordan Epstein, Sean Nicholson, Katherine Hempstead, and Sam Asin) estimates potential cost savings if consumers are willing to shop around for imaging services and take advantage of both insurer-negotiated prices and cash price options. We use price data from five private health insurers and cash prices across 142 imaging facilities in the San Francisco Bay area. Across different simulations, we estimate that patients could save 11–22% of their insurer's in-network prices by paying cash and could save even more (45–64%) if patients choose the lowest in-network or cash prices for an imaging service in the Bay area.

The technical memo provides an overview of the major patent classification systems and the basic ideas behind the categorization of patent classes. Patent classification systems and upper-level groupings have been widely used for research and entrepreneurial purposes but are insufficiently documented. I highlight recent institutional changes that disproportionately affect patents in specific categories and alternative categorizations used in the patent examination process. Finally, I update the National Bureau of Economic Research patent technological categorization based on the latest U.S. patent classification.

BIOGRAPHICAL SKETCH

Xiaolu (Lucy) Wang joined the doctoral program in the Department of Economics at Cornell University in the fall of 2014. Her research interests are in economics of innovation, health care economics, industrial organization, and public finance. She holds a Master of Arts in Economics from Duke University in 2012 and a Bachelor's degree in Economics (with a specialty in insurance) from Central University of Finance and Economics in Beijing, China. She was born and raised in Tongling City, Anhui Province, China.

This document is dedicated to my parents, Yong Wang and Ziyun Guo.

ACKNOWLEDGMENTS

I am deeply indebted to my advisors Michael Waldman, Sean Nicholson, Michael Lovenheim, and Chris Forman for their continuous guidance, encouragement and support in the past years. They have been incredibly helpful to my research and professional development as well as providing mentorship and support in numerous other ways. I am both fortunate and grateful to have each of them as a role model and they have had profound influence on my career. I owe much more to them than what is reflected in this thesis. Thank you!

I also thank other Cornell faculty members for many conversations and discussions that enriched my graduate studies, including Colleen Carey, John Cawley, Maria Fitzpatrick, Douglas Miller, Zhuan Pei, Evan Riehl, Nick Sanders, Seth Sanders, and Nicolas Ziebarth.

For essay 1, I am indebted to Sean Nicholson, Michael Waldman, Chris Forman, and Michael Lovenheim for invaluable advice. For helpful comments or discussions, I thank Panle Barwick, Charles Becker, Iain Cockburn, Wes Cohen, Jorge Contreras, Amanda Eng, Aija Leiponen, Josh Lerner, Ben Leyden, Doug Miller, Atul Nerkar, Chris Rider, David Ridley, Evan Riehl, Michael Roach, F.M. Scherer, Frank Sloan, Sarah Wolfolds, Nahim Zahur, and Rosemarie Ziedonis. Individuals from the MPP, World Health Organization, and Janssen provided valuable insights, especially Charles Gore, Erika Dueñas, Maica Trabanco, Sébastien Morin, and Frank Daelemans. I thank Dalton Price for excellent research assistance. I gratefully acknowledge funding from Cornell University (Economics, Policy Dept., and SC Johnson Business School, and Graduate School) and the Institute for Humane Studies.

For essay 2, I thank Sean Nicholson, Michael Waldman, Chris Forman, and Michael Lovenheim for invaluable support. For helpful comments or discussions, I thank Charles Becker, Larry Blume, Thomas Buchmueller, Colleen Carey, John Cawley, Aaron Chatterji, Amanda Eng, Avi Goldfarb, Don Kenkel, Esteban Méndez, Amalia Miller, Corbin Miller, Andrea Monge, Anita Mukherjee, Sarah Prenovitz, Jaeyong Shin, Kosali Simon, Frank Sloan, Katherine Wen, Barton Willage, and Nahim Zahur. I thank individuals from Boston Children's Hospital, Cornell

Health, Duke Hospital, Healthcare Cost and Utilization Project, Legal Science, National Association of Boards of Pharmacy, National Alliance for Model State Drug Laws, Office of the National Coordinator for Health Information Technology, and Surescripts for valuable insights. I appreciate travel grants from Cornell and the Institute for Humane Studies.

For essay 3 (co-authored with Jordan Epstein, Sean Nicholson, Katherine Hempstead, and Sam Asin), we thank Michael R. Richards for detailed comments and participants in a number of conferences and workshops for helpful suggestions and discussions. We gratefully acknowledge financial support from the Robert Wood Johnson Foundation (grant #73185).

In addition, I want to thank my other mentors, friends, and colleagues at Cornell and beyond. Graduate school is challenging, and I cannot image finishing a PhD without their intellectual and emotional support. It is always fun to be with my Friday dinner group members: Abhi Ananth, Jeehun Choi, Tilahun Emiru, Esteban Mendez, Yu She, Armand Sim, Roy Luoyi Su, Qi Wu, and Nahim Bin Zahur. I am always fond of the chats and discussions with my friends and officemates, in particular Anne Burton, Amanda Eng, Katelyn Heath, Andrea Monge, Grace Phillips, and Katherine Wen. I thank Penny Sanders for being an awesome speech coach for my department and guiding us all through the very stressful and exciting job market process. And, I am always grateful for my Duke mentors, Charlie Becker, David Dunson, Joseph V. Hotz, Frank Sloan, Andrew Sweeting, and Edward Tower, and my undergraduate advisor Yansu Hao at CUFE, all of whom helped start my journey in economics and research.

Furthermore, I am grateful for the institutional support across different departments and divisions at Cornell University, including the Economics Department, Department of Policy Analysis and Management, SC Johnson College of Business (Johnson Graduate School of Management and Dyson School of Applied Economics and Management), the Institute on Health Economics, Health Behaviors and Disparities, the Graduate School, Center for Teaching Innovation (CTI), Center for the Integration of Research, Teaching and Learning (CIRTL), and Cornell Health. Special thanks to the Cornell CIRTL director Colleen McLinn.

Finally, I thank my family, particularly my parents, for their unconditional love and support.

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CHAPTER 1

GLOBAL DRUG DIFFUSION AND INNOVATION WITH A PATENT POOL: THE CASE OF HIV DRUG COCKTAILS

Lucy Xiaolu Wang

Abstract: I study the impact of the first joint licensing platform for patented drugs, the Medicines Patent Pool, on global drug diffusion and innovation. The pool allows generic firms worldwide to license drug bundles cheaply and conveniently for sales in a set of developing countries. I construct a novel dataset from licensing contracts, public procurement, clinical trials, and drug approvals. Using difference-in-differences methods, I find that the pool leads to substantial increases in the generic supply of drugs purchased. In addition, there are positive responses in R&D inputs and outputs. Finally, I estimate a simple structural model to quantify welfare gains.

1.1. Introduction

Intended to reward innovation, patents can also impede the diffusion of affordable generic drugs and the development of new formulations. A patent owner has the right to exclude others from using and selling an invention for roughly two decades. In principle, patent licensing allows a manufacturer to produce and sell a drug before patent expiration by paying royalties. In practice, firms keep ever-green patents (Hemphill and Sampat, 2012), making it costly to license when each drug can be covered by hundreds of patents.[1] This situation has more severe impacts in developing countries, where many drugs remain unaffordable and unavailable decades after

[1] There is clear evidence of generic firms' comparative advantage in producing low-cost new cocktails. Before patent enforcement in developing countries, the first qualified single-pill HIV cocktail was created by generic firm Cipla in 2001 for $350 per patient-year, whereas the prices for the three standalone drugs were above $10,000. The cost dropped to about $140 per year after more generic entry (Hoen, 2016).

their initial approvals (Kremer, 2002; Cockburn *et al*., 2016).[2] When such drugs are available, substantial welfare gains can be achieved (Azomahou *et al*., 2016).

The tradeoff between patent protection and access to medicines can result in negative consequences to both patients and firms. One notable illustration of the consequences is the distribution and development of drugs to treat acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV). Standard treatments require the bundling of multiple drugs (i.e., cocktails) taken daily, of which each drug can be owned by a different firm. As of 2017, only about 59% of the 37 million people living with HIV worldwide had access to HIV drugs.[3] The lack of a stable supply of drugs and fixed-dose cocktail pills make it difficult for patients to adhere to the course of medical treatment, which further accelerates antimicrobial resistance. In response, governments and generic drug firms in developing countries infringe on and invalidate patents, which can further reduce innovation incentives.

In this paper, I study the effects of patent pools, which are institutions designed to ameliorate the tension between patent protection and the diffusion of technologies. As depicted in Figure 1.1, patent pools are joint licensing platforms that typically gather complementary patents from many patent owners and provide "one-stop shopping" to manufacturers. Historically, patent pools were commonly used in many sectors, including aircraft, railways, and radio (Lerner and Tirole, 2004). Patent pools disappeared after World War II as a result of regulatory changes and were revived in the late 1990s to spur the development of information and communication technologies. Although there is growing interest among practitioners and the

[2] Generic HIV drugs cost at least $200 per patient per year in the early 2000s, which was unaffordable in low-income countries that had average per capita health spending of $23 (Tirole, 2006).
[3] Source: https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics.

U.S. Patent and Trademark Office in creating biomedical patent pools (Clark *et al*., 2000; Van Overwalle, 2016), progress has been slow in the heavily regulated biomedical sector.

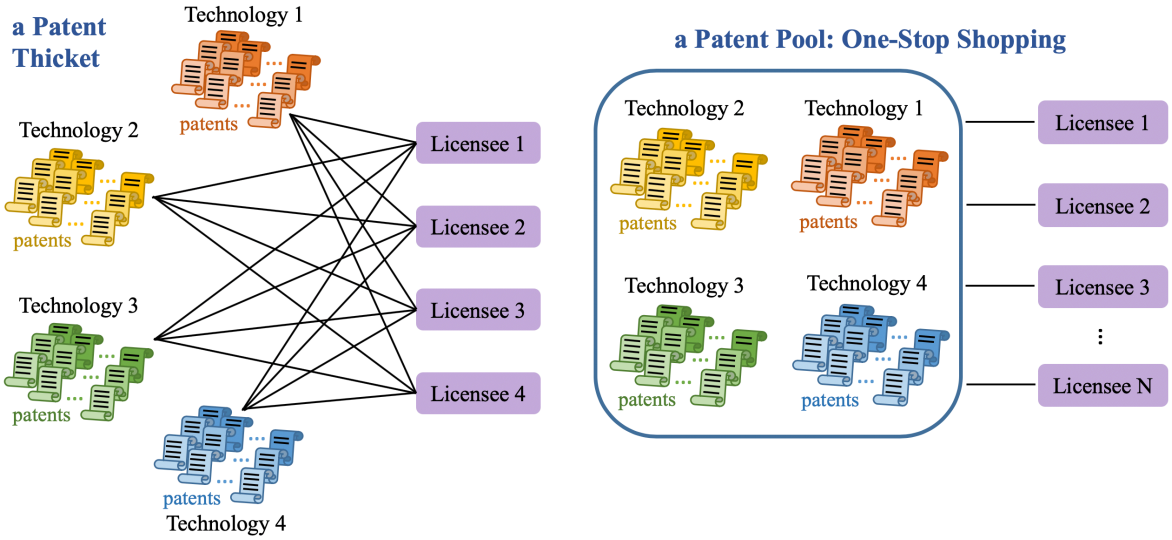


Figure 1.1: Graphical Structure of the Licensing Market without and with a Patent Pool

Notes: Author's graph. Each technology (e.g., a drug) has numerous underlying patents, and a complex technology (e.g., a drug cocktail) requires licensing multiple technologies for each licensee. The multiple patents involved and repeated negotiation with different patent owners create a patent thicket (left). A patent pool provides a one-stop shopping through a joint licensing platform (right). Therefore, more licensees can enter the market to develop and sell new products (e.g., new cocktails or formulations).

This paper investigates the first modern biomedical patent pool, the Medicines Patent Pool (MPP), which allows access to a set of HIV-related drug patents from multi-national firms with the goal of fostering the diffusion of generic drugs to developing countries and spurring innovation of new drugs. The MPP is a United Nations-backed non-profit organization founded in July 2010 in Geneva, Switzerland. The pool is an independent platform designed to facilitate generic licensing for all patents on pooled drugs in sales territories specified in the license. These MPP licenses cannot be used for sales in high-income countries. The pool targeted drugs for HIV at the early stage of its establishment, expanded to cover Hepatitis C and tuberculosis in late 2015, and is working on adding other disease areas. This institution offers an opportunity to explore the effects of biomedical patent pools and pool designs more broadly.

An illustrative example suggests that the MPP accelerates generic entry and new drug creation. A new compound, dolutegravir (DTG), was first approved in the U.S. in August 2013 and was added to the MPP in March 2014. Over a hundred patents on DTG were licensed from the pool by the generic firm Mylan in July 2014. The first DTG-based three-drug single-pill cocktail (TLD) made by Mylan was approved in 2017 for sales in developing countries; four other generic firms also obtained MPP licenses and drug approvals in 2018. Without the MPP, this process typically takes over a decade (Cockburn *et al*., 2016).

A patent pool can affect static efficiency (i.e., deadweight loss) and dynamic efficiency (i.e., innovation incentives) through different mechanisms. It can improve static welfare by addressing three economic problems: (1) transaction costs stemming from numerous patent negotiations with multiple drug owners; (2) hold-up problems where one failed negotiation is sufficient to prevent distribution of a generic cocktail; and (3) double-markup problems where downstream firms can also exert market power. The impact of a patent pool on dynamic efficiency is less clear. A pool can spur new drug creation from branded or downstream firms by reducing transaction and litigation costs, generating royalty revenue for branded firms which place drugs in the pool, and enabling downstream development of new products through broader licensing. However, a pool can stifle innovation with antitrust concerns of price-fixing and restrictive licensing terms that deter licensees from developing new products. Hence, the effect of a patent pool on innovation is ambiguous, underscoring the need for empirical analysis.

I examine the impact of the MPP on static and dynamic welfare. First, I ask whether the MPP increases the percentage of generic drug purchases in developing countries. Second, I investigate whether and how firms adjust R&D in response to the pool. Third, I estimate a static structural model of demand and supply to quantify welfare gains and simulate counterfactuals.

To examine how the MPP affects generic drug diffusion, I use the arguably exogenous variation in the timing of when a drug is included in the pool and thus available for generic licensing for sales in a given territory. I construct a novel dataset of drug sales in developing countries and use the generic share of HIV drug purchases as the main outcome variable. The pool-inclusion timing is driven by factors independent of changes in the outcomes of interest, such as firms' attitudes and administrative efficiency. Critically, I show that the timing is not determined by demand-side factors such as HIV prevalence and death rates. Because drugs are added to the pool at different times for different sales territories, I exploit variation regarding when a drug is added to the pool for a country and the impact on changes in the drug-country level share of generic drug purchases. Adding a drug in the MPP for a country increases generic drug share by about seven percentage points in that country, a result that is robust across various tests. I support the identifying assumptions using event studies, regression tests, and interviews which all indicate that the timing of entry to the MPP is exogenous to my outcomes of interest.

To further understand how firms strategically react to the MPP, I construct new data from all U.S.-registered global clinical trials of HIV drugs and HIV drug approvals by the two largest global drug approval agencies. The MPP can spur innovation if it creates a pro-competitive licensing environment for diffusion-oriented innovation. My analysis of clinical trials data indicates that the MPP increases follow-on innovation. Once a compound enters the pool, new clinical trials increase for drugs that include the compound and more firms participate in these trials. In particular, firms outside the pool increase late-stage trials to develop drug cocktails that include pooled compounds, and firms inside the pool invest more in new compound development. Post-approval trials that focus on long-term effects are shifted from pool insiders to pool outsiders. Furthermore, MPP-included compounds result in more new drug product

approvals, especially of generic drugs approved for sales in developing countries. These new products can be licensed back to branded firms and thus also benefit developed countries.

Finally, I estimate the welfare impact and cost-effectiveness of the pool. Specifically, I estimate a nested discrete choice model for the demand side, taking into consideration that HIV drugs are more substitutable within the same drug class, which are science-based measures of similarity used for drug regimen recommendations. I estimate the supply side in two broad cases: marginal cost pricing and Bertrand-Nash oligopolistic pricing. Both cases are motivated by and consistent with my previous findings that the MPP increases generic drug access without dampening innovation incentives. My counterfactual simulation of the no-MPP case suggests that the pool increases social welfare substantially over its first seven years of establishment. The MPP reduces marginal costs and results in consumer surplus gains of $0.7-1.4 billion (8.6-18.9% increases) across market structure assumptions. The MPP-induced rises in sales can also increase producer surplus by up to $181 million (a 4.5% increase). The total welfare gains far exceed the pool's total operating cost of $33 million during the same sample period (below $5million/year).

This paper contributes to three strands of literature. First, I extend research on innovation and the economy by studying a market-based institution designed to balance patent protection and access to medicines, particularly for treatments that require drug bundling. Prior studies find that innovation responds positively to market size (Acemoglu and Linn, 2004; Dubois *et al*., 2015).[4] In the global setting, *ex ante* analyses find patent enforcement can result in large welfare losses (Chaudhuri *et al*., 2006). *Ex post* studies are inconclusive, either finding little impact of drug patents on prices and sales (Duggan *et al*., 2016), or suggesting that patented drugs have higher prices and sales conditional on launch (Kyle and Qian, 2017). However, policies have

[4] The impacts of patents on innovation are ambiguous in theoretical predictions (Green and Scotchmer, 1995; Bessen, 2004) and mixed in empirical analyses (Williams, 2013; Sampat and Williams, 2019).

limited impact to sustainably scale up drug diffusion and innovation for diseases primarily affecting low-income countries. Similarly, in developed countries, patents can create hurdles to develop treatments that require inter-firm technology sharing (Heller and Eisenberg, 1998). The welfare effects of drug cocktails are ambiguous in merger simulations (Song *et al*., 2017), one of the inter-firm strategies closest to forming a patent pool. This paper provides a first evaluation of whether a market-based institution can effectively balance diffusion and innovation.

Second, this paper contributes to the patent pool literature as the first empirical analysis of a biomedical patent pool. Existing studies on patent pools are mostly theoretical. Early work emphasizes the importance of pooling complements (Cournot, 1838; Shapiro, 2001; Lerner and Tirole, 2004). A growing theoretical literature studies patent pools with both complementary and substitutable patents (Quint, 2014; Lerner and Tirole, 2015; Rey and Tirole, 2019). However, many theoretical predictions are difficult to test empirically, especially when measuring the degree of substitutability by *ex post* prices or litigation, which can be endogenous to the pool. To overcome this difficulty, I use drug classification as an *ex ante* measure of substitutability to explore the design and structure of the patent pool. In addition, empirical studies on patent pools are either historical (Lampe and Moser, 2013, 2015) or focus on modern software pools (Lerner *et al*., 2007; Vakili, 2016; Bekkers *et al*., 2017). The lack of detailed historical data can lead to under-estimated welfare impacts of a pool, and it is challenging even to measure diffusion from software patent pools.[5] I overcome these hurdles by utilizing the transparency of the MPP and compiling rich data from the biomedical sector.

Third, this paper adds to research on sharing through a business-to-business platform. A patent pool is an example of co-marketing arrangements (i.e., platforms) that facilitate sharing,

[5] The MPP is closer to traditional patent pools in history (i.e., with a small number of patent owners, not much ambiguity of who holds patent rights), compared to modern software patent pools.

including content bundling by cable operators and music performance rights licensed by streaming platforms (Lerner and Tirole, 2004; Gilbert, 2017). Whether such platforms can be welfare-enhancing depends on the institutional design (Ostrom, 1990). Evaluating the impact of these institutions is challenging and often relies on individual-based measures of research outputs, such as citation and publication (Furman and Stern, 2011). However, we understand little of how business-to-business platforms affect firms' economic activities in inputs and outputs. The MPP as a joint licensing platform for leading diseases with large markets provides a valuable setting to study, especially as it is expanding to more traditional disease areas.

The paper proceeds as follows. Section 2 lays out background and the conceptual framework. Section 3 describes the data. Sections 4 and 5 present empirical strategies and results for diffusion and innovation analyses, respectively. Section 6 estimates a static structural model of demand and supply. Section 7 discusses and concludes.

1.2. Background and Conceptual Framework

1.2.1 HIV and Drug Cocktails

Since the beginning of the AIDS pandemic in the 1980s, more than 35 million people have died from the disease and over 70 million people are infected with HIV globally. Today, AIDS remains a leading global cause of death, with almost two-thirds of the people living with HIV residing in Africa. HIV, the virus causing AIDS, cannot be eliminated once a person is infected. In the final stage of HIV's progression, AIDS destroys the immune system and makes the patient vulnerable to opportunistic infections—a set of over 20 illnesses. AIDS remained a fatal disease and a leading cause of death until the mid-1990s when highly active antiretroviral therapy (HAART) was discovered. Death rates dropped nearly 85% within a few years. Left

untreated, AIDS patients survive three years on average, and life expectancy drops to one year if an opportunistic infection strikes.

Despite the lack of a cure, daily HAART can turn HIV from a fatal to a chronic disease. The HAART typically uses a bundle of antiretrovirals from different drug classes based on the mechanisms of action, and each mechanism targets HIV at a different stage of its life cycle. If a patient cannot maintain medication adherence and develops resistance to a drug, that patient will be resistant to all drugs within that drug class. Within each drug class, drugs have different side effects, so a patient needs to switch to a different regimen once a side effect becomes intolerable. In sum, HIV compounds are complements due to bundling and substitutes due to side effect-induced switching. Therefore, both new cocktails and new compounds can improve current therapy. Although HIV treatment was the first case of a drug cocktail, this strategy has since been adopted in treating other diseases, such as hepatitis, tuberculosis, and certain cancers.

1.2.2 Patent Pools and the Medicines Patent Pool (MPP)

First used in 1856 to reduce patent litigations in the sewing machine industry, patent pools are institutions in which patent holders share rights for joint licensing with members or firms outside of the pool. There is no universal design for patent pools; thus, the pool design is case-specific. Public policy towards patent pools was extremely laissez-faire in the early twentieth century, and the pools were seen as exempt from regulatory scrutiny. However, patent pools almost disappeared after a 1945 U.S. Supreme Court decision regarding cartel behavior through joint marketing.[6] If not dissolved by courts, a patent pool expires when all patents in the pool expire. Although not historically used in the biomedical sector, the prevalence of HIV, the

[6] *Hartford-Empire Co. v. United States*, 323 U.S. 386 (1945); a case in the glass container industry.

lack of a cure, and the extensive patents associated with cocktail treatments provide a testing ground for a patent pool to reduce intellectual property (IP) issues in global health.

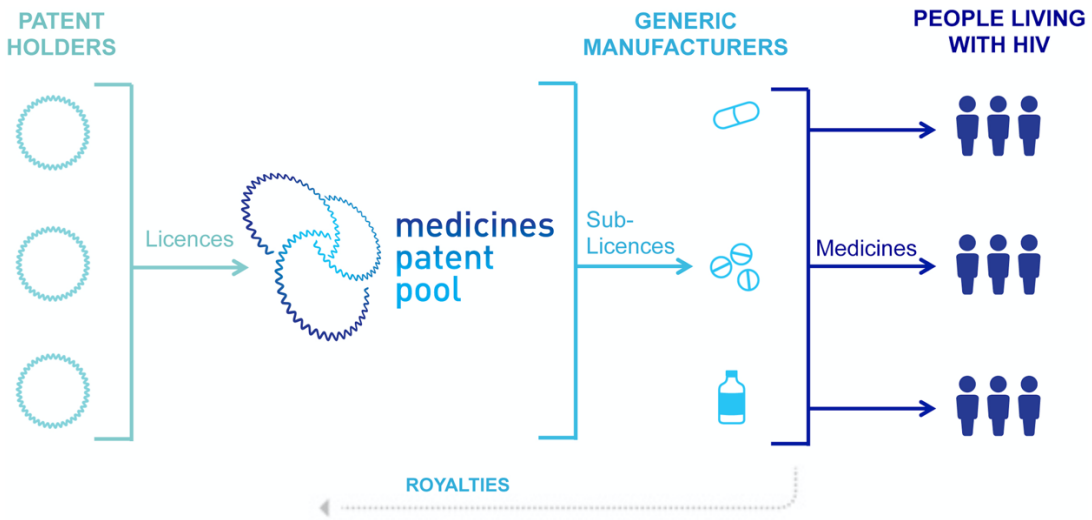


Figure 1.2: Licensing Structure for the Medicines Patent Pool

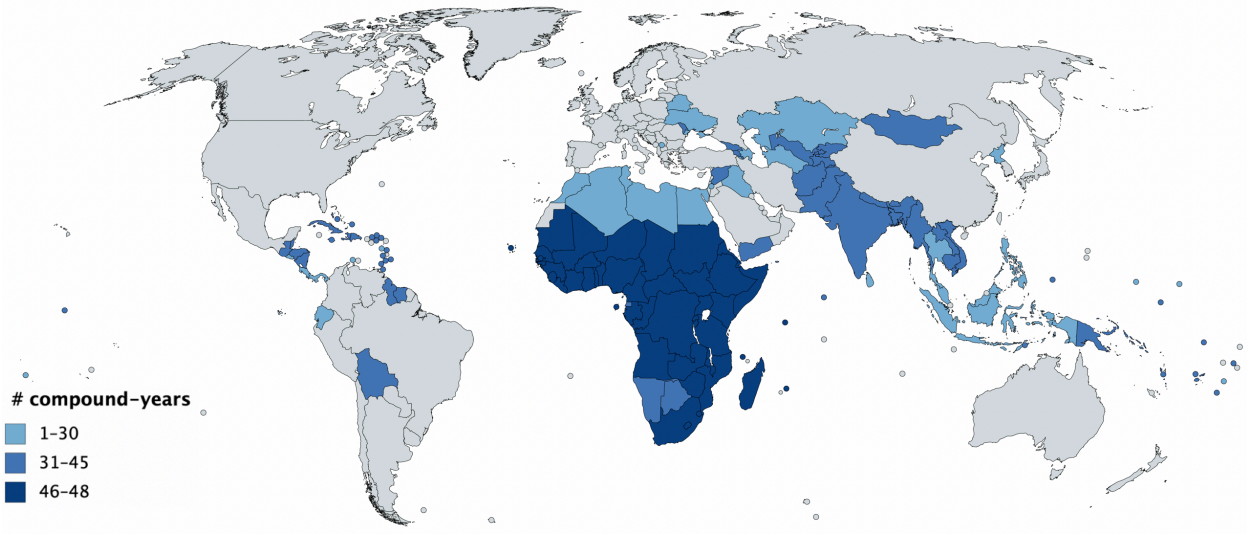
Notes: The figure depicts the basic structure of the MPP (form MPP official material). The MPP works as the intermediaries between branded drug firms and qualified generic licensees, and it prioritizes patients in resource-limited countries. Royalties are typically capped at 5% of revenue and are free in many cases.

The MPP aims to use market-based mechanisms to resolve coordination failure in the global medical supply chain, to spur generic licensing of patented drugs for sales in developing markets, and to avoid infringement or compulsory licensing.[7] As illustrated in Figure 1.2, the MPP negotiates with patent holders for drug licenses on HIV and related illnesses.[8] These licenses enable generic firms to develop new treatments, including fixed-dose cocktails and pediatric formulations. Any improvements in production or formulation by licensees can be non-exclusively granted back to the original patent holders. Generic firms can license a set of drugs

[7] With compulsory licensing, a government allows the production of a patented product without the consent of the patent owner. The MPP has gained support from the World Health Organization (WHO), the World Intellectual Property Organization (WIPO), and the World Trade Organization (WTO).
[8] The negotiation period can range from a few months to a few years. For instance, the MPP approached both Gilead and Janssen in 2010. Gilead joined the pool in 2011 and gradually licensed all of its HIV drugs, including two compounds that were not yet approved. In contrast, Janssen remained outside the MPP and agreed in 2015 to not enforce patent rights for the pediatric formulation of a drug it owns.

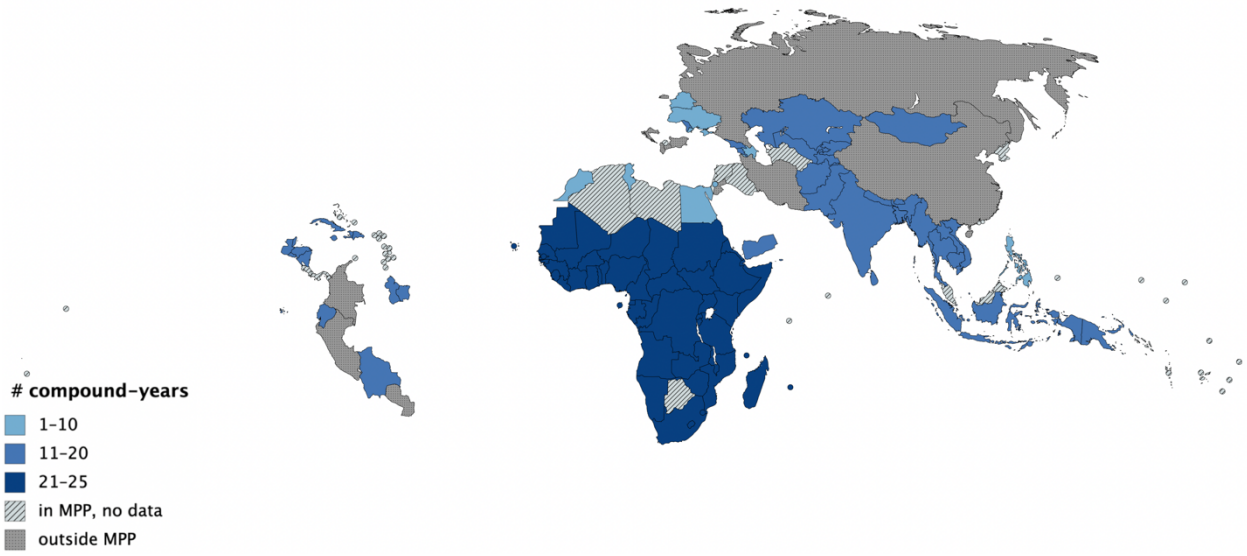
from the pool at once, and all patents on the set of drugs in the sales territory are included. Royalty rates are typically set at no more than 5% of revenue.[9] The MPP receives quarterly drug development updates from licensees and informs firms with de-identified progress of their competitors. Competition among generic firms can bring down prices and scale up drug access.

By the end of 2017, the MPP provided eligible licensing for 10 compounds covering four of the six HIV drug classes, and four out of the nine branded HIV drug providers had joined the MPP.[10] Figure 1.3 depicts the MPP sales territories; a detailed summary of MPP license terms is reported in the legal appendix (Appendix A.5). Generic drug industries are very heterogeneous across developing countries, with most large and competitive generic firms based in India, China, Brazil, and South Africa; while many sub-Saharan African countries lack local production and rely on imports. To assure branded firms that the intention of the MPP is to increase generic drug access in resource-limited countries, MPP licenses cannot be used for drug sales in high-income countries, and such activities need independent licensing outside the pool.



(a) MPP overall effective sales territory

[9] Five percent implicit cap of MPP royalty rates is relatively low compared to the average licensing price (five to eight percent) in the U.S. (Author's calculation based on the drug licensing database BioSciDB).
[10] As of early 2019, nine patent holders have pooled thousands of patents on 17 drugs. I exclude from my analysis those that are not for HIV, pediatric-only licenses, and non-sue agreements.



(b) MPP representation in the diffusion data

Figure 1.3: Geographic Penetration of the MPP: (a) Overall and (b) in the Diffusion Data

Notes: Figure 1.3 pictures the MPP effective sales territories by the end of 2017. Color groups represent the compound-year weighted intensity of impact. Panel (a) include all compound countries covered in the MPP sales territory, and panel (b) adapts the map to account for MPP compounds and countries in my data sets for the diffusion and structural analyses. Not all MPP-associated compounds appear in my data as many newer drugs need a couple of years to pass the production, registration, and distribution process.

1.2.3 Conceptual Framework: Incentives to Participate Across Firms

Below, I discuss how three types of firms with different incentives interact with the MPP: generic firms, branded firms in the pool, and firms outside the pool. Qualified generic firms can access pooled compounds with reduced licensing costs and obtain more and faster approvals of drugs with pooled compounds. Branded firms in the pool may shift resources to complementary R&D. Firms outside the pool may decide to develop new drug cocktails with pooled compounds.

Generic firms can utilize the MPP to overcome IP-related barriers. Given the specific context of HIV therapy, high royalties of patented compounds may deter generic firms from licensing and thus either exit the market or infringe patents and face costly litigations. If a generic firm already has two compounds but needs a third, patent-protected compound to develop a new single-pill cocktail, this development can be held-up by the branded firm in the

negotiation process. In addition, downstream firms may not be willing to negotiate with several branded firms to license many patents on multiple new compounds for sales in different countries. The transaction costs, for even a single compound, can be costly for both branded and generic firms alike. Once a generic firm overcomes the transaction cost and hold-up problem, the firm may have to pay multiple royalties to become the sole generic supplier for a drug and then use its downstream market power. In this type of market, prices are unlikely to fall until multiple generic firms begin to compete. The MPP makes licensing (multiple) drugs administratively easier, can reduce the cumulative royalty rates, and avoid unnecessary patent litigations.[11]

At the same time, branded firms in the MPP can benefit. Besides reducing administrative costs in licensing to generic firms, branded firms can use the pool to monitor compliance of licensees' sales behaviors (e.g., selling only in the allowed countries) and have an option to license back patentable improvements developed by the licensees.[12] It is worth noting that many branded firms are proactive in advancing drug access in developing countries, but it is difficult to set up marketing and sales teams in those countries. In fact, generic firms can sell more products in under-developed markets and therefore increase profit to branded firms from those markets via royalty fees.[13] If royalty income increases in these markets, branded firms may increase R&D in technically feasible trials (Finkelstein, 2004). However, branded firms could lose out from IP sharing without prior evidence about licensees' compliance. The situation is further complicated

[11] Although the discussion is mainly on patents, IP-related barriers include both patent and trade secrets (e.g., know-hows). Even for firms that try to sell in countries without issued patents, there can still be patents filed but pending grants. Licensing is always a safe option in the absence of complete information.
[12] Grant back provision means the licensor has a right to use patentable technology made by the licensee as a result of the initial license, possible through either an agreement or reverse licensing.
[13] Gilead intended to license to the MPP the blockbuster hepatitis C drug—sofosbuvir. But the MPP was not allowed to cover hepatitis C then due to the initial company mandate. Gilead has to set up an access program to facilitate generic licensing of sofosbuvir in developing countries. [interview with the MPP] Harvard Business School cases (# 9-510-029 and #9-515-025) elaborate on Gilead's access programs.

when pool participating firms hold partly substitutable drugs. Although a pool with price caps on royalty rates can be pro-competitive even with substitutable technologies, how firms would behave is ambiguous in theory and requires careful empirical work (Rey and Tirole, 2019).

In addition, a patent pool can generate spillover effects to upstream, research-oriented firms outside the pool (e.g., universities, public institutions). Employees at the MPP regularly present in medical conferences to disseminate information and communicate with scientists to encourage diffusion-oriented innovation. Inclusion in the MPP can indicate firms' openness to IP diffusion, and thus lower the litigation risks to research-oriented firms if a result enters the for-profit domain (Williams, 2013). This situation is similar to a patent commons (i.e., a pool with zero royalties) in open source software, where opening up IP can increase follow-on R&D and firm entry (Wen *et al.*, 2015). Often times, follow-on innovation by firms outside the pool can complement branded firms' R&D by discovering new or better use of approved drugs and by providing post-market surveillance. However, whether an access-oriented pool can effectively engage with the research community is an open empirical question.

1.3. Data

1.3.1 Data on HIV Drugs and MPP Licensing Contracts

I first collect data on all HIV drugs approved by the U.S. Food and Drug Administration (FDA), including both standalone compounds and multi-compound drug cocktails.[14] I obtain the data from the FDA and AIDS*info*.gov, which is a U.S. government agency providing information on HIV/AIDS. I convert branded names to generic names to standardize the coding, because the

[14] All existing HIV drugs are approved in the most lucrative U.S. market. Similarly, all clinical trials on new drug development (for U.S. drug approval or academic publications) must be registered in the U.S.

same drug can have different branded trade names in different countries. I then collect details about the MPP from its official website and the licensing contracts. The timing of a compound-country being included in the MPP is documented in the original contract and amendments.

Table 1.1: Approved Active Pharmaceutical Ingredients (Compounds) Treating HIV
(generic names marked with * are compounds no longer recommended in the U.S.)

Drug class	Generic name	Abbr.	Brand drug holder	date: FDA approval	date: add to MPP
NRTIs	abacavir	ABC	ViiV Healthcare	1998.12.17	2013.02.13[ped]
NRTIs	didanosine *	ddI	Bristol-Myers Squibb	1991.10.09	
NRTIs	emtricitabine	FTC	Gilead Sciences, Inc.	2003.07.02	2011.07.11
NRTIs	lamivudine	3TC	ViiV Healthcare	1995.11.17	
NRTIs	stavudine *	d4T	Bristol-Myers Squibb	1994.06.24	
NRTIs	tenofovir alafenamide	TAF	Gilead Sciences, Inc.	2015.11.05	2014.07.22
NRTIs	tenofovir disoproxil fumarate	TDF	Gilead Sciences, Inc.	2001.10.26	2011.07.11
NRTIs	zidovudine	ZDV	ViiV Healthcare	1987.03.19	
NNRTIs	doravirine	DOR	Merck & Co., Inc.	2018.08.30	
NNRTIs	efavirenz	EFV	Bristol-Myers Squibb	1998.09.17	
NNRTIs	etravirine	ETR	Janssen	2008.01.18	
NNRTIs	nevirapine	NVP	Boehringer Ingelheim	1996.06.21	
NNRTIs	rilpivirine	RPV	Janssen	2011.05.20	
PIs	atazanavir	ATV	Bristol-Myers Squibb	2003.06.20	2013.12.11
PIs	darunavir	DRV	Janssen	2006.06.23	
PIs	fosamprenavir	FPV	ViiV Healthcare	2003.10.20	
PIs	indinavir *	IDV	Merck & Co., Inc.	1996.03.13	
PIs	nelfinavir *	NFV	Agouron (ViiV)	1997.03.14	
PIs	lopinavir	LPV	AbbVie Inc.	2000.09.15	2014.11.24[ped]; 2015.12.17[adult]
PIs	ritonavir	r	AbbVie Inc.	1996.03.01	2014.11.24[ped]; 2015.12.17[adult]
PIs	saquinavir	SQV	Hoffman-La Roche	1995.12.06	
PIs	tipranavir	TPV	Boehringer Ingelheim	2005.06.22	
FIs	enfuvirtide	ENF	Hoffman-La Roche	2003.03.13	
EIs	Ibalizumab	IBA	TaiMed Biologics	2018.03.06	
EIs	maraviroc	MVC	ViiV Healthcare	2007.08.06	
IIs	bictegravir	BIC	Gilead Sciences, Inc.	2018.02.07	2017.09.26
IIs	dolutegravir	DTG	ViiV Healthcare	2013.08.12	2014.03.31[ped. & adult]
IIs	elvitegravir	EVG	Gilead Sciences, Inc.	2012.08.27	2011.07.11
IIs	raltegravir	RAL	Merck & Co., Inc.	2007.10.12	2015.02.20[ped]
Enhancers	cobicistat	COBI	Gilead Sciences, Inc.	2012.08.27	2011.07.11

Notes: (1) I excluded 3 compounds withdraw from the market before 2000 (APV, ddC, DLV). EVG and COBI were first approved as part of a cocktail; both standalone compounds were approved on 9/24/2014. Similarly, standalone TAF was approved on 2016.11.10 after its cocktail approval on 2015.11.05. (2) MPP license for ABC and RAL restrict to pediatric formulation. I treat DRV as not in the pool, albeit NIH put in part of DRV-related patents but not those owned by Janssen, resulting in no technology transfer and no sub-licensing so far. (3) drug classes are medical

groups based on the mechanism of action towards HIV virus. (4) DTG was marked as 8/12/2013 in FDA raw data but as 8/13/2018 on FDA websites. DTG enters the MPP on 3/31/2014 with different territory specified for adult and pediatric products. (5) Agouron is a subsidy of Pfizer since 1999 and Pfizer is part of the joint venture ViiV Healthcare (with GlaxoSmithKline and Shionogi).

Table 1.1 displays key information on all HIV compounds approved by 2018. There are six drug classes for HIV therapy, including 30 distinct compounds owned by nine branded entities from 11 firms. Among them, the market leaders are Gilead Science and ViiV Healthcare (i.e., a joint venture of GlaxoSmithKline, Pfizer, and Shionogi). I report the FDA approval dates for each compound and MPP addition dates for associated compounds by the end of 2018.

1.3.2 Drug Diffusion Data: Public Procurements, Patents, and Country-Year Controls

I use HIV drug purchase records from the Global Fund's Price and Quality Reporting, a large-scale public dataset that records procurement transactions made by Global Fund-supported programs. The non-profit Global Fund is the world's largest financier of health service programs for AIDS, tuberculosis, and malaria. Specifically, the Global Fund finances about 40 percent of all HIV drug purchases for low- and middle-income countries (LMIC).[15] The implementation relies on within-country partners such as ministries of health and country-specific committees, who report results to the Global Fund for monitoring purposes. My sample includes 29 HIV drugs involving 18 compounds purchased for 103 developing countries during 2007–2017.

I aggregate the raw data from purchasing records to create a country-drug-year level unbalanced panel dataset. The raw data report the transaction date, the quantity of drugs purchased in various strengths and dosage forms, prices, selling firm, and destination country. To measure the diffusion of generic HIV drugs, I calculate the proportion of drug purchases for each given drug-country-year that is generic. Specifically, I divide the number of purchases made

[15] Source: Global Fund publication, 2016, available at https://tinyurl.com/y4dgwy3w.

from generic firms by the total number of purchases for a drug within a country-year. I then convert each drug-purchase into a standardized dosing quantity in units of per patient-day, and I calculate the percentage of generic drug quantity at the drug-country-year level.[16] I calculate the number of distinct drug products—a combination of drug-strength-dosage form-firm—at the drug-country-year level as a proxy measure of within-drug market competitiveness. Table 1.2 Panel A provides summary statistics for the outcomes. During my sample period, the average shares of generic purchases and generic quantities are 84.3% and 85.6%, respectively.

I obtain HIV drug-country-specific international patent data from two sources. First, I use data from the MPP's own patent database, MedsPaL, which was created in collaboration with regional patent offices and provides the patent status (e.g., expiration date by country) of selected drugs. Second, I acquire data on all available international patents on HIV drugs from the Drug Patent Watch database, following Galasso and Schankerman (2014). A drug is covered by effective patents if there are any active patents for that drug in the country-year.

I collect country-year level control variables from two sources. First, I use population and income (GDP per capita) provided by the World Bank. I also use the World Bank Worldwide Governance Indicators, which are six continuous measures of voice and accountability, political stability and absence of violence, government effectiveness, regulatory quality, rule of law, and control of corruption. Second, I obtain HIV prevalence and age-adjusted death rates from Global Burden of Disease Study Life Tables provided by the Institute for Health Metrics and Evaluation and curated by Our World in Data from Oxford University.

[16] The U.S. standard adult daily dosing information is from FDA labeling and AIDS*info* and is reported in Appendix A.3 (Medical Appendix) Table III.A2. In the absence of perfect dosing data for each country, this conversion provides the best proxy measure. I use both the measure of the raw percentage of generics and the quantity-adjusted measures to ensure that my results are not driven by idiosyncratic factors.

Table 1.2: Summary Statistics of Outcome Variables

Variables	Unit of obs.	Obs.	Mean	Std. Dev.	Min	Max
Panel A: variables used in the diffusion analysis – cross-country panel analysis						
% generic orders (%)	drug-country-year	7,084	84.31	34.47	0	100
% generic quantity (%)	drug-country-year	7,084	85.63	34.16	0	100
# products	drug-country-year	7,084	1.72	1.04	1	10
% generic orders	comp.-country-year	6,485	79.82	36.94	0	100
% generic quantity	comp.-country-year	6,485	82.07	36.75	0	100
# products	comp.-country-year	6,485	2.53	1.94	1	21
Panel B1: variables used in the innovation analysis – clinical trials analysis						
# new trials	comp.-year	540	10.08	13.24	0	67
# firms in new trials	comp.-year	540	20.73	28.53	0	165
# new trials, MPP insiders	comp.-year	540	2.41	3.27	0	17
# new trials, MPP mix	comp.-year	540	1.99	3.49	0	23
# new trials, MPP outsiders	comp.-year	540	5.68	7.89	0	44
# firms in trials, MPP insiders	comp.-year	540	3.15	4.53	0	36
# firms in trials, MPP mix	comp.-year	540	5.92	10.52	0	69
# firms in trials, MPP outsiders	comp.-year	540	11.67	16.80	0	113
# new investigational trials	drug class-year	126	6.76	8.19	0	32
# firms in investigational trials	drug class-year	126	12.49	16.39	0	63
Panel B2: variables used in the innovation analysis – drug approval analysis						
# new approvals	drug-year	798	0.70	1.63	0	14
# new approvals, generic	drug-year	798	0.61	1.60	0	14
# new approvals, branded	drug-year	798	0.09	0.42	0	6
# new approvals	comp.-year	378	2.28	4.02	0	32
# new approvals, generic	comp.-year	378	2.01	3.97	0	31
# new approvals, branded	comp.-year	378	0.27	0.72	0	6

Notes: this table reports summary statistics for the main outcome variables used in the analysis. "Comp." is short for compound, the smallest chemical units of a standalone drug. Panel A is for drug-country-year and compound-country-year level variables over the time period 2007-2017. Panel B1 is for compound-year level variables from HIV clinical trials during 2000-2017. MPP insiders refers to branded firms participated in the MPP, MPP outsiders refers to non-MPP firms, and MPP mix indicates trials by a mix of MPP insiders and outsiders. Panel B2 is for drug-year and compound-year level variables from FDA and WHO original drug approvals during 2005-2018.

