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155 College Street
Toronto, Ontario

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Global Drug Diffusion and Innovation with the Medicines Patent Pool

Lucy Xiaolu Wang*[1,2,3]

[1] *Department of Resource Economics, University of Massachusetts Amherst, Amherst MA 01002, United States*
[2] *Max Planck Institute for Innovation and Competition, Marstallplatz 1, 80539 Munich, Germany*
[3] *Canadian Centre for Health Economics, Toronto, Canada*

Abstract

This paper 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, particularly in countries with stronger patent protection. In addition, there are some positive increases in clinical trials and drug product approvals after a compound enters the pool, mostly by firms outside the pool.

JEL Classification: O30; K20; I10
Keywords: drug cocktails; innovation and diffusion; patent pool; developing countries

*Assistant Professor, University of Massachusetts Amherst; Faculty Research Fellow, Max Planck Institute for Innovation and Competition; Faculty Associate, Canadian Centre for Health Economics. I am indebted to Sean Nicholson, Michael Waldman, Michael Lovenheim, and Chris Forman for valuable advice. For comments or discussions, I thank Panle Barwick, Charles Becker, Iain Cockburn, Wes Cohen, Jorge Contreras, Amanda Eng, Dietmar Harhoff, Josh Lerner, Ben Leyden, Doug Miller, Atul Nerkar, Chris Rider, David Ridley, Evan Riehl, Michael Roach, F.M. Scherer, Frank Sloan, Nahim Zahur, Rosemarie Ziedonis, and participants in CHITA 2018, IHS 2018, ISA 2019, CCC 2019, ASHEcon 2019, iHEA 2019, IPSC 2019, EPIP 2019, NEUDC 2019, WINDS 2019, INFORMS 2019, EGSC 2019, APPAM 2019, NBER productivity lunch 2019, ESWM 2019, AEA 2020, CES 2020, NBER entrepreneurship 2020, MaCCI 2021, SMYE 2021, ASHEcon 2021, iHEA 2021, AOM 2021, and seminars at Berkeley Haas, Columbia, Cornell, EuHEA, KU Leuven, MPI for Innovation, Medicines Patent Pool (MPP), Melbourne Institute, National Univ of Singapore, RAND, Shanghai International College of IP, UMass Amherst, U of Illinois at Chicago, U Sydney, US FDA, Cornerstone Research, and Charles River Associates. Individuals from the MPP, WHO, and Janssen provided valuable insights, especially Charles Gore, Erika Dueñas, Maica Trabanco, Sébastien Morin, and Frank Daelemans. Dalton Price provided excellent research assistance. I thank funding from Cornell and the Institute for Humane Studies. All errors are mine.

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 an invention and associated know-how for roughly two decades. In principle, manufacturers can license a patent to produce and sell a drug before patent expiration by paying royalties. In practice, firms "ever-green" patents (Hemphill and Sampat, 2012), making it costly to license when each drug can be covered by hundreds of patents (Shapiro, 2001). This situation has more severe impacts in developing countries, where many drugs remain unaffordable and unavailable decades after their initial approvals (Kremer, 2002; Cockburn *et al*., 2016).[1] 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 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 constituent 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.[2] The lack of a stable supply of drugs and fixed-dose cocktail pills make it difficult for patients to adhere to a 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.

This paper studies the Medicines Patent Pool, the first public health-oriented patent pool designed to reduce the tension between patent protection and technology diffusion. Patent pools are joint licensing platforms that typically gather complementary patents from patent owners and provide "one-stop shopping" to manufacturers (Figure 1). 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 regulation changed and revived in the late 1990s to spur the development of information and communication technologies. Although there

[1] Generic firms have comparative advantage in producing low-cost new cocktails. Before India started enforcing patents, the first qualified single-pill HIV cocktail was created by Cipla in 2001 for $350 per patient-year, whereas the prices for the three standalone drugs were above $10,000. The cost dropped to $140 per year after more generic entry (Hoen, 2016). Generic HIV drugs cost over $200 per patient-year in early 2000s, when low-income countries had average per capita health spending of $23 (Tirole, 2006).

[2] Source: https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics.

is interest among practitioners and federal agencies in creating medical patent pools (Clark *et al*., 2000; Van Overwalle, 2016), progress has been slow in the heavily regulated medical sector.

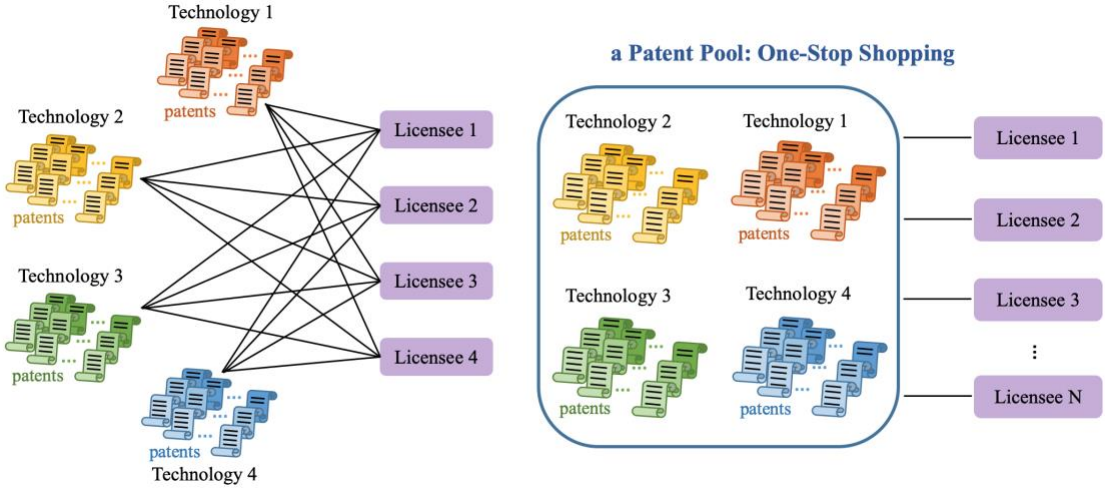


Figure 1: Graphical Structure of the Licensing Market without and with a Patent Pool

Notes: Each technology (e.g., a drug) has numerous underlying patents, and a drug cocktail requires licensing multiple compounds for each licensee. Royalty rate negotiations for multiple patents from one or more patent owners complicate the process (left). A patent pool provides a one-stop shopping through a joint licensing platform (right). Therefore, more licensees can enter the market.

This paper investigates the first modern biomedical patent pool, the Medicines Patent Pool (MPP), which allows easy access to a set of drug patents from multi-national firms with the goal of fostering the generic diffusion of drugs and development of new drugs for developing countries. Founded in Geneva, Switzerland in July 2010, the United Nations-backed, Unitaid-funded MPP aims to facilitate generic licensing for drugs that typically treat diseases that disproportionately affect