1.3.3 Drug Innovation Data: Clinical Trials, Drug Approvals, and Controls

I measure R&D inputs using clinical trials at the compound-year level from 2000–2017. I obtain clinical trials data from the U.S. registry, ClinicalTrials.gov, the most widely used database of global clinical trials. The registry was first released in 2000 and was maintained by

the National Library of Medicine (NLM) at the National Institutes of Health (NIH) to collect and share data on clinical trials.[17] To identify trials on HIV drugs, I obtain clinical trial identifiers provided by AIDS*info* of trials related to each FDA-approved HIV drug and pre-approval investigational drug. AIDS*info,* which is also maintained by the NLM, offers access to the latest federally approved HIV/AIDS medical information. I convert all branded drug names to their generic names to unify the coding. Table 1.2 Panel B reports the summary statistics for the clinical trials outcomes. On average, there are about 10 U.S.-registered new clinical trials that involved a HIV compound in a year, among which branded firms inside the MPP engaged in about 4.4 trials—2.4 trials in-house and two collaborated with firms outside the pool. There are about 21 firms engaged in these trials each compound-year, with a similar distribution pattern.

I also use FDA and WHO approval data for HIV drugs (branded and generic) as output measures of innovation from 2005–2018. These are the two largest agencies whose approvals are qualified for expediated registration in many developing countries. HIV drugs can be approved by the FDA via two channels: regular approval and the international program. I extract all FDA regularly-approved HIV drug product data from the Drugs@FDA database; I obtain international program approvals via the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), which began in 2004.[18] The two channels maintain the same safety, efficacy, and quality standards; however, the PEPFAR provides expedited reviews of generic versions of patented drugs to reduce the global burden of the AIDS epidemic. The WHO pre-qualification program is the other

[17] Before 2000, the registry collected and shared data on clinical trials conducted on experimental drugs with "serious or life-threatening diseases or conditions" (including HIV/AIDS-related drugs). The scope broadened over time to include all interventions: https://clinicaltrials.gov/ct2/about-site/history.
[18] Source: https://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm. Drugs approved via PEPFAR cannot be marketed in the U.S. I focus on all drug approvals and tentative approvals by the FDA and WHO during 2005–2018, because drug approval policies changed in 2004 and 2005 following the FDA's new initiative to expedite AIDS drug reviews and the end of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement's grace period for Indian generic firms, respectively.

common mechanism through which HIV drugs are approved for global distribution. Pre-qualified firms can then register a quality-assured drug in different countries. Table 1.2 Panel C reports the summary statistics for the R&D outputs. There are 0.7 approval per drug-year and about 2.3 approvals per compound-year, indicating the majority approvals are for cocktails.

I obtain U.S. patent data from DrugBank, which is an online drug database widely used for peer-reviewed research. The U.S. patent status is closely tied with a drug's owner perceived value, given that U.S. is the largest drug market. The data provider obtains compound-specific patent records from the FDA's Orange Book and further undertakes a manual curation process. I record the U.S. patent status based on the effective patent period for each compound (i.e., before the last granted patent expires), and I then assign drug-year level patent status accordingly.

1.4. Patent Pool and Global Diffusion of HIV Drugs

1.4.1 Empirical Strategy

To estimate the causal impact of the MPP on generic drug diffusion, I first define drugs "as they are"—either as standalone compounds or in fixed-dose single-pill drug cocktails. Pool inclusion timing is coded based on compound-level inclusion into the pool, because a compound is the lowest-level unit for standalone and cocktail drugs alike. I exploit variation in the timing of drug-country additions to the pool and estimate the difference-in-differences model as follows.

$$y_{dct} = \delta_{dc} + \delta_t + \boldsymbol{\beta} MPP_{dct} + \tilde{\gamma}\tilde{X}_{ct} + \eta X_{dct} + \varepsilon_{dct} \qquad (1)$$

Here, y_{dct} is an outcome variable aggregated to the drug-country-year level, including the share of generic transactions of a drug, the quantity-adjusted generic shares, and the number of distinct products purchased for a drug in a country-year. MPP_{dct} is an indicator for whether a drug d has

any compound included in the MPP in country c in year t. I also examine another MPP_{dct} measure using the share of MPP compounds in a drug for a country-year ct. The variable X_{dct} controls whether any effective patents on drug d exist in country c for a given year t.

Each regression contains fixed effects for drug-country pairs (δ_{dc}) and year (δ_t) to account for differences between drug-countries and years, respectively. The drug-country fixed effects capture differences in unobserved factors that correlate with the generic share of a drug in a country that are not recorded in observable data, such as response rate, resistance rate, and expected profit for each drug in each country. $\tilde{X}_{ct}$ contains a set of observed country-year level control variables, including institutional factors, HIV prevalence and death rates, log population, and GDP per capita.[19] Standard errors are two-way clustered at country and drug levels to allow for arbitrary autocorrelation within a country and a drug (Cameron *et al*., 2011).[20]

There are two identifying assumptions: common trends and lack of common shocks. I test the former using an event study model, and I support the latter by elaborating on why the data generating process is driven by factors arguably orthogonal to the outcomes of interest.

I test the common trends assumption using an event study framework. First, this framework helps to assess the validity of the assumption that the trend in the control group that is outside the MPP (drug-country-years outside the MPP) is a valid counterfactual for the treated group (drug-country-years in the MPP). Differential trends of outcome variables between the treatment and control groups in the pre-treatment period would suggest endogeneity in drug-country inclusion or, potentially, correlation with other shocks. Second, the event study measures the dynamic responses of outcomes to policies—whether the effects fade or build over time. The

[19] The institutional factors are the six worldwide governance indicators described in the data section. I also use two-way fixed effects instead of observable controls as a specification test to show robustness.
[20] Results are robust to alternative clustering methods at the country level and country-drug level.

MPP impacts could gradually build up (because diffusion takes time) and diminish over time since the dependent variable is bounded by 100%. I estimate event study models as follows:

$$y_{dct} = \delta_{dc} + \delta_t + \sum_{j \in T} \boldsymbol{\beta_j} 1\left\{ \begin{matrix} MPP\ event \\ time_j \end{matrix} \right\}_{dct} + \tilde{\gamma} \tilde{X}_{ct} + \eta X_{dct} + \varepsilon_{dct}. \qquad (2)$$

Here, β_j represents the difference between treatment and control units j years relative to when a drug-country was included in the MPP. For drug cocktails that have multiple compounds, I define the event time as years relative to when any compound was first included in the pool.

Next, I describe the data generating process to support the lack of common shocks assumption. First, which patented drugs are included in the pool results from perceived value and negotiation outcomes, and below I present evidence that drugs inside and outside the pool appear to be similar in quality and in initial approval year. In a learning-by-doing process, the MPP aims to target candidate drugs that are of high clinical and market values, but targeted drugs are not always added; firms can also voluntarily contribute other drugs to the pool. In principle, the MPP follows the WHO *Essential Medicine List* on marketed drugs that have demonstrated sufficient effectiveness.[21] In practice, the MPP also considers pre-approval drugs and aims to further speed up generic access. By the end of my sample period, patented drugs inside and outside the MPP are similar in terms of sales and approval time. Specifically, six HIV compounds are listed in the top 100 drugs by global sales in 2012, and three of the six HIV compounds are in the MPP (Table III.A3); the U.S. approval dates are similar for drugs in and outside the pool (Table 1.1).

Second, drug-specific MPP sales territories typically vary by the branded firm and always include sub-Saharan Africa and Djibouti; additional inclusion of countries roughly depends on

[21] The WHO list includes all approved HIV drugs except three pre-2000 withdrawals. They are all of high market values. The MPP broadly target any HIV drugs in early years to demonstrate the business model.

income groups, prior voluntary licensing status, and exercises in public relations.[22] When initially adding a drug, branded firms typically include over 90 countries in the MPP territory, and rarely add more countries later. Thus, territory decisions are not likely driven by temporary country-specific demand shocks that can induce higher generic supply without the pool. In many cases, firms had already issued bilateral generic licensing and voluntary free licensing before the MPP was established, and countries in pre-existing licenses are typically also included in the initial MPP territory (Juneja *et al.*, 2017). This situation can bias my estimates towards zero. In addition, the control variables account for the country-year level differences over time in HIV death rates, HIV prevalence, population, income, and institutional factors that are related to the demand and distribution for the drug. The outcomes in percentages further account for supply-side factors, because overall demand increases will affect both generic and branded drugs.

Third, the timing of when a drug-country is eligible for MPP licensing is partly affected by negotiation time and scientific discovery. The negotiation time is affected by firms' attitude and administrative efficiency. For example, Gilead Sciences used generic licensing years before the MPP was established and has gradually put all of their HIV drugs into the pool, including two investigational drugs in late-stage clinical trials. In contrast, Janssen was approached by the MPP early on but has never officially joined the MPP.[23] While I cannot perfectly determine what drives entry and when it happens, it is unrelated to factors that are most likely to cause a bias. To show this, I regress the MPP indicator on observables related to demand, demographics, income,

[22] I obtained the details from interviews with MPP employees in Geneva, Switzerland. A branded firm can follow the "low-income" defined by the World Bank or use its own per capita income cut-off value. One firm once split the name of an island country into two to boost the number of countries it helped. Another firm once left one sub-Saharan African country outside the MPP territory unintentionally and added it back once reminded. These factors are likely orthogonal to changes in my outcomes of interest.
[23] Janssen agreed on a covenant not to sue without further commitment in technology transfer and formal licensing. Janssen is unsure whether the MPP model would work [interview with Frank Daelemans].

institutional factors, and fixed effects at drug-country and year levels. As shown in Table A1, none of the key observables are significant predictors of the timing, and the goodness of fit barely increases when adding observables to the regression.[24] Empirical tests and institutional knowledge indicate that the timing is driven by factors orthogonal to my outcomes of interest.

Furthermore, the smallest treatment unit is at the compound level, while each purchase is at the drug level: as a standalone compound or a drug cocktail. As a robustness check for measurement error, I estimate a compound-country-year level model where drug cocktails are converted into compounds. This model is estimated using equation (1) but on compound-country-year (y_{act}) aggregated data, with fixed effects at the compound-country and year levels.

1.4.2 Does the MPP Foster Diffusion of Affordable Generic Drugs?

The main results from the drug-country-year analysis indicate that the MPP increases generic shares. Table 1.3 Panel A reports the baseline estimates using an indicator for MPP_{dct}. Column (1) controls for fixed effects at drug-country and year levels; columns (2)–(3) gradually adds observable controls at country-year and drug-country-year levels, respectively.[25] Across columns (1)–(3), coefficient stability reduces concerns on omitted variable bias and measurement errors on observables. The results indicate that adding a drug-country pair in the MPP increases the share of generic purchases of this drug in the country by about seven percentage points. This is a substantial increase given the already high generic coverage in developing countries (84% on average during my sample period). Columns (4)–(6) report results from regressions using the

[24] Similar, Figure A1 depicts trends of HIV death rates and prevalence; neither show spikes during my sample period. Civil society advocacy and compulsory licensing threats for the inclusion of additional countries into the MPP are typically outside my sample periods and affecting the comparison group.
[25] Because comprehensive global patent data are hard to obtain (Lerner & Seru, 2017), I demonstrate the robustness of my results across specifications with and without the drug-country-year patent control.

share of generic quantities purchased. Coefficient estimates are of similar magnitudes and precision to these in columns (1)–(3) and are stable across specifications. However, there is no statistically significant effect on the number of drug products purchased (columns 7–9). This result is consistent with the idea that countries may still purchase a subset of drug products when there are more options available and benefit from competition-induced price reductions.

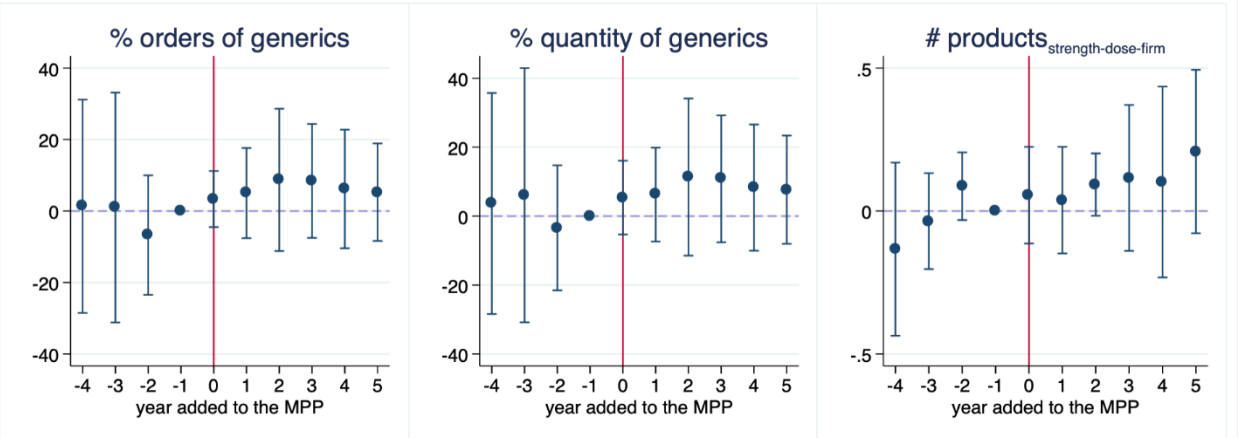
Table 1.3: MPP and Generic HIV Drug Diffusion in LMICs

Dept. Vars.	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	% generic orders (#)			% generic quantities (patient-year)			# products (strength-dose-firm)		
Panel A: Drug-Country-Year Analysis, MPP_{dct} as {0, 1} dummy									
MPP_{dct}	6.888**	7.223**	7.226**	6.653**	7.003**	7.010**	0.0739	0.0719	0.0717
	(3.178)	(2.933)	(2.932)	(3.035)	(2.802)	(2.796)	(0.113)	(0.104)	(0.104)
	[2.712]	[2.706]	[2.707]	[2.725]	[2.717]	[2.715]	[0.081]	[0.080]	[0.080]
Panel B: Drug-Country-Year Analysis, MPP_{dct} as % of MPP compounds									
MPP_{dct}	7.154**	7.403**	7.409**	6.916**	7.183**	7.194**	0.0929	0.0939	0.0937
	(3.270)	(2.983)	(2.984)	(3.123)	(2.858)	(2.857)	(0.124)	(0.113)	(0.112)
	[2.870]	[2.851]	[2.853]	[2.870]	[2.858]	[2.859]	[0.087]	[0.085]	[0.085]
drug-country FE	Y	Y	Y	Y	Y	Y	Y	Y	Y
year FE	Y	Y	Y	Y	Y	Y	Y	Y	Y
X_{ct} control		Y	Y		Y	Y		Y	Y
X_{dct} control			Y			Y			Y
LHS mean	84.3	84.3	84.3	85.6	85.6	85.6	1.7	1.7	1.7
Obs.	7,084	7,084	7,084	7,084	7,084	7,084	7,084	7,084	7,084
Panel C: Compound-Country-Year Analysis									
MPP_{act}	9.576**	9.977**	10.12***	10.09***	10.42***	10.55***	0.156	0.140	0.132
	(3.708)	(3.493)	(3.487)	(3.369)	(3.248)	(3.261)	(0.193)	(0.185)	(0.186)
	[3.088]	[3.050]	[3.076]	[3.227]	[3.204]	[3.226]	[0.115]	[0.114]	[0.110]
comp.-country FE	Y	Y	Y	Y	Y	Y	Y	Y	Y
year FE	Y	Y	Y	Y	Y	Y	Y	Y	Y
X_{ct} control		Y	Y		Y	Y		Y	Y
X_{act} control			Y			Y			Y
LHS mean	79.8	79.8	79.8	82.1	82.1	82.1	2.5	2.5	2.5
Obs.	6,485	6,485	6,485	6,485	6,485	6,485	6,485	6,485	6,485

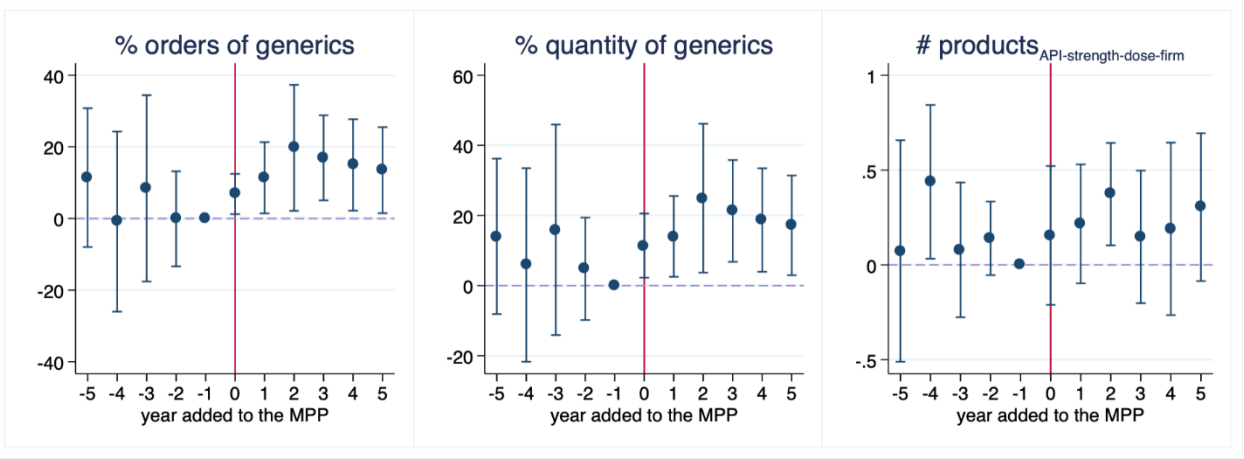
Notes: This table reports the results of estimating a difference-in-differences model using equation (1). "Comp." is short for compound. Each cell reports the coefficient of interest from a separate regression. Coefficient estimates for the treatment variables $MPP_{d(a)ct}$ are reported across three measures across panels. The specification controls for drug (compound)-country-year level effective patent status and country-year level observables. Fixed effects for drug (compound)-country pairs and years are always included. Robust standard errors are clustered using two-way clustering at the drug (compound) and country levels and are reported in () parenthesis. Robust standard errors clustering at the country level is reported in []. Two-way robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

The main results are robust to using alternative measures of the treatment variable, reported in Table 1.3 Panel B as the percentage of MPP compounds over total compounds for a drug in a country-year. The results are qualitatively similar to the indicator measure and slightly larger in magnitude. I mainly focus on the indicator measure below, because it captures the most salient changes at the extensive margin and favors simplicity in explanation.

The associated event studies support the main results discussed above and are reported in Figure 1.4. No pre-trends exist that violate the difference-in-differences assumptions. The lack of pre-trends is particularly clear for the outcomes of percentages of generic orders and generic quantities. The post-period trends for these outcomes rise from zero, consistent with the estimate of the significantly positive average treatment effects, despite the lack of power to precisely estimate the impact for each post-period. The effects gradually build after a drug enters the MPP and stabilize over time, consistent with time varying treatment effects that take time to establish and then bounded by 100%. The event study for product variety demonstrates a similar pattern.



(a) Drug-Country-Year Panel



(b) Compound-Country-Year Panel

Figure 1.4: Event Studies for Diffusion Analysis

Notes: These figures report event-study coefficient estimates using Equation (2). The units of observation for panel (a) and (b) are at drug-country-year (dct) and compound-country-year (act) levels, respectively. The dots are point estimates of differences in outcomes between treatment and control groups 4-5 years before MPP inclusion and 5 years after inclusion. The whiskers correspond to 95% confidence intervals.

In Table 1.3 Panel C, I report results after converting drug cocktails into compounds – the smallest treatment unit. The compound-country-year analysis further supports my main results with more precise estimates. In the full sample, adding a compound in the pool increases the percentages of generic drug orders and generic drug quantities ordered by about 10% across specifications; all estimates are statistically significant at the 1% level. The estimates from the product variety regressions are larger in magnitude than those in the drug-country-year results, but similarly are not statistically significantly different from zero at conventional levels. The associated event studies with the full set of control variables are presented in Figure 1.4 panel (b). Overall, there are no pre-trends from the event studies for the outcomes of interest. The post-period increases in the share of generic drug purchases and quantities are clear and significant. The graph for product variety is relatively less precise, which matches the results in Table 1.3.

1.4.3 Subsample Heterogeneity and Robustness Checks

Previous results show the overall treatment effects, and I now demonstrate that the results in subsamples vary by patent status. As discussed before, the MPP's impact is expected to be stronger in countries in which a drug is patented because a firm considering launching a generic drug in that country needs to secure a license (or licenses) or risk a lawsuit. Countries without patents can also benefit from the MPP through spillover effects, such as enhanced international trade. Table A2 reports the results, and they match the prediction: across specifications and measures, the percentage of generic drug orders increases more in countries where a drug placed in the MPP was patented. The MPP coefficient estimates are similar when using percentage of generic drug quantities purchased as the outcome variable. Similar to the baseline case, the impact of MPP inclusion on within-drug product varieties is statistically insignificant.

The above analyses all support the hypothesis that the MPP works as a market-based institution to increase generic utilization. Here, I provide additional analyses using price as a counterpart measure.[26] Simple analyses of price and quantities suggest that the MPP reduces prices and increases overall quantities accordingly. Table A3 reports the reduced-form evidence using price and quantities as outcome variables. Overall price per patient-year reduces by about $87, mainly from a substantial reduction in generic prices, and quantities react correspondingly. More comprehensive analyses on prices and quantities would consider more factors such as market structure and demand in the presence of substitutes. Therefore, I examine demand and supply more formally and estimate the welfare effects in section 6.

[26] Higher generic share is a sufficient but not necessary condition for lower prices, because the latter can be achieved by non-market strategies such as price ceiling and branded-firms' donations. Besides, price calculation involved strength and dosing conversion that makes it less straightforward in interpretation. Thus, I use generic shares and distinct products purchased as main measures in the diffusion analysis.

To further demonstrate the robustness regarding country territories and drugs included in the control group, Tables A4 and A5 report a set of tests designed to show that my results are robust to alternative definitions. Table A4 repeats the analyses in MPP-common territories for all drugs (47 countries: sub-Saharan Africa and Djibouti) and in the territories ever covered by any MPP drugs (92 countries). The results are similar to the main analysis. Table A5 reproduces the analyses on subsamples of drugs. Column (1) focuses on the first MPP addition of compounds and drugs in the same classes as these compounds. The first MPP addition is more likely to be unanticipated as this process is unprecedented. Column (2) drops drugs in the drug class without any MPP inclusion by the end of the sample period. Column (3) drops drugs with any of the four toxic compounds that are no longer recommended in the U.S., although they are still widely used in developing countries. Column (4) drops drugs approved before 1996, the year the oldest MPP compound was approved in the U.S. Column (5) keeps only drugs developed by branded firms inside the MPP. My results and conclusions are robust in all cases.

Furthermore, I test an alternative specification that includes a full set of country-year level fixed effects (Table A6). Country-year level observable controls are dropped in this specification due to collinearity. The country-year level fixed effects account for the differences between each country-year to capture unobserved demand or institutional shocks happened in a country-year beyond the feasible observable controls. All of the coefficient estimates are very similar in magnitude and statistical significance to those in my preferred main specification.[27]

In sum, I find that the MPP increases the percentage of generic HIV drug purchases in developing countries. The result is robust to alternative measures, specifications, and subsamples

[27] I also test a specification that further includes a full set of drug-year fixed effects. The MPP coefficients are not statistically significant and are smaller in magnitudes. This lack of power with three-way fixed effects is anticipated as MPP compounds enter 47 to 92 countries at the same time in my sample (e.g., see territory analyses in Table A4) and drug-year fixed effects would absorb treatment effects.

consisting of different comparison groups. However, an increase in generic diffusion can occur at the cost of innovation, and it is *ex ante* unclear how firms may react to this new institution in R&D. In the next section, I analyze how firms respond to the MPP in R&D.

1.5. Patent Pool and Innovation in HIV Drugs

1.5.1 Drug Innovation Process: Clinical Trials and Drug Approvals

I utilize detailed data to measure both R&D inputs and outputs. I measure R&D inputs using the number of clinical trials at the compound-year level. Before a new drug is marketed by a branded firm, it typically undergoes three phases of clinical trials. Phase I usually tests drug safety in multiple doses on healthy volunteers. Phase II tests drugs on patients with the disease of interest to assess efficacy and side effects. Phase III evaluates a drug's efficacy and safety on a large scale *versus* a control therapy. For HIV/AIDS, clinical trials often test a specific drug cocktail consisting of multiple compounds. Phase IV studies involve post-market surveillance to monitor drug use and determine a drug's long-term effects. Follow-on trials of drugs that have already been approved for the same or a different disease can skip phases I and II.[28] I use all clinical trials initiated between 2000 to 2017 that explicitly include HIV treatment compounds.

After a Phase III trial, a branded firm can submit a new drug application to the FDA, which decides whether to approve the drug and at what strength and dosage forms.[29] Generic

[28] An indication is a symptom or condition that requires medical treatment. Because HIV drugs are toxic, HIV trials often need to replace healthy volunteers with patients and combine three phases into two. A trial can take several months to years. HIV drug trials often use surrogate endpoints (e.g., viral load) instead of mortality to reduce trial time. About 10% of HIV trials do not have phases recorded, when the main purposes are not applicable to phases or for behavioral trials aimed to improve the use of a drug.
[29] Drugs for life-threatening conditions, including HIV/AIDS, typically enter fast-track review and are approved within six months. The time taken for FDA approval is not always publicly available. The FDA posted a set of first approval time for HIV drugs – most of them are approved within six months. Text available at: https://www.fda.gov/forpatients/illness/hivaids/treatment/ucm118915.htm.

drugs typically enter the market after the expiration of patents and market exclusivity, with a few exceptions. Generic firms are not required to conduct clinical trials for drug approvals as long as they provide sufficient evidence of the bioequivalence of their product to the reference drug.[30]

1.5.2 R&D Reactions in Clinical Trials: Empirical Strategy & Results

I start with aggregate measures and then consider how pool outsiders react to compounds being placed into the pool, how insiders reallocate R&D, and how these decisions vary across phases. The goal is to understand how the MPP affects R&D behaviors for different players.

1.5.2.1 Empirical Strategy

The logic behind the identification strategy is similar to that described in the diffusion analysis (section 4.2). Once a compound enters the pool, firms may increase trials for drugs that include the compound. The timing of new compound additions is uncertain at the aggregate level. An individual branded firm may agree to put a compound in the MPP when possible R&D opportunities are exhausted in-house, if the firm aims to use the MPP to attract additional outside investment, or simply for experimentation. I discuss potential concerns and why this entry process is orthogonal to my outcomes of interest. I then examine R&D behaviors across firm types by MPP-affiliation: branded firms inside the MPP, firms outside the MPP (such as research institutions and small private firms), and collaboration between the two in clinical trials. While it is interesting to show stratified results, I mainly focus on outsiders' reactions and do not claim causality for MPP insiders, as I am not able to disentangle planned and reactive behaviors.

[30] Generic firms can submit drug applications before the reference drug's patent expires through the FDA's tentative approval or international program, via a patent challenge, or via WHO pre-qualification. Generic firms can submit drug applications before the reference drug's patent expires through the FDA's tentative approval or international program, via a patent challenge, or via WHO pre-qualification.

I estimate a difference-in-differences model that exploits when a compound is added to the MPP to examine changes in R&D activities involving that compound over time:[31]

$$y_{at} = \delta_a + \delta_t + \beta MPP_{at} + \gamma X_{at} + \varepsilon_{at} \,. \qquad (3)$$

Here, y_{at} is an outcome aggregated at the compound-year (at) level, including the total number of new trials, the total number of participating firms, and the previous two outcomes stratified by MPP-affiliation, phase, and funding source. MPP_{at} indicates whether a compound at time t was included in the MPP. Each regression contains fixed effects for compound (δ_a) and year (δ_t) to account for unobserved differences between compounds and years, respectively. X_{at} controls for observed differences in compound-year characteristics, such as whether compound a was FDA-approved in year t and whether the compound is covered by a U.S. patent in year t. I cluster standard errors at the compound level to allow for arbitrary autocorrelation within a compound.

The two identifying assumptions are similar to those in the diffusion analysis, common trends and lack of common shocks, with two minor differences. First, the unit of analysis is at the compound-level to match innovation measures. Second, factors affecting innovation likely differ from those affecting diffusion. To empirically justify the first identifying assumption regarding common trends, I estimate corresponding event studies using the following equation:

$$y_{at} = \delta_a + \delta_t + \sum_{j \in T} \beta_j \, 1\left\{ \begin{matrix} MPP\ event \\ time_j \end{matrix} \right\}_{at} + \gamma X_{at} + \varepsilon_{at} \,. \qquad (4)$$

Here, β_j represents the difference between treatment and control units j years relative to when a compound was included in the MPP. I specify the event window to be six years before and four years after the event; sample sizes are small outside of this range.

[31] Following trial identifiers provided by AIDS*info*, trials covering multiple compounds are counted once for each compound. This logic is consistent with how Finkelstein (2004) defines disease-year trials.

The process of innovation and the institution design of the MPP are inconsistent with the existence of common shocks that would bias my results. One concern is that the MPP may target and obtain compounds that are likely to generate substantial follow-on innovation. In practice, though, the MPP is an institution with fewer than 20 employees, it mainly focuses on drug diffusion rather than innovation, and is not likely to have superior data regarding the value of a compound than HIV scientists and private firms. The clinical value of a compound is typically unclear until phase III completion, and the market value is further validated by FDA approval and U.S. patents. Most of the compounds included in the pool are approved and have been marketed for years.[32] Overall, compounds in and out of the pool are roughly of similar quality as described in section 4.1.

Another concern is that firms may be making decisions regarding when to enter the pool compound-by-compound in response to expected future value. However, it is theoretically ambiguous how a non-profit patent pool with imperfectly complementary drugs would affect R&D (Rey and Tirole, 2019).[33] Empirically, the data and my interviews indicate that branded firms are not making sophisticated compound-level decisions. For example, Gilead contributed six MPP compounds by the end of 2018—all the HIV compounds that Gilead owned. The first four compounds were added to the MPP in 2011 shortly after the MPP approached Gilead, and the two other compounds were added as early as possible.[34] One firm almost contributed all its

[32] The results are similar when excluding two Gilead drugs entering the MPP pre-approval.
[33] The theoretical setting is closest to section 4.2.3 and Figure 4 in Rey and Tirole (2019). The impact of a pool (with complements, price caps, and licensing outside the pool) on firm behaviors is ambiguous.
[34] Although the first four compounds were added to the MPP in the same year (as a cocktail), the approval years for them are 2001, 2003, and 2012 (for 2), respectively. The fact that Gilead contributed compounds to the MPP as early as possible (for fast diffusion) and did not distinguish compounds by age, class, and other factors alleviates the concern of endogenous timing for R&D.

drugs but did not due to a CEO change.[35] These anecdotes indicate that compound-level unobserved characteristics that make R&D more attractive for a compound do not necessarily cause a firm to become more likely to add the compound into the pool. As the first patent pool to focus on drug access to resource-limited countries with large disease burden but little profit potentials, most of the negotiations between the MPP and branded firms are diffusion-oriented.

1.5.2.2 Do Firms Invest More in Compounds that are in the MPP?

I find that firms respond to the inclusion of a compound in the MPP with more follow-on clinical trials. Table 1.4 Panel A reports results using the number of new clinical trials as the outcome variable. Column (1) indicates that the overall number of new trials on drugs including a given compound increases by 9.9 trials after the compound is added to the MPP, close to the mean annual trial rate for a compound during my sample period. The initial estimate is significant at the 5% level but loses statistical significance once I add observable controls. However, the coefficient magnitude remains close to the original specification. FDA approval has a significantly positive association with follow-on trials, while U.S. patent status does not have a significant coefficient. Results in column (4) indicate that branded firms inside the MPP collectively choose to initiate 1.6 more trials with MPP-associated compounds. However, the estimate is significant only at the 10% level. Similarly, column (8) indicates that MPP outsiders collectively increase new trials that include MPP-associated compounds, significant at the 10% level. The estimates from insider-outsider partnered trials are not statistically significant.

The results are qualitatively similar when using the number of firms that participated in trials as the outcome. In Table 1.4 Panel B, coefficient estimates are positive but not statistically

[35] According to the MPP administrators, the timing of inclusion for other firms is mostly affected by firm leadership and administrative efficiency.

significant at the 5% level in specifications that control for observables. Dividing coefficients from Panel A by their counterparts in Panel B provides a proxy for new clinical trials initiated per participating firm. The per-firm trial rate is about 0.9, 0.4, and 0.3 among insiders, outsiders, and mixed firms, respectively. These results need to be interpreted carefully across specifications when I control for observables. The cross-column coefficient estimates are less stable among MPP insiders than outsiders, as branded firms react strongly to FDA approvals—when drugs can be marketed; in contrast, branded firms' decisions to join the MPP are less clear and more likely experimentation to use this new business model for diffusion. Outsiders react more strongly to the MPP in total new trials, as the increased openness that the pool provides creates additional incentives for follow-on innovation given the lower costs, and the per-firm trial is smaller as the outsiders are typically smaller in size compared to insiders. Overall, the results from Table 1.4 indicate that firms, on the margin, react positively to the MPP in terms of follow-on innovation.

Table 1.4: Innovation Analysis - Clinical Trials: New HIV Trials & Firms Participated

Panel A: # new HIV clinical trials								
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dept. Vars.	# trials		# trials: $MPP_{insiders}$		# trials: MPP_{mix}		# trials: $MPP_{outsiders}$	
MPP_{at}	9.925**	8.093	2.098**	1.625*	1.672	1.100	6.155**	5.368*
	(4.534)	(4.831)	(0.883)	(0.859)	(1.025)	(1.051)	(2.848)	(3.084)
LHS mean	10.08	10.08	2.367	2.367	1.915	1.915	5.794	5.794
Panel B: # firms in new trials								
Dept. Vars.	# firms		# firms: $MPP_{insiders}$		# firms: MPP_{mix}		# firms: $MPP_{outsiders}$	
MPP_{at}	20.81**	17.75*	2.284**	1.747	5.366*	3.803	13.16**	12.20*
	(9.488)	(10.28)	(1.065)	(1.072)	(3.091)	(3.226)	(5.967)	(6.454)
LHS mean	20.73	20.73	3.104	3.104	5.754	5.754	11.87	11.87
comp. & year FEs	Y	Y	Y	Y	Y	Y	Y	Y
X_{at} control		Y		Y		Y		Y
Observations	540	540	540	540	540	540	540	540

Notes: This table reports the results of estimating a compound-year level difference-in-differences model using equation (3). Each cell reports the coefficient of interest from a separate regression. $MPP_{insiders}$ means all the participants of a trial are branded firms contributed to the MPP, $MPP_{outsiders}$ are trials by firms outside the MPP, and MPP_{mix} denotes trials that are collaborated by MPP insiders and outsiders. Controls variables include FDA

approval status, patent status, and fixed effects for compounds and years. Robust standard errors are clustered at the compound level and are reported in parenthesis. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

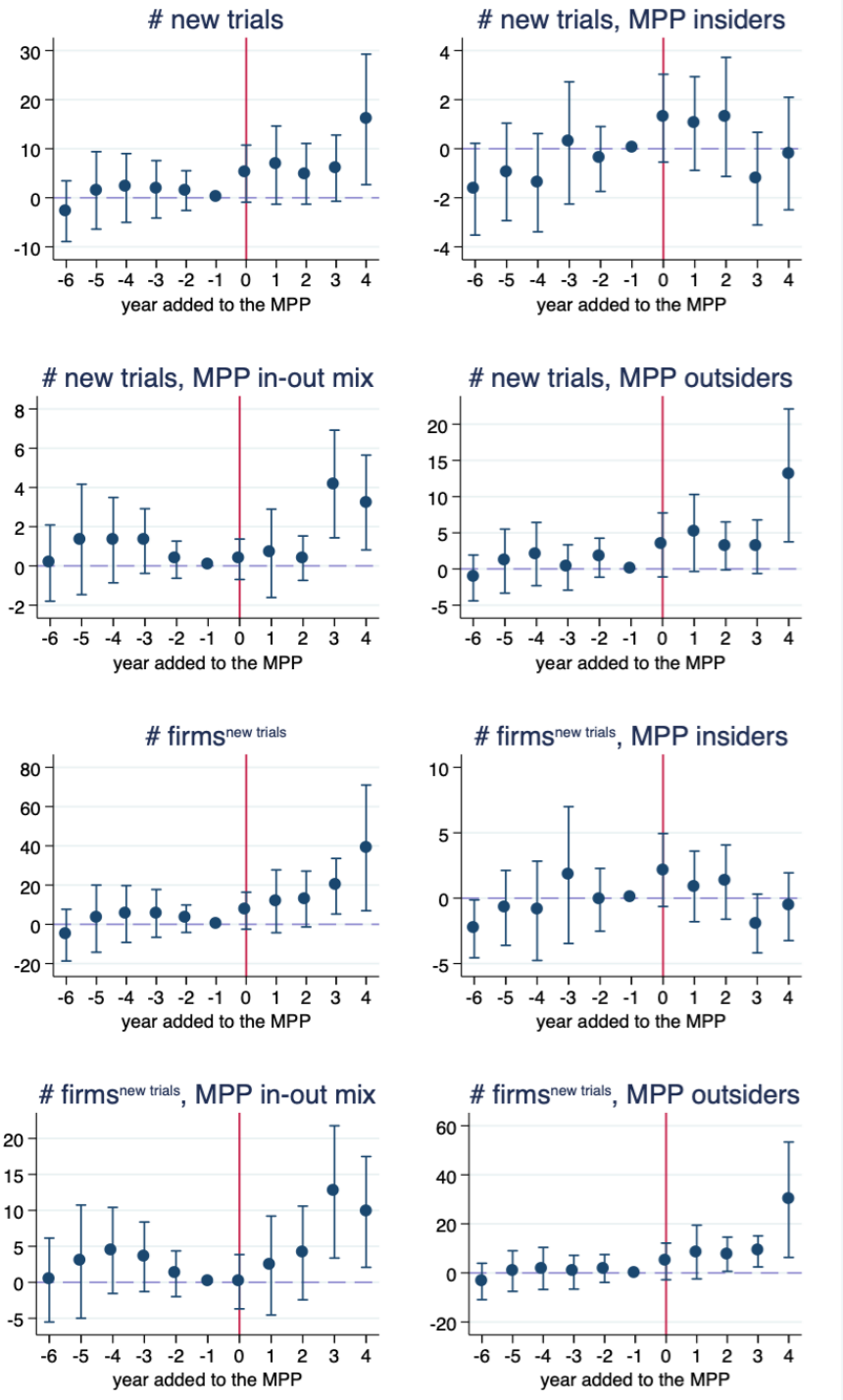


Figure 1.5: Event Studies for Innovation Analysis: New Clinical Trials and Firms Participated

Notes: These figures report event-study coefficient estimates using Equation (4). The dots are point estimates of differences in outcomes between treatment group and control groups 6 years before MPP inclusion and 4 years after inclusion. The whiskers correspond to 95% confidence intervals.

The event studies support the effects estimated above (Figure 1.5). The event study for the number of new trials has no pre-trend but a clear post-period increase in new trial initiations, especially four years after MPP entry. The next three event studies display results for the number of new trials by MPP-affiliation status. The pre-trends for MPP insiders, although not statistically different from zero, are noisier than those for outsiders and insider-outsider mixed trials. All event studies involving MPP outsiders demonstrate a pattern of post-period trial increases with a 3-4 years' lag. The event patterns are similar for the number of firms in new trials, and the post-period reactions are smoother and clearer in these cases, thus indicating that increases in post-MPP trials from MPP outsiders are primarily driven by more firm participation.

1.5.2.3 Heterogenous Effects on R&D Reallocation and by Funding Status

Across phases, firms respond to the MPP by starting more late-stage clinical trials, as reported in Table 1.5. One would not expect MPP addition to substantially affect phase I trials as these compounds are already tested for safety (except for new doses). Firms are more likely to invest more in phase III trials to create new or better drugs based on existing compounds. Panels A–D report results across phases I–IV. Results are not statistically significant for trials in phases I and II. The increases in new trials and firm participation for phase III trials are significant at the 1% level. Event studies in Figure A2 justify the results for phase III trials except fully in-house trials by MPP insiders. Notably, MPP insiders statistically significantly reduce phase IV post-market trials by about 0.4 per compound-year, with about 0.5 fewer firms participating, at 5% and 1% levels of significance, respectively. This reduction does not affect overall new phase IV trials, as the reduction is offset by firms outside the pool doing more phase IV trials (in-house or jointly with pool insiders). Event studies in the bottom panel of Figure A2 support this point.

Table 1.5: Innovation Analysis - Clinical Trials: HIV Trials by Phase

Dept. Vars.	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	# New HIV clinical trials				# Firms in new HIV clinical trials			
	total	$MPP_{insiders}$	MPP_{mix}	$MPP_{outsiders}$	total	$MPP_{insiders}$	MPP_{mix}	$MPP_{outsiders}$
Panel A. Phase I								
MPP_{at}	1.114	-0.0388	0.168	0.986	2.314	-0.0325	0.525*	1.822
	(0.866)	(0.135)	(0.108)	(0.778)	(1.693)	(0.211)	(0.279)	(1.449)
LHS mean	1.352	0.331	0.144	0.876	2.306	0.539	0.363	1.404
Panel B. Phase II								
MPP_{at}	0.925	0.466	-0.134	0.593*	1.120	0.527	-0.524	1.117*
	(0.646)	(0.290)	(0.131)	(0.312)	(1.120)	(0.360)	(0.370)	(0.596)
LHS mean	1.909	0.530	0.261	1.119	3.704	0.672	0.889	2.143
Panel C. Phase III								
MPP_{at}	3.374***	1.945***	0.0680	1.361**	4.585**	2.122***	-0.132	2.594*
	(1.066)	(0.569)	(0.192)	(0.503)	(1.862)	(0.657)	(0.565)	(1.331)
LHS mean	2.885	1.141	0.446	1.298	5.970	1.376	1.402	3.193
Panel D. Phase IV								
MPP_{at}	1.325	-0.385**	0.614	1.096	4.539	-0.481***	2.435	2.585
	(1.151)	(0.152)	(0.491)	(0.797)	(2.971)	(0.165)	(1.634)	(1.564)
LHS mean	2.463	0.269	0.752	1.443	5.578	0.320	2.302	2.956

Notes: This table reports the results of estimating equation (3) at the compound-year level. The number of observations is always 540 in this balanced panel data. Each cell reports the coefficient of interest from a separate regression. $MPP_{insiders}$ means all the participants of a trial are branded firms contributed to the MPP, $MPP_{outsiders}$ are trials by firms outside the MPP, and MPP_{mix} denotes trials that are collaborated by MPP insiders and outsiders. Panels A to D report results by trial phase. Controls variables include FDA approval status, patent status, and fixed effects for compounds and years. Robust standard errors are clustered at the compound level and are reported in parenthesis. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Firms' responses to the MPP also vary by funding type, where firms with public-sector funding react more strongly with follow-on clinical trials. Notably, most firms outside the MPP are academic or public institutions partly funded by grants. Table A7 reports the results. I expect clinical trials to increase in response to the MPP, as the pool increases openness and reduces costs for follow-on trials. The reactions can be particularly strong among trials that are not fully funded by industry and in phase III trials that involve multiple compounds. Privately funded trials are likely to reallocate post-market trials to the pre-market stage. Specifically, privately funded trials reallocated phases IV trials to pre-market development stages; and this reduction is more than offset by increases in publicly funded phase IV trials. Figure A4 reports the event studies; there are no pre-trends for all cases except a pre-period shift in insider phase III trials.

The results across clinical phases and across firm types provide new insights to findings in the literature. First, market-based institutions can generate results similar to those of non-market strategies, like those described in Finkelstein (2004)—policies that spur drug diffusion can spur technically feasible, follow-on clinical trials by 2.5-fold. My findings suggest that a market-based institution can generate about 40% of that effect (1-fold increase). Second, my results complement Williams (2013) and Sampat and Williams (2019):[36] in small molecule areas and a global setting, increased openness from privately owned IP (patents and data exclusivity) can foster follow-on innovation from outsiders, particularly in non-private sectors.

1.5.2.4 Do Firms Invest More in New Compound Development?

In previous sections, I analyzed clinical trials using approved compounds by the end of 2018 because trials on new compounds that had not been approved by the end of my sample period would not have unified names (i.e., generic names). However, it is also important to understand the interaction of compounds' addition to the pool and firms' R&D activities in developing new compounds that have not been approved but can further complement existing drugs. To account for the fact that these pre-approved compounds would not have a unified name, I aggregate HIV investigational drug trials to the drug class-year level for this analysis. First, the trend in clinical trials on HIV investigational drugs in Figure A5 suggests no reduction in overall innovation incentives to explore new drugs. Second, Table A8 and event studies in Figure 1.6 confirm the hypothesis that in general, the MPP weakly increases overall R&D activity in investigational drugs. In addition, the phase-specific event studies (Figure A6) justify

[36] For gene technology, data restriction hinders follow-on innovation (Williams, 2013), but patents do not importantly affect follow-on innovation quantitatively (Sampat and Williams, 2019).

that MPP insiders and industry-funded trials are increasing particularly for phase III trials. This result, together with previous results, indicates that MPP insiders and industry trial funders invest more in new compounds that can further complement existing drugs.

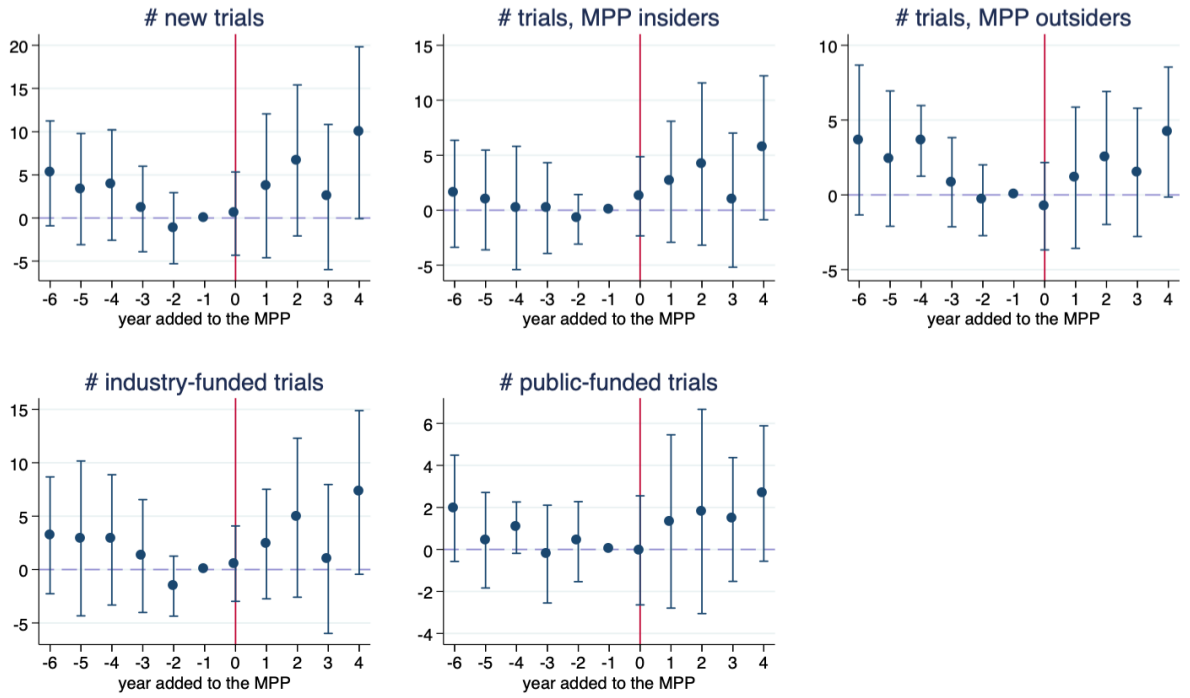


Figure 1.6: Event Studies for Innovation Analysis: Clinical Trials for HIV Investigational Drugs

Notes: These figures report event-study coefficient estimates using Equation (4), at drug class-year level. The dots are point estimates of differences in outcomes between treatment group and control groups 6 years before and 4 years after MPP inclusion. The whiskers correspond to 95% confidence intervals.

1.5.3 R&D Results in New Drug Approvals

1.5.3.1 Innovation and Imitation: Overview and Exploratory Analysis

I next use HIV drug approvals to analyze R&D outputs in reaction to the MPP. All of the HIV drug approvals that I examine are original FDA and WHO approvals of a new product at the drug-strength-dosage form-firm level. These approvals are obtained by either branded or generic firms and include tentative generic approvals that only allow for sales in developing countries. At the drug level, a drug innovation is either an original approval of a new compound or the first

approval of a cocktail that bundles different compounds, whereas a drug imitation is a follow-on product from the same drug at a chemical level but at a different strength-dosage form or by different manufacturers. At the drug product level, defined as a drug-strength-dosage form combination, a product innovation is the first approval of a drug in a formulation (strength-dosage form) by the first applicant firm, while product imitations include any follow-on approvals of the same drug product by other firms. Not all approvals allow for marketing in the U.S., but all of these approvals reflect the qualifying status of approved products.

Although branded drug makers are leaders in the development of new compounds, generic firms develop many new cocktails and products. As reported in Table A9, of the 30 first approvals of new drugs with already-approved compounds, twenty-seven are new drug cocktails. Among these 27, thirteen new cocktails were first created by generic firms. Moreover, all of the new cocktails first created by generic firms have bundled compounds, owned by 2.31 branded firms on average. In contrast, new branded cocktails have bundled compounds owned by 1.47 branded firms on average, either via intra-firm bundling or cross-licensing between two firms. This pattern highlights the often-underappreciated role that generic firms play in drug innovation, particularly regarding the comparative advantage in cross-firm bundling. The overall pattern is similar at the drug product level, where generic firms capture a higher share of new drug products approved when strength and dosage forms are considered.

I analyze the association between MPP status and "time to first generic" using histograms, survival, and regression analyses. I focus on the sample where a drug product is first approved generically for a given drug-strength-dose form after all of its underlying compounds are approved (i.e., it is technically feasible to produce a drug generically). Figure A7 reports histograms of the "time to first generic," with and without MPP compounds, in the full sample

(2005–2018) and the sample since MPP establishment (2010–2018). In both samples, the average "time to first generic" product is smaller for drugs with MPP compounds: three to four years faster than the counterparts without MPP compounds. Table A9 reports Cox proportional hazard models and linear models that regress "time-to-generic" on an MPP indicator and fixed effects at year and drug class levels. The results suggest that products with MPP compounds have higher odds for an approval (positive coefficient in Panel A) than do the alternatives, and the "time-to-generic" is shorter for a drug with MPP compounds (negative coefficient in Panel B). These analyses provide evidence that the MPP is associated with faster generic approvals.

1.5.3.2 Does the Patent Pool Induce More Follow-on Drug Approvals?

I then analyze whether the MPP accelerates more follow-on drug product approvals. The empirical strategy is identical to that used in the analysis of clinical trials except the outcomes are now the number of new approvals at the drug and compound levels.[37]

I find that firms have obtained more follow-on drug product approvals for compounds in the pool relative to those that enter the pool later or outside the pool, including generic approvals of new cocktails (innovation) and more generic firms gain approvals to market existing drugs with pool-covered compounds (imitation). At the drug-year level, Table 1.6 Panel A measures MPP treatment as an indicator, and Panel B measures treatment as the share of the number of compounds in a drug that are in the MPP. In Panel A columns (1)–(2), the MPP-induced increase in new drug product approvals is about 0.5 more approvals per year in pool-associated drugs and is robust across specifications. Moreover, the increased product approvals are primarily driven

[37] I adjust the event windows to be five years before and after the event to account for the shorter sample periods 2005–2018, in contrast to 2000–2017 in the clinical trials sample.

by generic firms, which create both new drug cocktails and existing products at lower costs. The results are consistent with the regulatory standards that exempt generic firms from conducting new clinical trials when the underlying compounds have been previously approved. In Panel B, the coefficient estimates are statistically more precise when the MPP treatment is measured at the percentage level to capture changes in both the extensive and intensive margins.

Table 1.6: Innovation Analysis - Drug Approvals

Dept. Vars.	(1) # new approvals	(2) # new approvals	(3) # new approvals ^{generic}	(4) # new approvals ^{generic}	(5) # new approvals^{branded}	(6) # new approvals^{branded}
Panel A: Drug-Year Analysis, MPP_{dct} as {0, 1} dummy						
MPP_{dt}	0.555**	0.517*	0.445	0.508*	0.110**	0.00870
	(0.261)	(0.280)	(0.271)	(0.278)	(0.0482)	(0.0550)
Panel B: Drug-Year Analysis, MPP_{dct} as % compounds in the pool						
MPP_{dt}	0.749**	0.711**	0.616*	0.670*	0.133**	0.0410
	(0.321)	(0.341)	(0.338)	(0.341)	(0.0604)	(0.0641)
drug & year FEs	Y	Y	Y	Y	Y	Y
X_{dt} control		Y		Y		Y
LHS mean	0.70	0.70	0.61	0.61	0.09	0.09
Observations	798	798	798	798	798	798
Panel C: Compound-Year Analysis						
MPP_{at}	2.418**	2.607**	2.034**	2.478**	0.383**	0.129
	(0.908)	(0.993)	(0.961)	(0.980)	(0.143)	(0.140)
comp. & year FEs	Y	Y	Y	Y	Y	Y
X_{at} control		Y		Y		Y
LHS mean	2.28	2.28	2.01	2.01	0.27	0.27
Observations	378	378	378	378	378	378

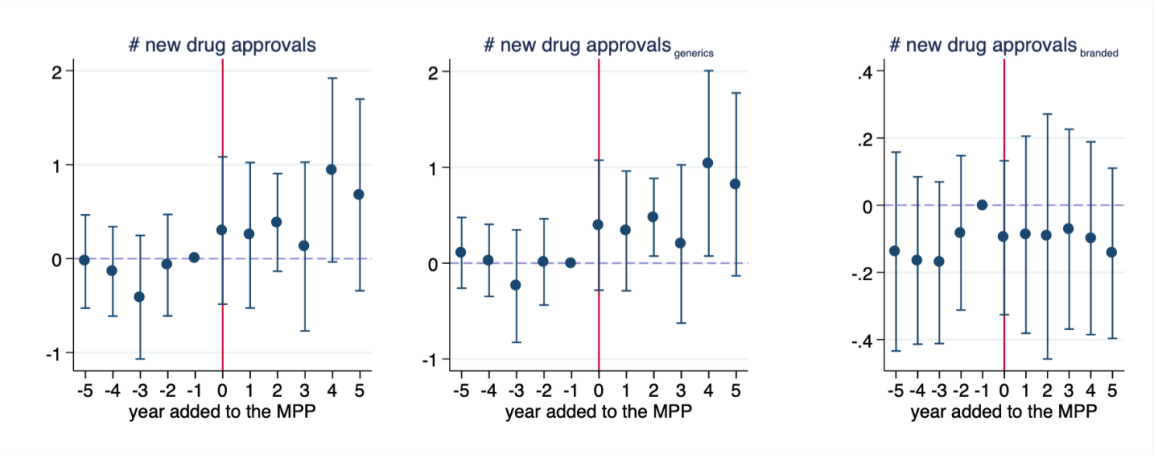
Notes: This table reports the results of estimating a difference-in-differences model using equation (3). Each cell reports the coefficient of interest from a separate regression. Each adjacent two columns share the same dependent variable in different specifications. Panel A and Panel B differ in how the treatment variable is defined: as an indicator or percentage measure. Robust standard errors are clustered at the drug level and are reported in parentheses. Robust p-value: *** p<0.01, ** p<0.05, * p<0.1.

These findings are robust to a sample where drugs are de-bundled to the compound level, and the coefficient estimates become larger. This result is expected as now the MPP effect captures the increase in total follow-on drug product approvals involving a compound in either standalone or cocktail form. Table 1.6 Panel C reports the analysis of new approvals at the

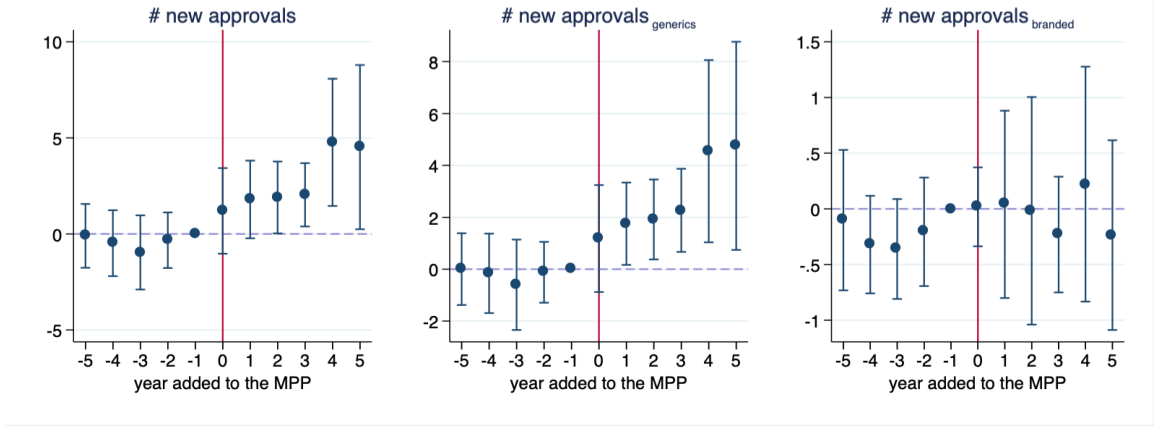
compound-year level. These results are consistent with the hypothesis that follow-on approvals with pooled compounds are often developed as drug cocktails instead of as simple imitations at the compound-level, thereby suggesting higher social values derived through increased competition among new and more completed cocktail products.[38] These results also provide new empirical insights regarding innovation and competition. Increasing competition is associated with more innovation when the level of competition is low (Aghion *et al*., 2005), as in my case, where the generic competition is relatively low for patented new compounds.

Event studies support the drug approval analyses and are illustrated in Figure 1.7. In both cases, there are no pre-trends in total new approvals and those by generic firms. For follow-on approvals by branded firms, the pre-trends do not significantly differ from zero but are noisy. Comparing the columns of graphs within the same panel, most of the new drug or compound-level approvals are driven by follow-on product approvals by generic firms, suggesting large imitation-based investment responses from generic firms. Once I control for initial approvals, new approvals by branded firms do not substantially change in these figures. Some compounds are already in the pool before final approval, and it can take years for branded firms to obtain approvals for new drugs that require new clinical trials. Across panels, the event study responses are larger when drug cocktails are de-bundled into compounds. Overall, the responses in trial initiation and firm participation suggest that firms outside the pool are responsive to increases in the expected return to technologically feasible products once barriers to entry are reduced.

[38] I also implement a count data model using conditional negative binomial to demonstrate robustness of the results (reported in Table A11), given that the mean dependent variable is small for drug approvals.



(a): new drug approvals in drug-year panel



(b): new approvals in compound-year panel

Figure 1.7: Event Studies for Innovation Analysis: New Drug Product Approvals

Notes: These figures report event-study coefficient estimates using Equation (4). The dots are point estimates of differences in outcomes between treatment group and control groups 5 years before MPP inclusion and 5 years after inclusion. The whiskers correspond to 95% confidence intervals.

1.5.3.3 Case Studies: R&D Decisions and Outputs

To supplement the innovation results, I provide a few qualitative cases on new generic drugs that have stemmed from the MPP and firms' decisions or reactions during the process. Although ex ante unclear, new products created by MPP generic licensees can benefit branded firms by offering a higher market value in developing countries outside the MPP territories. For example, the new single-pill once-daily cocktail TLD was first approved by a generic firm in 2018 and recommended by the WHO as a starting therapy for treatment naïve patients in the

same year. This WHO recommendation can potentially increase branded sales in other middle-income countries that are not covered by the pool.

Branded firms are not active in developing pediatric formulations, partly because most pregnant women in the U.S. are tested for HIV. Mother-to-children transmission can then be prevented by suppressing the viral load during pregnancy with HIV drugs. The lack of a pediatric version mainly affects developing countries and low-income populations in developed countries. Under such a circumstance, pooled licensing can induce socially beneficial innovation by allowing generic firms to develop localized solutions. For example, the first pediatric granules formulation for lopinavir/ritonavir (LPV/r) was developed by generic firms with MPP licenses and gained FDA approvals in 2018. If needed, branded firms can be granted back low-cost non-exclusive licenses for patents on this new formulation.

Once participating in the pool, branded firms may adjust R&D strategies accordingly. The case of Gilead's pool participation and R&D decisions illustrate this point. Gilead joined the MPP in July 2011 and contributed several approved drugs, including tenofovir disoproxil fumarate (i.e., TDF, a prodrug of tenofovir).[39] Gilead then started phase II trials of tenofovir alafenamide fumarate (i.e., TAF, a prodrug of TDF) in December 2011, collected primary results in October 2012, and started phase III trials in December 2012. The phase III trials on a TAF cocktail were completed with main results in 2014, and TAF was licensed to the MPP in the same year, before the 2015 FDA approval. It is worth noting that the earliest clinical trial of TAF was completed in 2003. Although a firm's phase III trial decision can be affected by many factors, the timeline suggests that Gilead is at least not reducing R&D after MPP participation.[40]

[39] Prodrug is an inactive compound that can be metabolized into a pharmacologically active form within the body. In many cases, prodrug can improve the absorption of a drug with lower dose and side-effects.
[40] Furthermore, Gilead started phases II/III trials on tenofovir-based microbicides in 2012, while the phase I trials were finished in 2008. Those trials are joint with partners in the public sector from South Africa.

In addition, discussions with practitioners suggest that drug access programs can benefit branded firms by improving corporate image. This change can increase employee retention and attract institutional investors (e.g., pension funds) who would invest in firms that actively make a social impact. Generic licensing via the MPP can be a cost-effective way to reach these goals.

Overall, results from the innovation analysis suggest that firms react to the MPP with higher R&D inputs and outputs. The increases in R&D inputs of new clinical trial initiations and firm participation come from both pool insiders and outsiders. While pool outsiders increase trials on drugs with pooled compounds, pool insiders invest more in new compound development and shift post-market trials to outsiders. The increases in R&D outputs of new drug product approvals are primarily driven by generic versions of existing drugs and new formulations.

1.6. Welfare Analysis – A Simple Model of Demand and Supply

This section reports the welfare analysis of the MPP. The goal is to examine whether the MPP is cost-effective in achieving the current results. I first provide an overview of the basic set-up, followed by a formalization of the demand and supply equations. I then report estimation results and results of counterfactual simulations.

1.6.1 Overview: Basic Intuition

Quantifying the cost-effectiveness of a patent pool is challenging, as most products are sold globally despite relatively concentrated innovation activities. In my case, the MPP separates the market into sales territories and, based on my previous results, increases diffusion and R&D, so a welfare analysis for the developing countries in my diffusion sample is conservative yet

Because microbicides belong to a new drug class that is more valuable to developing countries, Gilead's decision may reflect a combination of factors, among which can be its engagement with the MPP.

informative for calculating cost-effectiveness. Another challenge of studying patent pools is the difficulty in categorizing technologies with clear *ex ante* measures of their intrinsic substitution patterns. My setting allows me to measure substitutability based on drug classes. The decision of HIV drug purchases can be premised on sequential choices: first, choice of a drug class, and then choice of drugs within the chosen class. Regardless of whether a drug purchased is a standalone compound or a cocktail, the treatment requires multi-compound bundling.[41] The MPP would not directly enter patients' preferences towards a drug. Including the MPP as a marginal cost shifter is related to my previous findings and the conceptual framework that the pool lowers licensing costs and royalty rates.[42] My counterfactuals examine what would happen in the absence of the MPP and with an expanded MPP. I then compare welfare changes to the MPP operating costs.

1.6.2 A Simple Model of Demand and Supply

1.6.2.1 Demand-Side: Nested Discrete Choice Model

Patients in each country choose whether to take drugs and choose among available choices following physicians' suggestions. The choice sets of drugs vary across countries and over time. Denote D_{ct} as the set of HIV drugs available from my data source in country c at year t, and index drug by j. Each patient-physician pair in a country in a given year decides whether to take a drug in the choice set $D_{ct} = \{1,2,..,d_{ct}\}$ or use outside options – taking no drugs or from other sources outside my sample. Each drug j belongs to drug class $g(j)$ based on its

[41] I observe drug purchases but not how patients use them, which limits the richness of the demand model I can estimate. Besides, my sample period (2007-2017) is not sufficient to model new drug launches, as most of them have not entered my data, resulting in conservative welfare estimations. I also abstract away from branded-generic interactions with the drug-country-year level aggregate data. Thus, my exercise is best viewed as an empirical illustration of the idea of drug cocktails in the context of a patent pool.
[42] The marginal cost assumption is institutionally backed as royalty rates are defined as % sales here.

mechanism of action. Specifically, each patient-physician pair i in country c at year t chooses drug j from the $D_{ct} + 1$ options to maximize the conditional indirect utility function as below:

$$u_{ijct} = \underbrace{X_{jct}\beta - \alpha p_{jct} + \xi_{jct}}_{\delta_{jct}} + \zeta_{ig(j)ct} + (1-\sigma)\varepsilon_{ijct}. \quad (5)$$

Here, δ_{jct} is the mean utility of drug j in country-year market ct. X_{jct} is a vector of observables, including the number of compounds in a drug, number of distinct products for a drug in each country-year, HIV prevalence and death rates, income, log(population), institutional factors, and fixed effects at country and year levels. p_{jct} is the average price of drug j in country c and year t. The parameter ξ_{jct} is the unobserved quality of drug j from the perspective of country c patients and can differ across country-year. ε_{ijct} is an independent taste shock following the extreme value distribution, $\zeta_{ig(j)ct}$ is a group specific taste of the patient-physician pair, and $(1-\sigma)$ measures the relative weight of idiosyncratic and group preferences.

Given the functional forms associated with nested logit models, the market share of each product for any set of product qualities δ_j can be calculated à la Berry (1994).[43] With aggregate data, the estimation equation is as follows:

$$\ln(s_j) - \ln(s_0) = \sigma \ln(s_{j|g(j)}) + \underbrace{X_j\beta - \alpha p_j + \xi_j}_{\delta_j - \delta_0}, \quad (6)$$

where $s_{j|g(j)}$ is drug j's share of its nest in a given country-year market ct. I estimate the model using two-stage least square with instruments for conditional market share $\ln(s_{j|g(j)})$ and price p_j. I include three instruments: patent status, the number of distinct manufacturers for a given

[43] To explore the robustness of the results to the demand model specifications, I also implemented a plain logit model. In the empirical implementation, I define the market size as 30% of the population. I test the sensitivity of the results to other market size definitions and report those results in Table A12.

drug in a country-year market, and the number of distinct competing products (i.e., drug product and manufacturer combinations for other drugs in the same drug class). The latter two are "BLP instruments" following Berry *et al.* (1995).[44] I discuss relevant tests in the results section (6.3). Standard errors are clustered at drug-country level to allow for arbitrary autocorrelation within a drug-country pair. Using parameters from the demand estimation, the nested logit model allows researchers to calculate expected consumer surplus in each market using equation (7) below:

$$E(CS_{ct}) = \frac{1}{\alpha} \ln \left\{ \Sigma_g \left[\Sigma_{j \in g} \exp \left(\frac{\delta_j}{1-\sigma} \right) \right]^{1-\sigma} \right\}. \qquad (7)$$

Here, the choices among nests (i.e., drug classes) depend only on their inclusive values $\delta_j = X_j\beta - \alpha p_j + \xi_j$, as there are no nest-specific observables entering the utility function. The total consumer surplus during my sample period can be calculated as the summation of market-size weighted expected consumer surplus values across markets. Therefore, the baseline consumer surplus with the MPP can be calculated independent of the supply-side estimation.

1.6.2.2 Supply-Side Pricing: Competitive Pricing & Bertrand-Nash Game

In this section, I describe two simple cases in modeling supply and how each case is motivated by previous findings. The first case models supply using a constant marginal cost pricing equation as in Bertrand competition. The second case uses a Bertrand-Nash game in an oligopolistic setting. In both cases, the MPP affects pricing by lowering marginal costs as the MPP lower royalty rates in joint licensing and injunctions are also typically calculated on a per

[44] The BLP instruments are valid as long as the drug characteristics are exogenous. The justification is that drug characteristics are determined at the time of trials, and once approved, firms cannot change the characteristics in the short-run. The instruments are relevant, as a drug that has close competitors (drugs within the same drug class work through the same mechanism of action) is likely to be priced lower.

unit basis.[45] Each case has advantages and limitations. The actual market structure is in between – oligopolistic pricing with a competitive fringe and threats of compulsory licensing – a structure that is infeasible to model directly.[46] I aim to provide a simple and conservative estimation.

In the first case, I estimate the supply side using a marginal cost pricing scheme. This set-up captures the realistic feature that generic firms produce at marginal costs and generic market shares are high in developing countries. My previous results from the diffusion and innovation analyses support competitive pricing in that there are increases in the generic shares and new drug product approvals. I use *j* to denote drug-country pair and estimate the following equation.

$$p_j = mc_j = X_j\gamma + \beta MPP_j + \omega_j \qquad (8)$$

Here, MPP indicates whether a drug-country is in the MPP in a year. X_j is a vector of drug-country-year level controls including whether a drug is effectively patented in a country-year, number of drug products and competitors for a drug in a country-year, country-year level HIV prevalence and age-adjusted death rates, population, income, institutional factors, country and year fixed effects. Quantity is not included in this baseline competitive case, because firms do not face capacity constraints in a competitive market with many generic firms. Once the pricing equation is estimated, counterfactual prices can be simulated by changing the MPP indicator.

In the second case, I estimate supply with oligopolistic pricing in a static Bertrand–Nash game with differentiated products. Firms can have market power in the short-run before reaching the competitive equilibrium in the long-run. Each firm acts as either a single-product or multi-product drug firm where each drug belongs to a nest based on its drug class. This design captures

[45] Due to the lack of complete HIV drug sales and entry data, I cannot back out the fixed costs and separately identify additional MPP-induced cost reduction. This suggests my cost results are conservative.
[46] I do not have sufficiently rich data to model a dynamic pricing game. In common with the prior literature (Song *et al*., 2017), I model drug pricing as a static game.

the realistic feature that the brand ownership of a drug does not matter as much for generic drug makers, but the "business stealing effect" comes from drugs with similar characteristics (i.e., drugs in the same class). Each country-year is a separate market, and a firm maximizes profit from all drugs they produce using the equation below:

$$\Pi = \Sigma_j(p_j - mc_j) \times s_j(p_j) \times M. \qquad (9)$$

Here, j indexes drug j in a country-year market, and M represents the same market size measure used in the demand estimation. Note that the substitution patterns between drugs j and k are affected by their corresponding drug classes g_j and g_k. The first-order condition yields

$$\mathrm{s_j}(p_j) + \Sigma_k(p_k - mc_k) \times \frac{\partial s_k(p)}{\partial p_j} = 0. \qquad (10)$$

I define the price derivative matrix as $\Delta_{jk} = -\frac{\partial s_k}{\partial p_j}$, following Berry *et al*. (1995). Here, f_j indicates that drug *j* is owned by firm *f*. I estimate two structures. First, I estimate a single product oligopoly, where each representative firm owns one product. Second, I estimate a multi-product oligopoly with drug-level ownership, where I assign a cross-firm cocktail owner to a separate entity. Derivation of Δ_{jk} and additional results are provided in Appendix A.3.

$$\Delta_{jk} = \begin{cases} \alpha s_j\left(\frac{1}{1-\sigma} - \frac{\sigma}{1-\sigma}s_{j|g} - s_j\right) & ,j = k \\ -\alpha s_j\left(\frac{\sigma}{1-\sigma}s_{k|g} + s_k\right) & ,j \neq k, g_j = g_k, f_j = f_k \\ -\alpha s_j s_k & ,j \neq k, g_j \neq g_k, f_j = f_k \\ 0 & ,o.w.(i.e., f_j \neq f_k) \end{cases} \qquad (11)$$

Rewrite the F.O.C as $s - \Delta[p - mc] = 0$; it then follows that $p = mc + \Delta^{-1}s$. The new estimation equation is as below, suppressing the country-year subscript and indexing drug with j:

$$mc_j = p_j - \Delta^{-1}s_j = X_j\gamma + \beta MPP_j + \eta q_j + \omega_j\ . \qquad (12)$$

Here, the covariate X_j specification is the same as that in equation (8), except I include quantity q in the regression to capture firms' capacity constraints in oligopolistic settings. I instrument q using the number of competing products in the same class (Berry *et al*., 1995; Song *et al*., 2017).

1.6.3 Results and Counterfactuals

I first report results from the demand and supply estimation, respectively. Then, a welfare analysis is reported using estimated parameters from the demand and supply sides. The basic idea is to simulate scenarios by changing the MPP quasi-experiment. For example, I shut down the MPP parameters in the estimated oligopolistic marginal cost curve. I then simulate counterfactual equilibrium prices and quantities by solving the new first-order condition and update for each market. New consumer and producer surpluses are computed accordingly. Details on the counterfactual simulation are reported in Appendix A.3 (Mathematical Appendix).

Demand estimation results are consistent with model assumptions. Table 1.7 column (1) reports results using ordinary least square (OLS) and columns (2)–(3) report the main results using nested logit models. In the nested logit model, the coefficient estimates of within-group market share is 0.863 and statistically significant at the 1% level. This result supports the nested logit assumption that drugs are closer substitutes within a group than between groups. A comparison of the price coefficients between OLS and the nested logit model reveals that there is a positive correlation between price and demand shocks and that the instrumental variables mitigate the problem. The price coefficient increases in absolute value from -0.137 in the OLS model to -1.946 in the nested logit model, and in all models the price coefficients are significant at the 1% level. The first-stage Kleibergen–Paap F-statistic of the excluded instruments for both

endogenous variables is 19.30, and the Sanderson–Windmeijer multi-variate first-stage F-statistics for each endogenous variable are much larger.

Table 1.7: Results from the Demand Estimation

	(1) OLS	(2) Nested logit	(3) Logit
$\ln(s_{j\|g(j)})$	0.702***	0.862***	
	(0.0144)	(0.0814)	
p_j	-0.137***	-1.946***	-3.483***
	(0.0227)	(0.243)	(0.441)
drug age	0.0119*	-0.196***	-0.449***
(U.S. appr.)	(0.00637)	(0.0404)	(0.0838)
prod. variety	0.345***	-0.00503	0.434**
	(0.0335)	(0.122)	(0.179)
regulatory	0.00194	-0.0646***	-0.121***
quality	(0.00558)	(0.0208)	(0.0378)
rule of law	0.0226***	0.0507***	0.0532*
	(0.00546)	(0.0162)	(0.0291)
control of	-0.00783*	0.0361**	0.0785***
corruption	(0.00446)	(0.0148)	(0.0272)
Kleibergen-Paap F statistic		19.50	
1st stage $(s_{j\|g})$		104.42	
1st stage (p_j)		46.91	54.56
country FE	Y	Y	Y
year FE	Y	Y	Y
X_j controls	Y	Y	Y
Observations	7,084	7,084	7,084

Note: This table presents results of estimating the nested logit demand model as in equation (6) and compares it with OLS and plain logit. The instruments for conditional market share and price are: (1) whether a drug is effectively patented in the country-year, (2) the number of manufacturers for the same drug in a country-year, and (3) the number of competing products, i.e., drug product-firm combinations for other drugs in the same drug class. IVs for the plain logit do not include the second instrument to avoid over-identification. Only main parameters of interests are reported for simplicity. Observable controls, X_j include within-drug product variety in a country-year, number of compounds within a drug, number of years since a drug's U.S. approval, country-year level HIV prevalence and age-adjusted death rates, institutional factors (i.e., the six world governance indicators), log(population) and GDP per capita. The excluded instruments are at drug-country-year level: patent status, number of competitors and number of close competitors in the same drug class. The first-stage statistics displayed immediately under coefficients-of-interests are the Kleibergen-Paap F statistic that robust to heteroskedasticity. The first-stage F statistics for each endogenous variable is the Sanderson-Windmeijer multivariate F test of excluded instruments. Standard errors are clustered at drug-country level. Robust p-value: *** p<0.01, ** p<0.05, * p<0.1.

Table 1.8: Estimations of Pricing Equations

Dept. var: marginal cost ($)	(1) MC pricing flat MC	(2) Bertrand-Nash Oligopoly single-prod. firm	(3) Bertrand-Nash Oligopoly multi-prod. firm
MPP_j	-0.642***	-1.908***	-1.952***
	(0.112)	(0.524)	(0.539)
Q_j		3.60e-07***	3.83e-07***
		(1.27e-07)	(1.31e-07)
#variety	-0.209***	0.445*	0.495**
	(0.0616)	(0.234)	(0.244)
$\#firms_{dct}$	-0.310***	-1.584***	-1.662***
	(0.0398)	(0.480)	(0.494)
$Patent_{dct}$	-0.173	0.210	0.198
	(0.192)	(0.255)	(0.262)
year FE	Y	Y	Y
country FE	Y	Y	Y
X_j controls	Y	Y	Y
Kleibergen-Paap rk Wald F-stat		16.66	16.66
Observations	7,084	7,084	7,084

Notes: this table reports the results from estimating competitive marginal cost pricing and oligopolistic pricing on the drug-country-year diffusion sample using equations (8) and (12), respectively. Only main parameters of interests are reported for simplicity. X_j is a vector of drug-country-year level controls including whether a drug is effectively patented in a country-year, number of drug products and competitors for a drug in a country-year, country-year level HIV prevalence and age-adjusted death rates, population, GDP per capita, and institutional factors. Country and year fixed effects are always included. Quantity variable is instrumented by the number of competing products in the same drug class within a market (country-year). Standard errors are clustered at drug-country level to allow for arbitrary autocorrelation within a drug-country pair. The first-stage F-statistics reported are adjusted for heteroskedasticity clustering. Robust p-value: *** p<0.01, ** p<0.05, * p<0.1.

Supply-side estimates provide evidence that the MPP reduced drug costs and are robust to various assumptions concerning market structure. As shown in Table 1.8, results under constant marginal cost pricing are similar to these given oligopolistic pricing, all indicating significant marginal cost reductions from the MPP at the 1% level. Specifically, the MPP reduces marginal cost by $0.6 per patient-day under competitive pricing and by $1.9 under oligopolistic pricing across ownership assumptions. The estimated quantity coefficients are positive yet small. These quantity estimates are consistent with the fact that supply curves are upward sloping, as oligopolistic firms face some capacity constraint as quantity goes up. In cases where marginal

costs are not independent of quantity, drug patent protection increases marginal costs, and the number of competitors in the market reduces marginal costs. These results are robust to the inclusion of country-year level observable controls and to statistical tests on the BLP instrument.

Table 1.9: Welfare Estimation: Consumer & Producer Surpluses

welfare estimates ($ M)	MC pricing flat MC	Bertrand-Nash Oligopoly single-prod. firm	Bertrand-Nash Oligopoly multi-prod. firm
$\widehat{CS_0}$	7,354.5	8,055.1	8,025.8
$\widehat{CS}$	8,747.7	8,747.7	8,747.7
$\widehat{CS_1}$	8,883.3	8,821.5	8,816.4
Δ$: $\widehat{CS_0}$	1,393.2	692.6	721.9
Δ%: $\widehat{CS_0}$	18.94%	8.60%	8.99%
Δ$: $\widehat{CS_1}$	135.6	73.8	68.7
Δ%: $\widehat{CS_1}$	1.55%	0.84%	0.78%
$\widehat{PS_0}$	0	3,998.1	4,194.8
$\widehat{PS}$	0	4,179.5	4,309.6
$\widehat{PS_1}$	0	4,320.7	4,462.0
Δ$: $\widehat{PS_0}$	0	181.4	114.8
Δ%: $\widehat{PS_0}$	0	4.54%	2.74%
Δ$: $\widehat{PS_1}$	0	141.2	152.4
Δ%: $\widehat{PS_1}$	0	3.38%	3.54%

Notes: this table reports estimating the gains in consumer and producer surpluses with the MPP. Here, $\widehat{CS}$ denote the total consumer surplus cross-markets. $\widehat{CS_0}$ is the counterfactual consumer surplus without the MPP. Similarly, $\widehat{PS}$ and $\widehat{PS_0}$ denote the actual and counterfactual producer surpluses, respectively. $\widehat{CS_1}$ and $\widehat{PS_1}$ denote the counterfactual consumer and producer surpluses with a fully expanded MPP (covering all developing countries in my sample for a compound in the pool), respectively.

The welfare and counterfactual results in Table 1.9 further quantify how much the MPP increases both consumer and producer surpluses in dollar values. Consumers benefit from cost savings induced by the MPP via joint licensing, and producers can benefit from market expansion in developing countries and increased sales via the generic network. The estimated current consumer surplus across all markets (country-year) during my sample period is $8.7 billion, on the same order of magnitude as the total revenue during my sample period ($4.3

billion) and consistent with demand being elastic. Compared to the counterfactual cases without a patent pool, the MPP results in $0.69-1.39 billion consumer surplus gains across market structure specifications. These are equivalent to 8.60-18.94% increases from the counterfactual consumer surpluses. Overall, the benchmark level of consumer welfare gains I estimate is similar to the MPP's estimates of cost savings ($1.06 billion).[47] The estimated producer surplus gains are up to $181 million and are consistent with theories in which producers can also benefit from cost-reducing technologies.

The costs of operating the patent pool can be incorporated using a back-of-the-envelope cost-benefit type welfare calculation. Given the limited data on modern patent pools, there is limited understanding of the costs directly associated with the intermediary. I overcome this issue with transparent, audited financial statements from the MPP.[48] The total operating cost of the MPP is about $33 million from its establishment in July 2010 to the end of 2017 (less than $5 million per year). This amount is small compared to the welfare gains estimated above. These counterfactual results, together with the diffusion and innovation analyses, suggest that the MPP is an effective business model in a LMIC setting with elastic demand. Lower prices from generic licensing generate larger responses in terms of quantity increases, which can further increase profits. This calculation is conservative as both branded and generic firms also benefit from reduced administrative costs that are not incorporated here.

[47] They multiply quantities sold by the price differences between the lowest branded and generic prices.
[48] Year-specific financial data collected are reported in Table A13. As a reference, $5 million annual operating costs is comparable to that for a regional NPO program such as "Girl Scout Cookies."

1.7. Discussion and Conclusion

I find that the first joint licensing platform in medicine, the MPP, increases the diffusion of affordable generic versions of pool-associated drugs by about seven percentage points. The results are stronger in countries where a drug has been patented and when drug cocktails are de-bundled to the compound level. The results are robust to a set of robustness and sensitivity tests. In addition, the pool also fosters a pro-competitive environment with R&D increases in both follow-on clinical trials and drug approvals. Branded firms inside the pool decide to reallocate clinical trials to drugs close to the market and new compound development. Firms outside the pool increase trials with pooled compounds. And generic firms obtain more drug approvals with pool-associated compounds. Overall, the MPP increases welfare by lowering the costs of licensing and offers new channels of marketing in previously underdeveloped markets.

Although I focus on a pool with HIV drug cocktails, the nature of the disease and treatment regimen are broadly related to other disease areas. For example, the MPP expanded in 2015 to work on hepatitis C and tuberculosis, which are also chronic conditions that require cocktail treatment and with higher disease prevalence globally. As the MPP further expanded in 2018 to work on all small molecule drugs in the WHO's essential medicine list, more research is needed to understand the long-term impact of the patent pool. In addition, many diseases started from developing countries and became prevalent in the U.S., making it mutually beneficial to develop institutions to facilitate diffusion and innovation that can benefit all countries. In the presence of rising anti-microbial resistance, market-based institutions such as patent pools can unite global talent to tackle urgent global issues. Furthermore, the MPP is ready to support access to HIV drugs that may be effective in the treatment of the current coronavirus pandemic.

In addition, the MPP provides some insights into inter-firm alliances from a mechanism design perspective. This pool carries several features that appeared in historical patent pools with modern twists. First, the MPP is a non-profit pool with for-profit patent holders. The public-private partnership makes it natural to consider diffusion and innovation in coordinated manners. This partnership is similar to the aircraft patent pool during WWI that spurred the growth of the U.S. aircraft industry. Second, the lowest licensing unit is at the compound level, and all relevant territory patents are included in the MPP licenses. This compound-based all-patent package eliminates selection in patents. Third, the pool segments the market to preserve lucrative high-income territories for branded firms and uses implicit price caps for low-income territories to deter price fixing. The geographic separation allows branded firms to maintain prior strategies in lucrative markets and to broaden well-compliant patent licensing in developing countries.

Focusing on the first modern biomedical patent pool has clear advantages and some limitations. I take the pool design as given and cannot extrapolate if the pool design changes drastically and becomes completely profit driven. One needs to be careful about the external validity of a global pool with an economic development focus. The substantial internal validity of the MPP is worth noting, and more research is needed to evaluate pools with complex biologic products. Besides, because a patent pool is designed to reduce multiple frictions in the market for patent licensing, it is difficult to quantify the relative magnitude of each mechanism precisely.

This paper has multiple implications for innovation, antitrust policy, and firm strategies, particularly given the ongoing expansion of the MPP and the increasing intention to use patent pools in biomedical sciences. First, branded firms can use patent pools to collaboratively expand the global market and reduce costs. Second, effective technology diffusion involves detailed licensing designs that allow for broad use of patents and the preservation of licensor's rights in

the preferred sales territory. Third, a patent pool can be an institutional innovation to align public and private interests to increase profits and improve welfare. Fourth, for diseases with heavy global burdens, technology diffusion can benefit both consumers and firms by leveraging comparative advantages across branded and generic firms in the global economy.

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CHAPTER 2

THE COMPLEMENTARITY OF HEALTH INFORMATION AND HEALTH IT FOR REDUCING OPIOID-RELATED MORTALITY AND MORBIDITY

Lucy Xiaolu Wang

Abstract: In response to the opioid crisis, each U.S. state has implemented a prescription drug monitoring program (PDMP) to collect data on controlled substances prescribed and dispensed in the state. I study whether health information technology (HIT) complements the availability of patient data in PDMPs to reduce opioid-related mortality and morbidity. I construct a novel dataset that records state policies that integrate PDMP with HIT and facilitate interstate data sharing. Using difference-in-differences models, I find that PDMP-HIT integration policies reduce opioid-related mortality and morbidity. The reductions in inpatient morbidity are substantial in states that established integration without ever mandating the use of a PDMP. The impacts are strongest for the most vulnerable groups – middle-age, low- to middle-income patients, and those with public insurance. I find suggestive evidence that interstate data sharing further complements integration despite not having a significant impact independently. The total benefits from integration far exceed the associated costs.

2.1. Introduction

Following a substantial long-term decline in mortality and morbidity rates since 1900, the United States has experienced a striking mortality and morbidity reversal for middle-aged white non-Hispanic Americans since the late 1990's (Cutler et al., 2006; Case and Deaton, 2015, 2017). This deterioration in health is so substantial that overall mortality and morbidity rates have increased in recent years, with drug poisonings being a leading factor behind this health

deterioration (Case and Deaton, 2017). As the biggest cause of drug poisoning, opioid-induced death rate has more than tripled from 2000 to 2014 (Rudd et al., 2016). Moreover, most opioid-related deaths occur among those between the ages of 25 to 54, leading to large productivity losses and a future burden for Medicare (CDC, 2016). Opioid-related annual social costs are estimated to be between $294 billion and $622 billion (CEA, 2017).

To reduce opioid-related poisonings, each U.S. state has implemented a *Prescription Drug Monitoring Program* (PDMP, or PMP), and some states mandated its use. The PDMPs are state-run electronic databases that provide prescription histories for controlled substances. Health care providers can use this database to identify drug-seeking behavior, avoid inappropriate prescribing, and conduct early interventions. Independently, the adoption of health information technologies (HITs) can reduce drug poisoning as part of general quality improvement. HITs are clinical software and systems that facilitate physicians' clinical decisions by storing, processing, and analyzing patients' health and medical services received. While both PDMP and HITs have drawn significant attention separately, their complementarity has been overlooked.

In this paper, I study policies that integrate PDMP and HITs to allow better data access and utilization within and across states. Until recent years, most states' PDMPs were stand-alone web portals using technology standards different from those in clinical software. Exploring a patient's medical history can be time-consuming and inaccurate without HITs; requesting opioid prescription history from a separate site that requires extra verification creates further hurdles. Moreover, some non-opioid prescription drugs that can interact dangerously with opioids are not recorded in a PDMP nor are they easy to identify or analyze without assistance from HITs. For instance, the psychoactive drug benzodiazepines (benzos) are not always recorded in PDMPs, are

often prescribed to opioid users, and can result in dangerous interactions. Analytic functions embedded in HIT can help overcome these challenges.[49]

To reduce technological hurdles, the U.S. Office of the National Coordinator for Health Information Technology (ONC) collaborated with states and the private sector since 2011 to initiate pilot projects linking drug monitoring portals to medication histories within HITs.[50] These PDMP-HIT integration pilots effectively reduced opioid prescription and improved associated treatment, and some of these projects were expanded into statewide programs (CDC, 2017). At the state-level, Nebraska and Maryland were aware of this issue up front and built PDMPs within their existing statewide HIT portals to create an integrated system. The impact of these statewide integration policies has not been studied systematically in the academic literature.

In addition, PDMPs are administered and managed independently by states, but patients with drug overdose histories frequently doctor-shop across state lines (McDonald and Carlson, 2014). Exchanging PDMP data across states is a challenging process. State privacy laws can impose legal barriers to interoperable technology diffusion (Miller and Tucker, 2009). This legal constraint prevented New York and New Jersey from sharing PDMP data until April 2016 and restricted Florida's attempts to integrate PDMP in 2012 even with a federal grant. Furthermore, a lack of funds can prevent PDMP data sharing as once occurred in North Carolina.[51]

[49] Benzos are Schedule IV drugs. Some state PDMPs do not record Schedule III-V drugs. As of 2013, Pennsylvania monitors Schedule II drugs only and Rhode Island monitors Schedules II and III (source: https://www.bja.gov/Publications/PDMP_PPR_Jan-Dec13.pdf). Even when benzo and opioids are both recorded, it is not easy to use multi-drug records for a patient without HIT analytics (Zaman *et al*., 2018).
[50] Pilot projects involve extensive collaboration with electronic health record vendors, such as Appriss Health, Epic, Dr. First, and NextGen. Project details are available via https://www.healthit.gov/PDMP.
[51] The legislative information is collected from a combination of public sources, numerous phone calls, and email communications with legal experts and state PDMP/HIT agencies.

This paper evaluates the impact of statewide PDMP-HIT integration policies, controlling for other PDMP policies and interstate data sharing. I link state integration policies to opioid-related mortality rates and hospital discharge rates. The policy data are collected from state legal and regulatory documents, press releases, and discussions with state HIT and PDMP agencies. My mortality data include mortality rates caused by any opioids and illicit opioids; my morbidity data include hospital discharges with diagnoses including poisoning by any opioids. Because states implemented integration policies at different dates, I exploit variation in when these policies were implemented and use difference-in-differences models to estimate causal impacts. To my knowledge, this is the first paper examining the impact of PDMP-HIT integration, a design feature of PDMPs, on opioid-related outcomes.

I find that PDMP-HIT integration effectively reduces opioid-related hospitalization and mortality rates. The results are particularly strong among opioid-related inpatient discharges. On average, the morbidity and mortality reductions from integration are about 17 percent and 10 percent of the mean of associated outcomes during my sample period. The event studies confirm a lack of pre-trends in outcomes in states with integrated PDMPs relative to control states, and the post-period policy impacts are significant and build over time. Heterogeneity analyses reveal that the policy impacts are strongest for the most vulnerable groups, including middle-age patients, low-income patients, and patients with public insurance. All of these results suggest that PDMP-HIT integration offers decision support for providers to identify risky patients for early intervention and allows insurers to make progress in helping enrollees during the opioid crisis.

Subsample results indicate that the inpatient morbidity reductions are substantial in states that integrated PDMPs without ever mandating PDMP access during my sample period, suggesting that making PDMPs user-friendly via integration encourages effective utilization. I

am not able to test whether mandate and integration policies are complements or substitutes due to data limitations. My results are robust to controlling for confounding policies, placebo tests, and alternative policy measures. As another technology-oriented PDMP design feature, interstate data sharing can further complement PDMP-HIT integration, despite the lack of an independent impact. Although I cannot more precisely investigate PDMP interstate data sharing given the nature and limitation of the data available, my results provide suggestive evidence of its value in further enhancing PDMPs. A back-of-the-envelope calculation indicates that the total annual benefits that would be generated from a national integration policy are approximately $30-$60 billion per year, which far exceeds any plausible estimates of the associated costs.

This study contributes to two strands of the literature. First, I extend the literature on drug monitoring program evaluations with a new mechanism of PDMP-HIT integration. Although some studies show that PDMP implementation is associated with reduced opioid prescriptions (Bao et al., 2016; Dowell et al., 2016; Kilby, 2016; Patrick et al., 2016), most find little impact on health outcomes, such as overdose mortality (Li et al., 2014; Meara et al., 2016). To increase the use of PDMPs, several states mandated that providers must access a PDMP before any new opioid prescription. Buchmueller and Carey (2018) find that opioid prescriptions declined among Medicare patients in states with a PDMP mandate, but they also show that a mandate does not reduce opioid poisoning and can drive up cross-state opioid doctor-shopping. Dave et al. (2017) find some evidence that mandates reduce opioid treatment program admission of young adults. Mandate is one of the most widely studied design feature of PDMPs.

I study an alternative design to encourage PDMP utilization – making it user-friendly through HIT integration. Most physicians are aware of PDMPs but find them difficult to access (Fleming et al., 2014; Rutkow et al., 2015). The time-consuming data requests and frustrating

cross-system data interpretation crowd-out treatment time, resulting in prescriber opposition and low compliance rates to PDMP mandates (Haffajee et al., 2015; Blum et al., 2016). PDMP-HIT integration can resolve these technology challenges and further improve decision support.

Second, this paper contributes to studies on digitization in health care with an emphasis on complementary assets. Identifying and using complementary assets to improve health care is difficult but important (McCullough et al., 2010, 2016; Dranove et al., 2014). Although most drug-related poisonings in the past two decades have involved controlled substances, these drugs were not recorded nor analyzed by most HITs.[52] Not surprisingly, there is little evidence that HITs independently reduce adverse drug events (Agha, 2014). In contrast, HITs can complement prescriber education to improve antibiotic use (Meeker et al., 2016) and substantially reduced opioid utilization in federally funded pilot projects when integrated with PDMPs (CDC, 2017). This paper provides systematic validation of these project results at the state-level and highlights the value of integrating complementary assets in an era with massive yet segmented patient data.

The paper proceeds as follows. Section II describes the background and data. Section III presents empirical strategies and results. Section IV reports robustness checks. The final section concludes and discusses policy implications.

[52] Electronic Prescription for Controlled Substances (EPCS) has been legal only since June 2010, when the Drug Enforcement Agency revised the rules (DEA, 2010). According to Surescripts®, fewer than 1% of physicians enabled EPCS by the end of 2015 in most states. I abstract away from this issue in this study.

2.2. Background and Data

2.2.1. Do Physicians React to Inter-Connected PDMPs and HIT?

Anecdotal evidence suggests PDMP-HIT integration greatly increases PDMP utilization.[53] For example, in a federally-funded pilot hospital, the PDMP data requests increased 145-fold the year after integration, with a 22% decrease in hospital opioid prescriptions. During the same period, the PDMP data request rate increased by 28% statewide, with a 13% increase in hospital opioid prescriptions (CDC, 2017). In another example, two years after Kansas implemented interstate data sharing, the out-of-state data requests from in-state physicians increased from zero to 25.2% (CDC, 2017). Realizing these benefits, the Centers for Medicare & Medicaid Services (CMS) issued a letter in 2018 highlighting the importance of leveraging technology to combat the opioid crisis.[54] Given the lack of detailed data on illicit opioid use that substitute for opioid prescriptions, in this study I focus on patient health outcomes rather than prescription volume.

2.2.2. Legal Coding on PDMPs

I include state-quarter level indicators on whether a state has implemented an operational PDMP, whether a further modernized PDMP has been implemented (Horwitz et al., 2018), and whether a state has a mandate requiring providers to access the PDMP before writing a new opioid prescription. I define a PDMP as operational when its core functionality as electronic data

[53] A quote from a physician was reported on healthIT.gov: "I have to say that this is probably one of the more genius moves of the 21st century . . . having easy access to [the PDMP] without going to a totally different website and have it pop up instantly has taken a lot of time off of decision making for me."
[54] Source: https://www.medicaid.gov/federal-policy-guidance/downloads/smd18006.pdf.

of controlled substances becomes available to authorized users. Some states mandate that all eligible providers must access PDMP for each new patient.[55] Others encourage voluntary access.

I cross-checked three data sources to code PDMP-related operational and mandate dates. First, I obtained PDMP regulatory data provided by the National Alliance for Model State Drug Laws (NAMSDL), a federally funded non-profit institution that works in coordination with the Office of National Drug Control Policy. Second, I acquired legislative data collected by Legal Science, LLC in the Prescription Drug Abuse Policy System (PDAPS), using grants from the National Institute on Drug Abuse. Third, I used the resources and state profiles stored in the Prescription Drug Monitoring Program Training and Technical Assistance Center (PDMP TTAC) managed by Brandeis University.[56] In addition, I controlled for when a PDMP became "modern system operational," as provided by Horwitz et al. (2018).[57]

2.2.3. PDMP-HIT Integration, PDMP Interstate Data Sharing, and HIT Adoption Rates

State autonomy in PDMP database design results in many PDMP data formats that are often incompatible with clinical data standards. In contrast, most HITs are developed following industry standards to transfer clinical data securely and confidentially. The timings of integration are plausibly exogenous given the multilateral coordination of agencies involved.

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[55] I coded mandates under "broad circumstances" following Buchmueller and Carey (2018) using updated data. I recoded the Delaware PDMP mandate date to its operational date, as this mandate was issued before the Delaware PDMP started operating and thus could not be enforced without an operating PDMP.

[56] Due to differences in raw data sources and terminology, there are inconsistencies in the policy dates, and many records are at the year level. For each inconsistent or potentially inaccurate date, I researched statutes, administrative codes, state documents, and consulted legal professionals and state PDMP managers to improve coding accuracy.

[57] I define a PDMP as operational when the core functionality of the electronic PDMP database becomes available to users (in line with the three main sources and the view of practitioners/providers). The definition in Horwitz et al. (2018) often includes sophisticated system updates and expansion in access methods to existing PDMPs. My results are robust to including either one of the two operational measures; both are important conceptually. Results are available upon request.

I define "integration" as a policy integrating PDMP into HITs to streamline access and analysis with clinical data.[58] I focus on integration that can facilitate statewide access to PDMP within HITs without an external login. I collected data from multiple sources. First, I collected reports from federally-funded integration pilot projects that document the progress and whether/ when the integration extends to the state-level. Second, I checked PDMP websites and training documents to ascertain timing and, when necessary, discussed particular details with state PDMP and/or HIT managers. Third, I searched press media releases from stakeholders involved in the integration. For example, Appriss Health releases states' contracting status with their data solution products.[59] For each state I checked whether it had integrated a PDMP or experienced barriers to integration during my sample period (2005-2015). A PDMP is always considered to be integrated if a state built the PDMP directly within the state health information exchange.[60]

I define interstate sharing as cross-state PDMP data exchange through the national hub – "PMP InterConnect."[61] The hub links the participating states' PDMPs via secured and encrypted channels. State PDMPs need a single memorandum of understanding (MoU) to join the hub instead of negotiating bilateral MoUs with each participating state. The National Association of Boards of Pharmacy provided the date a state "goes live" and starts interstate data sharing via the hub.[62] This measure is superior for identifying when cross-state PDMPs become connected to

[58] I do not distinguish between specific HIT intermediaries utilized across states in the integration. The ability to integrate data into the HITs is an informative measure of the extensive margin of integration.
[59] Anecdotes indicate that the time of doctors' data access can be reduced from 5-10 minutes to 2 seconds with their technology. https://app.brainshark.com/appriss/vu?pi=zI0zuhlD0zUwYDz0&nodesktopflash=1
[60] This definition does not include narrow integration, such as pilot integrations that were limited to a set of EHR users (e.g., Kentucky), or a program that became problematic and was suspended (e.g., Indiana).
[61] The PMP InterConnect is also referred to as PDMPi Hub – the earliest and only national hub started in 2011. There is an alternative RxCheck Hub with only three non-bordering participating states by the end of 2015 (AL, KY, and ME); KY also jointed the PMP InterConnect. I do not have data on this hub. Their collective data exchange is minimal in scale, and my results are robust to dropping these three states.
[62] The state must have transferred data with *at least one* hub-participating state once it went live; this does not ensure data transfer between *all* bordering states. The timings of pairwise sharing are not available.

alternative measures that record the date when a state allows PDMP data sharing. The lack of restriction in PDMP sharing can have little relationship to actual sharing implementation, as the details are subject to legal interpretation. Table 2.1 reports the policy implementation dates.

In addition, I include a control for state HIT levels to account for changes in health care quality through channels independent of opioid-related treatments, such as a timely process of regular medical data and clinical decision support. HIT adoption has risen dramatically in recent decades independent from substance control as most states had not included PDMP integration into their performance measures ("meaningful use" criteria) during my sample period. The best available proxy measure for states' HIT levels is states' adoption rates for electronic health records (i.e., EHR, the most universally used HITs), which is also most relevant to hospital diagnostic and treatment that are closely associated with health outcomes. I obtained data from the American Hospital Association Annual Survey IT database.[63]

Table 2.1: State Prescription Drug Monitoring Program Laws & Related Health IT Policies

state name	state	PDMP	mandate	integrate	interstate share
Alabama	AL	2006q2			
Alaska	AK	2011q3			
Arizona	AZ	2008q4			2012q2
Arkansas	AR	2013q1		2015q3	2013q4
California	CA	pre-2005			
Colorado	CO	2007q3		2015q3	2013q2
Connecticut	CT	2008q3	2015q4		2012q1
Delaware	DE	2012q3	2012q3		2013q4
District of Columbia	DC	2016q3			
Florida	FL	2011q3			
Georgia	GA	2013q3			
Hawaii	HI	pre-2005			
Idaho	ID	pre-2005		2014q2	2014q1
Illinois	IL	pre-2005			2013q1
Indiana	IN	pre-2005	2014q3		2011q3
Iowa	IA	2009q1			2015q2

[63] I linearly interpolated the rates to the quarter-level. Basic EHRs are the most widely used HITs, and basic EHR adoption rates are most representative of HIT levels in terms of clinical support. Advanced HITs that add business functions are less relevant in my case. My results are robust to alternative measures such as EHR incentive payments, with post-2010 data available from the CMS.

Kansas	KS	2011q1		2013q4	2012q2
Kentucky	KY	pre-2005	2012q3		2013q1
Louisiana	LA	2008q1	2014q3	2015q4	2013q1
Maine	ME	pre-2005		2014q2	
Maryland	MD	2013q4		2013q4	2015q3
Massachusetts	MA	pre-2005	2014q3		
Michigan	MI	pre-2005			2012q1
Minnesota	MN	2010q1			2013q4
Mississippi	MS	2006q2		2015q2	2013q4
Missouri	MO				
Montana	MT	2012q1			
Nebraska	NE	2011q2		2011q2	
Nevada	NV	pre-2005	2015q4	2015q1	2014q1
New Hampshire	NH	2014q3			
New Jersey	NJ	2011q3	2015q4		2014q2
New Mexico	NM	2005q1	2012q3	2015q2	2012q3
New York	NY	pre-2005	2013q3		
North Carolina	NC	2007q3			
North Dakota	ND	2007q3	2014q4	2014q2	2012q1
Ohio	OH	2006q3	2015q4	2015q4	2011q3
Oklahoma	OK	pre-2005	2015q4	2014q2	2015q1
Oregon	OR	2011q2			
Pennsylvania	PA	pre-2005			
Rhode Island	RI	pre-2005			2014q4
South Carolina	SC	2008q1		2015q3	2012q1
South Dakota	SD	2011q4		2015q3	2013q1
Tennessee	TN	2006q4	2013q2	2015q4	2013q3
Texas	TX	pre-2005	2015q3		
Utah	UT	pre-2005			2014q3
Vermont	VT	2009q1	2015q2		
Virginia	VA	2003q3	2015q3	2015q2	2011q3
Washington	WA	2011q4		2014q4	
West Virginia	WV	pre-2005	2012q3	2015q3	2014q1
Wisconsin	WI	2013q2			2013q3
Wyoming	WY	2004q3			

Notes: This table reports dates of interest, cross-checked specifically for my analytical sample from 2005q1 to 2015q4; effective dates before 2005 are recoded as pre-2005. The data collection is based on information available by 2017q1.

2.2.4. Outcome Data: Opioid-related Mortality and Morbidity

State-quarter level mortality data are aggregated from the restricted-access U.S. death certificates administered by the Division of Vital Statistics within the National Center for Health Statistics. Each death certificate of U.S. resident contains a broad underlying cause of death and up to twenty detailed multiple causes (including the contributing ones). I follow Ruhm (2018) to compute and correct underreporting in opioid-related mortality caused by any opioids and illicit opioids (i.e., heroin/synthetic opioids) in particular. The death rates per 100,000 population are

calculated with supplementary population data from the Surveillance, Epidemiology, and End Results Program.[64]

Morbidity measures include opioid-related inpatient stays and emergency room visits at the state-quarter level and available from the Healthcare Cost and Utilization Project (HCUP) Fast Stats opioid topic. The data are also stratified by age group, community income quartiles, patient location, and expected payers.[65] The underlying data are all discharges diagnosed with any opioid-related illnesses in the State Inpatient Databases and State Emergency Department Databases that record hospital inpatient discharges and hospital-affiliated emergency department discharges.[66] The data do not distinguish between prescription and illicit opioids (including synthetic opioids, e.g., fentanyl) and are intended to capture all opioid-related diagnoses.[67] My sample is an unbalanced panel from 2005 to 2015. Table B1 reports detailed data availability.

2.2.5. Descriptive Statistics

The pairwise correlations between PDMP, mandate, integration, and interstate sharing are all below 0.5. Identifying variation comes from differences in which states implemented policies and when these policies became effective. Figure 2.1 depicts the policy variation. Many PDMPs became operational before 2005, yet most of the other policies started after 2010. Figure 2.2 shows the rapid increase of integration policy adoption and states' entry into the sharing hub. By

[64] I linearly interpolate quarterly population from the annual SEER data, following Evans et al. (2017).
[65] The expected payer-specific measures are only available in counts instead of rates from HCUP. I calculated the denominators using the insurance coverage data by insurance type from the Census' Current Population Survey (2005-2012) and American Community Survey (2013-2015).
[66] The ER data captures hospital visits that do not result in admission, and those ER visits result in inpatient admission are recorded in the inpatient data (i.e., patients with more severe conditions).
[67] I do not stratify outcomes by opioid types (prescription or illicit) because these data are not available. According to the HCUP, it is not possible to extract illicit opioid morbidity in most diagnosis code series.

the end of my sample period in 2015, a total of 20 states had implemented PDMP-HIT integration. In addition, 30 states are making growing efforts in interstate PDMP data sharing.

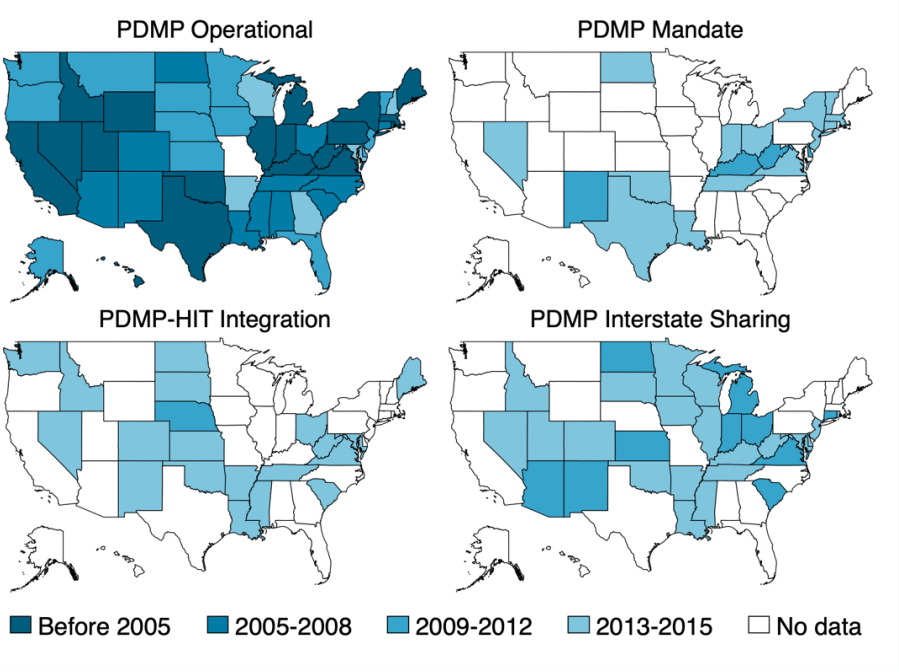

Figure 2.1: Variation in PDMP and PDMP-specific HIT Policies

Notes: this figure displays policy implementations for PDMPs, PDMP user mandates, policies facilitate integration between PDMP and clinical software, and states' participation in the national hub to share data across states. My analytic sample period covers 2005 to 2015.

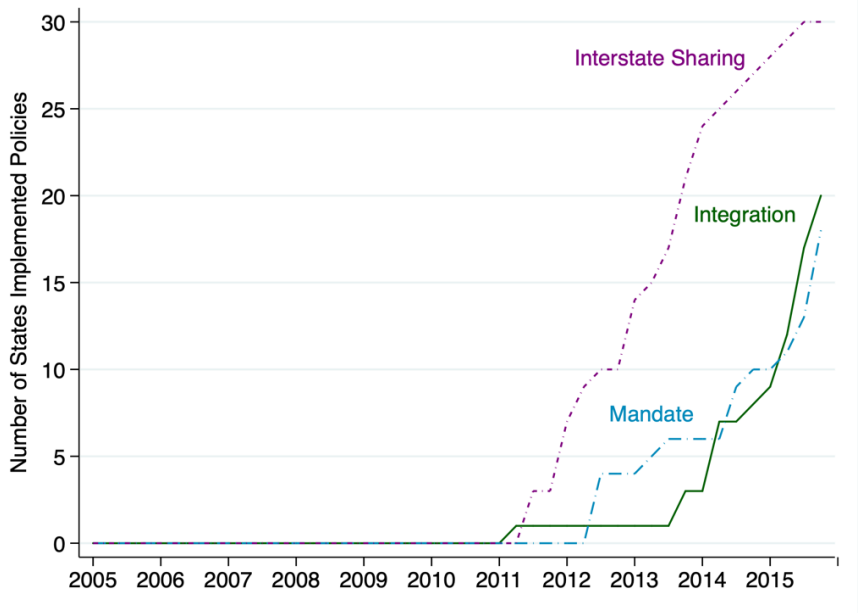

Figure 2.2: Trends of PDMP Integration, Interstate Sharing, and Mandate

Notes: This graph depicts trends of how many states have effectively implemented PDMP-HIT integration, PDMP mandate, and PDMP interstate data sharing hub participation. During this sample period, mandate and integration are the two most salient PDMP policies.

Table 2.2: Summary Statistics

Variables	Obs.	Mean	Std. Dev.	Min	Max
Opioid-induced Mortality Rates (per 100,000 population)					
All opioid deaths	2,244	2.50	1.18	0	10.13
Illicit opioid deaths	2,244	0.88	0.78	0	6.95
Opioid-Related Inpatient Stays (per 100,000 population)					
Total Inpatient Stays	1,856	190	90	40	474
Age Group: 25-44	1,851	275	164	30	895
Age Group: 45-64	1,850	260	152	48	1307
Age Group: 65+	1,822	211	88	34	791
community income quartile 1	1,641	308	287	43	2067
community income quartile 2	1,700	208	129	46	929
community income quartile 3	1,694	170	83	36	536
community income quartile 4	1,483	132	54	27	513
Expected Payer: Medicare	1,784	89	35	23	237
Expected Payer: Medicaid	1,741	96	79	12	523
Expected Payer: Private	1,789	15	5	4	35
Opioid-Related Emergency Room Visits (per 100,000 population)					
Total Emergency Visits	1,256	130	75	16	501
Age Group: 25-44	1,241	246	169	26	1206
Age Group: 45-64	1,222	132	77	25	720
Age Group: 65+	1,051	51	27	9	208
community income quartile 1	1,090	219	174	31	1436
community income quartile 2	1,143	156	112	22	782
community income quartile 3	1,124	123	75	20	566
community income quartile 4	979	93	49	21	340
Expected Payer: Medicare	1,112	33	17	7	98
Expected Payer: Medicaid	1,090	64	49	8	338
Expected Payer: Private	1,137	10	5	2	28

Notes: Each observation is a crude rate at the state-quarter level. HCUP-provided opioid-related morbidity outcomes are only available in counts when stratified by expected payer, so I calculated the rates by dividing these discharge counts by the number of people covered by each expected payer. Since there are more unclear discharges in terms of expected payers (the missing appears to be random), outcome stratified by expected payers are overall smaller than other stratified measures.

Table 2.2 reports summary statistics for the outcome variables at the state-quarter level. The means of all opioid-induced and illicit opioid-induced mortality rates are 2.5 and 0.88 per 100,000, respectively. During my sample period, the overall opioid-related discharge morbidity

rates are, on average, 190 per 100,000 in inpatient stays and 130 in ER visits. For stratified outcomes, opioid-related rates of inpatient discharges are almost always higher than those of emergency department visits. In both the inpatient and ER data, the highest opioid-related morbidity rates occur among 25- to 44-year-old patients followed by those between the ages of 45 and 64. Stratified by community income, the opioid-related morbidity rates are highest among low- to middle-income populations in the first and second quartiles. Patients with Medicare and Medicaid as expected payers have much higher inpatient morbidity rates among insured patients.

The mortality data cover all 50 states and the District of Columbia. The morbidity data set is an unbalanced panel data with inpatient data from the 44 states and ER data from the 34 states that ever participated in the HCUP data project during my sample period. Because states participated at different years, I empirically test whether there are policy-relevant differences in state-quarters with missing data versus those without. I find that the missing data are not policy-relevant and are likely missing at random.[68]

2.3. Empirical Analysis and Results

2.3.1. Empirical Strategies

My primary analysis evaluates the impact of state policies on state-quarter aggregates of opioid-related mortality and hospital discharges in inpatient and ER settings.[69] I hypothesize that

[68] To test whether the data are missing at random, I constructed an indicator variable for each outcome to record whether an observation is missing. I then estimated a regression for each indicator on the policy variables and fixed effects. None of the coefficients are significant. The data provider stated that the pattern of missing data stems from the completeness of the data provided by the individual states.

[69] In all of the specifications, I run the analysis on both the full sample and on the sample excluding states without an operational PDMP during my sample period. All states except Missouri had enacted PDMPs by the end of 2016, and the District of Columbia started operating its PDMP in late 2016. The results are similar in both samples, indicating that the two states are not drastically different from the other states. I report results using the full sample for simplicity and in order to maintain a larger sample size.

a PDMP is more effective when data can be accessed and analyzed within HIT, which allows providers to access PDMP data more quickly and thus effectively analyze patients' disease history and drug interactions involving opioids (within a PDMP) and other drugs (within HITs). Because states implemented integration policies at different dates, I exploit within-state changes in health outcomes and cross-state variation in when policies were implemented to estimate difference-in-differences models. The regression model is:

$$y_{st} = \delta_s + \delta_t + \alpha PDMP_{st} + \beta integration_{st} + \gamma mandate_{st} + \eta X_{st} + \varepsilon_{st} \qquad (1)$$

where y_{st} is a state-quarter-level outcome variable. $PDMP_{st}$ indicates whether state s in quarter t has implemented a $PDMP$. The key variable of interest, $integration_{st}$, indicates whether a state at time t has implemented PDMP-HIT integration. $mandate_{st}$ controls for whether a state requires providers to access PDMP data in a year. X_{st} is a set of control variables including PDMP interstate sharing, baseline HIT adoption levels measured as the percentage of hospitals that adopted any EHR system,[70] whether a modern PDMP system is implemented, and other policies studied in the current literature, including the unemployment rate, large pill mill crackdowns, naloxone access laws, Good Samaritan overdose prevention laws, medical marijuana dispensary laws, and Medicaid expansion (Powell et al., 2015; Doleac and Mukherjee, 2017; Hollingsworth et al., 2017; Rees et al., 2017; Horwitz et al., 2018; Wen et al., 2020). Fixed effects for states (δ_s) and year-quarters (δ_t) are included to account for fixed differences between states and year-quarters, respectively. Standard errors are clustered at the state-level.[71]

[70] EHR is the most common type of HITs adopted and is often used to represent the broad scope of HITs used in clinical settings. This is also the only consistently measured HIT variable in the AHA IT sample.
[71] My estimates of standard errors are likely conservative for the mortality analysis according to new methodological developments that emphasize design-based approaches to clustering (Abadie et al., 2017).

There are two identifying assumptions: common trends and a lack of common shocks. I evaluate these assumptions within an event study framework for two reasons. First, this framework helps assess the validity of the assumption that the trend in control group (state-quarters without integrated PDMPs yet) is a valid counterfactual for the treated group (state-quarters with integrated PDMPs). Differential trends of outcome variables between the treatment and control groups in the pre-treatment periods would suggest policy endogeneity or correlation with other shocks. Event studies with zero coefficients on event indicators prior to a policy provide evidence in support of the identifying assumptions. Second, the event study measures the dynamic responses of outcomes to policies. The integration policy could improve over time through more effective treatment, or it may have an instant impact that diminishes over time as patients switch to illicit opioids. The event study estimates the following equation:

$$y_{st} = \delta_s + \delta_t + \alpha PDMP_{st} + \sum_{j\in[-12,12]} \beta_j 1\left\{\begin{matrix} integration \\ event\ time_j \end{matrix}\right\}_{st} + \gamma mandate_{st}^{PMP} + \eta X_{st} + \varepsilon_{st} \qquad (2)$$

where β_j denotes the difference between treatment and control units in the period j quarters relative to when an integration policy was implemented. The period before implementation, j= –1, is omitted as the reference period. I specify the event window to be 12 quarters before and 8 quarters after the event.[72] Sample sizes are small outside of this range.

2.3.2. Baseline Results

Table 2.3 reports the results of the difference-in-difference estimation. I first report the results from the overall mortality and morbidity regressions and then I provide hypotheses and

[72] Data more than three years before and more than two years after an event are recoded to j= –12 and j=6, respectively. The results are similar if I drop the data outside of the event window.

corresponding morbidity results in stratified sub-populations. The integration policy is estimated to reduce overall opioid deaths by -0.253 and illicit opioid deaths by -0.303 per 100,000 people, respectively, although only the latter is statistically significant at the 10% level. The relative magnitudes suggest that integrated PDMPs can help providers detect high-risk opioid misusers, which allows them to provide treatment to avoid patients' switching to illicit opioids. Figure 2.3 depicts the associated event studies and indicates a lack of statistical power, despite downward trends in post-period point estimates and the absence of obvious pre-trends. The lack of statistical precision is understandable because mortality rates are extreme outcomes.

Table 2.3: Baseline Regression Results

outcomes	overall opioid deaths		overall morbidity		Inpatient rate, by age group		
	any	illicit	inpatient	ER visits	25-44	45-64	65+
PDMP	-0.113	-0.0505	6.163	-21.00**	7.209	5.171	6.601
	(0.163)	(0.131)	(8.594)	(8.665)	(21.27)	(10.18)	(13.69)
mandate	0.409*	0.387**	13.68	4.082	53.49*	7.347	-12.11
	(0.208)	(0.184)	(12.67)	(8.882)	(30.40)	(15.45)	(11.01)
integration	-0.253	-0.303*	-33.86***	-2.102	-54.33**	-42.34**	-35.27
	(0.197)	(0.173)	(11.95)	(9.340)	(22.71)	(13.55)	(21.14)
interstate	0.0129	-0.0804	-6.823	5.489	-9.956	-9.551	-17.94
	(0.152)	(0.142)	(8.313)	(6.905)	(17.68)	(11.77)	(14.06)
LHS mean	2.50	0.88	190	130	275	260	211
N	2,244	2,244	1,856	1,256	1,851	1,850	1,822
outcomes	inpatient rate, by income quartile				inpatient rate, by expected payer		
	Q1	Q2	Q3	Q4	Medicare	Medicaid	Private
PDMP	-0.265	-8.950	4.702	5.375	3.272	15.32	0.655
	(18.37)	(12.40)	(8.067)	(5.623)	(4.876)	(12.57)	(0.840)
mandate	13.75	21.20	14.08	-2.633	2.690	15.70	0.311
	(17.27)	(14.68)	(10.09)	(6.477)	(4.692)	(14.07)	(0.639)
integration	-59.98*	-30.75**	-10.22	-17.62***	-16.64**	-31.21**	-0.724
	(29.75)	(13.57)	(9.387)	(6.394)	(6.687)	(13.87)	(0.945)
interstate	-13.93	-10.04	-11.29	-11.27**	-6.483	-2.131	-0.120
	(15.75)	(11.08)	(7.520)	(4.482)	(4.683)	(10.01)	(0.810)
LHS mean	308	208	170	132	89	96	15
N	1,641	1,700	1,694	1,483	1,784	1,741	1,789

Notes: This table reports the results of the baseline model using equation 1. Each column name represents a dependent variable in a separate regression. Fixed effects for states and year-quarters are always included. Robust standard errors are clustered at the state level and are reported in parenthesis. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

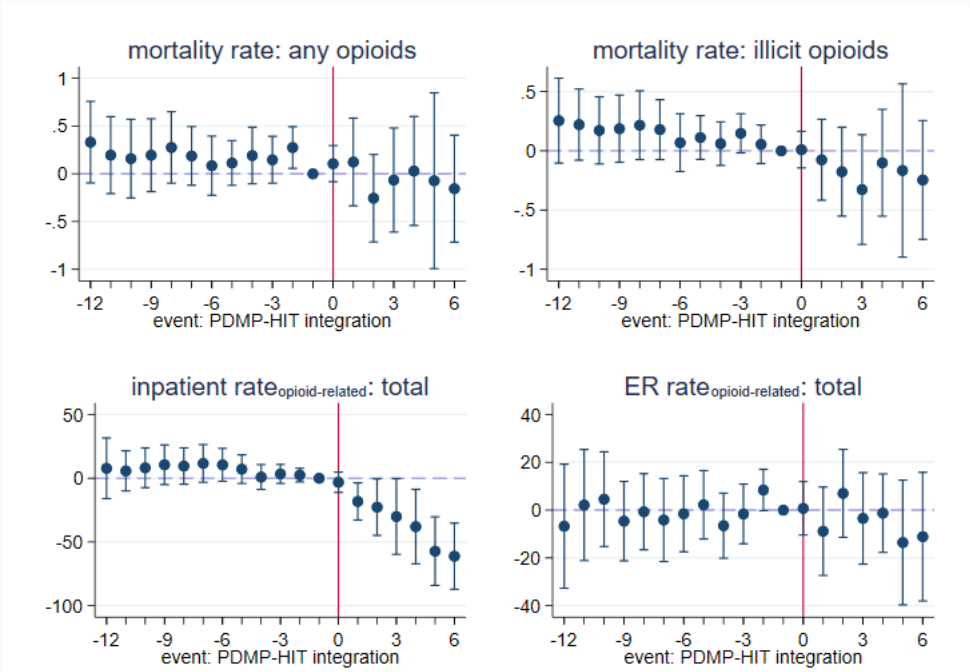

Figure 2.3: Event Studies: Integration on Opioid-Related Mortality and Overall Morbidity

Notes: These figures report event-study coefficient estimates using Equation 2. The dots are point estimates of differences in outcome variables between treatment and control groups 12 quarters before and 6 quarters after implementation. The whiskers correspond to 95% confidence intervals.

For overall morbidity, the integration estimate is about 34 fewer hospital discharges per 100,000 for opioid-related inpatient stays and is statistically significant at the one percent level. The associated event study (Figure 2.3) supports the lack of a pre-trend for treated and control groups, and the post-period reductions occur quickly and build over time. Intuitively, admitted patients are usually severely ill and require substantial treatment. For doctors treating these patients, integrated PDMPs can be particularly helpful in providing opioid-related data and can provide decision support functions via HITs. In contrast, the regression results from total opioid-related ER visits is estimated to be -2, but this is not statistically significant. The related event study (Figure 2.3) is noisy, with approximately zero coefficient estimates of differences between treated and control groups in all periods. Intuitively, ER visits are likely less responsive to policies because ER physicians are usually exempted from PDMP use (Blum et al., 2016).

Next, I analyze stratified opioid-related inpatient morbidity rates in Table 2.3 and Figure 2.4. I examine groups where there is a plausible hypothesis for why the policy effect might differ: adult age groups, community-income quartiles, and patients with different types of insurance. These measures are closely related to patients' socioeconomic status, and thus might isolate vulnerable sub-populations. Due to data availability issues, I lack state-quarter mortality rates stratified by demographics, so I am not able to provide a stratified mortality analysis.[73]

Across adult patient age groups, middle- to old-aged patients can benefit more from an integrated policy presumably because they require greater treatment intensity and use more hospital resources. Specifically, patients of working age (the 25-64 age groups) are most vulnerable based on mean inpatient morbidity rates, and old-age patients are less time-constrained for inpatient treatment. From the regression results, the integration coefficient point estimates are 54, 42, and 35 fewer inpatient discharges per 100,000 for patients aged 25-44, 45-64, and 65 and older, respectively (corresponding to 19%, 16%, and 16% of mean morbidity rate). Based on the event studies, there does not appear to be significant pre-period differences between the treated and control groups for age groups 25-44 and 65+. The post-period responses are almost immediate for the 25-44 age group whereas they take a few periods to build up for the elderly. Although the pre-trend for patients between ages 45-64 are slightly above zero, post-period estimates clearly diverge downward.

[73] There is no clear hypothesis concerning stratified ER outcomes, and note that the coefficient estimate is not statistically significant for opioid-related total ER visits as discussed above. The regression results and associated event studies using stratified ER outcomes are reported in Table B6 and Figure B1.

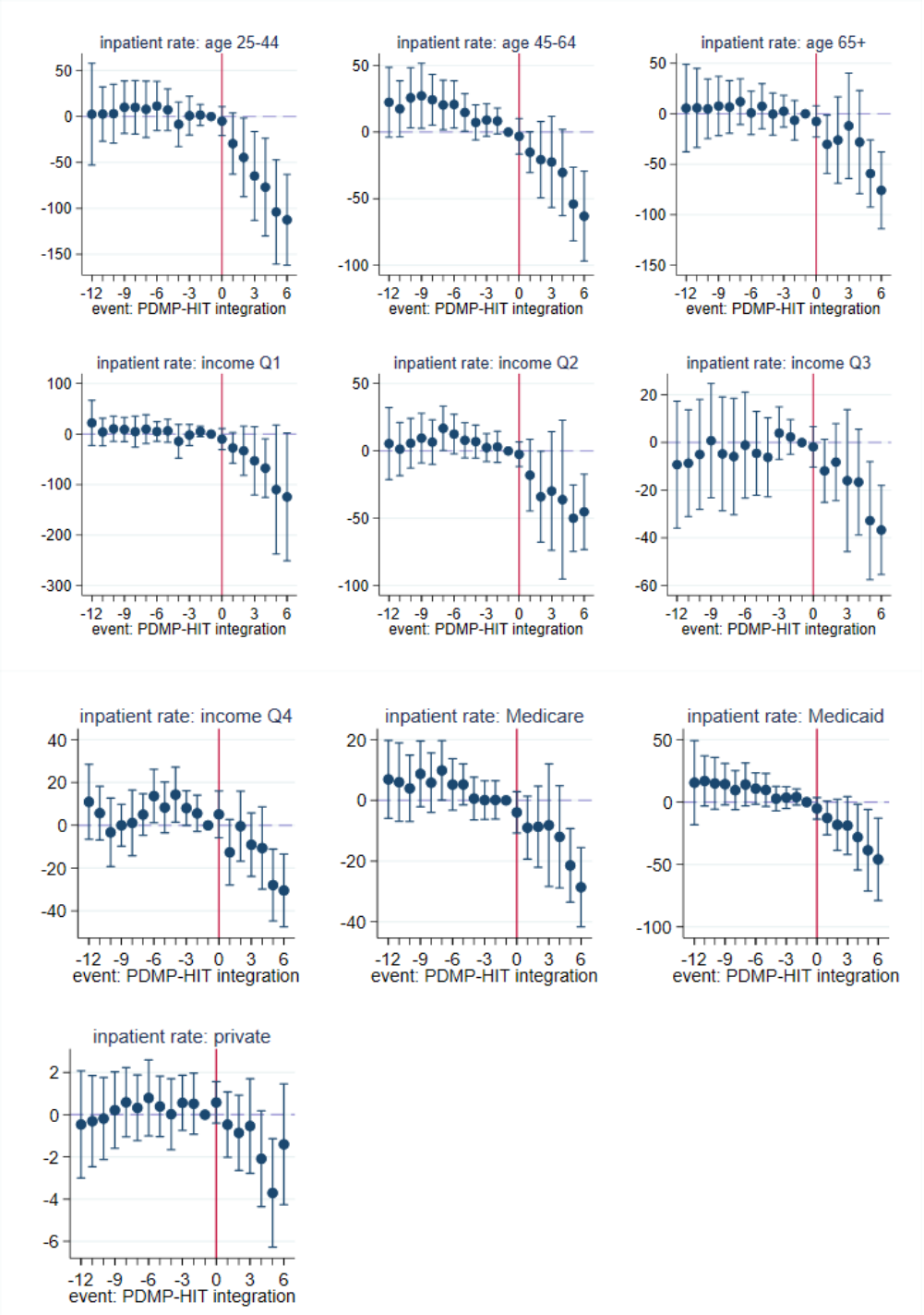

Figure 2.4: Event Studies: Integration on Opioid-Related Inpatient Morbidity, Stratified

Notes: These figures report event coefficient estimates using Equation 2. Outcome variables are the rates of hospital inpatient discharge per 100,000, stratified by adult age group, community-level income quartile, and expected payer. The dots are point estimates of differences in outcome variables between treatment group and control groups 12 quarters before implementation and 6 quarters after implementation. The whiskers correspond to 95% confidence intervals.

Across community-level income quartiles, patients from low- and middle-income communities have the highest opioid inpatient rates and might be most responsive to PDMP integration. Patients from high-income communities, on the other hand, have more resources to travel across states and might therefore be more impacted by cross-state data sharing. In fact, patients from the two lowest community-income quartiles have the largest responses to the integration policy, with estimates of about 60 and 31 fewer inpatient discharges per 100,000. Patients in the highest income quartile have about 18 fewer discharges per 100,000 (13% of the mean) from integration and experience 11 fewer discharges associated with interstate sharing. The estimate for patients in the third income quartile is 10 fewer discharges but not statistically significant. The upward trending, statistically insignificant point estimates in the pre-period of the event study for this group suggest that the integration estimate is conservative. Event studies for other groups show lack of pre-trends and post-period integration effects that grow over time.

A patient's insurance status may capture both provider's treatment incentives and personal characteristics that affect the health production function. Specifically, Medicare and Medicaid patients may over-use opioids under lenient reimbursement policies but can also benefit more from integrated PDMPs when e-billing data can be used to detect overuse. Combining results from regressions and event studies, Medicare and Medicaid patients are estimated to have the largest responses to the integration policy: -17 and -31 fewer inpatient discharges, respectively. Estimates for privately insured patients are imprecise but follow a similar pattern. Morbidity rates across expected payers have smaller magnitudes compared to other stratified outcomes in the raw data. Therefore, these integration estimates are also of smaller magnitudes and are likely to be lower bounds of the actual quantitative effects.

There are also a few supporting results. First, although the interstate sharing coefficients are not statistically significant in most regressions, most of these estimates are negative, as expected, and large. Most states participated in the interstate sharing hub before implementing integration policies, and the impact of sharing is not likely to reach its full potential without integration. Second, I test the hypothesis that integration matters more in states with higher EHR penetration by interacting integration and EHR adoption rates rather than including both variables separately. All the main results hold, and the integration estimates are larger than the baseline estimates, confirming the hypothesis above.[74] Third, I also perform stratified analyses across rural-urban classifications. I find that rural and median-sized metropolitan residents are most responsive to integration policies, likely because they can benefit more from enhanced treatment while experiencing substantial opioid problems due to a sluggish local economy.[75]

Overall, I find that PDMP-HIT integration can improve opioid-related health outcomes, particularly among vulnerable populations with the highest morbidity rate. The lack of pre-trends supports the identifying assumption that the integration policies are exogenous; the policy on average takes two to three periods to materialize and its impact gradually builds over time. It is worth noting that the overall effects of a PDMP can be further calculated by adding up all PDMP related coefficients, including integration and other control coefficients. I abstract away from this summation when discussing results. Instead, I focus on the integration estimate (β in equation (1)) that captures the PDMP-HIT complementarity, which is the main contribution of this paper.

[74] This specification assumes a linear effect of percentage EHR adoption. Appendix Table B2 reports the results. I maintain equation (1) as the preferred specification with weaker and more standard assumptions.
[75] Along this line, I find that the impact of integration is stronger in the more populous Northeast/East and Midwest regions than that in the South and West regions. Results are available upon request.

2.3.3. Subsample Analysis in States without a PDMP Mandate

By the end of 2015, 20 states had implemented integrated PDMPs, 30 states had joined the national interstate sharing hub, and 18 states had issued PDMP user mandates. I repeat the previous analysis in subsamples of states that had never issued a mandate during my sample period to isolate the effects of integration in the absence of a PDMP mandate.[76]

Theoretically, mandate and integration policies can be substitutes for inducing PDMP utilization through different mechanisms. Mandate requires providers to access the PDMP data (with penalties for non-compliance) while integration lowers the costs of data use voluntarily. In principle, this substitution holds if a mandate policy is well-enforced with strong oversight. In practice, the compliance rate of a mandate policy can be under 50% (Blum et al., 2016). In this case, PDMP integration can complement a mandate to increase compliance by further reducing the costs of accessing PDMPs. An integrated PDMP is easier to use and can harness the power of both a PDMP and HIT, especially in high risk cases where HIT analytics can be used to generate automatic alerts. Most states started with one or the other policy but eventually move towards adopting both a mandate and integration. Hence, states likely treated the two policies as substitutes initially but increasingly see them as complements.

Empirically, I cannot directly test whether these two policies are complements or substitutes given the lack of sufficient independent variation during my sample period. Therefore, I report the results in subsamples of states without PDMP mandates to isolate the effects of integration (Table 2.4). In mortality regressions, none of the negative integration estimates are statistically significant at the five percent level. For opioid-related total inpatient

[76] 17 states have *both* PDMP integration and interstate sharing, and an integration is typically the later one being implemented. Among the 29 states with either an integration or a PDMP mandate, 11 of them had integration without a mandate, 9 had a mandate without integration, and 9 states had both integration and a mandate - among those, 5 states implemented PDMP integration at the same time or before a mandate.

morbidity, the integration estimate indicates 52 fewer opioid-related inpatient stays per 100,000, corresponding to about 29 percent of mean morbidity. Similar to the baseline specification, estimates for total ER visits are negative but not statistically different from zero.

Table 2.4: Subsample Analysis in States without PDMP Mandates

outcomes	overall opioid deaths		overall morbidity		inpatient rate, by age group		
	any	illicit	inpatient	ER visits	25-44	45-64	65+
integration	-0.128	-0.178	-51.92***	-6.592	-81.83***	-56.53**	-56.59
	(0.240)	(0.201)	(18.16)	(11.15)	(29.09)	(21.19)	(33.32)
interstate	-0.118	-0.232	-18.31	0.881	-22.86	-27.16*	-39.45*
	(0.202)	(0.193)	(10.91)	(7.425)	(18.96)	(15.20)	(20.55)
LHS mean	2.29	0.78	179	112	242	259	225
N	1,452	1,452	1,160	832	1,155	1,154	1,130
outcomes	inpatient rate, by income quartile				inpatient rate, by expected payer		
	Q1	Q2	Q3	Q4	Medicare	Medicaid	Private
integration	-106.5**	-40.32**	-13.94	-17.58**	-22.96**	-49.95**	-1.536
	(46.03)	(19.52)	(13.73)	(7.658)	(10.34)	(18.79)	(1.483)
interstate	-24.06	-21.75	-27.46***	-13.76**	-10.61	-14.15	0.132
	(22.55)	(13.44)	(9.133)	(5.649)	(6.655)	(13.03)	(1.187)
LHS mean	312	200	162	128	91	93	15
N	1,005	1,056	1,050	919	1,132	1,089	1,142

Notes: This table reports the results of subsample regressions of equation 1 in states that never mandated PDMP access during my sample period. Only coefficients of interests are reported for simplicity. Each column name represents a dependent variable in a separate regression. Fixed effects for states and year-quarters are always included. Robust standard errors are clustered at the state level and are reported in parenthesis. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Across stratified inpatient outcomes, the estimates indicate that integration policies work well for most of the subpopulations in states that never mandated PDMP use during my sample period. All of the integration estimates are negative and most of them are statistically significant at the five percent or one percent levels. Across results from stratified regressions in this subsample, most of the integration estimates range from about 20-30% of the associated means.

The hypotheses across stratified populations follow the same idea as discussed in the previous section: at-risk populations should benefit more from a well-integrated system under the PDMP-HIT integration policy. Indeed, the reductions are most substantial among the most

vulnerable groups: middle-age patients (especially those in prime working age), patients from low- to middle-income communities, and publicly insured patients. Per 100,000 population, patients in the 25-44 and 45-64 age groups have 82 and 57 fewer inpatient discharges; patients in income quartiles 1, 2, and 4 have 107, 40, and 18 fewer discharges, respectively. Patients in income quartiles 3 and 4 are also estimated to have fewer discharges associated with interstate sharing at 1 and 5 percent levels, respectively. Integration policies are estimated to reduce inpatient discharges of Medicare and Medicaid patients by about 23 and 50 per 100,000. The magnitudes of these estimates are larger than the counterparts in the main specifications.

I also run an alternative test using the sample of all states without observations in post-mandate state-quarters and find consistent results. Prior studies suggest no systematic differences between pre-mandate period outcomes in states that ever or never issued a PDMP mandate (Buchmueller and Carey, 2018; Dave et al., 2017). Thus, this exercise aims to provide estimates for integration policy effects net of the post-mandate effects while maintaining a larger sample with more state-quarters. All the coefficients of interest are negative, and most results from inpatient morbidities are statistically significant at the 5 or 1% level. The pattern of integration estimates is similar to that in the subsample results described above and are more precisely estimated. The magnitudes of these estimates are between those in the subsample of states without mandates and the baseline estimates. Results are available upon request.

In the context of the existing literature, my results complement Buchmueller and Carey (2018), who mentioned the importance of integration, but were not able to measure it explicitly due to the lack of data in the earlier time period. Their finding that PDMP mandate can drive up prescription shopping in neighboring states also suggested the importance of integration and interstate sharing. These policies can be complements given the emerging illicit opioid use and

patients' behavior adaptation. Quantifying the relationships between policies remains an open question and is beyond the scope of the present analysis.[77] My results are also consistent with Alpert et al. (2018) in the sense that supply-side policies alone can have unintended consequences in the presence of illicit substitutes to prescription opioids. In contrast, technology-based policies can mitigate these concerns by improving treatment and prevention to help close the gap between supply-side policies and demand-side patient behavior adjustments.

2.3.4. Limitations

The use of an aggregate, stratified hospital discharge data set provides clear advantages in capturing overall opioid-related morbidity that incorporates the substitution between different types of opioids, but it also has some limitations. Because the underlying data are at the discharge-level instead of the patient-level, I cannot distinguish between reduced hospital visits among patients with an opioid use history versus fewer opioid initiations. Also, due to patient privacy protection, my data set is aggregated at the state level and does not have individual identifiers, so I cannot directly estimate the precise amount of reduction in cross-state doctor-shopping. Finally, the integration policy indicates when a state implements any infrastructure for providers to use PDMPs within any HITs in their workflow. Detailed data on the heterogeneity of what type of HIT system is integrated with the PDMP and the extent of integration are not available.

[77] In the absence of detailed morbidity data, I cannot examine how integration affects morbidity related to drug switching/shopping behaviors. I also tried a two-layered event study to estimate a mandate-integration interaction beyond the two baseline policies, but my sample does not provide enough power.

2.4. Robustness Checks and Alternative Measures

2.4.1. Testing Confounding Policies

An assumption in my empirical analysis is that the integration policy variable is not capturing impacts generated by other related policies implemented concurrently. I justify this assumption both qualitatively and quantitatively. I searched state regulations on both health and technology but found no other policies creating similar mechanisms as defined by "integration" in this paper. I confirmed my investigation with legal experts and state PDMP/HIT managers. The pairwise correlations between integration and other policies (mentioned in section III.A) are all below 0.25, suggesting these policies work through different mechanisms at different times. I also drop these other policies from my main model to empirically test the sensitivity of my main results. The results (Table B3) are not much different from those of the main specification. This test supports the idea that these policies are unrelated to integration.

2.4.2. Placebo Tests

I estimate a set of placebo regressions that test for the effect of PDMP-HIT integration on a set of morbidity rates for a few common types of reasons: total inpatient stays not involving opioids, total inpatient stays caused by injuries not involving opioids, inpatient stays for mental health, and inpatient stays for asthma.[78] The rationale is that if the integration policy is somehow correlated with general trends in morbidity, then I might incorrectly attribute the change in health outcomes to the integration policy. Thus, the placebo outcomes should be health conditions not directly related to controlled substances that usually do not require advanced treatments where

[78] Data are aggregated from HCUP Fast Stats State Trends in Hospital Use (Inpatient Stay). Ideally, the placebo outcomes may also have similar incidences as opioid-related outcomes. However, the opioid crisis is unique and no other diseases are creating a similar problem with comparable magnitude.

PDMP-HIT integration can generate spillover effects. When I repeat the analyses on the placebo outcomes (Table B4), none of the estimates on integration are similar to those found in my main analysis.

2.4.3. Alternative Measures: Complementarity between Integration & Interstate Sharing

Integration and interstate sharing are technology-based design features to improve PDMPs. While integration lowers the costs of accessing and analyzing PDMP data, interstate sharing improves PDMP data quality. The impacts from integration and interstate sharing are likely larger when implemented together. The state-quarter level correlation between the integration policy and interstate sharing participation is about 0.26, and both gradually rolled out as shown in Figure 2.2.[79] Since most of the integrations are implemented relatively late compared to interstate sharing, there is some state-quarter level variation for a test on the relationship between these two technology-based PDMP designs.

To do so, I include three mutually exclusive variables to replace the integration and interstate sharing variables in the baseline regression: "integration & interstate," "integration only," and "interstate only." Table B

5 reports the results and indicates that there is some complementarity between integration and interstate sharing. The overall pattern of the results is similar to that of the baseline analysis, except now much of the effects are captured by the coefficient "integration & interstate;" while "integration only" has smaller independent effects. Although these results provide suggestive evidence that integration could work better with high-quality data shared with other states, these

[79] By the end of 2015, 17 states implemented both integration and interstate sharing, three states only have integration without interstate sharing, and 13 states have only interstate sharing without integration.

results need to be interpreted with caution because the test is more correlational than casual in nature.

2.5. Conclusion and Discussion

I find strong evidence that policies enabling PDMP-HIT integration effectively reduces opioid-related mortality and inpatient morbidity rates. The estimated reductions are robust in stratified morbidity outcomes and are about 18% of the mean of corresponding outcomes. The reductions are substantial in states with integrated PDMPs that never mandated PDMP access during my sample period. Specifically, the policy impacts are strongest among the most vulnerable groups in this crisis: middle-aged patients (between the ages of 25 to 64), people residing in low- to middle-income communities, and patients with public insurance. Since my sample period was a time of active policy experimentation, I show that my results are robust to either including or excluding other policy controls.

Although many states have demonstrated significant effort in integrating PDMPs with HIT, there are substantial lags in some states. For instance, Florida neither took action on integration nor shared the Florida PDMP data with other states until 2018. Meanwhile, the estimated annual social cost of the opioid crisis ranges from $293.3 billion to $622.1 billion, using a wide range of statistical values of life (CEA, 2017). Thus, a conservative estimate of a 10% reduction in mean mortality and morbidity can generate annual savings of $29.3-62.2 billion. Even an exaggerated $500 million/state investment to implement integration policies would generate savings far exceeding the associated costs.

My results suggest that a PDMP can be more effective when combined with technology-oriented design features including PDMP-HIT integration. States that proactively implemented

PDMP integration benefited from mortality reductions, yet this process was delayed in other states due to cybersecurity concerns and state privacy laws. More research and data are needed to systematically evaluate the best practices and strategies in improving PDMPs with technology. Practitioners, engineers, and policymakers may want to consider working together to improve PDMP policy designs to enhance their joint impact. Once PDMPs become more user friendly and fully integrated into clinical workflow, providers may voluntarily use it more frequently and effectively; therefore, the compliance rates for other PDMP-related policies may also increase. All of these can help providers to make more informed decisions quickly for patients with opioid-related issues.

Although this paper focuses on PDMP-HIT integration that can streamline physicians' data access and analysis, other innovations in digital health can help mitigate the opioid crisis in broader dimensions, such as electronic prescription of controlled substances and direct-to-consumer behavior nudges through mobile applications. These promising innovations mostly came after my sample period and are fairly small in scale, so I do not include them in this analysis. In addition, individual providers can further design their HIT analytics to use integrated PDMPs more effectively. Overall, the potential of leveraging health IT to combat the opioid crisis is substantial and thus deserves more practical investments and academic investigation.

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CHAPTER 3

THE SECRET MENU IN HEALTH CARE: A CASH MARKET FOR IMAGING IN CALIFORNIA

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Abstract: In addition to the prices they negotiate with private health insurers, most providers also have a cash price schedule for patients who have the wherewithal to ask and are willing to pay in full when they receive a service. This is the first study that estimates the potential benefits of allowing privately-insured consumers to observe both in-network negotiated prices and cash prices, which is of particular interest given the growing importance of high-deductible health plans. Using data from five private health insurers and 142 imaging facilities in the San Francisco Bay Area, we estimate that patients could save between 10 percent and 22 percent of their insurer's in-network price by paying cash. Potential savings are much larger (between 45 percent and 64 percent of their insurer's in-network price) if consumers observe both cash and in-network prices and select the facility in the region offering the lowest price for a particular service.

3.1. Introduction

Despite increasing interest, price dispersion and new payment options for medical services are still not well understood. Given the current insurance scheme, how much can patients save by utilizing price information and new payment options? In this paper, we use a proprietary dataset of imaging services across facilities and payment options in the San Francisco

Bay area to simulate cost saving potentials from price shopping and the cash price option – paying cash instead of out-of-pocket prices even for insured patients. This is the first study to our knowledge that examines the potential short-run benefits of allowing privately-insured consumers to observe both in-network prices and cash prices.

How much does an MRI cost? The answer depends on which provider is being asked and whether the patient plans to use her private health insurance or is willing to pay cash on the spot. Few consumers realize that prices vary for providers within their private health insurance network. In a recent survey of 2,000 adults, only 44 percent and 46 percent were aware that prices vary across physicians and hospitals, respectively (Schleifer et al., 2017). Even fewer consumers realized that providers often have a separate price schedule if a patient is willing to pay cash rather than using insurance.

Health care providers included in a private health insurer's network usually negotiate a fee/price schedule with that private insurer, specific to each service the provider performs. The provider agrees to accept the negotiated price as the complete payment for the service, which is then divided between the insurer and the patient, with the latter in the form of a deductible, copayment, and/or coinsurance. Rarely posted directly, but generally provided if consumers ask, most providers also have a cash price schedule for patients who have the wherewithal to ask and are willing to pay in full when they receive a service. Cash prices, which are almost always distinct and lower than the standard chargemaster rate or "list price" charged for each service, can be paid via cash, check, tax-advantaged health account, or credit/debit card.

Both privately-insured consumers and health providers have incentives to utilize cash prices. A consumer who is likely to end the year below her deductible can save money if the cash price is lower than her insurer negotiated price. Consumers beyond their deductibles can

also benefit if cash prices are lower than their required out-of-pocket payment. Besides, providers might be willing to accept a cash payment lower than the insurer negotiated price for an insured consumer, if they prefer an instant fixed payment to a payment delayed for months with a possibility of reduction or rejection and administrative efforts. In contrast, physicians get paid by an insurer about 40 days after providing care and spend an estimated $68,000 per year per physician on administrative costs associated with interacting with insurers (Casalino et al., 2009).

In addition, providers that offer low cash prices may be able to attract additional patients who expect to end the year below their deductible, impatient to wait for their insurer's prior approval process or are denied, or seek services outside of their insurance coverage. The latter situation is more likely to occur if insured consumers know the cash prices and the prices private insurers have negotiated with providers, and insurers provide incentives for consumers to price shop. Based on confidential communication with providers in the Bay area, fewer than 10 percent of imaging transactions are cash payments.

In this paper, we use a new proprietary dataset of the imaging market in the San Francisco Bay Area to explore the implications for consumers and insurers if insurance and cash prices are transparent. We focus on imaging services because they are common, often moderately expensive, have relatively homogeneous quality across providers, and customers usually have time to price shop. First, we compare cash and insurance prices for the same service at the same imaging facility and find that about 60 percent of cash prices are set below the corresponding in-network insurance prices. We then estimate that privately-insured patients could save up to 22 percent of their in-network prices if they pay the lower of the two prices for a service at a given facility. Due to the lack of data on transactions, we focus on short term

savings instead of the dynamic general equilibrium effects. Finally, we estimate savings if consumers observe cash and insurance prices at all facilities and choose the facility in the county or region with the lowest price. We find that the service-volume weighted average cost saving for a privately insured patient can be as high as 47 percent if she shops within her county and takes advantage of the cash prices.

Understanding the dispersion in private prices and cash prices offers opportunities to reduce medical spending. On one hand, patients increasingly have substantial "skin in the game" in the form of high deductibles, copayments, and coinsurance rates. In 2017, twenty-eight percent of employees were enrolled in a high-deductible health plan, up from four percent in 2006, according to a 2016 Kaiser/HRET Survey of Employer-Sponsored Health Benefits. On the other hand, health care prices are, finally, becoming more transparent. For example, the Center for Medicare and Medicaid Services has posted charge and payment information for all physician and hospital services in recent years; several states are developing all-payer claims data bases; start-up companies such as Castlight Health, non-profit organizations such as Minnesota Health Scores, and certain states (e.g., New Hampshire) post the prices that providers accept from private health insurers for specific procedures. As consumers become savvier about shopping for medical care, hospitals and outpatient medical centers can benefit by offering large discounts if insured patients pay cash instead.

Existing price transparency studies have not looked at cash prices and typically focus on what happens, or could happen, if privately-insured consumers observe the prices their health insurers negotiated with in-network providers. Some studies find that providing consumers with transparent prices before choosing a provider could substantially reduce medical spending (White et al., 2014), especially when consumers with a high-deductible health plan shift from an

above-medium to a median-priced provider (Brot-Goldberg et al., 2017). A number of studies point out that most consumers are not aware of nor use price transparency tools (Brot-Goldberg et al., 2017; Desai et al., 2017; Schleifer et al., 2017), but none of the tools mentioned in the prior literature include cash prices as an option. Improving access to price transparency platforms can reduce spending by 13–17 percent, presumably by facilitating choices among advanced tests or lower-priced providers (Whaley et al., 2014; Lieber, 2017). However, two other studies find no impact of price transparency on spending (Desai et al., 2017; Whaley et al., 2019), although the latter study does find an effect when a reference pricing insurance feature is added.

Our study contributes to the literature of price transparency by examining cash prices as a new channel for cost savings. None of the existing studies consider the new option – cash prices – for insured patients to reduce medical spending. Cash prices can align incentives between patients and their insurers and spur new strategies for joint cost savings. From a policy perspective, the popularity of high deductible health plans and the increasing burden of medical spending calls for payment innovation, including a wider adoption of cash prices. Understanding the cash market for medical care also offers business opportunities for organizations to develop new tools to help consumers access and use them effectively.

3.2. Data and Descriptive Analysis

We use a unique dataset developed by Stroll Health by assembling claims data, cash prices, and private and public payer fee schedules for the San Francisco Bay Area for imaging services. Stroll Health is a San Francisco-based company that helps consumers and physicians to search for a patient's required out-of-pocket cost for a specific imaging service at a range of local outpatient imaging facilities. The raw data are acquired from a variety of sources including web

scraping payer sites, medical claims, and asking facilities directly for their fee schedules and cash prices.

The dataset includes information on how much Medicaid, Medicare, and five major private insurance companies reimburse for 194 radiology procedures (Current Procedural Terminology, or CPT, codes) to 142 imaging facilities between 2014 and 2016. The data used in this study are bundled at the procedure level, meaning that professional, technical, contrast, and other potential modifiers are grouped into a single negotiated price. The unit of observation in our analysis is a price (cash or from a private insurer) for a service at an imaging facility. Our final sample includes facility-service pairs with all five private insurer prices and cash prices available. Those facilities provide over 70 percent of imaging services available in the market.

Table 3.1: Sample Statistics

Facility-Service-Level Data:				
	# observations	Mean	Std. Dev.	
Medicaid price	6,818	$245.6	$283.4	
Medicare price	7,595	$262.4	$215.6	
Private insurance price	7,811	$491.5	$694.9	
Cash price	7,811	$528.4	$1,127.1	
Consumers' Insurance Benefits and Use of In-Network Medical Care				
	Individual Policies (n=700)		Family Policies (n=556)	
Period: 1/1/2015-12/27/2015	Mean	Std. Dev.	Mean	Std. Dev.
Deductible	$996	$1,188	$2,106	$2,391
Out-of-pocket maximum	$3,349	$1,636	$6,761	$3,333
Deductible remaining on 12/27/15, conditional on a positive balance	$1,022	$1,272	$1,556	$2,203
% with deductible remaining on 12/27/15	63.3%		73.4%	

The private insurance prices are the in-network allowed amounts that consist of the patient's required payment plus the insurer's payment to the provider. The average private insurance price is calculated as the average price that the five private health insurers pay a

particular facility for a particular service. We weight each of the five private insurers equally. Table 3.1 reports descriptive statistics. Medicare and Medicaid prices, which are set rather than negotiated, are much lower than the private insurance prices in this market.

The five private insurers in the sample collectively covered 42.4 percent of the commercially-insured population in the San Francisco Bay Area, according to data from AIS Health's Directory of Health Plans for January 2014. The market shares ranged from a low of 1.6 percent to a high of 17.0 percent. The only major health insurer in Northern California not included in our data is Kaiser, an insurer integrated with health providers that covered 48.1 percent of the commercially-insured population in January of 2014. So, the five insurers in our sample cover about 82 percent of the non-Kaiser commercially-insured population. Figure 3.1 indicates the distribution of imaging facilities in the sample by county.

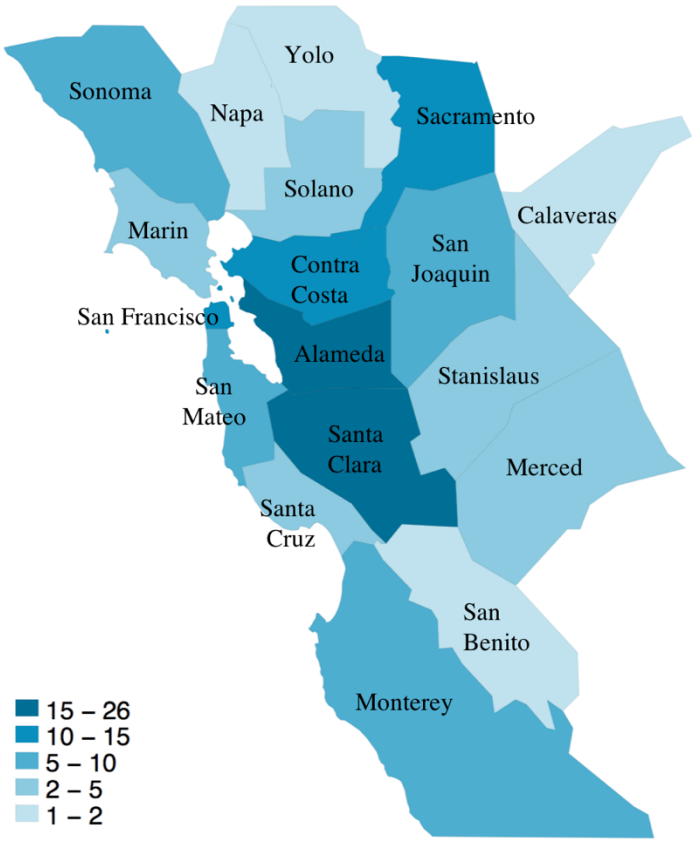

Figure 3.1: Distribution of Imaging Facilities in the Greater San Francisco Bay Area

In addition, we use benefit data from Stroll Health to determine the percentage of people who ended a year without exhausting their deductible. This dataset has information on insurance benefits and use of medical services for 753 people under 65 years of age who were covered by one of the five private insurers in the sample throughout 2015, and for 556 families with a family policy from one of these insurers. These people can expect to capture the savings and thus will have the strongest incentives to pay a cash price when it is less than the insurance price. A consumer who has exhausted her deductible will have an incentive to pay the cash price if it is less than her copayment or coinsurance rate, or her insurer provides incentives to do (i.e. by more than crediting her expenditure).

3.3. Method: Simulations

We perform three simulations to estimate how much patients and their private insurers could save if all prices were transparent. In the first simulation we assume that one privately-insured patient arrives at an imaging facility for a service and pays the lesser of the insurer-negotiated in-network price or the imaging facility's cash price. We report the level and percentage of savings relative to the in-network price for patients holding plans from each of the five private insurers. The patient saves nothing if the cash price exceeds the in-network price, and saves the difference between the in-network price and the cash price when the latter is smaller than the former. We aggregate the savings by placing a weight on each facility type (i.e., hospital-based versus in a physician office or freestanding) – service pair based on the volume of imaging services received by California Medicare patients in 2014.

For each case in simulation one, we report an upper-bound and a more conservative savings estimate to account for patients' incentives to price shop. The upper-bound estimate is

likely to be achieved if: 1) patients can observe in-network prices and cash prices; and 2) insurers credit a cash price toward the person's deductible and share savings when a patient is beyond her deductible. In this case, patients have both the information and incentives to price shop. In a more conservative scenario, in contrast, patients are only willing to search for and use lower in-network prices or cash prices if they actually ended the plan year below their deductible.

This lower-bound situation is likely to occur where: 1) providers sometimes stipulate that if a patient pays the cash price she agrees not to submit the claim to her insurer, in order to prevent the discount from being extended to all enrollees covered by the patient's insurer, and to satisfy the insurer's requirement to collect a copayment in order to channel patients to in-network providers (Muir et al., 2013); and 2) insurers do not provide incentives for patients who are beyond their deductible to shop for lower prices, because these consumers are much less likely to search for provider prices than patients below their deductible (Lieber, 2017). The inability to pay cash prices and then seek reimbursement from their insurer weakens the incentives for consumers to pay cash prices because doing so often displaces the insurer's payment, thereby saving money for their insurer but not for themselves.

We calculate the more conservative savings as a proportion of the upper-bound estimates using the proportion of enrollees who do not exhaust their deductible by the end of the year. By the end of the year in the benefits dataset, sixty-three percent of the enrollees with an individual health insurance policy did not exhaust their deductible, and 73 percent with family policies did not exhaust their family deductible (Table 3.1). Among the patients who ended the 2015 plan year without reaching their deductible, the mean deductible balance was $1,022 for individual policy members, and $1,556 for enrollees in a family policy. The actual savings could be lower than the conservative estimate if prices are not transparent or consumers do not believe they will

recoup the savings from price shopping. Conversely, the actual savings may exceed the conservative estimate if patients respond to "spot prices" – the price of care on the date of a service based on the person's current deductible, cost sharing requirements, and prior use – rather than "shadow prices" – the price of care based on their end-of-year use. That is, patients may search for lower prices today even though it only saves their insurer money but not themselves by the end of the year. Recent studies show that patients place considerable weight on spot prices (Brot-Goldberg et al., 2017; Abaluck et al., 2018).

In the second and third simulations, we assume that patients price shop in a geographic region, instead of comparing prices offered by a given facility. In the second simulation we estimate how much patients and private insurers could save if patients were treated by the facility with the lowest in-network price within the county where they live. We report results separately for a situation where a patient is willing to travel further and searches for the lowest-price facility in the entire Bay Area. In the third simulation we estimate how much patients and private insurers could save if patients were treated by the imaging facility with the lowest price (in-network price or cash price) within either the county where they live or (separately) the Bay Area. This simulation is relevant if an insurer or intermediary provided patients with both the in-network and cash prices at each facility. The actual savings in the second and third simulations would be smaller if consumers believe the quality of imaging services differ meaningfully between facilities and if travel costs are substantial.

3.4. Results

3.4.1 Variation in In-network Negotiated Prices across Facilities

There is substantial price dispersion in insurer-specific negotiated in-network prices and cash prices across imaging facilities for the same service. For three common imaging services, Figure 3.2 displays price dispersion across facilities separately for the in-network prices negotiated with five private insurers and cash prices. The bottom and top of the rectangular boxes in Figure 3.2 refer to the prices at the 25th and 75th percentiles, respectively; the horizontal line in the rectangle indicates the median price across the facilities; and the horizontal lines outside of the boxes refer to the 5th and 95th percentiles. For private insurer 2, for example, the median price for a neck MRA without contrast (CPT code 70547) is $339, whereas the prices range across facilities from $217 at the 25th percentile to $544 at the 75th percentile. This means that patients could save a substantial amount of money if they observed the full set of in-network prices, were willing to travel, if perceived quality was similar across facilities, and insurers could determine how to share savings with patients who price shop.

For the three procedures depicted in Figure 3.2, the median cash price is sometimes higher than the median private prices (CPT code 70547), sometimes similar (CPT code 72190), and sometimes lower (CPT code 76830). For all three procedures, the distribution of cash prices is tighter than for private prices, indicating smaller price dispersion when consumers pay cash instead of using insurance.

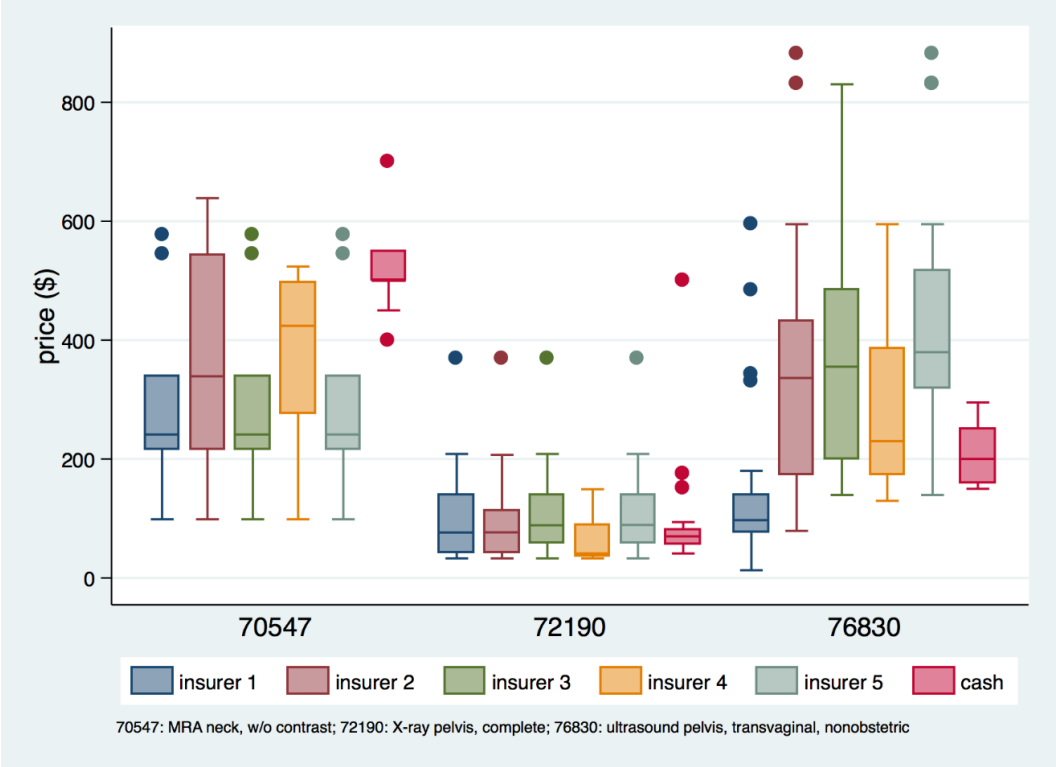

Figure 3.2: Variation of In-Network Prices and Cash Prices

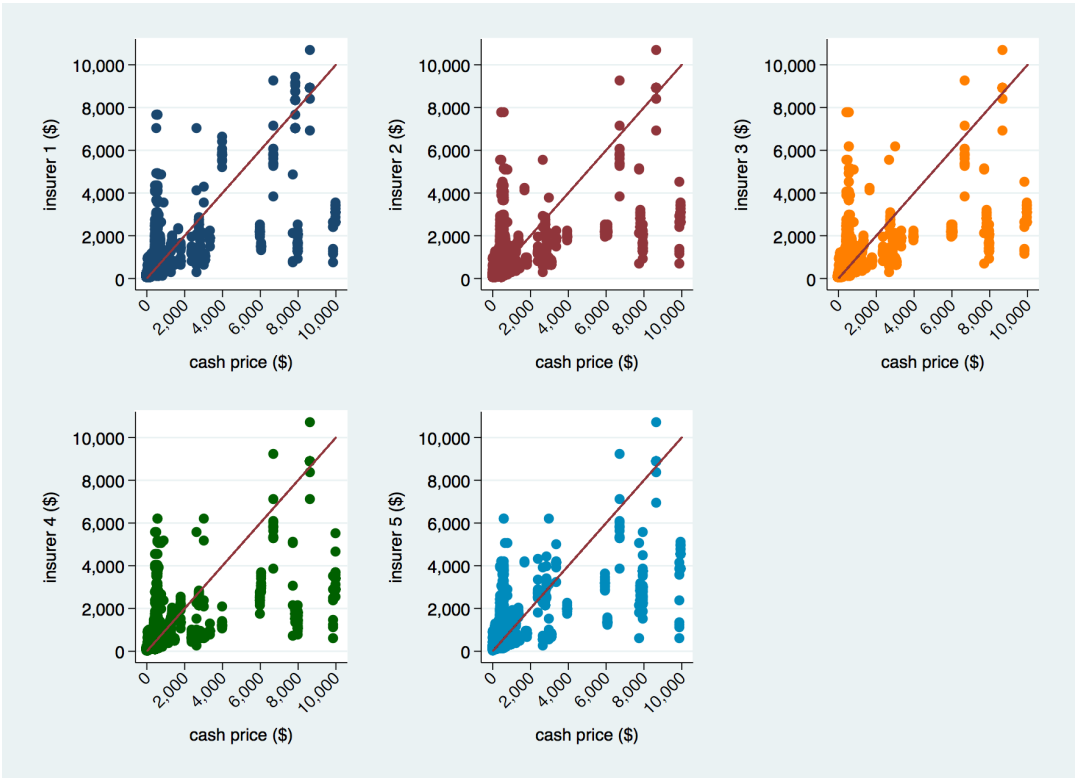

Figure 3.3: Comparison of Private Prices versus Cash Prices, at the Procedure-facility Level

3.4.2 Comparing Cash Prices to In-Network Private Insurance Prices

In Figure 3.3 we compare cash to in-network negotiated prices for each service-facility observation, separately for each of the five private insurers. Cash prices are measured on the x-axis and in-network prices on the y-axis. Observations that are below the 45-degree line are situations where an imaging facility charges a higher cash price than they accept from a private insurer, and observations above the 45-degree line indicate the opposite is true. Across all facilities, services, and private insurers, the cash price is less than the average of the five private insurance prices 57.6 percent of the time. In these situations, the cash price is $203 less than the private insurance price, on average, or 31.2 percent less than the private insurance price. Conversely, in the other 42.4 percent of instances, the cash price is $362 higher than the private insurance price on average, or 74.4 percent higher than the private insurance price.

3.4.3 Savings when Patients Pay the Lesser of the Cash Price or the In-Network Private Price

In the first simulation reported in Table 3.2, we assume that, for each imaging service and each of the five private insurers, one patient arrives at an imaging facility in the Bay Area that provides that service and pays the lesser of the in-network price their health plan has negotiated or the imaging facility's cash prices. Across the five private insurers, patients could save between $40 and $96, on average, or between 10.1 percent and 22.2 percent of their insurer's in-network price. This includes instances where the facility's cash price is greater than the in-network price, and thus there is no savings. We also ran a simulation where patients do not observe prices ahead of time and adopt a strategy to ask for and always pay the cash price at an

imaging facility. Always paying the cash price produces total spending that is fairly close to always paying the in-network price. This is consistent with the data displayed in Figure 3.3.

Table 3.2: Cost Simulation Results

Simulation 1: Patients Pay the Lesser of the Cash Price or the In-Network Private Price

	Saving measures	Insurer 1	Insurer 2	Insurer 3	Insurer 4	Insurer 5
Upper-bound	average per service	$58	$77	$96	$40	$81
	as % of in-network price	15.0%	18.1%	22.2%	10.1%	21.5%
More conservative	average per service	$37	$49	$61	$25	$51
	as % of in-network price	9.5%	11.5%	14.1%	6.4%	13.6%

Simulation 2: Patients Pay the Lowest In-Network Price in County or Bay Area

	Saving measures	Insurer 1	Insurer 2	Insurer 3	Insurer 4	Insurer 5
County	per service	$172	$178	$203	$130	$182
	as % of in-network price	38.3%	37.0%	41.5%	26.5%	39.5%
Bay Area	per service	$258	$257	$280	$191	$280
	as % of in-network price	64.0%	58.8%	63.0%	45.4%	63.2%

Simulation 3: Patients Pay the Lowest In-Network or Cash Price in County or Bay Area

	Saving measures	Insurer 1	Insurer 2	Insurer 3	Insurer 4	Insurer 5
County	per service	$184	$194	$220	$147	$212
	as % of in-network price	41.7%	40.8%	46.9%	30.8%	46.7%
Bay Area	per service	$259	$258	$283	$196	$284
	as % of in-network price	64.1%	59.1%	63.9%	46.8%	64.0%

3.4.4 Savings when Patients Pay the Lowest In-Network Price in the County or Bay Area

In the second simulation reported in Table 3.2, we estimate how much patients and private insurers could save if patients were treated by the imaging facility with the lowest in-network price within the county where they live, or in the entire Bay Area. In this simulation, consumers do not observe cash prices. Across the five private insurers, patients who are willing to travel within their county could save between $130 and $203 per service, on average, or between 27 percent and 42 percent of their insurer's in-network price. Potential savings are larger if patients are willing to search for, and travel to, the lowest-priced imaging facility in the

San Francisco Bay Area. Specifically, the estimated savings per service would be between $191 and $280, on average, or between 45 percent and 64 percent of their insurer's in-network price.

3.4.5 Savings when Patients Pay the Lowest In-Network or Cash Price in the County or Bay Area

In the third simulation reported in Table 3.2, we estimate how much patients and private insurers could save if they were treated by the facility with the lowest price (in-network or cash price) within the county where they live, or the Bay Area. When the market is defined as the entire Bay Area, there is little difference in the savings between the second and third simulations. That is, when patients are willing to price shop across a broad geographic area, the opportunity to use cash prices in addition to in-network prices does not present a significant additional savings opportunity. However, if patients are only to search within their county, adding cash prices to the choice set does increase savings opportunities. Specifically, patients can save about an extra $20 per service when searching for the lowest in-network or cash price (simulation 3, county market) versus the lowest in-network price only (simulation 2, county market). With traffic in the Bay Area, a trip from Oakland to San Francisco (a distance of 10 miles) often takes more than an hour, and a trip from San Francisco to San Jose (a distance of 50 miles) often takes two-and-a-half hours. It seems unlikely, therefore, that a patient would traverse the Bay Area in search of better prices. The more conservative savings estimates for all three simulations, where only patients who expect to end the year below their individual deductible are willing to pay cash prices, are 63.3 percent of the upper-bound savings.

3.5. Discussion

We find large saving opportunities in imaging services, given the large price dispersion in cash and private prices across facilities for the same procedure. About 60 percent of cash prices are set below the corresponding in-network private insurance prices. We estimate consumers could save up to 22 percent of their insurer's in-network price by paying cash on the spot at the same facility for the same service if prices are transparent and insurers determine how to create incentives for consumers to price shop. This baseline estimate is similar in magnitude to studies that estimate savings associated with price shopping across facilities in in-network prices. The potential savings are much larger (45-64 percent of the corresponding in-network price) if a privately-insured patient shops over in-network and cash prices within a county.

Providing consumers with information on cash prices provides savings opportunities beyond those of in-network prices given the large price dispersion across imaging facilities. Specifically, searching for the minimum in-network or cash price provides savings about three to five percent below those available from searching for the lowest in-network prices only if one restricts the available imaging centers to those in a consumer's county. Although our analyses focus on the San Francisco Bay Area, the emerging trend in advocating cash prices for imaging services is national and has led to hospital self-pay programs (e.g., in Colorado and Florida), multiple region-specific online crowdsourcing imaging price calculators (e.g., clearhealthcosts.com), and others. As high deductible plans continue to grow, paying in cash may present a significant savings opportunity for both patients and insurers.

More research is needed to better understand this opportunity, including examining the effect of narrow networks, understanding how and where doctors refer their patients, incorporating non-pricing factors like interoperability and patient experience, applying copay,

coinsurance, and out-of-pocket maximum levels, and to test tools that will enable consumers to effectively navigate these channels. Policymakers and payers should examine legislation, rules, and contracts that inhibit providers from offering and patients from using cash prices. The current limited understanding of the cash market in health care also provides promising business opportunities for organizations to create and adopt technologies that can expedite the search and comparison of cash and private prices.

There are some limitations. First, we estimate cost savings from price-shopping across facilities without measuring consumers' travel costs. Modeling travel costs is difficult given the housing patterns and proliferate travel options in the Bay area. Second, we study the rather homogenous radiology industry without differentiating quality metrics across facilities. This is reasonable given that the technological status of radiology is based on equipment and radiologist training, but there can be unobserved quality differences. Third, our analyses take the listed prices as given and focus on short-run cost savings. In the long-run, if private and cash prices become more transparent and consumers search more actively, providers may respond by changing the composition of their service network and pricing strategies. In the absence of better data, our analysis offers a first step for understanding the under-studied cash market for medical services.

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CHAPTER 4

PATENT CLASSIFICATION SYSTEMS AND TECHNOLOGICAL CATEGORIZATION: AN OVERVIEW AND UPDATE

Lucy Xiaolu Wang

Abstract: Patent classification systems and upper-level groupings have been widely used for research and entrepreneurial purposes but are insufficiently documented. This article provides an overview of the major patent classification systems and the basic ideas behind categorization of patent classes. I highlight recent institutional changes that disproportionately affect patents in specific categories and alternative categorizations used in the patent examination process. Finally, I update the National Bureau of Economic Research patent technological categorization based on the latest U.S. patent classification. The resulting datasets can be used in numerous follow-up analyses using patent data to investigate innovation and entrepreneurship.

A comprehensive patent classification is a system that allows patent examiners (employees at a patent office) to classify patent-related documents based on the features of the underlying subject matter. Patent classification systems were originally developed to sort patent documents in paper form into different classes. They are now widely used to facilitate search in electronic patent-related databases to find patent disclosure documents on pre-commercialized technologies, check originality (e.g., patentability) of new products before patent filing, track technological changes, and identify infringement of existing patents, among other uses. The languages and standards in a given patent classification system are typically developed independently by the organization that issues patents in each jurisdiction.

The three most widely used patent classification systems are the United States Patent Classification (USPC), International Patent Classification (IPC), and Cooperative Patent Classification (CPC). The USPC is the official patent classification system developed and maintained by the United States Patent and Trademark Office (USPTO), an institution that has existed for over 200 years. As of January 2018, there are 475 classes in the USPC, of which 440 are utility patents (i.e., non-design, non-plant patents that cover inventions on machines, methods, manufacture, and composition).[80] The IPC was established in 1971 by the Strasbourg Agreement, a treaty administered by the World Intellectual Property Office (WIPO) in Geneva Switzerland, to provide alphanumeric symbols that divide patent subject matter into eight groups with about 70,000 subgroups (WIPO, 2018). Youngest among the three systems and developed based on the IPC, the CPC was initiated in 2010 as a partnership between the USPTO and the European Patent Office to harmonize their existing classification systems (CPC, 2013).

Each of the above systems is independent, resulting in no clear mapping between systems. Mapping from the USPC to the CPC and IPC can be identified case-by-case using the USPTO web-based search algorithm.[81] Due to data availability issues, most of the empirical literature uses patent data from the USPTO where the patent documentation and research methods are relatively most well developed. The USPC system is also the only classification system that, by construction, distinguishes utility and non-utility (design and plant) patents; in contrast, both IPC and CPC integrated design and plant patents within their internal grouping rules. Since January 2013, the USPTO stopped updating the USPC code in transition to use the

[80] Each class refers to a major component of the subject matter; a subclass may be assigned for a minor component (USPTO, 2012). I follow the literature and focus on the categorization of the major classes.
[81] Available at: https://www.uspto.gov/web/patents/classification/index.htm.

IPC code, but the USPC classification system is still employed to examinate patent applications.[82]

Using the existing patent classification systems, researchers often must group the granular patent data into much broader categories for empirical analysis. The USPC does not assign technology categories to individual patent classes, and researchers have been using the "NBER technological categories" based on 1999 USPC and developed in Hall, Jaffe, and Trajtenberg (2001).[83] The authors construct higher-level codes to aggregate about 400 patent classes into 36 technological sub-categories and six main categories. In contrast, based on European standards that are updated periodically, IPC and CPC have nine and eight alphabetical categories, respectively, and each has hundreds of sub-categories and underlying classes. Although the top-level alphabetical categories used in CPC and IPC are similar, a significant portion of patent classes exist in only one of these two relatively recent systems.[84] Therefore, I focus on the USPC-based categorization since it is also the most widely used in the economics of innovation literature as well as many industry databases.

The six main technologies categories for utility patents are: Chemical, Computers & Communications, Drugs & Medical, Electrical & Electronics, Mechanical, and Others (Hall et al., 2001).[85] Over the past two decades, new technologies have emerged, such as scanning-probe techniques/apparatus (e.g., scanning probe microscope), information security, robots, and

[82] Patents issued post 2015 may no longer have an USPC class number but were simply recorded with USPC class number 1 ("undetermined and unclear patent classes").
[83] The authors focus on the patent classes (not subclasses) as those are likely the most relevant information for the vast majority of users in their research application.
[84] For example, a quick glance at the CPC scheme - section A can be informative enough of the problems in using the two relatively new systems: https://www.uspto.gov/web/patents/classification/cpc/html/cpc-A.html. For completeness and a quick reference, I list the pre-existing high-level categories in IPC and CPC systems in Appendix Table C1 and Table C2, respectively.
[85] The initial categories are constructed based on the USPC 1999 patent classes, which have been updated via several iterations in subsequent years.

electronic funds transfer, and others. Those new technologies resulted in 22 new patent classes in the latest USPC code. I first assign technological categories and sub-categories to those new utility patent classes based on the similarity in the patent class description (class title) between each new patent class and the NBER pre-categorized old patent classes. Then, for those that cannot be easily categorized, I search patent claims (i.e., the text content describing the patented subject matter) to obtain a sufficient sample of granted patents under those new classes and compare the similarity of the sample to the NBER pre-categorized technology categories and sub-categories. Last, I hand check the NBER Patent Data Project to replicate the thought process applied in that categorization method. [86]

In addition, I include non-utility patent classes and categorize them into three groups: Design, Plants, and Miscellaneous.[87] The rationale is that for specific research questions, such as patent infringement and litigation, design patents can be an informative measure of creativity that can be used in combination with function-oriented utility patents. On the one hand, the number of design patent issuances and litigations have risen in recent years; on the other hand, high-profile court cases in recent years affected court rulings in a way that ties design patents more closely with product patents. For example, the U.S. Supreme Court's decision in *Samsung Electronics Co., Ltd. v. Apple Inc*. allows patent owners to recover the total infringement profits even if only a subset of a multi-component article is infringed (Rapacke Law Group, 2018). Therefore, including non-utility patents in addition to the widely used utility patents in the analytical sample is essential for exploring a variety of research questions related to innovation. In my updated categorization, I also include previously excluded non-utility patents.

[86] The NBER Patent Data Project non-periodically incorporates updates from the research community but does not document the changes systematically (Hall et al., 2010). I recoded a few irregular categories.
[87] Hall, Jaffe, and Trajtenberg (2001) exclude non-utility patents (design and plant patents) given their collectively small share of total patents at that time.

I retrieve the latest USPC patent classes (class numbers and titles) from the USPTO's official website (USPTO, 2018), and I document the final technological categorizations in Tables 1 and 2. Table 4.1 mirrors the format of Appendix 1 in Hall, Jaffe, and Trajtenberg (2001) and reports the classification of patent classes into upper-level technological categories and sub-categories. To provide potential users with a transparent demonstration on the recoded patent classes, I report how I re-categorize new patent classes into (sub-)categories in Table 4.2. In eight cases, although the patent class numbers have not changed over time, the corresponding patent class titles have evolved. I list these modified patent class titles in Table 4.3 to support my point that the minor changes in patent titles do not meaningfully affect the patent class categorization.[88] There are no substantial differences in the subject matters described by these slightly different patent titles apart from minor changes in their descriptions, and thus I maintain the current categorization for those patent classes.[89]

Beside technological categorization, the USPTO has another administrative grouping for patent examination purposes. The USPTO centrally assigns patent application numbers, patent class, and patent subclass codes according to technology types described in the application. Each application is assigned, based on class and subclass numbers, to about 300 Art Units (consisting of specialized examiners) to review whether an application deserves a patent grant (Sampat and Williams, 2019). Patent applications within a given Art Unit are assigned to individual examiners by supervisory patent examiners appointed within corresponding Art Units. Furthermore, Art Units are grouped into technology centers (TCs) at the USPTO to which the incoming patent applications are broadly assigned (Marco et al., 2014). I summarize the current

[88] In another 64 cases, there are trivial format changes in patent class titles purely due to extra space inserted in the text between words – I fixed the format and re-include them.
[89] The final data files can be requested from the author or directly downloaded from the data repository, available at: https://github.com/LucyXiaoluWang/patents_tech_categorization.

technology centers and their roles in Table 4.4, and I report in Table 4.5 the clusters and descriptions of Art Units within the broad TCs and their subgroups.[90]

This article aims to provide an overview and description of the updated classification for technological categorization of patents classes. The categorization based on USPC is likely the most widely used since USPC offers the longest historical record of patent data. Maintaining a USPC-based consistent measure of evolving technological categories can be helpful for understanding a broad range of issues such as product bundling with complements or substitutes, venture capital investment related to technological bundling or novelty, cross-sector patent infringement and litigation, among others. It is worth noting that in many industries, such as pharmaceuticals and biotechnology, each drug product can include hundreds of patents (globally or domestic), and each patent can cover multiple patent classes (across technological categories). As granted patents have proliferated globally in the past two decades, cross-category and cross sub-categories measures can be used to construct new measures for increasingly-complex multi-functional technologies. Technological categorization for a multi-class patent into both a primary patent class and additional (cross-reference) patent classes offers opportunities to define primary and secondary technological areas of underlying inventions.

[90] Legal professionals frequently refer to Art Units in 10s unit (reported in Table 4.5), e.g., using 1620s to represent Art Units 1620-1629 that covers patent classes and subclasses related to Organic Chemistry.

Table 4.1: Classification of 2018 U.S. Patent Classes into Technological Categories & Sub-Categories

(Logic and structure following Hall, Jaffe, and Trajtenberg, 2001)

Cat. Code	Category Name	Sub-Cat. Code	Sub-Category Name	Patent Classes
1	Chemical	11	Agriculture, Food, Textiles	8, 19, 71, 127, 442, 504
		12	Coating	106, 118, 401, 427
		13	Gas	48, 55, 95, 96
		14	Organic Compounds	532, 534, 536, 540, 544, 546, 548, 549, 552, 554, 556, 558, 560, 562, 564, 568, 570, 987
		15	Resins	520, 521, 522, 523, 524, 525, 526, 527, 528, 530
		19	Miscellaneous-chemical	23, 34, 44, 102, 117, 149, 156, 159, 162, 196, 201, 202, 203, 204, 205, 208, 210, 216, 222, 252, 260, 261, 349, 366, 416, 422, 423, 430, 436, 494, 501, 502, 506, 510, 512, 516, 518, 585, 588
2	Computers & Communications	21	Communications	178, 333, 340, 342, 343, 358, 367, 370, 375, 379, 385, 455
		22	Computer Hardware & Software	341, 380, 382, 395, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 712, 713, 714, 715, 717
		23	Computer Peripherials	345, 347
		24	Information Storage	360, 365, 369, 711, 720
		25	Electronic Business Methods & Software	718, 719, 725, 726, 902
3	Drugs & Medical	31	Drugs	424, 514
		32	Surgery & Med Inst.	128, 600, 601, 602, 604, 606, 607, 850
		33	Biotechnology	435, 800, 930
		39	Miscellaneous–Drgs & Med	351, 433, 623
4	Electrical & Electronic	41	Electrical Devices	174, 200, 327, 329, 330, 331, 332, 334, 335, 336, 337, 338, 392, 439
		42	Electrical Lighting	313, 314, 315, 362, 372, 445
		43	Measuring & Testing	73, 324, 356, 374
		44	Nuclear & X-rays	250, 376, 378, 976
		45	Power Systems	60, 136, 290, 310, 318, 320, 322, 323, 361, 363, 388, 429
		46	Semiconductor Devices	257, 326, 438, 505, 716
		49	Miscellaneous-Elec	191, 218, 219, 307, 346, 348, 377, 381, 386, 903
5	Mechanical	51	Mat. Proc & Handling	65, 82, 83, 125, 141, 142, 144, 173, 209, 221, 225, 226, 234, 241, 242, 264, 271, 407, 408, 409, 414, 425, 451, 493

		52	Metal Working	29, 72, 75, 76, 140, 147, 148, 163, 164, 228, 266, 270, 413, 419, 420
		53	Motors & Engines + Parts	91, 92, 123, 185, 188, 192, 251, 303, 415, 417, 418, 464, 474, 475, 476, 477, 901
		54	Optics	352, 353, 355, 359, 396, 398, 399
		55	Transportation	104, 105, 114, 152, 180, 187, 213, 238, 244, 246, 258, 280, 293, 295, 296, 298, 301, 305, 410, 440
		59	Miscellaneous-Mechanical	7, 16, 42, 49, 51, 74, 81, 86, 89, 100, 124, 157, 184, 193, 194, 198, 212, 227, 235, 239, 254, 267, 291, 294, 384, 400, 402, 406, 411, 453, 454, 470, 482, 483, 492, 508, 977
6	Others	61	Agriculture, Husbandry, Food	43, 47, 56, 99, 111, 119, 131, 426, 449, 452, 460
		62	Amusement Devices	273, 446, 463, 472, 473
		63	Apparel & Textile	2, 12, 24, 26, 28, 36, 38, 57, 66, 68, 69, 79, 87, 112, 139, 223, 450
		64	Earth Working & Wells	37, 166, 171, 172, 175, 299, 405, 507
		65	Furniture, House Fixtures	4, 5, 30, 70, 132, 182, 211, 256, 297, 312
		66	Heating	110, 122, 126, 165, 237, 373, 431, 432
		67	Pipes & Joints	138, 277, 285, 403
		68	Receptacles	53, 206, 215, 217, 220, 224, 229, 232, 383
		69	Miscellaneous-Others	~~1,~~ 14, 15, 27, 33, 40, 52, 54, 59, 62, 63, 84, 101, 108, 109, 116, 134, 135, 137, 150, 160, 168, 169, 177, 181, 186, 190, 199, 231, 236, 245, 248, 249, 269, 276, 278, 279, 281, 283, 289, 292, 300, 368, 404, 412, 428, 434, 441, 462, 503, 968, 984
10	Non-Utility	101	Design	D01, D02, D03, D04, D05, D06, D07, D08, D09, D10, D11, D12, D13, D14, D15, D16, D17, D18, D19, D20, D21, D22, D23, D24, D25, D26, D27, D28, D29, D30, D32, D34, D99
		102	Plants	PLT
		109	Miscellaneous-Non-Utility	G9B

Notes: this categorization is based on the USPC system as of 1/31/2018 and includes all patent classes available as of that date. This USPC system is also probably the latest public USPC system in history as the USPTO decided not to issue USPC code for new patents after 2015. Patent class 1 was originally included in category 6 but it is rarely formally listed in USPC. The title for class 1 is "**

Classification Undetermined **" and thus it can bias the sample if included in the same manner as other patent classes. I suggest excluding patents that are only categorized with class 1.

Furthermore, there are three patent classes that I decided to include in sub-categories different from the NBER Patent Data Project (2010): class numbers 987, 703, and 720.

The patent class title for patent class no. 987 is "Organic compounds containing a bi, sb, as, or p atom or containing a metal atom of the 6th to 8th group of the periodic system." I categorize it into the sub-category of "Organic Compounds" together with other patent classes of "Organic compounds" instead of leaving it in "Miscellaneous-chemical" as in the *Patent Data Project*.

For patent class no. 703 with the title "Data processing: structural design, modeling, simulation, and emulation," I put it into the sub-category 22 for "Computer Hardware & Software" that contains other seven "Data Processing" related patent classes (701-702 and 704-707). This class no. 703 is in sub-category 25 of "Electronic Business Methods & Software" in the *Patent Data Project*. Note that the sub-category 25 does not exist in Hall, Jaffe, and Trajtenberg (2001), and is added as a new sub-category.

For patent class no. 720 with the title "Dynamic *optical* information storage or retrieval," I put it into the sub-category 24 for "Information Storage" that contains two other closely tied patent classes: 360 "Dynamic *magnetic* information storage or retrieval" and 369 "Dynamic information storage or retrieval" as well as two other classes for information processing systems. The Patent Data Project include class no. 720 in the sub-category 25 of "Electronic Business Methods & Software."

Table 4.2: Recoded New Patent Classes and Related Technological (Sub-)Categories
(based on the Patent Classification System as of 1/31/2018)

Cat.	Cat. Name	Sub-Cat.	Sub-Cat. Name	Class No.	Class Title
1	Chemical	14	Organic Compounds	532	Organic compounds -- part of the class 532-570 series
				987	Organic compounds containing a bi, sb, as, or p atom or containing a metal atom of the 6th to 8th group of the periodic system
		19	Miscellaneous-chemical	506	Combinatorial chemistry technology: method, library, apparatus
2	Computers & Communications	22	Computer Hardware & Software	703	Data processing: structural design, modeling, simulation, and emulation
				715	Data processing: presentation processing of document, operator interface processing, and screen saver display processing
				717	Data processing: software development, installation, and management
		24	Information Storage	720	Dynamic optical information storage or retrieval
		25	Electronic Business Methods & Software	718	Electrical computers and digital processing systems: virtual machine task or process management or task management/control
				719	Electrical computers and digital processing systems: interprogram communication or interprocess communication (ipc)
				725	Interactive video distribution systems
				726	Information security
				902	Electronic funds transfer
3	Drugs & Medical	32	Surgery & Med Inst.	850	Scanning-probe techniques or apparatus; applications of scanning-probe techniques, e.g., scanning probe microscopy [spm]
		33	Biotechnology	930	Peptide or protein sequence
4	Electrical & Electronic	44	Nuclear & X-rays	976	Nuclear technology
		46	Semiconductor Devices	716	Computer-aided design and analysis of circuits and semiconductor masks
		49	Miscellaneous-Elec	903	Hybrid electric vehicles (hevs)
5	Mechanical	53	Motors & Engines + Parts	901	Robots
		54	Optics	398	Optical communications
		59	Miscellaneous-Mechanical	977	Nanotechnology
6	Others	69	Miscellaneous-Others	968	Horology
				984	Musical instruments

10	Non-Utility	101	Design	D01	Edible products
				D02	Apparel and haberdashery
				D03	Travel goods and personal belongings
				D04	Brushware
				D05	Textile or paper yard goods; sheet material
				D06	Furnishings
				D07	Equipment for preparing or serving food or drink not elsewhere specified
				D08	Tools and hardware
				D09	Packages and containers for goods
				D10	Measuring, testing, or signalling instruments
				D11	Jewelry, symbolic insignia, and ornaments
				D12	Transportation
				D13	Equipment for production, distribution, or transformation of energy
				D14	Recording, communication, or information retrieval equipment
				D15	Machines not elsewhere specified
				D16	Photography and optical equipment
				D17	Musical instruments
				D18	Printing and office machinery
				D19	Office supplies; artists and teachers materials
				D20	Sales and advertising equipment
				D21	Games, toys, and sports goods
				D22	Arms, pyrotechnics, hunting and fishing equipment
				D23	Environmental heating and cooling; fluid handling and sanitary equipment
				D24	Medical and laboratory equipment
				D25	Building units and construction elements
				D26	Lighting
				D27	Tobacco and smokers' supplies
				D28	Cosmetic products and toilet articles
				D29	Equipment for safety, protection, and rescue
				D30	Animal husbandry
				D32	Washing, cleaning, or drying machine
				D34	Material or article handling equipment
				D99	Miscellaneous
		102	Plants	PLT	Plants
		109	Miscellaneous-Non-Utility	G9B	Information storage based on relative movement between record carrier and transducer

Notes: This table list patent classification of patent classes not previously recorded in the NBER patent classification crosswalk. Category and sub-category codes for non-utility patents are user-assigned values to maintain the structure of technological categories while set distance from those of utility patents.

Table 4.3: Class Title Modifications Reflected in 2018 USPC

Class Title 2018	Class Title 1999
miscellaneous hardware (e.g., bushing, carpet fastener, caster, door closer, panel hanger, attachable or adjunct handle, hinge, window sash balance, etc.)	miscellaneous hardware
192 clutches and power-stop control	clutches and power-stop control
aeronautics and astronautics	aeronautics
computer graphics processing and selective visual display systems	computer graphics processing, operator interface processing, and selective visual display systems
optical: systems and elements	optics: systems (including communication) and elements
motion video signal processing for recording or reproducing	television signal processing for dynamic recording or reproducing
fabric (woven, knitted, or nonwoven textile or cloth, etc.)	web or sheet containing structurally defined element or component (428/221)
electrical computers and digital processing systems: multicomputer data transferring	electrical computers and digital processing systems: multiple computer or process coordinating

Notes: the table lists patent titles with identical underlying patent class number and non-identical patent class titles. As shown in above, there are no meaningful differences in the title descriptions between the 2018 edition and the 1999 edition. I recoded "192 clutches and power-stop control" to "clutches and power-stop control" as the "192" is a visible typo which refers to the patent class number 192.

Table 4.4: Technology center and their roles

Technology Center	Description
1600	Biotechnology and Organic fields
1700	Chemical and Materials Engineering fields
2100	Computer Architecture Software and Information Security
2400	Computer Networks, Multiplex, Cable and Cryptography/Security
2600	Communications
2800	Semiconductors, Electrical and Optical Systems and Components
2900	Designs
3600	Transportation, Electronic Commerce, Construction, Agriculture, Licensing and Review
3700	Mechanical Engineering, Manufacturing and Products

Notes: The current nine technology centers can be simplified to six technology centers for utility patents. Specifically, technology centers 2100, 2400, and 2600 were originally one center on computer related patents. Technology center 2900 for design patents is of minimum relevance to studies on utility patents.

Table 4.5: Art Units Clusters and Descriptions

TC	Art units	Descriptions on Art Units (USPTO clusters)
1600	1610-1619	1610 Organic Compounds: Bio-affecting, Body Treating, Drug Delivery, Steroids, Herbicides, Pesticides, Cosmetics, and Drugs
	1620-1629	1620 Organic Chemistry
	1630-1639	1630 Molecular Biology, Bioinformatics, Nucleic Acids, Recombinant DNA and RNA, Gene Regulation, Nucleic Acid Amplification, Animals and Plants, Combinatorial/ Computational Chemistry
	1640-1649	1640 Immunology, Receptor/Ligands, Cytokines Recombinant Hormones, and Molecular Biology
	1650-1659	1650 Fermentation, Microbiology, Isolated and Recombinant Proteins/Enzymes
	1660-1669	1660 Plants
	1670-1679	1670 Process, Nucleic acid, Protein, Carbohydrate Chemistries and Diagnostics
1700	1710-1719	1710 Coating, Etching, Cleaning, Single Crystal Growth
	1720-1729	1720 Fuel Cells, Battery, Flammable Gas, Electrophotography, Photolithography
	1730-1739	1730 Metallurgy, Metal Working, Inorganic Chemistry, Catalyst
	1740-1749	1740 Tires, Adhesive Bonding, Glass/Paper making, Plastics Shaping & Molding
	1750-1759	1750 Electrochemistry, Solar Cells, Thermoelectrics
	1760-1769	1760 Organic Chemistry, Polymers, Compositions
	1770-1779	1770 Chemical Apparatus, Separation and Purification, Liquid and Gas Contact Apparatus
	1780-1789	1780 Food, Miscellaneous Articles, Stock Material
	1790-1799	1790 Food, Analytical Chemistry, Sterilization, Biochemistry
2100	2110-2129, 2180-2189	2110/2120/2180 Computer Architecture & Miscellaneous Computer Applications
	2130-2139	2130 Memory Access and Control
	2140-2149, 2170-2179	2140/2170 Graphical User Interface and Document Processing
	2150-2169	2150/2160 Data Bases & File Management
	2190-2199	2190 Interprocess Communication and Software Development
2400	2410-2419, 2460-2469, 2470-2479	2410/2460/2470 Multiplex and VoIP
	2420-2429	2420 Cable and Television
	2430-2439, 2490-2499	2430/2490 Cryptography and Security
	2440-2459	2440/2450 Computer Networks
	2480-2489	2480 Recording and Compression
2600	2610-2619	2610 Computer Graphic Processing, 3D Animation, Display Color Attribute, Object Processing, Hardware and Memory
	2620-2629	2620 Selective Visual Display Systems
	2630-2639	2630 Digital and Optical Communications
	2640-2649	2640 Telecommunications: Analog Radio Telephone; Satellite and Power Control; Transceivers, Measuring and Testing; Bluetooth; Receivers and Transmitters; Equipment Details
	2650-2659	2650 Videophones and Telephonic Communications; Audio Signals; Digital Audio Data Processing; Linguistics, Speech Processing and Audio Compression
	2660-2669	2660 Digital Cameras; Image Analysis; Applications; pattern Recognition; Color and Compression; Enhancement and Transformation
	2670-2679	2670 Facsimile; Printer; Color; halftone; Scanner; Computer Graphic Processing; 3-D Animation; Display Color; Attributes; Object Processing; Hardware and Memory

	2680-2689	2680 Telemetry and Code Generation; Vehicles and System Alarms; Selective Communication; Dynamic Storage Systems; Mechanical parts of Disk Drives; Signal Processing and Control Processing in Disk Drives
	2690-2699	2690 Selective Visual Display Systems
2800	2810-2829, 2890-2899	2810/2820/2890 Semiconductors/Memory
	2830-2849	2830/2840 Electrical Circuits and Systems
	2850-2869	2850/2860 Printing/Measuring and Testing
	2870-2889	2870/2880 Optics
2900	2900-2929	Design
3600	3610-3619	3610 Surface Transportation
	3620-3629	3620 Business Methods - Incentive Programs, Coupons; Operations Research; Electronic Shopping; Health Care; Point of Sale, Inventory, Accounting; Cost/Price, Reservations, Shipping and Transportation; Business Processing
	3630-3639	3630 Static Structures, Supports and Furniture
	3640-3649	3640 Aeronautics, Agriculture, Fishing, Trapping, Vermin Destroying, Plant and Animal Husbandry, Weaponry, Nuclear Systems, and License and Review
	3650-3659	3650 Material and Article Handling
	3660-3669	3660 Computerized Vehicle Controls and Navigation, Radio Wave, Optical and Acoustic Wave Communication, Robotics, and Nuclear Systems
	3670-3679	3670 Wells, Earth Boring/Moving/Working, Excavating, Mining, Harvesters, Bridges, Roads, Petroleum, Closures, Connections, and Hardware
	3680-3689	3680 Business Methods - Incentive Programs, Coupons; Electronic Shopping; Business Cryptography, Voting; Health Care; Point of Sale, Inventory, Accounting; Business Processing, Electronic Negotiation
	3690-3699	3690 Business Methods - Finance/Banking/ Insurance
3700	3710-3719	37A Amusement and Education Devices
	3720-3729, 3765, 3781, 3782, 3788	37BC Sheet Container Making, Package Making, Receptacles, Shoes, Apparel, and Tool Driving or Impacting; Manufacturing Devices and Processes, Machine Tools and Hand Tools
	3730-3739; 3760-3764, 3766-3769, 3770-3779; 3786	37DEF Medical and Surgical Instruments, Treatment Devices, Surgery and Surgical Supplies; Medical Instruments, Diagnostic Equipment, and Treatment Devices; Body Treatment, Kinestherapy, and Exercising
	3740-3759	37GHI Thermal and Combustion Technology, Motive and Fluid Power Systems; Fluid Handling and Dispensing; Refrigeration, Vaporization, Ventilation, and Combustion

Notes: information in this table is summarized from USPTO Patent Technology Centers Management (main web page is available at https://www.uspto.gov/patent/contact-patents/patent-technology-centers-management). Additional patent class and art unit crosswalks are updated periodically at two USPTO classification sites. (1) "classes arranged by art unit" (https://www.uspto.gov/patents-application-process/patent-search/understanding-patent-classifications/patent-classification). (2) "classes arranged numerically with art unit and search room locations" (https://www.uspto.gov/patents-application-process/patent-search/understanding-patent-classifications/classes-arranged-0). Note that the broad technology center and art unit groups are relatively stable, while the crosswalk is fuzzier given the amount of patent class abandoned and created (class-specific mapping can be partly retrieved via USPTO historical documents).

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APPENDIX A

APPENDICES FOR CHAPTER 1

Appendix A.1: Data Construction

This appendix provides more details concerning how I construct the analytical samples. I describe the process of compiling the data for diffusion analysis and innovation analysis, respectively. For more information on certain generic data products generated in this process, I provide more detail in the supplementary online appendix.

A.1.1 Drug-country-year panel of HIV drug access

The *Price and Quality Reporting Data* provide information on procurement transactions made by Global Fund-supported programs.[91] Starting from the raw data, I follow the data caveats document and drop clearly duplicated transaction records. At the country-level, I construct a listing file with all countries in the dataset and assign the appropriate International Organization for Standardization (ISO) three-digit alphabetical country code. This procedure guarantees that a country will be consistently treated regardless of the variation in spelling (e.g., "Viet Nam" vs. "Vietnam"; "DR Congo" vs. "Congo (Democratic Republic)") and to facilitate data merging across different datasets. I also dropped the redundant regional-level summary data (e.g., "Western Asia" and "World").

At the firm level, I unify manufacturing firm names to correct inconsistency induced by different spellings (e.g., "Cipla" vs. "Cipla Ltd." vs. "Cipla Inc."). I assign a transaction-level indicator for generic drugs if the drug is purchased from a generic manufacturer. At the drug

[91] Available at https://www.theglobalfund.org/en/sourcing-management/price-quality-reporting//. Data last accessed in 8/2018, when I request all available yearly data by 2017 from the online system. The data request system has been updated in 2019 and requires additional conversion from Tableau files.

level, I focus on generic names (international names of compounds within a drug), as branded names vary across countries, depending partly on trademark registration. For drugs with multiple compounds, I unify the order of compounds within the drug to avoid over-counting of drug varieties; corresponding adjustments applied to all variables that are order-sensitive, such as milligram (mg) strength for each compound within a drug. For each drug in my database, I collected standard U.S. adult daily doses from FDA, AIDS*info*, and WHO, and I report the information in Appendix A.4 (medical appendix) Table A16.[92]

I calculate the percentage of generic transactions by dividing the number of transactions made with generic manufacturers for a country and a given drug in a year by the total number of transactions made at the same country for the same drug in the same year. I then calculate the percentage of generic quantity purchases following the same idea. Since different drug products may have different strengths (e.g., "10mg/mL", "300 mg"), I calculate the effective strength for each smallest unit – stock keeping unit (SKU). I then calculate the total strength supplied in a transaction by multiplying strength per SKU with the number of SKU in a pack and the number of packs. The percentage of quantity ordered is calculated as the number of patient-years supplied by generic manufacturers for a drug-country-year to the total patient-years purchases for the same drug-country-year. Last, for product variety purchases, I count the number of unique drug-formulation (strength-dosage form)–manufacturer combinations in a country-year.

In the compound-country-year level analysis, I aggregate compound-specific information from multi-compound drugs into country-year levels. For example, I calculate the numbers of generic and total transactions related to a given compound in a country-year. I then reshape the

[92] I focus on U.S. standard adult daily doses for two practical reasons. First, although it is ideal to collect country-specific dosing standards, it is practically impossible to collect this data across over 100 countries. Second, adult doses are more standard and comparable compared to pediatric doses that depend on age and weight. Realizing the caveats, I also use a quantity-free percentage of transaction measure.

data to the compound-country-year level and divide the two to get the percentage of generic transactions for a compound in a country-year. The same logic follows for other procedures.

A.1.2 Compound-year panel of HIV clinical trials

Clinical trials data are available from clinicaltrials.gov, the largest peer-reviewed clinical trials registry in the world and the most widely used by scientists. This U.S.-based trial registry accepts trial registration globally, particularly as multi-national companies typically conduct trials in multi-country clinical sites.[93] Each clinical trial has a unique identifier (i.e., an NCT number) and a set of data recorded and updated periodically.[94] Researchers can typically use Medical Subject Headings (MeSH) terms in the programming processes to pinpoint trials for specific disease conditions, but such processes are not always accurate to locate specific drugs. Therefore, I obtain compound-specific NCT numbers from AIDS*info* to identify HIV-related trials. I collect NCT numbers for all FDA-approved HIV drugs and investigational HIV drugs.

To keep a comprehensive record, I create a variable to store values for each trial based on the compound references in AIDS*info*. For trials referenced in AIDS*info* by brand names, I assign the associated generic name to unify the record. The number of new trials initiated for a compound-year is calculated based on the trial starting date reported and verified in the database. For each trial, I calculate the number of distinct firms collaborating in the trial. I then calculate the number of firms participated in a compound-year by computing the total number of firms collaborated in trials on a given compound in a year. This value captures the intensive margin of firms' trial participation on the compound-year level, including a firm's multiple participations

[93] Researchers can retrieve a zipped file with all trials included in XML format or request certain trials with advanced search options. The site has been updated over time and users are recommended to check the latest XML schema and/or data request options (data last accessed: 11/2018).
[94] A descriptive webpage with data element definitions and mandatory information disclosure requirement in trials is available at: https://prsinfo.clinicaltrials.gov/definitions.html.

across trials. For investigational trials, there are no generic names to facilitate unification, so I further collect the associated drug classes (mechanisms of action) for related aggregation.

A.1.3 Drug-year and compound-year panel of HIV drug product approvals

From the Drugs@FDA online database, I request "All Approvals by Month" (approvals, tentative approvals, and supplements) and append the data.[95] To pinpoint all approvals for HIV drugs, I convert the "active ingredients" variable all to lower-case and perform a text match: keep the record if the active ingredients of a drug include any compounds used in HIV treatment. Next, I subset the most relevant approvals—original approval of a drug product produced by a firm (submission code "ORIG-1") instead of supplements to approved applications (submission code including "SUPPL"). As a final check to avoid over-inclusion, I drop a few records of drugs approved for hepatitis C treatment with any antiretroviral compounds. In addition, the WHO pre-qualification program is the other largest drug approval and qualification agency.[96] The list is comprehensive and relatively clean. The other steps follow the same logic as described above.

One must be cautions in calculating the period between the first-ever approval of a drug and its follow-on approvals, either cumulative innovation or straightforward imitation. For standalone drugs with a single compound, each compound has a unique date for its first-ever approval. For drug cocktails, I calculated a first-ever technically feasible date as the date all the underlying compounds are approved in any format. I also record the first actual approval dates for cocktails with existing compounds. These approval dates can help us understand follow-on innovation in multiple respects: approvals of new cocktails and formulations *versus* imitations.

[95] Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Note there are other ways to obtain the underlying data that involve merging across segmented files. I use this conservative data request method due to the lack of detailed instruction concerning alternatives. Last accessed: 1/20/2019.
[96] Available at https://extranet.who.int/prequal/content/prequalified-lists/medicines.

Appendix A.2: Additional Figures and Tables

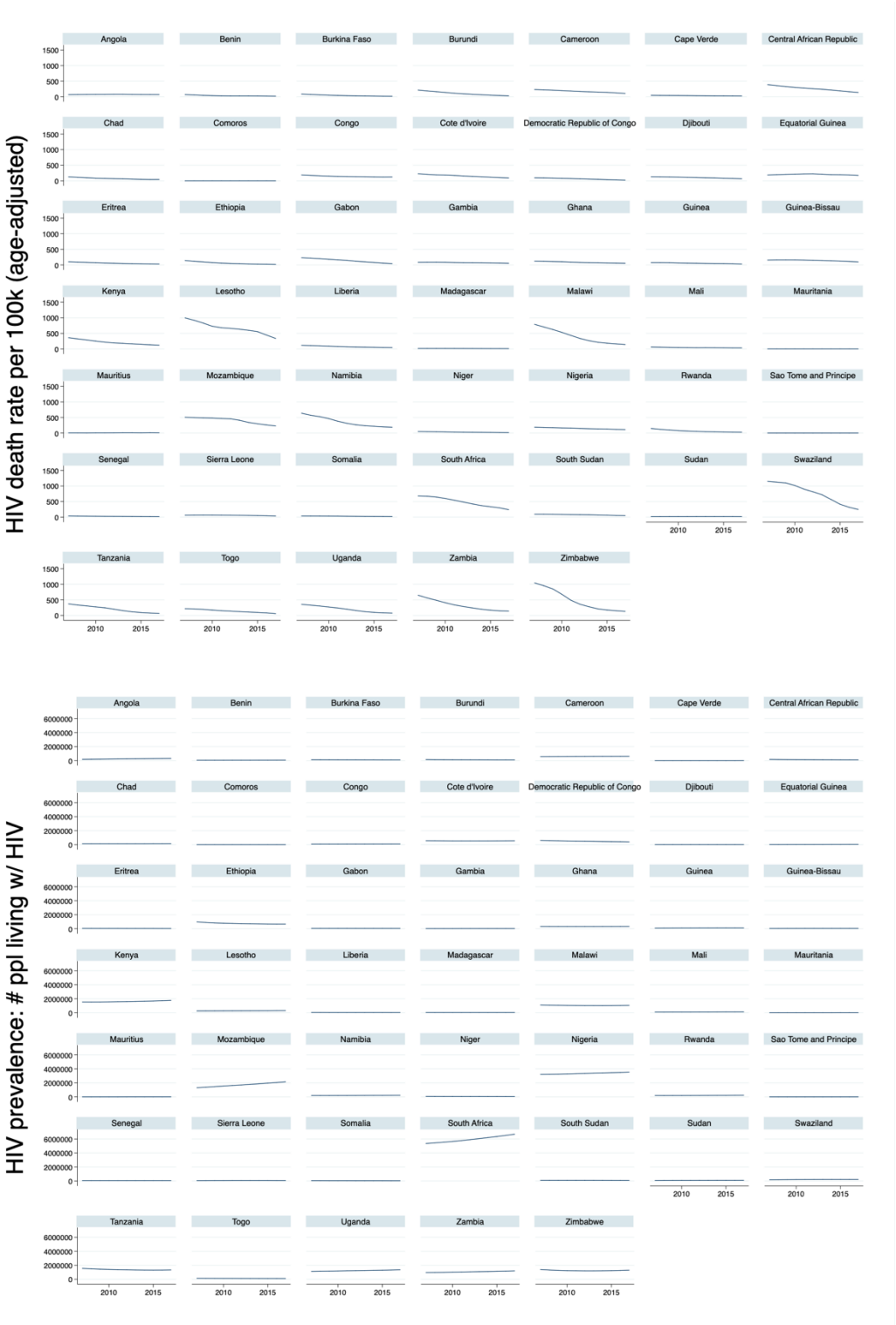


Figure A1: HIV death rate and prevalence, across MPP common territories

Notes: This figure visualize age-adjusted HIV death rate (per 100k population) and HIV prevalence in MPP common sales territory. In particular, there are no disease-related events generating exogenous shocks to HIV/AIDS mortality during the sample periods of my diffusion analysis.

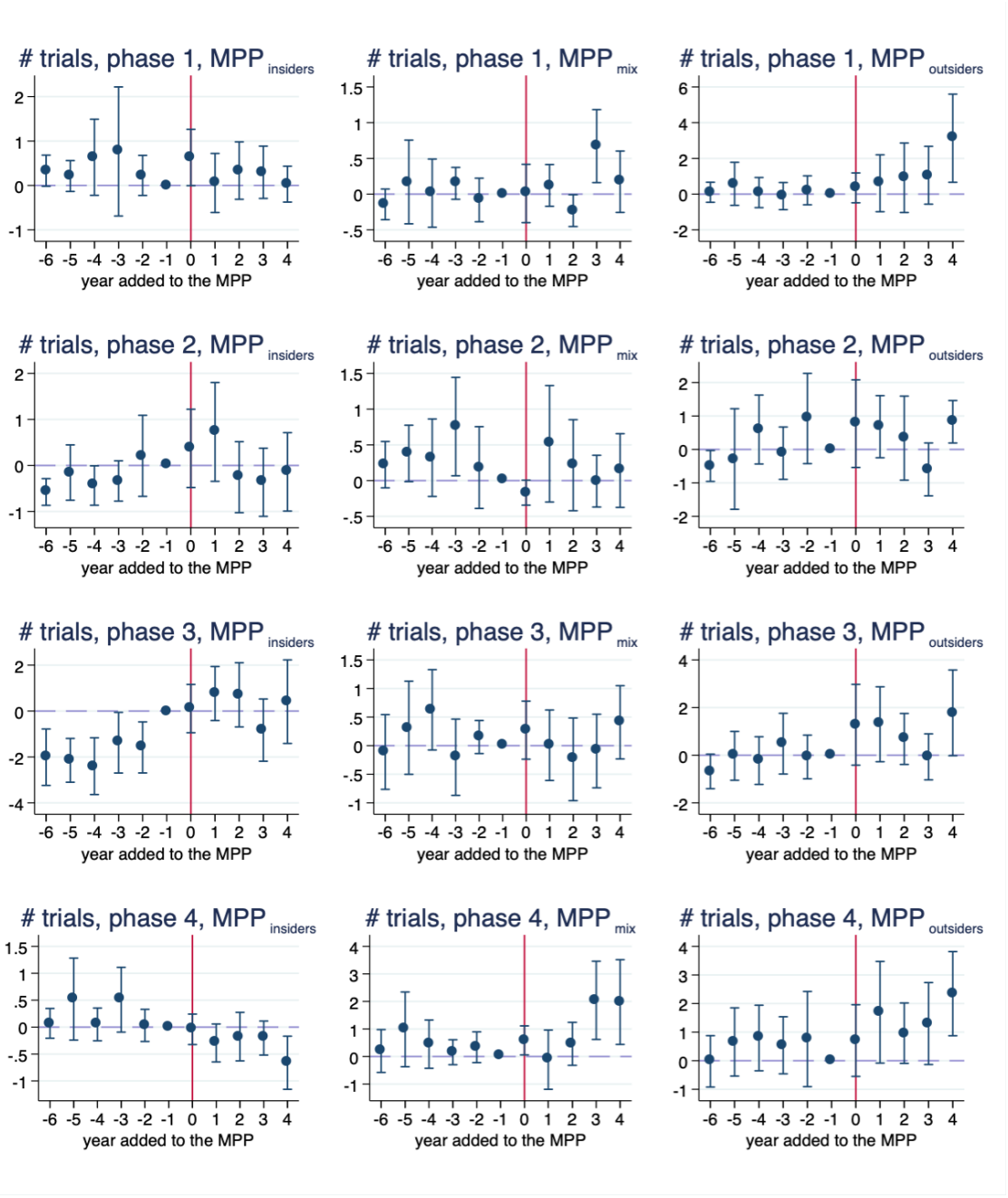


Figure A2: Event Studies for Innovation Analysis: Clinical Trials, by Firm and Phase

Notes: These figures report event-study coefficient estimates using Equation (4). The dots are point estimates of differences in outcomes between treatment group and control groups 6 years before MPP inclusion and 4 years after inclusion. The whiskers correspond to 95% confidence intervals.

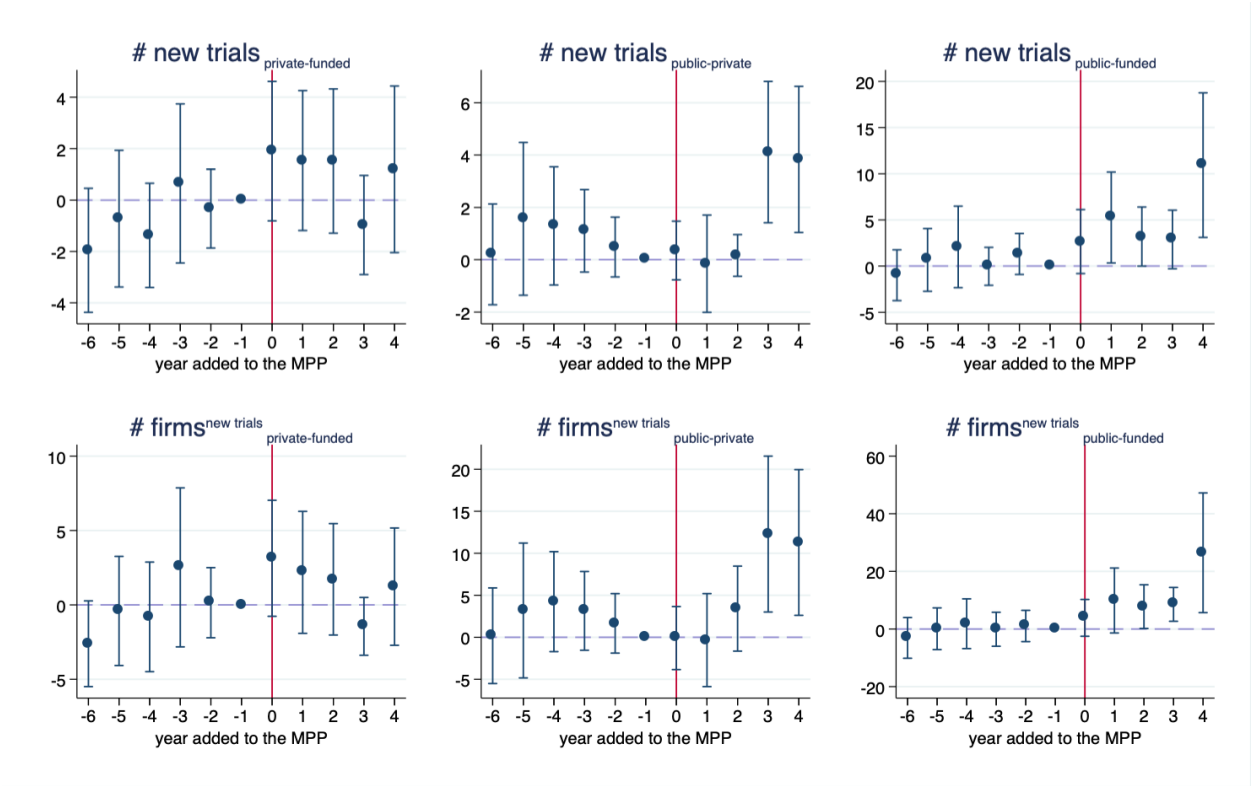


Figure A3: Event Studies for Innovation Analysis: Clinical Trials by Funding Type

Notes: These figures report event-study coefficient estimates using Equation (4). The dots are point estimates of differences in outcomes between treatment group and control groups 6 years before MPP inclusion and 4 years after inclusion. The whiskers correspond to 95% confidence intervals.

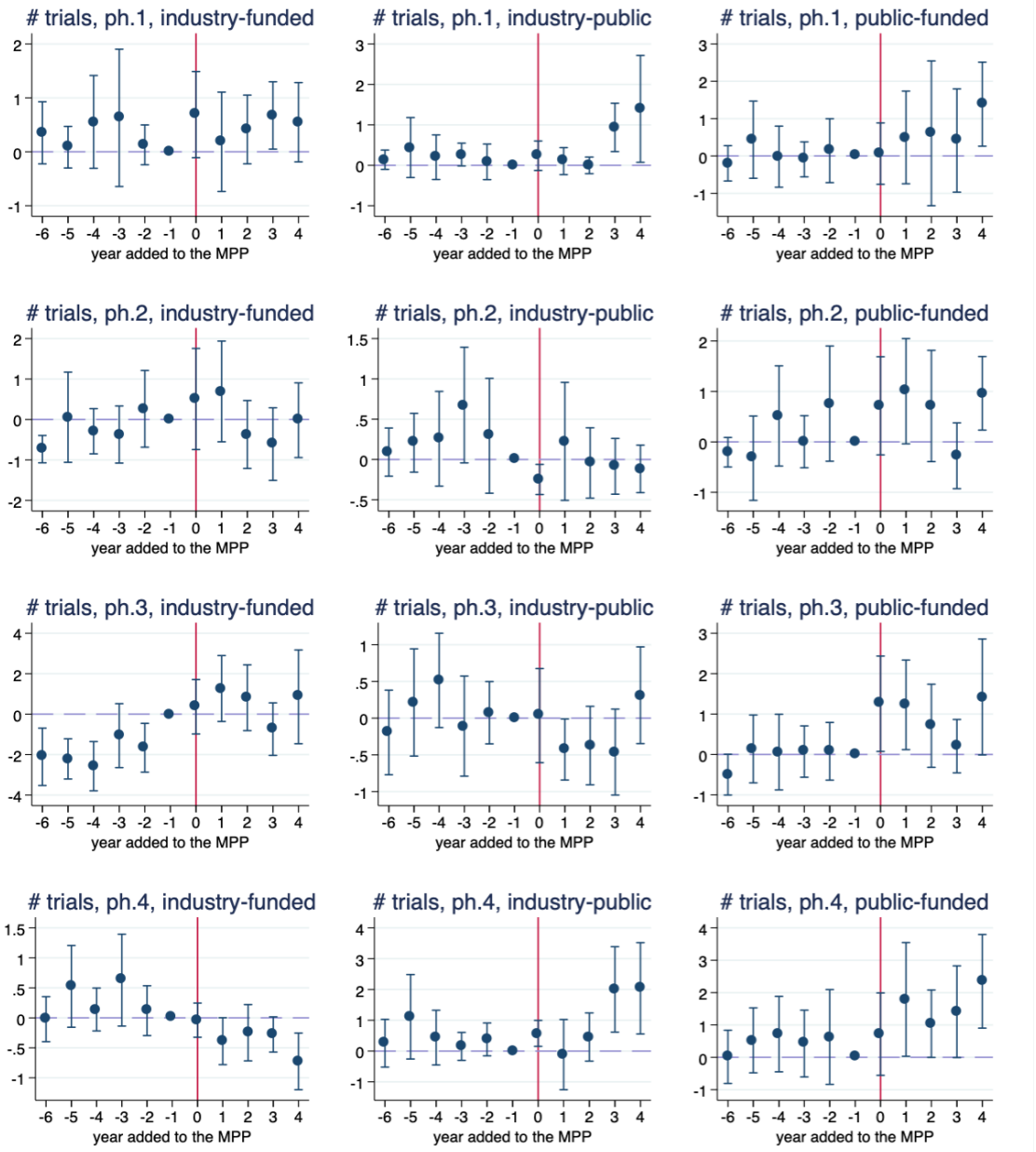
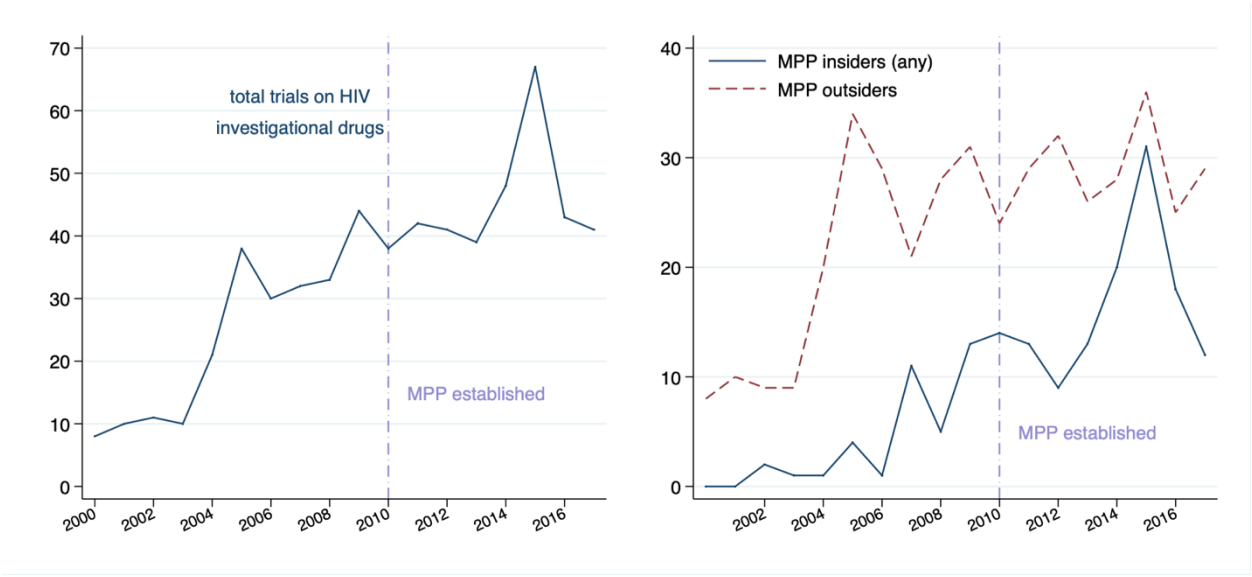
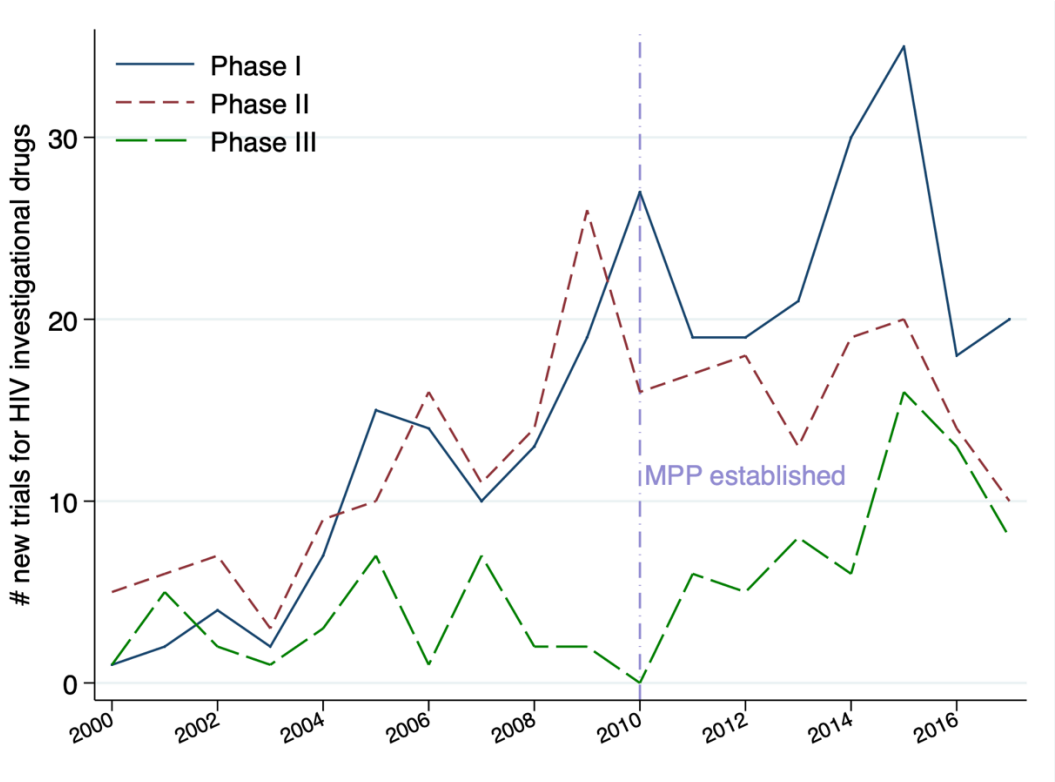


Figure A4: Event Studies for Innovation Analysis: Clinical Trials, by Funder and Phase

Notes: These figures report event-study coefficient estimates using Equation (4). The dots are point estimates of differences in outcomes between treatment group and control groups 6 years before MPP inclusion and 4 years after inclusion. The whiskers correspond to 95% confidence intervals.



(a) Total Trials on HIV Investigational Drugs, and across MPP-affiliation



(b) Investigational Trials by Phases (I-III)

Figure A5: Descriptive Trends: # New Trials on HIV Investigational Drugs (pipeline)

Notes: This graph visualizes the trends of the number of new clinical trials initiated per year on HIV investigational drugs, i.e., new compounds that have not been approved (majority 90%, as in phases I-III) or investigational use of existing drugs (beyond approved antiretrovirals) for new HIV treatment purposes. The vertical dash line indicates the time when the Medicines Patent Pool established.

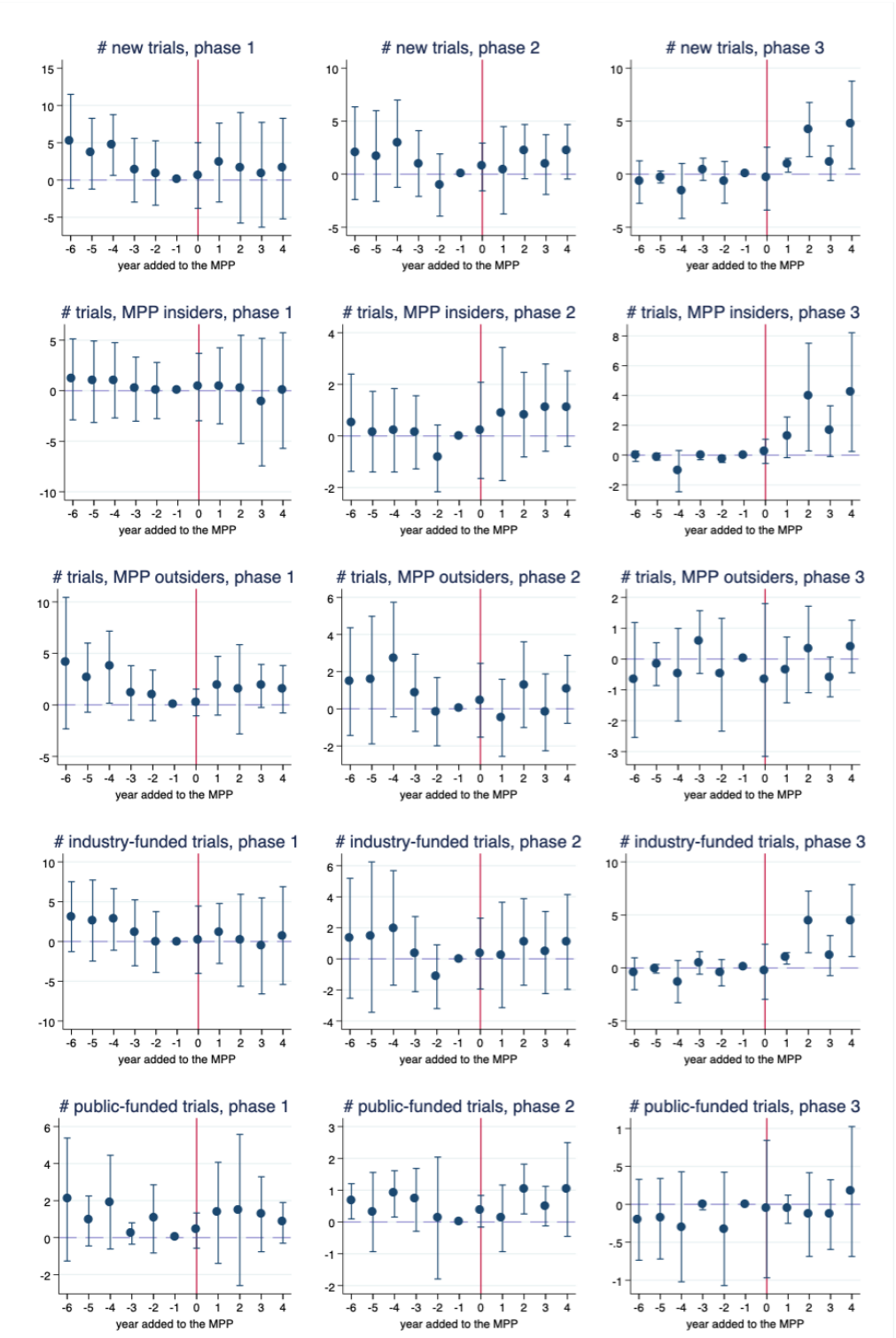


Figure A6: Event Studies: Clinical Trials for HIV Investigational Drugs, by Phase

Notes: These figures report event-study coefficient estimates using Equation (4), at drug class-year level. The dots are point estimates of differences in outcomes between treatment group and control groups 6 years before and 4 years after MPP inclusion. The whiskers correspond to 95% confidence intervals.

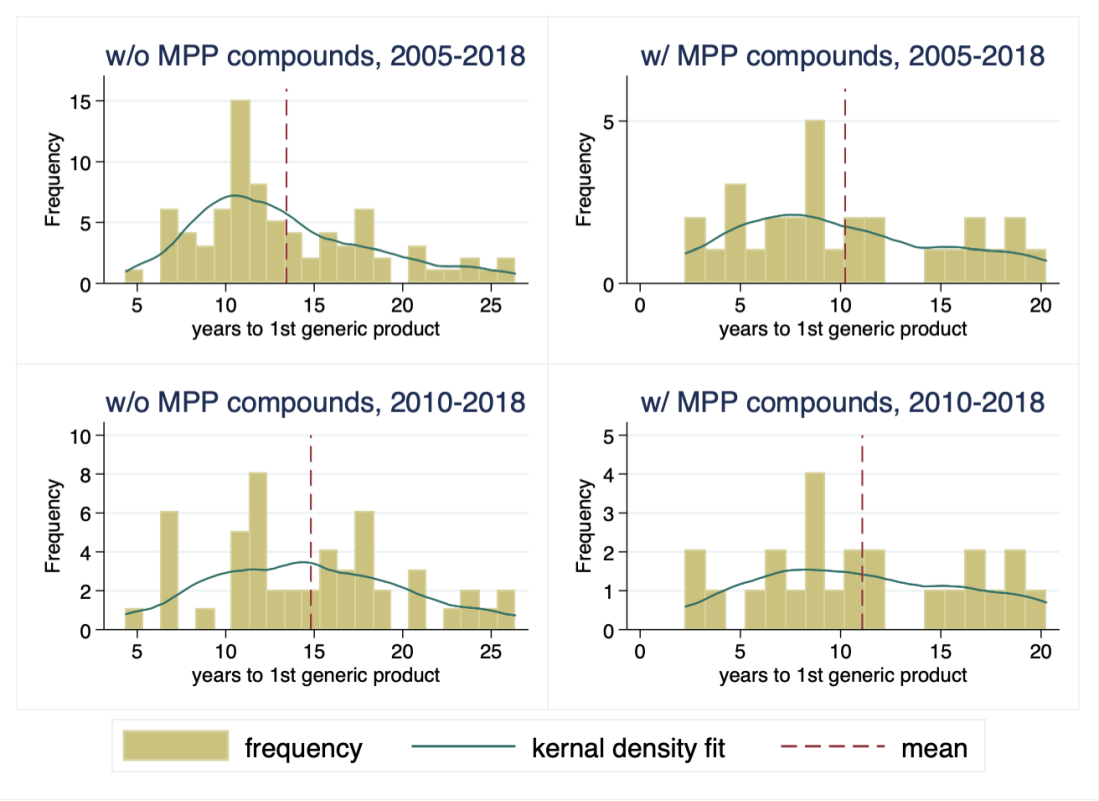


Figure A7: Histograms of Time-to-Generic by MPP Status

Notes: this set of figures pictures the association between time-to-generic and MPP status. Time-to-generic is measured as the years (continuous variable) between when all original compounds were approved and when the first generic (combination) of existing compounds is approved in a given strength-dosage form. The upper panel uses the full sample (2005-2018) and the bottom panel displays the sample where MPP has been established (2010-2018).

Table A1: Regressing MPP Indicator on Observables

	(1)	(2)	(3)
R^2 (two-way s.e.)	0.820	0.821	0.821
R^2 (one-way s.e.)	0.827	0.828	0.828
HIV death rate		-0.000137	-0.000139
(age-adjusted,		(0.000228)	(0.000229)
per 100k pop.)		[7.49e-05]	[7.56e-05]
HIV prevalence		4.10e-08	4.12e-08
		(1.20e-07)	(1.20e-07)
		[3.61e-08]	[3.63e-08]
log(population)		0.193	0.196
		(0.420)	(0.425)
		[0.153]	[0.153]
GDP per capita		7.16e-06	7.09e-06
		(6.02e-06)	(6.32e-06)
		[5.82e-06]	[5.86e-06]
voice and		0.000692	0.000715
accountability		(0.00116)	(0.00126)
		[0.00106]	[0.00106]
political stability		0.000450	0.000438
and lack of		(0.000610)	(0.000636)
violence		[0.000504]	[0.000503]
government		-0.000310	-0.000305
effectiveness		(0.000790)	(0.000876)
		[0.000721]	[0.000722]
regulatory		0.00126*	0.00125
quality		(0.000740)	(0.000763)
		[0.00102]	[0.00102]
rule of law		-0.00105	-0.00106
		(0.000632)	(0.000624)
		[0.000965]	[0.000964]
control of		0.000653	0.000665
corruption		(0.000677)	(0.000713)
		[0.000839]	[0.000835]
$patent_{dct}$			0.0139
			(0.0791)
			[0.0360]
country-drug & year FEs	Y	Y	Y
X_{ct} controls		Y	Y
X_{dct} controls			Y
Observations	7,084	7,084	7,084

Notes: this table reports a diagnostic regression on whether the MPP inclusion decision can be predicted by changes in observed characteristics during my sample period. As shown above, none of the observables are significant predictors of when a drug-country pair is added to the MPP and available for bundled licensing. In addition, the disease rate and prevalence, population, income, and institution-related factors do not effectively increase predictive power of the MPP inclusion indicator, net of fixed effects. Robust standard errors are two-way clustered at the drug and country levels and are reported in parenthesis (). Robust standard errors clustered at the country level is reported in []. Two-way robust p-values: * $p<0.1$.

Table A2: Subsample Diffusion Analysis: Ever vs Never Patented

	(1)	(2)	(3)	(4)	(5)	(6)
Dept. Vars.	% generic orders (#)		% generic ordered (p.p.y)		# product-manufacturers	
Subsample	$Pat.$=1	$Pat.$=0	$Pat.$=1	$Pat.$=0	$Pat.$=1	$Pat.$=0
Panel A: drug-country-year subsamples						
MPP_{dct}	20.65**	4.360	18.03*	4.675*	-0.0122	0.0887
	(9.771)	(2.696)	(9.321)	(2.709)	(0.0886)	(0.126)
	[7.667]	[2.678]	[7.079]	[2.770]	[0.118]	[0.0924]
LHS mean	83.73	84.54	84.42	86.12	1.75	1.70
Observations	2,029	5,055	2,029	5,055	2,029	5,055
Panel B: compound-country-year subsamples						
MPP_{act}	19.85***	4.601	17.29***	6.699	-0.193	0.372*
	(3.665)	(3.735)	(3.600)	(3.962)	(0.176)	(0.198)
	[4.321]	[3.537]	[4.351]	[3.941]	[0.152]	[0.176]
LHS mean	84.19	85.54	84.99	87.33	1.75	1.72
Observations	3,328	3,157	3,328	3,157	3,328	3,157
two sets of FEs	Y	Y	Y	Y	Y	Y
X_{ct} control	Y	Y	Y	Y	Y	Y
$X_{d(a)ct}$ control	Y		Y		Y	

Notes: This table reports the results of the model using equation (1), across subsamples in countries where a drug (Panel A) or compound (Panel B) is ever patented or never patented during my sample period. Each cell reports the coefficient-of-interest from a separate regression. The specification also controls effective patent status and country-year level observable factors. Fixed effects for drug(compound)-country pairs and years are always included. Robust standard errors are two-way clustered at the compound and country levels and are reported in parenthesis (). Robust standard errors clustered at the country level is reported in []. Two-way robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table A3: Diffusion Analysis: Reduced-form Price and Quantity Regressions

	(1)	(2)	(3)	(4)	(5)	(6)
	Prices (Per Patient Year)			Quantity (Patient-Year Served)		
Dept. Vars.	Overall	Generic	Branded	Overall	Generic	Branded
MPP_{dct}	-105.8	-86.73***	91.51	294.2	464.0	-169.8**
	(79.15)	(28.48)	(139.9)	(2,279)	(2,270)	(77.96)
	[46.09]	[23.82]	[202.0]	[1,000]	[1,042]	[134.2]
FEs	Y	Y	Y	Y	Y	Y
X_{ct} control	Y	Y	Y	Y	Y	Y
X_{dct} control	Y	Y	Y	Y	Y	Y
LHS mean	375.17	158.37	1696.03	6289.15	6198.92	90.23
# Obs.	7,084	6,167	1,351	7,084	7,084	7,084

Notes: This table reports the results of estimating equation (1) using prices and quantities as outcome variables. Each cell reports the coefficient-of-interest from a separate regression. Fixed effects for drug-country pairs and years are always included. The specification also controls drug-country-year level effective patent status and country-year level observables. The LHS mean for branded quantity is small because of the zeros exist in many units; the mean for non-zeros branded quantity is 473.12 instead. Robust standard errors reported in () are clustered using two-way clustering at the drug and country levels. Robust standard errors reported in [] are clustered at the country level. Two-way robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table A4: Diffusion Analysis in Sample Territories

	(1)	(2)	(3)	(4)	(5)	(6)
Samples	MPP common territories			MPP ever-covered territories		
Dept. Vars.	% generic	%Q generic	# products	% generic	%Q generic	# products
Panel A: drug-country-year level analysis						
MPP_{dct}	5.011*	5.312**	0.115	7.528**	7.280**	0.0730
	(2.851)	(2.553)	(0.148)	(2.913)	(2.761)	(0.104)
	[3.318]	[3.423]	[0.121]	[2.690]	[2.699]	[0.0802]
LHS mean	88.65	89.74	1.77	85.68	87.00	1.73
# obs.	3,547	3,547	3,547	6,829	6,829	6,829
Panel B: compound-country-year level analysis						
MPP_{act}	8.378**	10.06**	0.228	10.54***	10.89***	0.129
	(3.922)	(3.546)	(0.266)	(3.593)	(3.334)	(0.190)
	[3.867]	[4.084]	[0.143]	[3.064]	[3.213]	[0.111]
LHS mean	84.34	86.33	2.77	81.29	83.53	2.57
# obs.	3,221	3,221	3,221	6,202	6,202	6,202
FEs	Y	Y	Y	Y	Y	Y
X_{ct} control	Y	Y	Y	Y	Y	Y
X_{dct} control	Y	Y	Y	Y	Y	Y

Notes: This table reports the results of estimating equation (1) in subsamples of MPP common territories (countries in every drug's territory) and MPP ever-covered territories (eligible for at least one drug). Each cell reports the coefficient-of-interest from a separate regression. Fixed effects for drug-country pairs (Panel A), compound-country pairs (Panel B), and years are always included. The specification also controls drug-country-year level effective patent status and country-year level observables. Robust standard errors reported in () are clustered using two-way clustering at the drug and country levels. Robust standard errors reported in [] are clustered at the country level. Two-way robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table A5: Diffusion Analysis in Sample Drugs

Samples	(1) drug class in 1st pool addition	(2) drop one drug class	(3) drop U.S. not recommended	(4) drugs approved since 1996	(5) drugs by MPP insider firms
Panel A: % generic orders as dependent variable					
MPP_{dct}	11.13***	7.030**	7.415**	6.848**	7.304**
	(3.586)	(2.951)	(2.967)	(2.938)	(2.842)
	[3.471]	[2.773]	[2.687]	[2.705]	[2.706]
LHS mean	94.80	82.77	83.92	83.41	86.64
# Obs.	4,463	5,828	6,316	5,786	6,127
Panel B: % generic quantity ordered (patient year) as dependent variable					
MPP_{dct}	10.32***	6.520**	7.234**	6.620**	7.145**
	(3.366)	(2.874)	(2.838)	(2.823)	(2.727)
	[3.335]	[2.781]	[2.693]	[2.702]	[2.709]
LHS mean	95.44	84.11	85.25	84.64	88.13
# Obs.	4,463	5,828	6,316	5,786	6,127

Notes: This table reports the results of estimating equation (1) in subsamples changing drugs in the comparison groups. Each cell reports the coefficient-of-interest from a separate regression. Fixed effects for drug-country pairs and years are always included. The specification also controls drug-country-year level effective patent status and country-year level observables. Robust standard errors reported in () are clustered using two-way clustering at the drug and country levels. Robust standard errors reported in [] are clustered at the country level. Two-way robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table A6: Diffusion Analysis in Alternative Specification

	(1)	(2)	(3)	(4)	(5)	(6)
Dept. Vars.	% generic orders		% generic quantities		# products	
MPP_{dct}	7.526**	7.535**	7.250**	7.254**	0.0623	0.0629
	(3.355)	(3.347)	(3.123)	(3.122)	(0.113)	(0.113)
	[2.700]	[2.700]	[2.734]	[2.736]	[0.0747]	[0.0746]
country-drug FE	Y	Y	Y	Y	Y	Y
country-year FE	Y	Y	Y	Y	Y	Y
X_{dct} control		Y		Y		Y
LHS mean	84.3	84.3	85.6	85.6	1.7	1.7
Observations	7,084	7,084	7,084	7,084	7,084	7,084

Notes: This table reports the results of estimating the MPP causal impact on drug-country-year level generic drug diffusion with an alternative specification. All the country-year level observables are replaced with a full set of country-year level fixed effects. Fixed effects for drug-country pairs are always included. Drug-country-year level effective patent status are included in the last set of columns to demonstrate coefficient stability. Each cell reports the coefficient-of-interest from a separate regression. Robust standard errors reported in () are clustered using two-way clustering at the drug and country levels. Robust standard errors reported in [] are clustered at the country level. Two-way robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table A7: Innovation Analysis - Clinical Trials: by Funding Types

	(1)	(2)	(3)	(4)	(5)	(6)
	# new HIV trials funded by			# firms in new HIV trials funded by		
Dept. Vars.	industry	ind.&pub.	public	industry	ind.&pub.	public
Total						
MPP_{at}	2.296*	0.898	4.899*	2.750*	3.231	11.77*
	(1.227)	(1.026)	(2.759)	(1.572)	(3.082)	(6.144)
LHS mean	3.417	1.996	4.663	4.494	5.880	10.36
Panel A. Phase I						
MPP_{at}	0.197	0.313	0.604	0.251	0.930	1.133
	(0.199)	(0.201)	(0.532)	(0.292)	(0.608)	(0.924)
LHS mean	0.546	0.209	0.596	0.774	0.546	0.985
Panel B. Phase II						
MPP_{at}	0.504	-0.244**	0.665**	0.556	-0.852**	1.416*
	(0.397)	(0.113)	(0.275)	(0.473)	(0.328)	(0.694)
LHS mean	0.806	0.291	0.813	1.007	0.941	1.756
Panel C. Phase III						
MPP_{at}	2.275***	-0.129	1.228***	2.743***	-0.664*	2.506*
	(0.721)	(0.0981)	(0.434)	(0.900)	(0.358)	(1.288)
LHS mean	1.524	0.393	0.969	1.943	1.256	2.772
Panel D. Phase IV						
MPP_{at}	-0.424**	0.574	1.174	-0.547***	2.352	2.735*
	(0.164)	(0.481)	(0.805)	(0.185)	(1.584)	(1.601)
LHS mean	0.354	0.796	1.313	0.444	2.402	2.731

Notes: This table reports the results of estimating equation (3). The number of observations is always 540 given the balanced panel data structure by design. Each cell reports the coefficient-of-interest from a separate regression. Industry-funded means the trial is 100% industry funded, while "ind.&pub." means the trial is private-public jointly funded. Controls variables include FDA approval status, patent status, and fixed effects for compounds and years. Robust standard errors are clustered at the compound level and are reported in parenthesis. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table A8: Innovation Analysis - Clinical Trials on HIV Investigational Drugs

Dept. Vars.	(1) # new trials	(2) # trials, MPP insiders	(3) # trials, MPP outsider	(4) # industry-funded trials	(5) # public-funded trials
Total					
MPP_{at}	4.230	2.959	1.271	2.871*	1.360
	(2.254)	(1.529)	(1.071)	(1.229)	(1.072)
LHS mean	8.58	3.30	5.29	5.67	2.91
Panel A. Phase I					
MPP_{at}	-0.582	-0.440	-0.142	-0.823	0.241
	(1.305)	(0.855)	(0.762)	(0.918)	(0.605)
LHS mean	3.45	0.81	2.64	1.95	1.51
Panel B. Phase II					
MPP_{at}	0.553	0.888	-0.335	0.280	0.273
	(0.474)	(0.629)	(0.444)	(0.267)	(0.227)
LHS mean	3.23	1.18	2.06	2.34	0.89
Panel C. Phase III					
MPP_{at}	2.770*	2.504*	0.266	2.599**	0.170
	(1.230)	(1.097)	(0.284)	(1.051)	(0.195)
LHS mean	1.98	1.37	0.60	1.81	0.17

Notes: This table reports the results of estimating equation (3), at drug class-year level. The number of observations is always 91 with the balanced panel data structure. There are totally seven drug classes in the analysis, where six of them are drug classes with existing compounds approved and one drug class capturing the set of new drug classes without existing products for HIV treatment, such as gene therapy, biological antibody, etc. Each cell reports the coefficient-of-interest from a separate regression. Industry-funded means the trial at least partly funded by industry. Controls variables include FDA approval status, patent status, and fixed effects for compounds and years. Robust standard errors are clustered at the drug class level and are reported in parenthesis. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table A9: 1st Time New HIV Drug Approvals with Existing Compounds

drug	firm	ymd	branded compound owners	#	type
Panel A: 1st Time New Drug Approvals by Branded Firms					
3tc+zdv	ViiV	1997.09.26	ViiV+ViiV	1	cocktail
abc+3tc+zdv	ViiV	2000.11.14	ViiV+ViiV+ViiV	1	cocktail
abc+3tc	ViiV	2004.08.02	ViiV+ViiV	1	cocktail
ftc+tdf	Gilead	2004.08.02	Gilead+Gilead	1	cocktail
efv+ftc+tdf	Gilead	2006.07.12	BMS+Gilead+Gilead	2	cocktail
ftc+rpv+tdf	Gilead	2011.08.10	Gilead+Janssen+Gilead	2	cocktail
abc+dtg+3tc	ViiV	2014.08.22	ViiV+ViiV+ViiV	1	cocktail
cobi	Gilead	2014.09.24	Gilead	1	standalone
evg	Gilead	2014.09.24	Gilead	1	standalone
atv+cobi	BMS	2015.01.29	BMS+Gilead	2	cocktail
cobi+drv	Janssen	2015.01.29	Gilead+Janssen	2	cocktail
3tc+ral	Merck	2015.02.06	ViiV+Merck	2	cocktail
ftc+rpv+taf	Gilead	2016.03.01	Gilead+Janssen+Gilead	2	cocktail
ftc+taf	Gilead	2016.04.04	Gilead+Gilead	1	cocktail
taf	Gilead	2016.11.10	Gilead	1	standalone
dtg+rpv	ViiV	2017.11.21	ViiV+Janssen	2	cocktail
cobi+drv+ftc+taf	Janssen	2018.07.17	Gilead+Janssen+Gilead+Gilead	2	cocktail
Panel B: 1st Time New Drug Approvals by Generics					
3tc+nvp+zdv	Pharmacare	2005.01.24	ViiV+BI+ViiV	2	cocktail
3tc+zdv+efv	Aurobindo	2006.03.06	ViiV+ViiV+BMS	2	cocktail
3tc+d4t+nvp	Cipla	2006.11.17	ViiV+BMS+BI	3	cocktail
3tc+d4t	Cipla	2007.01.19	ViiV+BMS	2	cocktail
d4t+3tc+efv	Strides	2007.06.01	BMS+ViiV+BMS	2	cocktail
3tc+tdf	Hetero	2009.11.05	ViiV+Gilead	2	cocktail
efv+3tc+tdf	Mylan	2010.10.25	BMS+ViiV+Gilead	3	cocktail
3tc+tdf+nvp	Matrix Labs	2011.09.08	ViiV+Gilead+BI	3	cocktail
atv+r	Matrix Labs	2011.11.18	BMS+AbbVie	2	cocktail
atv+r+3tc+zdv	Mylan	2014.09.04	BMS+AbbVie+ViiV+ViiV	3	cocktail
ftc+tdf+nvp	Mylan	2014.09.12	Gilead+Gilead+BI	2	cocktail
dtg+3tc+tdf	Mylan	2017.08.02	ViiV+ViiV+Gilead	2	cocktail
dtg+ftc+taf	Mylan	2018.02.09	ViiV+Gilead+Gilead	2	cocktail

Notes: This table summarizes the first approvals of HIV drugs based on existing compounds, reported for originators and generics in different panels and chronologically ordered within each panel. These first-time follow-on new approvals are typically for drug cocktails, except in three cases where the originators first created new compounds approved as part of a cocktail before the new standalone compound is approved. BI stands for Boehringer Ingelheim. The column of # count distinct brand owners of each underlying drug. Note that first-time new generic cocktails are not reported before 2005 because of a combination of international patent enforcement in India since then and new FDA approval initiatives. This table, together with Table 1.1, complete the list of first-approval information for all HIV drugs by end of 2018.

Table A10: Survival and Regression Analyses on Time-to-Generic

	(1)	(2)	(3)	(4)
Panel A: Cox Proportional Hazard Model				
MPP	0.532**	0.647**	1.019**	0.371
	(0.222)	(0.257)	(0.397)	(0.472)
Panel B: Regression Analysis				
MPP	-3.204***	-3.727***	-1.827	-0.157
	(1.117)	(1.317)	(1.102)	(1.738)
sample	2005-2018	2010-2018	2005-2018	2010-2018
year FE			Y	Y
drug class FE			Y	Y
LHS mean	12.57	13.62	12.57	13.62
Observations	108	75	108	75

Notes: this table reports results of analysis the association between time-to-generic and MPP status. Time-to-generic is measured as the years (continuous variable) between when all original compounds were approved and when the first generic (combination) of existing compounds is approved in a given strength-dosage form. The main variable of interest is an indicator variable of whether a first approved generic product has any MPP compound. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table A11: Count Model Results for Innovation Analysis – Drug Approvals

	(1) # approvals	(2) # appr.^{generic}	(3) # appr.^{branded}
Panel A: drug-year new approvals			
MPP_{dt}	1.014***	1.212***	0.772
	(0.262)	(0.287)	(0.786)
LHS mean	0.70	13.22	1.95
Observations	798	518	518
Panel B: compound-year new approvals			
MPP_{at}	1.067***	1.115***	0.969**
	(0.227)	(0.259)	(0.477)
LHS mean	2.28	39.95	4.29
Observations	378	266	336
FEs	Y	Y	Y
controls	Y	Y	Y

Note: This table reports innovation results in drug approvals using conditional negative binomial regressions. Fixed effects are at drug and year levels for Panel A and at compound and year levels for Panel B. I run this exercise to test whether drug approval results in Table 1.6 (using linear models) are robust to using count data models. The number of observations dropped in columns (2) – (3) to adjust for different drug approved by generics and branded—drugs/compounds always have zero approvals by the corresponding firm type create no variation and dropped to account for different focus in actual investment areas.

Table A12: Sensitivity Analysis of Demand Estimation to Market Size

	(1)	(2)	(3)	(4)	(5)
market size measures	10% population	30% population	50% population	70% population	pop*pr. HIV $death_{15to59}$
$\ln(s_{j\|g})$	0.862***	0.861***	0.861***	0.861***	0.863***
	(0.0826)	(0.0812)	(0.0810)	(0.0809)	(0.0811)
p_j	-1.968***	-1.942***	-1.938***	-1.937***	-1.941***
	(0.247)	(0.243)	(0.242)	(0.242)	(0.243)
1st stage $_{joint}$	19.50	19.50	19.50	19.50	19.50
1st stage $(s_{j\|g})$	104.42	104.42	104.42	104.42	104.42
1st stage (p_j)	46.91	46.91	46.91	46.91	46.91
country FE	Y	Y	Y	Y	Y
year FE	Y	Y	Y	Y	Y
X_j controls	Y	Y	Y	Y	Y
Observations	7,084	7,084	7,084	7,084	7,084

Note: This table presents results of estimating the nested logit demand model as in equation (6), and each column demonstrates robustness of the estimation to alternative market size measures. Observable controls, X_j include within drug product variety in a country-year, number of compounds within a drug, number of years since a drug's U.S. approval, country-year level HIV prevalence and age-adjusted death rates, institutional factors (i.e., the six world governance indicators), log(population) and GDP per capita. The excluded instruments are at drug-country-year level: patent status, number of competitors and number of close competitors in the same drug class. The first-stage statistics displayed immediately under coefficients-of-interests are the Kleibergen-Paap F statistic that robust to heteroskedasticity. The first-stage F statistics for each endogenous variable is the Sanderson-Windmeijer multivariate F test of excluded instruments. Each j denotes drug-country (dc) for simplicity in notations. Robust p-value: *** p<0.01, ** p<0.05, * p<0.1.

Table A13: Pool Operating Expenses from Financial Statement

time period	use of the funds (raw $/SFr.)	CHF/USD (annual)	MPP costs ($ current)
2010.7-2011.12	$ -4,254,666	NA	-4,254,666
2012.1-2012.12	SFr. -4,086,052	0.9377	-4,357,526
2013.1-2013.13	SFr. -4,271,467	0.9269	-4,608,336
2014.1-2014.12	SFr. -4,332,580	0.9147	-4,736,613
2015.1-2015.12	SFr. -4,759,073	0.9628	-4,942,951
2016.1-2016.12	SFr. -4,568,395	0.9848	-4,638,906
2017.1-2017.12	SFr. -4,974,406	0.9842	-5,054,263

Notes: I obtain the MPP operating costs from the financial statements in the "Annual Reports" from the MPP. Specifically, I use "use of the funds" within the "statement of changes in capital" to measure the costs of this platform. This calculation is similar to manually summing up the personnel and administrative costs (the two main categories of MPP expenditure). The annual foreign exchange rate of Swiss Francs to one U.S. Dollar is provided by the Federal Reserve Bank of St. Louis.

Appendix A.3: Mathematical Appendix

A.3.1. Derive price substitution matrix

I derive substitution matrix by taking partial derivatives of market share *k* w.r.t price *j*. Here, I derive the general expression for the price derivatives from the demand side. With information from the supply-side, the relevant elements from the matrix is the products owned by the same branded firm in a given market (i.e., subset products owned by the same firm).

Given that

$$\hat{s}_j = \frac{e^{\frac{\delta_j}{1-\sigma}}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma}}{\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}},\ \hat{s}_k = \frac{e^{\frac{\delta_k}{1-\sigma}}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}}{\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}},\ \text{and}\ \hat{s}_{k|g} = \frac{e^{\frac{\delta_k}{1-\sigma}}}{\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}} = \frac{\hat{s}_k}{\hat{s}_g}$$

$$\frac{ds_k}{dp_j} = \frac{d}{dp_j}\left[\frac{e^{\frac{\delta_k}{1-\sigma}}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}}{\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}}\right]$$

$$= \frac{\left(e^{\frac{\delta_k}{1-\sigma}}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\right)'\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right] - e^{\frac{\delta_k}{1-\sigma}}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]'}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]^2}$$

$$= \frac{\overbrace{\left(e^{\frac{\delta_k}{1-\sigma}}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\right)'}^{\equiv A}}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]} - \frac{e^{\frac{\delta_k}{1-\sigma}}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\overbrace{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]'}^{\equiv B}}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]^2}$$

$$= \frac{A}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]} - \hat{s}_k \times \frac{B}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]}, \qquad \text{eqn. (III.1)}$$

where $A \equiv \left(e^{\frac{\delta_k}{1-\sigma}}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\right)' = \left(e^{\frac{\delta_k}{1-\sigma}}\right)'\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma} + e^{\frac{\delta_k}{1-\sigma}}\left(\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\right)'$

and $B = \left[\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]'\ if\ g(k) = g(j);\ = \left[\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]'\ if\ g(k) \neq g(j).$

In the following part, I derive the analytic forms of the price derivatives for three cases. In each case, I first derive the expressions for A and B and then plug them back into eqn. (III.1).

Simplification note: that $\left(e^{\frac{\delta_k}{1-\sigma}}\right)' = 0$ if $j \neq k$ and $\left(\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\right)' = 0$ if $g(j) \neq g(k)$.

Case 1: $j=k$ (diagonal elements)

$$A = \left(e^{\frac{\delta_j}{1-\sigma}}\right)' \left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma} + e^{\frac{\delta_j}{1-\sigma}} \left(\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma}\right)'$$

$$= -\frac{\alpha}{1-\sigma} e^{\frac{\delta_j}{1-\sigma}} \left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma} + e^{\frac{\delta_j}{1-\sigma}} \times \frac{\alpha\sigma}{(1-\sigma)} \times \left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma} \times \frac{\overbrace{e^{\frac{\delta_j}{1-\sigma}}}^{=\hat{s}_{j|g}}}{\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}}$$

$$= -\frac{\alpha}{1-\sigma} e^{\frac{\delta_j}{1-\sigma}} \left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma} \left(1-\sigma\hat{s}_{j|g}\right)$$

$$= -\frac{\alpha}{1-\sigma} \hat{s}_j \left(1-\sigma\hat{s}_{j|g}\right) \times \left[\sum_{g=0}^{G} \left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]$$

$$B = \left[\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]' = (1-\sigma)\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma} \left(e^{\frac{\delta_j}{1-\sigma}}\right)'$$

$$= -\alpha e^{\frac{\delta_j}{1-\sigma}} \left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma} = -\alpha\hat{s}_j \times \left[\sum_{g=0}^{G} \left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]$$

Plug back to equation (III.1),

$$\frac{ds_j}{dp_j} = \frac{-\frac{\alpha}{1-\sigma}\hat{s}_j\left(1-\sigma\hat{s}_{j|g}\right)\times\left[\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]} - \hat{S}_j \times \frac{-\alpha\hat{s}_j\times\left[\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]}$$

$$= -\frac{\alpha}{1-\sigma}\hat{s}_j\left(1-\sigma\hat{s}_{j|g}\right) - \alpha\hat{s}_j\hat{s}_j$$

$$= -\alpha\hat{s}_j\left(\frac{1}{1-\sigma} - \frac{\sigma}{1-\sigma}\hat{s}_{j|g} + \hat{s}_j\right)$$

Case 2: $j \neq k, g(j) = g(k)$ (different alternatives within the same nest)

$$A = \overbrace{\left(e^{\frac{\delta_k}{1-\sigma}}\right)'}^{=0} \left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma} + e^{\frac{\delta_k}{1-\sigma}} \left(\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\right)'$$

$$= e^{\frac{\delta_k}{1-\sigma}}(-\sigma)\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma-1} e^{\frac{\delta_j}{1-\sigma}} \times \frac{-\alpha}{1-\sigma}$$

$$= \frac{\alpha\sigma}{1-\sigma} \times \underbrace{\frac{e^{\frac{\delta_k}{1-\sigma}}}{\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}}}_{\hat{s}_{k|g}} \times \underbrace{e^{\frac{\delta_j}{1-\sigma}} \times \left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}}_{\hat{s}_j\times\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}} = \frac{\alpha\sigma}{1-\sigma}\hat{s}_{k|g}\hat{s}_j \times \sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}$$

$$B = \left[\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]' = (1-\sigma)\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\left(e^{\frac{\delta_j}{1-\sigma}}\right)'$$
$$= -\alpha\hat{s}_j \times \left[\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]$$

Plug back to equation (III.1),

$$\frac{ds_k}{dp_j} = \frac{\frac{\alpha\sigma}{1-\sigma}\hat{s}_{k|g}\hat{s}_j \times \sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]} - \hat{s}_k \times \frac{-\alpha\hat{s}_j \times \left[\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]} = \alpha\hat{s}_j\left(\frac{\sigma}{1-\sigma}\hat{s}_{k|g} + \hat{s}_k\right)$$

Case 3: $j \neq k, g(j) \neq g(k)$ (different alternatives in different nests)

$$A = \overbrace{\left(e^{\frac{\delta_k}{1-\sigma}}\right)'}^{=0}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma} + e^{\frac{\delta_k}{1-\sigma}}\overbrace{\left(\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{-\sigma}\right)'}^{=0} = 0$$

$$B = \left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]' = \left[\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]' = -\alpha\hat{s}_j \times \left[\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]$$

Plug back to equation (III.1),

$$\frac{ds_k}{dp_j} = -\hat{s}_k \times \frac{-\alpha\hat{s}_j \times \left[\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}\right]}{\left[\sum_{g=0}^{G}\left(\sum_{k\in g} e^{\frac{\delta_k}{1-\sigma}}\right)^{1-\sigma}\right]} = \alpha\hat{s}_j\hat{s}_k$$

Summary: Finally, I summarize the three cases together.

$$\frac{ds_k}{dp_j} = \begin{cases} -\alpha\hat{s}_j\left(\frac{1}{1-\sigma} - \frac{\sigma}{1-\sigma}\hat{s}_{j|g} + \hat{s}_j\right) & j = k \\ \alpha\hat{s}_j\left(\frac{\sigma}{1-\sigma}\hat{s}_{k|g} + \hat{s}_k\right) & j \neq k, g(j) = g(k) \\ \alpha\hat{s}_j\hat{s}_k & j \neq k, g(j) \neq g(k) \end{cases}$$

Notes: (1) here α is the absolute value of the price coefficient. (2) when calculating the $\widehat{\Delta}_{jk} = -\frac{ds_k}{dp_j}$, one also needs to put an extra condition $f_j = f_k$ in each case to index for drug ownership.

A.3.2. Counterfactual Estimation Procedures

Two counterfactual situations are evaluated: 1) without a patent pool; 2) with a fully expanded patent pool (once a compound enters, no geographic segmentation within my sample period). The goal is to use estimated demand and supply parameters to simulate counterfactual prices and quantities in each scenario (under different market structure assumptions) and compute changes in consumer and producer surpluses.

In section 6, I investigate two broad cases in the supply-side market structure: marginal cost pricing and Bertrand-Nash game. In the first case of marginal cost pricing, one can either assume marginal cost curves to be flat or increasing in quantity. Counterfactual regarding the case with flat marginal cost curves are fairly straightforward as counterfactual prices can be simulated by adjusting the counterfactual values of the MPP variable. In this case, consumers obtain all the social surplus. Alternatively, when assume marginal cost increases in quantity, a shift (down) in the supply curve will also affect equilibrium quantity. Regarding this case of competitive pricing with upward sloping marginal cost curve, I simulate counterfactuals using fixed point iterations.

In the second case of Bertrand-Nash game, I simulate counterfactual prices, quantities, and marginal costs by optimization in each country-year market. This case is then break down to three sub-cases: single product oligopoly and multi-product oligopoly. The major difference across three cases lays in how I define the ownership matrix. In the single product case, only the diagonal elements in the substitution matrix are relevant to a firm's pricing decision. In the multi-product case, I assign ownership based on branded-firm's drug ownership and treat cross-firm cocktail as owned by a separate firm.

In the following part, I described more details regarding how to use fixed point algorithm or optimization to solve for the equilibrium values in relevant scenarios.

Fixed point iteration: competitive pricing with upward sloping MC curve

$$\hat{q}_j = \Pr_j(\hat{p}_j) \times M = \hat{s}_j(\hat{p}_j) \times M \quad (1)$$

$$\hat{p}_j = mc_j(\hat{q}_j) = \beta MPP_j^{cf} + X_j\gamma + \eta\hat{q}_j + \omega_j \quad (2)$$

To fix ideas, I use $MPP_j^{cf} = 0, \forall j$ (counterfactual: without the MPP) to elaborate below. Note that the MPP only enters through supply side but not via the demand side. The analytical form for $\hat{s}_j$ in equation (1) is as below.[97]

$$\hat{s}_j = \frac{e^{\frac{\delta_j}{1-\sigma}}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma}}{\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}}, \text{ where } \delta_j(\hat{p}_j) = X_j\beta + \xi_j - \alpha\hat{p}_j$$

[97] More details are available from the book by Kenneth Train (2009) "Discrete Choice Methods with Simulation."

Now, obtain *counterfactual* equilibrium price and quantity using *fixed point algorithm*:

For each market (country-year), find $\left(\hat{p}_j, \hat{q}_j\right)\ s.t.$ (1) and (2) hold. Start with a guess p_j^0 close to the true value with a random component, e.g., $p_j^0 = p_j(0.95 + 0.1 * uniform(1))$.

Iteration #1:

$$\hat{q}_j^1 = \hat{s}_j(\hat{p}_j) \times M$$
$$\hat{p}_j^1 = \underbrace{X_j\gamma + \omega_j}_{p_j - \eta q_j} + \eta\hat{q}_j^1$$

… iteration # $l+1$:

$$\hat{q}_j^{l+1} = \hat{s}_j(\hat{p}_j) \times M$$
$$\hat{p}_j^{l+1} = X_j\gamma + \omega_j + \eta\hat{q}_j^{l+1}$$

Continue until $\left\|p_j^{l+1} - p_j^l\right\| < \varepsilon$

Numerical optimization: oligopolistic pricing, with single/multi-product firms

$$\hat{p}_j = argmin_{p_j} \left\| \hat{p}_j - \widehat{mc}_j - \underbrace{\widehat{\Delta}_{jk}^{-1} \times \hat{s}_j}_{\widehat{makeup}_j} \right\|^2 \quad (1)$$

$$\hat{q}_j = \Pr_j(\hat{p}_j) \times M = \hat{s}_j(\hat{p}_j) \times M \quad (2)$$

$$mc_j\left(\hat{q}_j\right) = \beta MPP_j^{cf} + X_j\gamma + \eta\hat{q}_j + \omega_j \quad (3)$$

$$\hat{s}_j = \frac{e^{\frac{\delta_j}{1-\sigma}}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{-\sigma}}{\sum_{g=0}^{G}\left(\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}\right)^{1-\sigma}}, \text{ where } \delta_j\left(\hat{p}_j\right) = X_j\beta + \xi_j - \alpha\hat{p}_j \quad (4)$$

$$\widehat{\Delta}_{jk} = \begin{cases} \alpha\hat{s}_j\left(\frac{1}{1-\sigma} - \frac{\sigma}{1-\sigma}\hat{s}_{j|g} - \hat{s}_j\right) & ,j = k \\ -\alpha\hat{s}_j\left(\frac{\sigma}{1-\sigma}\hat{s}_{k|g} + \hat{s}_k\right) & ,j \neq k, g_j = g_k, f_j = f_k \\ -\alpha\hat{s}_j\hat{s}_k & ,j \neq k, g_j \neq g_k, f_j = f_k \\ 0 & ,o.w.(i.e., f_j \neq f_k) \end{cases} \quad (5)$$

$$\hat{s}_{j|g} = \frac{e^{\frac{\delta_j}{1-\sigma}}}{\sum_{j\in g} e^{\frac{\delta_j}{1-\sigma}}}, \text{ where } \delta_j\left(\hat{p}_j\right) = X_j\beta + \xi_j - \alpha\hat{p}_j \quad (6)$$

Here, for each market, a profit maximization decision is built within (1) to ensure that the counterfactual new price is generated from Bertrand-Nash game by minimizing the squared distance between the price and the sum of marginal cost and markup. The latter two are simultaneously updated using (2) and (3) within the fmincon minimization within (1). I impose mild conditions that prices are positive and less than twice the actual non-counterfactual prices to ensure that price search is within a realistic range.

More specifically, the algorithm starts with an initial guess of $\hat{p}_j$ for each country-year market. It then calculates the objective function using $\hat{p}_j$, relevant demand and supply parameters, and the counterfactual marginal cost. The optimal new prices (from the first-order condition) is obtained using fmincon. The quantity and marginal cost are then updated with the above equation system.

Other counterfactuals

One can also obtain counterfactual estimations of oligopoly price setting with flat marginal cost curves. These results can be obtained with flexible adaptation to the above optimization code by revising the quantity part (set the quantity coefficients to zero) and use supply-side parameters from corresponding estimations (with flat marginal cost assumption).

Additional notes on alternative estimation approach

Alternatively, one can get the quantity equation (1) using a simulation approach (less efficient).

One can obtain equation (1) by simulating demand from the nested logit utility function.

$$u_{ijct} = \underbrace{X_{jct}\beta - \alpha p_{jct} + \xi_{jct}}_{\delta_{jct} = \ln(s_j) - \ln(s_0) - \sigma \ln(s_{j|g})} + \zeta_{ig(j)ct} + (1-\sigma)\varepsilon_{ijct}$$

Therefore, the utility from counterfactual prices for a given ct can be expressed as below. Where the $\zeta_{ig(j)} + (1-\sigma)\varepsilon_{ij}$ cannot be simulated with the independent GEV simulator in MATLAB but shall be simulated using the inverse CDF approach based on the nested logit CDF (Train book, p. 79, equation (4.1)).

$$u_{ij}(\hat{p}_j) = \underbrace{X_j\beta + \xi_j}_{\delta_j - \alpha p_j} + \alpha\, \hat{p}_j + \zeta_{ig(j)} + (1-\sigma)\varepsilon_{ij}$$

To simulate the utility for N_{sim} =100,000 consumers across drugs in a given market (country-year), draw $N_{sim} \times J$ nested logit errors from the Generalized Extreme Value (GEV) distribution. Here $j \in \{0,1,\dots,J\}$ indicates distinct drugs within a market, including the outside option 0. For each simulated consumer i, (1) calculate the $u_{ijct}, \forall j$, (2) find the j that maximizes utility for i, and (3) define the realized choices for person i as $z_j(i) = 1$ if i choses j.

With the realized choices, one can calculate $\hat{s}_j = \frac{\sum_i^{N_{sim}} z_j(i)}{N_{sim}}$ and $\hat{q}_j = M \times s_j$ for a single market. Then, repeat the process for each country-year market and save the results into a vector for (2).

A.3.3. Graphic representation of model fit, and additional results

To test the performance of the optimization and fixed-point algorithm, I use actual data instead of counterfactual values to test whether I can reproduce actual prices and quantities. In addition, I run the algorithm multiple times and confirmed the results are not sensitive to the initial guess. The numeric precision is about 99% in all these placebo tests. I report graphic representation below. In all cases, the placebo prices and quantities well fit with the 45-degree lines.[98]

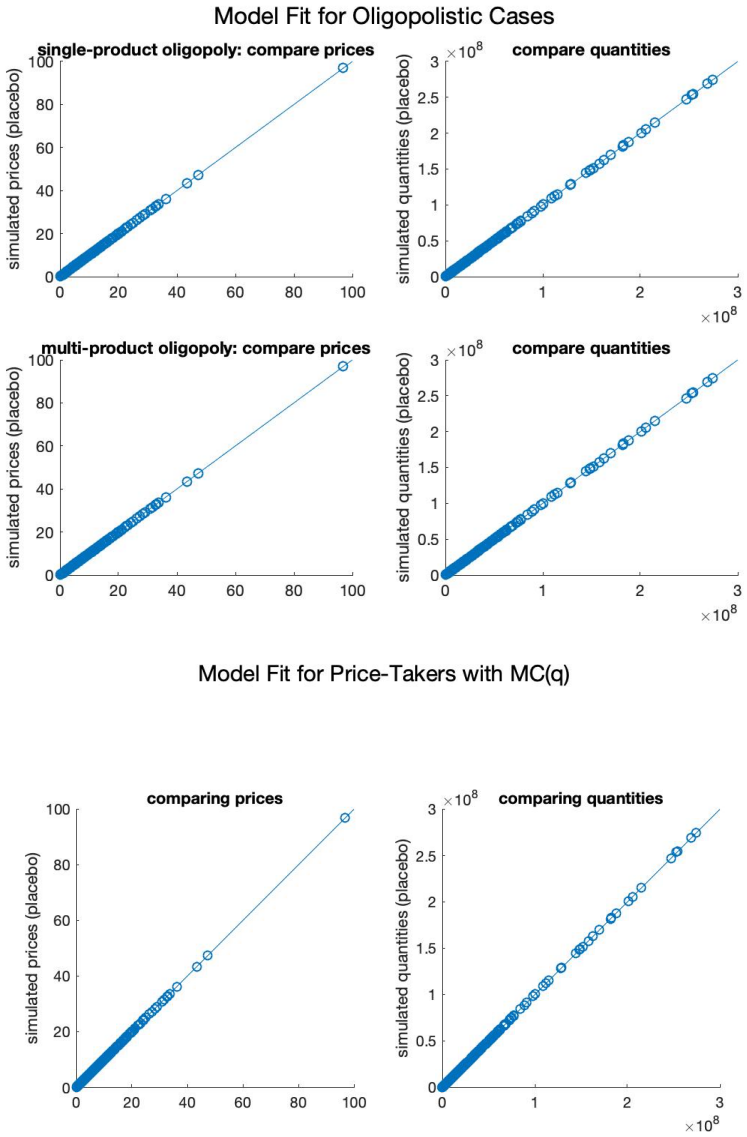


Figure A8: Visualization of Model Fit (across assumptions)

[98] I also produced corresponding graphs for "actual *vs.* counterfactual" and they are available upon request.

Additional results with alternative marginal cost assumptions

In the main analyses, I use flat marginal cost for competitive pricing and increasing marginal cost for oligopolistic pricing. These assumptions are good choices to capture the differences that compacity constraints matter in the two cases I study. This also provides more conservative estimates of the welfare gains from the MPP to consumers and producers.

As an additional exercise and comparison, I also produced the opponent counterfactuals. Specifically, price-taking firms with increasing marginal cost curves and oligopolistic pricing with flat marginal cost curves. From a realistic standpoint, the former case is more interesting as a transition stage of the two cases I discussed in the main text. However, it is worth noting that "price-takers with increasing marginal cost curve" is a typical case where the counterfactual producer surplus can explode. The reason is that when extrapolating the MC(q=0) point that is needed for calculating the producer surplus triangle, MC(q) curve would generate many negative prices with small quantities that would not be observed in the data. In other words, the in-sample fit can be fine, but the 0.5*beta(q)*q^2 provide overly large estimation for producer surplus (grey numbers), despite the still reasonable estimates of relative changes. The "oligopolistic pricing with flat MC" case uses strong assumptions that firms actively optimize and extract profit in LMICs without any capacity constraint, which contradicts reality and thus generate larger divisions in counterfactual cases. I report them below for a comparison.

Table A14: Welfare Re-Estimation: Additional results- alternative MC assumptions

welfare estimates ($ M)	MC pricing MC(q)	Oligopolistic Pricing (w/ flat MC) single-prod. firm	multi-prod. firm
$E(\widehat{CS_0})$	8,112.5	6,409.2	6,246.4
$E(CS)$	8,747.7	8,747.7	8,747.7
$E(\widehat{CS_1})$	8,836.3	8,821.1	8,811.5
Δ$: CS_0	635.2	2,338.5	2,501.3
Δ%: CS_0	7.83%	36.49%	40.04%
Δ$: CS_1	88.6	73.4	63.8
Δ%: CS_1	1.01%	0.84%	0.73%
$E(\widehat{PS_0})$	252$B	3,071.3	3,315.2
$E(PS)$	266$B	4,179.5	4,309.6
$E(\widehat{PS_1})$	267$B	4,271.8	4,392.1
Δ$: PS_0	14.1$B	1,108.2	994.4
Δ%: PS_0	5.58%	36.08%	30.00%
Δ$: PS_1	338.4	92.3	82.5
Δ%: PS_1	0.13%	2.21%	1.91%

Additional graphs regarding these additional cases are available upon request.

Appendix A.4: Medical Appendix

Brief Explanation of the Background and Classes of Antiretroviral Therapy

Human immunodeficiency virus (HIV) infects the immune system's cells, resulting in the impairment or destruction of their functions. Such an infection leads to the progressive deterioration of the immune system, generating *immune deficiency*. This deficiency can be defined as the condition in which the immune system can no longer fight any infection or disease. Unlike certain other viruses, HIV does not allow the human body to disinfect itself completely. Once a patient infected with HIV, that patient will have it for life. Consequently, acquired immunodeficiency syndrome (AIDS) can develop when HIV is left untreated. This stage of infection occurs when one's immune system is badly damaged, making one vulnerable to *opportunistic infections* – infections that occur more frequently and severely among people with weakened immune system. Such infections include tuberculosis and several cancers. Although AIDS is the final stage of HIV infection, not everyone who has HIV advances to this stage. An HIV infection can be contracted through three main routes: (1) unprotected sexual intercourse; (2) the sharing of contaminated syringes, needles, surgical equipment or other sharp instruments and transfusion of contaminated blood; (3) from a mother to her infant during pregnancy, childbirth, and breastfeeding.

People with AIDS and left untreated typically survive about three years on average. Once dangerous opportunistic illnesses develop, an infected person's life expectancy without treatment falls to about one year. Although medical treatment is necessary to prevent the death of AIDS patients, no effective cure currently exist. However, with proper treatment, it is possible to control HIV. The medicine used for the treatment of HIV is antiretroviral therapy (ART). According to the WHO guidelines, standard ART consists of a combination of drugs to maximally suppress HIV and inhibit the disease's progression. In addition, this therapy prevents further transmission of HIV. As a result, huge reductions in death rates and infection rates have been documented when using a potent ART regimen, especially in the early stages of the disease. The WHO recommends that people with HIV undergo ART as soon as possible after diagnosis without restrictions of the CD4 counts (a type of immune cells greatly reduced in HIV patients). It also recommends pre-exposure prophylaxis for people at high risk of HIV infection as an additional option among other non-drug based comprehensive prevention plans.

Table A15: ART drug classes

Drug class (abbr.)	Simple description (mechanisms of action explanations)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	block reverse transcriptase, an enzyme HIV needs to make copies of itself.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	bind to and later alter reverse transcriptase, an enzyme HIV needs to make copies of itself.
Protease Inhibitors (PIs)	block HIV protease, an enzyme HIV needs to make copies of itself.
Fusion inhibitor (FIs)	block HIV from entering the CD4 cells of the immune system, e.g., HR1.
Entry inhibitor (EIs)	block proteins on the CD4 cells that HIV needs to enter the cells, CCR5.
Integrase Inhibitors (IIs)	stop HIV from making copies of itself by blocking a key protein that allows the virus to put its DNA into the healthy cell's DNA.
Enhancers	help other ART work better by enhancing the blood levels.

Notes: (1) the distinctions between FIs and EIs are not substantial, mainly on which protein the drug binds to block HIV virus from entering the CD4 cells. In many cases they are grouped together into one broader class. (2) Entry inhibitors have multiple sub-classes, e.g., CCR5 inhibitor, post-attachment inhibitor (the new compound, IBA), etc.

Table A16: Clinical Guidelines on ART Standard Dosing (U.S. adult daily doses)

drug API code	adult daily dose	Notes
ABC	600 mg	
ATV	300 mg	
DRV; TCM	800 mg	
ddI	400 mg	250mg/d if weight <60kg
DTG	50 mg	
EFV	600 mg	
FTC	200 mg	
ENF; T20	180 mg	
ETR; ETV	400 mg	
FPV	1400 mg	
IDV	1600 mg	
3TC	300 mg	
MVC	600 mg	
NFV	2500 mg	2250 mg when taken 3 times/day
NVP	400 mg	Phase in: 200mg in the first 14 days
RAL	800 mg	
r; RTV	200 mg	The avg./mode: 100-400mg/d; depends on other compounds used
SQV	2000 mg	
d4T	80 mg	60mg if weight <60kg.
TDF	300 mg	
TPV	1000 mg	
ZDV; AZT	600 mg	FDA: 600mg; WHO 250-300mg
ABC+3TC	600+300 mg	
ABC+3TC+ZDV	600+300+600 mg	
ATV+r	300+100 mg	
EFV+FTC+TDF	600+200+300 mg	
EFV+3TC+TDF	600+300+300 mg	
EFV+3TC+ZDV	600+300+600 mg	
FTC+TDF	200+300 mg	
3TC+NVP+d4T	300+400+80 mg	if <60kg, then 300+400+60 mg
3TC+NVP+ZDV	300+400+600 mg	
3TC+d4T	300+80 mg	
3TC+TDF	300+300 mg	
3TC+TDF+NVP	300+300+400 mg	
3TC+ZDV	300+600 mg	
LPV+r	800+200 mg	

Notes: This table is used to convert active pharmaceutical ingredients (API) into standardized U.S. adult drug daily doses as a quantity-adjusted measure. Five observations in grey are dropped from the sample as they only appear in the data for a handful of times. I checked drug dosing guidelines using AIDS*info* and FDA labeling, and consulted WHO guidelines for global standards. The above measures are recorded as adult daily dosing for a representative patient weighted over 60 kg (the average adult weights are above 60 kg in most countries but can be smaller in low-income and developing countries). The localized doses can be smaller than the U.S. guideline in resource-limited developing countries. In the absence of country-specific clinical guidelines, I use this U.S. adult-based conversion as one outcome of interest.

Table A17: 2017 and 2012 top selling HIV drugs and MPP status

The two tables here are used to demonstrate top-selling HIV drugs.

Table A17.1: HIV drugs among 2017 top 200 drugs by global sales

rank 2017	HIV drugs among top 200 drugs by global sales, 2017	generic abbreviations	MPP status (by 12/31/2017)	sales ($M)
24	Genvoya	EVG+TAF+FTC+COBI	all in	3,730
31	Triumeq	ABC+DTG+3TC	out*+in+out	3,172
32	Truvada	FTC+TDF	all in	3,169
72	Prezista/Prezcobix/Rezolsta	[Prezista]: DRV; [Prezcobix/Rezolsta for US/Europe]:DRV+COBI	out$; out$+in	1,821
74	Tivicay	DTG	in	1,810
75	Atripla	EFV+FTC+TDF	out+in+in	1,806
100	Descovy	FTC+TAF	in	1,300
109	Isentress and Isentress HD	RAL	out*	1,204
120	Odefsey	FTC+RPV+TAF	out+in	1,106
126	Stribild	EVG+COBI+FTC+TDF	all in	1,054
129	Viread	TDF	in	1,046
139	Complera/Eviplera	[US/European]: RPV+FTC+TDF	out+in+in	966
191	Sustiva franchise (includes sales of bulk efavirenz)	EFV	out	729
196	Edurant/rilpivirine	RPV	out	714

Table A17.2: HIV drugs among 2012 top 100 drugs by global sales

rank 2012	HIV drugs among top 100 drugs by global sales, 2012	generic abbreviations	MPP status (by 12/31/2017)	sales ($M)
26	Atripla	EFV+FTC+TDF	out+in+in	3574
29	Truvada	FTC+TDF	all in	3,303
67	Sustiva franchise (includes sales of bulk efavirenz)	EFV	out	1,527
68	Reyataz	ATV	in	1521
71	Isentress	RAL	out*	1515
76	Prezista	DRV	out$	1414

Notes: out* means restrictive MPP licenses (pediatric-only) and treated as outside the pool for conservative estimates. out$ means the corresponding drug is not officially in the pool but have price arrangements with the MPP. The top selling drug list is obtained from Med Ad News report and has been used in previous studies. For more details regarding the source, see Duggan and Scott Morton (2006).

Reference: Duggan, M., & Scott Morton, F. M. (2006). The distortionary effects of government procurement: evidence from Medicaid prescription drug purchasing. *The Quarterly Journal of Economics*, *121*(1), 1-30.

Appendix A.5: Legal Appendix

Table A18: Key MPP license contract terms
(Simple explanations of abbreviations are listed at the end of the table)

API code	firm	eligibility for sublicenses (manufacturing)	sales scope: # countries	sales outside territory	royalty rates (in territory)	technology transfer	additional flexibilities
ABC (ped.)	ViiV	worldwide	121	permitted if no granted patents or non-infringing	0%	n/a	challenge
ATV	BMS	worldwide	122	enables those not relying on BMS tech to sell if not infringe granted patents	3%: adult forms in countries w/ patents; 0%: ped., or sub-Saharan/ India sales	provided to all sublicensees, no obligation to use	n/a
BIC	Gilead	China, India, South Africa	116	permitted if compulsory license issued	5% of FP net sales. 0% on API/ped. formulation.	one time for Indian & South-African sub-licensees	terminate; challenge
COBI	Gilead	China, India, South Africa	116	permitted if compulsory license issued	5% of FP net sales. 0% on API/ped. forms.	one time for Indian & South-African sub-licensees	terminate; challenge
DTG (adult; ped.)	ViiV	worldwide	adult: 94; ped.: 121	permitted if no granted patents or non-infringing	0%: all ped. & adults in 82 countries; 5%: Philippines, India, Vietnam, Moldova; 7.5%: Egypt, Indonesia, Morocco, Armenia, Ukraine, Mongolia, Tunisia; 10%: Turkmenistan	n/a	challenge
EVG	Gilead	China, India, South Africa	109	permitted if compulsory license issued	5% of FP net sales. 0% on API/ped. sales	one time for Indian sub-licensees	terminate; challenge
FTC	Gilead	China, India, South Africa, & licensed on TDF, TAF, COBI, EVG, even if terminated	116	possible if not infringe any granted patents	0%; there may be royalties on other components of any specific combination	n/a	licensees terminated TDF can still benefit from no-sue on tdf/ftc, taf/ftc, & tdf/ftc/efv
LPV/r (adult; ped.)	AbbVie	worldwide	adult: all 54 African; ped.: 102	permitted if not infringe granted patents	0%	n/a	challenge
RAL (ped.)	MSD	worldwide	92	permitted if not infringe granted patents	0%	n/a	challenge
TAF	Gilead	China, India, South Africa	116	permitted if compulsory license issued	5% of FP net sales. 0% on API/ped. sales	one time for Indian sub-licensees	terminate; challenge
TDF	Gilead	China, India, South Africa	116	permitted if compulsory license issued	3-5% of FP net sales. 0% on API/ped. sales.	one time for Indian & South-African sub-licensees	terminate

Notes: (1) common information omitted in the table: all of these licenses allow flexible compound combinations, all waive data exclusivity, all agree patents pooled include all pending and granted patents, and all agree to let WHO or a stringent regulatory authority (SRA), such as U.S. FDA, to help with quality-assurance. (2) A typical example for sales outside of territory when non-infringing is in the presence of compulsory license. (3) the sublicensing territory defines the manufacturing territory and the sales scope defined the countries available for sales using MPP licenses. (4) The "countries" defined in the sale scope (geographic territory) are economy/countries as in the World Bank/United Nations definition, but not necessarily a sovereign state (e.g., certain commonwealths are treated as an independent "country" in measures of economics/development). (5) API = Active Pharmaceutical Ingredient (i.e., compound, for small molecule drugs). FP = finished products. (6) Contracts regarding "manufacturing" in the MPP typically do not distinguish between API vs. FP manufacturers. (7) In the last column, "challenge" = allow patent challenges; "terminate" = allow termination of licensing agreements.

Source: The Medicines Patent Pool official website product page (https://medicinespatentpool.org/what-we-do/global-licence-overview/licences-in-the-mpp/), collected from each compound's key features and detailed/corrected a few incidences with raw information from the MPP (sub-)licensing contracts. Last updated: December 31, 2018.

Panel A19: Drug-Territory Coverage Final Panel (by end of 2018)

Country names	code	ldc	atv	bic	cobi	dtg	evg	ftc	lpv/r	taf	tdf
Afghanistan	AFG	1	2013	2017	2011	2014	2011	2011		2014	2011
Algeria	DZA	0	2017						2015		
Angola	AGO	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Anguilla	AIA	0		2017	2011		2011	2011		2014	2011
Antigua and Barbuda	ATG	0	2013	2017	2011		2011	2011		2014	2011
Armenia	ARM	0	2013	2017	2011	2016	2011	2011		2014	2011
Aruba	ABW	0		2017	2011			2011		2014	2011
Azerbaijan	AZE	0	2013								
Bahamas	BHS	0		2017	2011		2011	2011		2014	2011
Bangladesh	BGD	1	2013	2017	2011	2014	2011	2011		2014	2011
Barbados	BRB	0		2017	2011		2011	2011		2014	2011
Belarus	BLR	0	2013	2017	2017			2017		2017	2017
Belize	BLZ	0	2013	2017	2011		2011	2011		2014	2011
Benin	BEN	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Bhutan	BTN	1	2013	2017	2011	2014	2011	2011		2014	2011
Bolivia	BOL	0	2013	2017	2011	2014	2011	2011		2014	2011
Botswana	BWA	0	2013	2017	2017	2014	2017	2011	2015	2014	2011
British Virgin Islands	VGB	0		2017	2011		2011	2011		2014	2011
Burkina Faso	BFA	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Burundi	BDI	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Cambodia	KHM	1	2013	2017	2011	2014	2011	2011		2014	2011
Cameroon	CMR	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Cape Verde	CPV	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Central African Republic	CAF	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Chad	TCD	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Comoros	COM	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Cook Islands	COK	0	2017								
Costa Rica	CRI	0	2013								

Côte d'Ivoire	CIV	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Cuba	CUB	0	2013	2017	2011		2011	2011		2014	2011
Dem. Republic of the Congo	COD	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Djibouti	DJI	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Dominica	DMA	0	2013	2017	2011		2011	2011		2014	2011
Dominican Republic	DOM	0	2013	2017	2011			2011		2014	2011
Ecuador	ECU	0	2013	2017	2017		2017	2011		2014	2011
Egypt	EGY	0	2017			2014			2015		
El Salvador	SLV	0	2013	2017	2017	2014	2017	2011		2014	2011
Equatorial Guinea	GNQ	0	2017	2017	2011	2014	2011	2011	2015	2014	2011
Eritrea	ERI	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Ethiopia	ETH	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Fiji	FJI	0	2013	2017	2011		2011	2011		2014	2011
Gabon	GAB	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Gambia	GMB	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Georgia	GEO	0	2013	2017	2011	2014	2011	2011		2014	2011
Ghana	GHA	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Grenada	GRD	0	2013	2017	2011		2011	2011		2014	2011
Guatemala	GTM	0	2013	2017	2011	2014	2011	2011		2014	2011
Guinea	GIN	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Guinea-Bissau	GNB	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Guyana	GUY	0	2013	2017	2011	2014	2011	2011		2014	2011
Haiti	HTI	1	2013	2017	2011	2014	2011	2011		2014	2011
Honduras	HND	0	2013	2017	2011	2014	2011	2011		2014	2011
India	IND	0	2013	2017	2011	2014	2011	2011		2014	2011
Indonesia	IDN	0	2017	2017	2017	2014	2017	2011		2014	2011
Iraq	IRQ	0	2013								
Jamaica	JAM	0	2013	2017	2011		2011	2011		2014	2011
Kazakhstan	KAZ	0	2013	2017	2017		2017	2011		2014	2011
Kenya	KEN	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Kiribati	KIR	1	2013	2017	2011	2014	2011	2011		2014	2011
Korea Dem. Republic	PRK	0	2013			2014					
Kosovo	XKX	0				2014					
Kyrgyzstan	KGZ	0	2013	2017	2011	2014	2011	2011		2014	2011
Lao PDR	LAO	1	2013	2017	2011	2014	2011	2011		2014	2011
Lebanon	LBN	0									
Lesotho	LSO	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Liberia	LBR	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Libya	LBY	0	2013						2015		
Madagascar	MDG	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Malawi	MWI	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Malaysia	MYS	0	2017	2017	2017			2017		2017	2017
Maldives	MDV	0	2013	2017	2011		2011	2011		2014	2011
Mali	MLI	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Marshall Islands	MHL	0	2013								
Mauritania	MRT	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Mauritius	MUS	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Micronesia	FSM	0	2013			2014					

Moldova	MDA	0	2013	2017	2011	2016	2011	2011		2014	2011
Mongolia	MNG	0	2013	2017	2011	2014	2011	2011		2014	2011
Montserrat	MSR	0		2017	2011			2011		2014	2011
Morocco	MAR	0	2017			2016			2015		
Mozambique	MOZ	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Myanmar	MMR	1	2013	2017	2011	2014	2011	2011		2014	2011
Namibia	NAM	0	2013	2017	2017	2014	2017	2011	2015	2014	2011
Nauru	NRU	0	2013	2017	2011		2011	2011		2014	2011
Nepal	NPL	1	2013	2017	2011	2014	2011	2011		2014	2011
Nicaragua	NIC	0	2013	2017	2011	2014	2011	2011		2014	2011
Niger	NER	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Nigeria	NGA	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Niue	NIU	0	2017								
Pakistan	PAK	0	2013	2017	2011	2014	2011	2011		2014	2011
Palau	PLW	0	2013	2017	2011		2011	2011		2014	2011
Palestine	PSE	0	2013			2014					
Panama	PAN	0	2013								
Papua New Guinea	PNG	0	2013	2017	2011	2014	2011	2011		2014	2011
Philippines	PHL	0	2017	2017	2017	2014		2017		2017	2017
Republic of the Congo	COG	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Rwanda	RWA	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Samoa	WSM	0	2013	2017	2011	2014	2011	2011		2014	2011
Sao Tome and Principe	STP	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Senegal	SEN	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Seychelles	SYC	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Sierra Leone	SLE	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Solomon Islands	SLB	1	2013	2017	2011	2014	2011	2011		2014	2011
Somalia	SOM	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
South Africa	ZAF	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
South Sudan	SSD	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Sri Lanka	LKA	0	2013	2017	2017	2014	2017	2011		2014	2011
St Lucia	LCA	0	2013	2017	2011		2011	2011		2014	2011
St. Kitts and Nevis	KNA	0	2013	2017	2011		2011	2011		2014	2011
St. Vincent & the Grenadines	VCT	0	2013	2017	2011		2011	2011		2014	2011
Sudan	SDN	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Suriname	SUR	0	2013	2017	2011		2011	2011		2014	2011
Swaziland	SWZ	0	2013	2017	2011	2014	2011	2011	2015	2014	2011
Syrian Arab Republic	SYR	0	2013	2017	2011	2014	2011	2011		2014	2011
Tajikistan	TJK	0	2013	2017	2011	2014	2011	2011		2014	2011
Tanzania	TZA	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Thailand	THA	0		2017	2017		2017	2011		2014	2011
Timor-Leste	TLS	1	2013	2017	2011	2014	2011	2011		2014	2011
Togo	TGO	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Tonga	TON	0	2013	2017	2011		2011	2011		2014	2011
Trinidad and Tobago	TTO	0		2017	2011		2011	2011		2014	2011
Tunisia	TUN	0	2017			2014			2015		
Turkmenistan	TKM	0	2013	2017	2017	2014	2017	2011		2014	2011
Turks and Caicos Islands	TCA	0		2017	2011		2011	2011		2014	2011

Tuvalu	TUV	1	2013	2017	2011	2014	2011	2011		2014	2011
Uganda	UGA	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Ukraine	UKR	0	2017	2017	2017	2016		2017		2017	2017
Uzbekistan	UZB	0	2013	2017	2011	2014	2011	2011		2014	2011
Vanuatu	VUT	1	2013	2017	2011	2014	2011	2011		2014	2011
Vietnam	VNM	0	2017	2017	2011	2014	2011	2011		2014	2011
Yemen	YEM	1	2013	2017	2011	2014	2011	2011		2014	2011
Zambia	ZMB	1	2013	2017	2011	2014	2011	2011	2015	2014	2011
Zimbabwe	ZWE	0	2013	2017	2011	2014	2011	2011	2015	2014	2011

Notes: The above table include the complete licensing territories for adult formulations specified in MPP contracts by end of 2018. Among all the countries that ever covered in the MPP territory, only three are not developing countries by the World Bank 2018 classifications: Belarus, Moldova, and Ukraine. The country code reported in the table and used in the analysis is the ISO three-digit alphabetical code that uniquely identify a country. Given the multiple ways of country name spellings and historical country name changes (e.g., most recently in Apr. 2018, Swaziland to eSwatini), the most rigorous way is to merge any country-involved data set using country code instead of country names.

List of the 103 countries (and code) covered in the Global Fund data in the Diffusion Analysis:

Afghanistan (AFG), Albania (ALB), Angola (AGO), Armenia (ARM), Azerbaijan (AZE), Bangladesh (BGD), Belarus (BLR), Belize (BLZ), Benin (BEN), Bhutan (BTN), Bolivia (Plurinational State) (BOL), Bulgaria (BGR), Burkina Faso (BFA), Burundi (BDI), Cambodia (KHM), Cameroon (CMR), Cape Verde (CPV), Central African Republic (CAF), Chad (TCD), China (CHN), Colombia (COL), Comoros (COM), Congo (COG), Congo (Democratic Republic) (COD), Croatia (HRV), Cuba (CUB), CÃ´te d'Ivoire (CIV), Djibouti (DJI), Dominican Republic (DOM), Ecuador (ECU), Egypt (EGY), El Salvador (SLV), Equatorial Guinea (GNQ), Eritrea (ERI), Ethiopia (ETH), Gabon (GAB), Gambia (GMB), Georgia (GEO), Ghana (GHA), Guatemala (GTM), Guinea (GIN), Guinea-Bissau (GNB), Guyana (GUY), Haiti (HTI), Honduras (HND), India (IND), Indonesia (IDN), Iran (Islamic Republic) (IRN), Jamaica (JAM), Jordan (JOR), Kazakhstan (KAZ), Kenya (KEN), Kyrgyzstan (KGZ), Lao (Peoples Democratic Republic) (LAO), Lesotho (LSO), Liberia (LBR), Macedonia (Former Yugoslav Republic) (MKD), Madagascar (MDG), Malawi (MWI), Mali (MLI), Mauritania (MRT), Mauritius (MUS), Moldova (MDA), Mongolia (MNG), Morocco (MAR), Mozambique (MOZ), Myanmar (MMR), Namibia (NAM), Nepal (NPL), Nicaragua (NIC), Niger (NER), Nigeria (NGA), Pakistan (PAK), Palestine (PSE), Papua New Guinea (PNG), Paraguay (PRY), Peru (PER), Philippines (PHL), Russian Federation (RUS), Rwanda (RWA), Sao Tome and Principe (STP), Senegal (SEN), Sierra Leone (SLE), Somalia (SOM), South Africa (ZAF), South Sudan (SSD), Sri Lanka (LKA), Sudan (SDN), Suriname (SUR), Swaziland (SWZ), Tajikistan (TJK), Tanzania (United Republic) (TZA), Thailand (THA), Timor-Leste (TLS), Togo (TGO), Tunisia (TUN), Uganda (UGA), Ukraine (UKR), Uzbekistan (UZB), Viet Nam (VNM), Yemen (YEM), Zambia (ZMB), Zimbabwe (ZWE)

APPENDIX B

APPENDIX FOR CHAPTER 2

Table B1: HCUP Fast Stat Opioid-Topic Years of Data Availability (by Outcome Groups)

State	Opioid-Related Inpatient Stays					Opioid-Related Emergency Room Visits				
	Total	Ages	Income	Location	Insurer	Total	Ages	Income	Location	Insurer
AZ	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
AR	05-15	05-15	06-15	05-15	05-15	13-15	13-15	13-15	13-15	13-15
CA	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
CO	05-15	05-15	06-15	05-15	05-15	NA	NA	NA	NA	NA
CT	05-15	05-15	06-15	05-15	NA	05-15	05-15	06-15	05-15	NA
DC	13-15	13-15	13-15	NA	NA	14-15	14-15	14-15	14-15	NA
FL	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
GA	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
HI	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
IL	05-15	05-15	06-15	05-15	05-15	09-15	09-15	09-15	09-15	09-15
IN	05-15	06-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
IA	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
KS	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
KY	05-15	05-15	06-15	05-15	05-15	08-15	08-15	08-15	08-15	08-15
LA	08-15	08-15	08-15	08-15	08-15	NA	NA	NA	NA	NA
ME	06-15	06-15	06-15	06-15	06-15	06-14	06-14	06-14	06-14	06-14
MD	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
MA	05-15	05-15	06-15	05-15	05-15	05-14	05-14	06-14	05-14	05-14
MI	05-15	05-15	06-15	05-15	05-15	NA	NA	NA	NA	NA
MN	05-15	06-15	05-15	05-15	05-15	05-15	05-15	05-15	05-15	05-15
MO	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
MT	09-15	09-15	09-15	09-15	09-15	14-15	14-15	14-15	14-15	14-15
NE	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
NV	05-15	05-15	06-15	05-15	05-15	10-15	10-15	10-15	10-15	10-15
NJ	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
NM	08-15	08-15	08-15	08-15	08-15	NA	NA	NA	NA	NA
NY	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
NC	05-15	05-15	06-15	05-15	05-15	07-15	07-15	07-15	07-15	07-15
ND	11-15	11-15	11-15	11-15	11-15	11-15	11-15	11-15	11-15	11-15
OH	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	NA
OK	05-15	05-15	05-15	05-15	05-15	NA	NA	NA	NA	NA
OR	05-15	05-15	06-15	05-15	05-15	NA	NA	NA	NA	NA
PA	08-15	08-15	08-15	08-15	08-15	NA	NA	NA	NA	NA
RI	05-15	05-15	06-15	05-15	05-15	06-15	06-15	06-15	06-15	06-15
SC	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
SD	05-15	05-15	06-15	06-15	05-15	05-15	07-15	07-15	05-15	07-15
TN	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
TX	05-15	05-15	06-15	05-15	05-15	NA	NA	NA	NA	NA
UT	05-15	05-15	06-15	05-15	05-15	05-14	05-14	06-14	05-14	05-14
VT	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
VA	06-15	06-15	06-15	06-15	06-15	NA	NA	NA	NA	NA
WA	05-15	05-15	06-15	05-15	05-15	NA	NA	NA	NA	NA
WV	05-15	05-15	06-15	05-15	05-15	NA	NA	NA	NA	NA
WI	05-15	05-15	06-15	05-15	05-15	05-15	05-15	06-15	05-15	05-15
WY	07-15	07-15	07-15	07-15	07-15	14-15	14-15	14-15	14-15	14-15

Notes: During my sample period, 34 states participated in the HCUP State Emergency Department Database and 44 states participated in the State Inpatient Database (last accessed: Dec. 2017). This table records total opioid-related discharge data availability information at group-level. There is different degree of missing across stratified outcomes. A color-coded spreadsheet documenting variable-level data availability is available upon request.

Table B2: Integration Policy interact with EHR% Adoption

outcomes	overall opioid deaths		overall morbidity		inpatient rate, by age group		
	any	illicit	inpatient	ER visits	25-44	45-64	65+
integration	-0.323	-0.374	-41.60**	-0.317	-68.43**	-52.42***	-39.81
xEHR%	(0.278)	(0.243)	(17.10)	(13.44)	(31.65)	(19.35)	(29.70)
interstate	0.0184	-0.0842	-6.621	5.579	-9.607	-9.583	-17.11
	(0.150)	(0.139)	(8.294)	(6.817)	(17.53)	(11.57)	(14.05)
N	2,244	2,244	1,856	1,256	1,851	1,850	1,822
outcomes	inpatient rate, by income quartile				inpatient rate, by expected payer		
	Q1	Q2	Q3	Q4	Medicare	Medicaid	Private
integration	-81.33*	-38.17*	-9.310	-19.55**	-19.54**	-40.29*	-0.965
xEHR%	(42.71)	(19.14)	(12.93)	(9.149)	(9.429)	(20.56)	(15.38)
interstate	-13.87	-10.40	-11.19	-10.71**	-6.150	-3.297	0.0135
	(15.73)	(10.82)	(7.435)	(4.498)	(4.720)	(10.17)	(0.833)
N	1,641	1,700	1,694	1,483	1,784	1,741	1,137

Notes: This table reports the re-estimated results of the baseline model using equation 1 replace the integration and HIT control variables with integration interacting with HIT, where HIT is measured as % of state-quarter EHR adoption (0-1). Only coefficients of interests are reported for simplicity. Each column name represents a dependent variable in a separate regression. Fixed effects for states and year-quarters are always included. Robust standard errors are clustered at the state level and are reported in parentheses. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table B3: Policy Impact in the Absence of Potential Confounders

outcomes	overall opioid deaths		overall morbidity		inpatient rate, by age group		
	any	illicit	inpatient	ER visits	25-44	45-64	65+
Baseline: Full Set of Controls							
integration	-0.253	-0.303*	-33.86***	-2.102	-54.33**	-42.34**	-35.27
	(0.197)	(0.173)	(11.95)	(9.340)	(22.71)	(13.55)	(21.14)
interstate	0.0129	-0.0804	-6.823	5.489	-9.956	-9.551	-17.94
	(0.152)	(0.142)	(8.313)	(6.905)	(17.68)	(11.77)	(14.06)
Limited Controls							
integration	-0.329	-0.424*	-34.11***	-4.440	-56.39***	-41.55***	-31.95*
	(0.235)	(0.221)	(10.50)	(16.80)	(20.03)	(12.55)	(18.43)
interstate	0.0234	-0.0619	-5.957	5.848	-6.209	-9.759	-18.95
	(0.158)	(0.156)	(8.276)	(9.224)	(18.93)	(11.17)	(14.12)

outcomes	inpatient rate, by income quartile				inpatient rate, by expected payer		
	Q1	Q2	Q3	Q4	Medicare	Medicaid	Private
Baseline: Full Set of Controls							
integration	-59.98*	-30.75**	-10.22	-17.62***	-16.64**	-31.21**	-0.724
	(29.75)	(13.57)	(9.387)	(6.394)	(6.687)	(13.87)	(0.945)
interstate	-13.93	-10.04	-11.29	-11.27**	-6.483	-2.131	-0.120
	(15.75)	(11.08)	(7.520)	(4.482)	(4.683)	(10.01)	(0.810)
Limited Controls							
integration	-56.43**	-34.84***	-12.87	-20.32***	-15.55**	-30.93**	-0.956
	(26.81)	(12.92)	(12.37)	(5.933)	(5.827)	(12.15)	(0.888)
interstate	-10.93	-10.01	-10.93	-11.66**	-6.642	2.804	-0.451
	(15.46)	(11.13)	(8.415)	(5.157)	(4.395)	(10.13)	(0.902)

Notes: This table reports the results using equation 1, excluding other policy controls. The panel with limited controls excludes the group of other policy controls: unemployment rate, large pill mill crackdowns, naloxone access laws, Good Samaritan overdose laws, medical marijuana dispensary laws, and Medicaid expansion. Each column name represents a dependent variable in a separate regression. Fixed effects for states and year-quarters are always included. Robust standard errors are clustered at the state level and are reported in parentheses. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table B4: Estimating Policy Impacts on Placebo Outcomes

Inpatient outcomes	opioid-related	total non-opioid	total non-opioid injury	mental health	asthma
integration	-33.86***	-43.33	8.394***	8.184*	-1.121
	(11.95)	(31.42)	(2.550)	(4.281)	(0.690)
interstate	-6.823	20.20	3.810	2.651	-0.0597
	(8.313)	(20.42)	(2.377)	(2.579)	(0.395)
LHS mean	190	1989	60	64	16
N	1,856	1,800	1,768	1,788	1,726

Notes: This table reports the baseline results of the integration policy and interstate sharing on inpatient outcomes and the re-estimated coefficients using placebo outcome variables. Each column reports the results of a separate regression. All dependent variables are discharge rates per 100,000 population. Fixed effects for states and year-quarters are always included. Robust standard errors are clustered at the state level and are reported in parentheses. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table B5: Testing Complementarity between Integration and Interstate Sharing

outcomes	overall opioid deaths		overall morbidity		inpatient rate, by age group		
	any	illicit	inpatient	ER visits	25-44	45-64	65+
integration & interstate	-0.368	-0.491**	-35.81***	-1.768	-52.75*	-52.62***	-58.41***
	(0.247)	(0.237)	(12.33)	(11.79)	(26.37)	(14.97)	(19.10)
integration only	0.00782	-0.0832	-42.13**	7.454	-73.95**	-41.11*	-26.42
	(0.338)	(0.306)	(20.48)	(12.51)	(33.87)	(23.75)	(40.76)
interstate only	0.0618	-0.0392	-8.468	7.085	-13.86	-9.305	-16.17
	(0.161)	(0.151)	(8.102)	(6.998)	(18.28)	(12.04)	(13.88)
LHS mean	2.50	0.88	190	130	275	260	211
N	2,244	2,244	1,856	1,256	1,851	1,850	1,822
outcomes	inpatient rate, by income quartile				inpatient rate, by expected payer		
	Q1	Q2	Q3	Q4	Medicare	Medicaid	Private
integration & interstate	-59.71**	-41.32***	-22.12**	-27.38***	-23.22***	-22.01*	-0.488
	(25.48)	(12.62)	(10.40)	(7.508)	(6.677)	(12.28)	(1.298)
integration only	-84.84*	-29.80	-9.136	-19.96*	-16.49	-50.44**	-1.333
	(42.39)	(26.72)	(18.03)	(10.69)	(12.44)	(19.87)	(1.570)
interstate only	-18.93	-9.849	-11.07	-11.80***	-6.450	-6.152	-0.248
	(16.53)	(11.05)	(7.215)	(4.086)	(4.755)	(10.56)	(0.841)
LHS mean	308	208	170	132	89	96	15
N	1,641	1,700	1,694	1,483	1,784	1,741	1,789

Notes: This table reports the results of estimating equation 1 using three mutually exclusive variables. Each column name represents a dependent variable in a separate regression. Fixed effects for states and year-quarters are always included. Robust standard errors are clustered at the state level and are reported in parenthesis. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table B6: Results of Opioid-Related ER Visits, Stratified Outcomes
(unit: *per 100,000 population*)

	ER rate, by age group			ER rate, by income quartile				ER rate, by expected payer		
	25-44	45-64	65+	Q1	Q2	Q3	Q4	Medicare	Medicaid	Private
Panel A: full sample										
PDMP	-49.46*	-11.04	-2.354	-5.949	-18.20	-17.45*	-15.21*	-0.783	-5.515	-0.308
	(25.07)	(7.217)	(5.469)	(21.38)	(11.91)	(9.955)	(8.630)	(3.096)	(6.200)	(0.911)
mandate	17.31	-1.891	-0.553	-23.23	-12.88	19.31*	6.985	3.336	-2.691	-0.861
	(27.53)	(10.69)	(6.124)	(27.05)	(13.20)	(10.43)	(6.679)	(3.222)	(9.370)	(0.853)
integration	-21.98	12.02	-0.230	61.49	7.124	9.756	4.442	-2.439	2.583	-0.143
	(17.80)	(19.76)	(6.441)	(64.72)	(18.48)	(15.34)	(6.610)	(4.675)	(16.88)	(0.988)
interstate	6.301	8.725	0.995	1.769	8.293	-2.022	-4.839	2.747	8.924	0.440
	(19.44)	(7.324)	(4.526)	(19.28)	(14.74)	(6.759)	(5.122)	(2.248)	(6.682)	(0.659)
LHS mean	246	132	51	219	156	123	93	33	64	10
N	1,241	1,222	1,051	1,090	1,143	1,124	979	1,112	1,090	1,137
Panel B: in subsample of no-mandate states										
integration	-27.24	17.21	-7.363	61.87	17.52	21.01	-0.286	-4.800	7.050	-0.561
	(23.08)	(19.28)	(6.735)	(62.73)	(19.95)	(18.06)	(8.295)	(4.676)	(18.41)	(0.932)
interstate	0.896	0.846	-1.836	2.043	-9.484	-8.218	-7.426	1.606	4.629	-0.219
	(18.66)	(9.466)	(5.634)	(25.81)	(8.705)	(6.972)	(5.639)	(2.128)	(9.008)	(0.554)
LHS mean	203	124	55	190	134	104	81	31	58	10
N	817	801	688	717	751	735	626	785	757	801

Notes: This table reports the results of the baseline model using equation 1 in full sample and in states never mandated PDMP access during my sample period. In Panel B, only coefficients of interests are reported for simplicity. Each column name represents a dependent variable in a separate regression. Fixed effects for states and year-quarters are always included. Robust standard errors are clustered at the state level and are reported in parenthesis. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

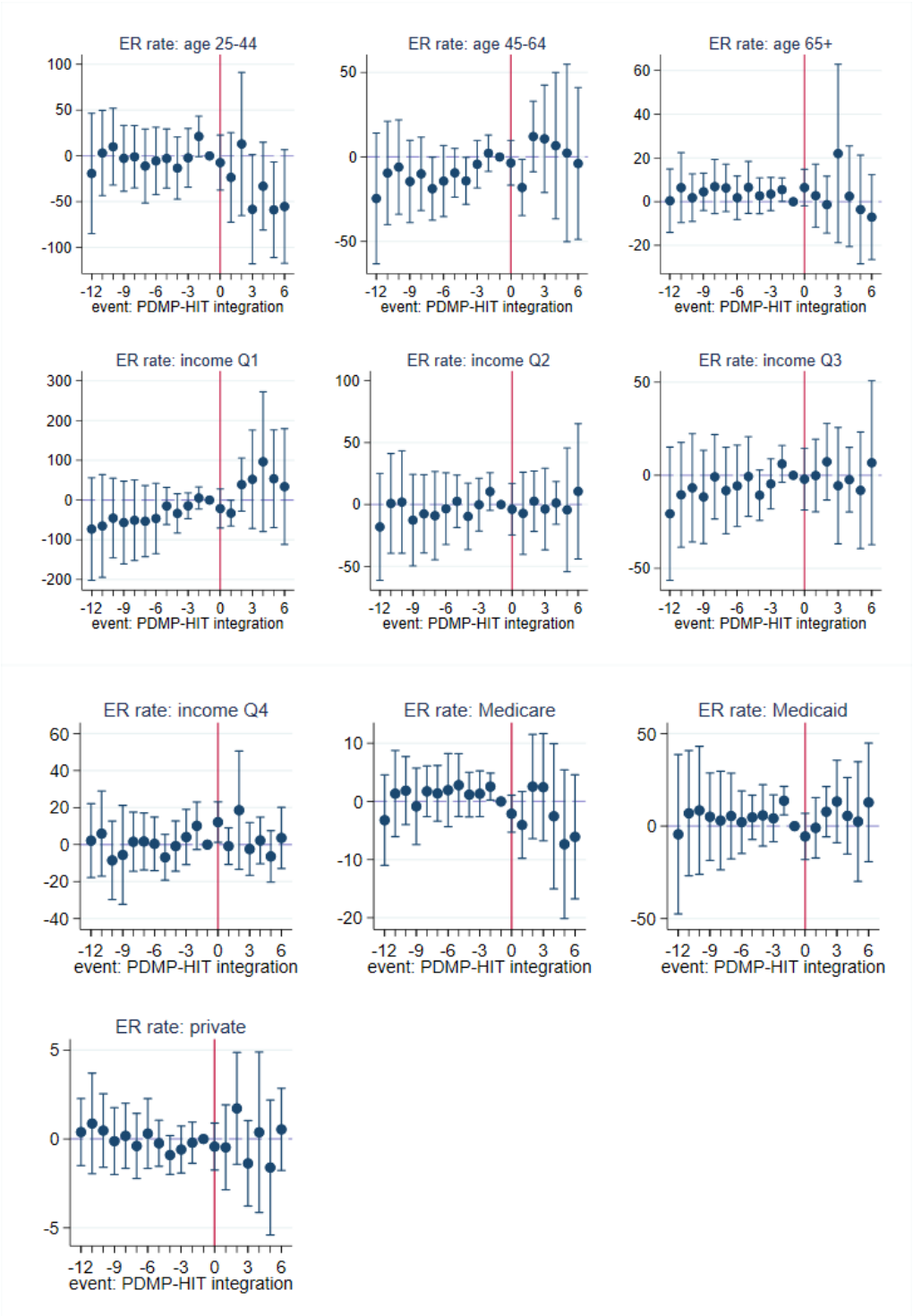


Figure B1: Event Studies: ER Visits, Stratified by Age, Income, and Expected Payer

Notes: These figures report event-study coefficient estimates using Equation 2. Outcome variables are the rates of hospital ER discharge per 100,000 population, stratified by adult age group, community-level income quartile, and expected payer. The dots are point estimates of differences in outcome variables between treatment group and control groups 12 quarters before and 6 quarters after implementation. The whiskers correspond to 95% confidence intervals.

APPENDIX C

APPENDIX FOR CHAPTER 4

Table C1: International Patent Classification (IPC) Scheme

Cat. code	WIPO Cat. Description
A	Human Necessities
B	Performing operations; Transporting
C	Chemistry; Metallurgy
D	Textiles; Paper
E	Fixed constructions
F	Mechanical engineering; Lighting; Heating; Weapons; Blasting
G	Physics
H	Electricity

Table C2: Cooperative Patent Classification (CPC) Scheme

Cat. code	WIPO Cat. Description
A	Human Necessities
B	Performing operations; Transporting
C	Chemistry; Metallurgy
D	Textiles; Paper
E	Fixed constructions
F	Mechanical engineering; Lighting; Heating; Weapons; Blasting
G	Physics
H	Electricity
Y	General tagging of new technological developments; General tagging of cross-sectional technologies spanning over several sections of the IPC; Technical subjects covered by former USPC cross-reference art collections (XRACs) and digests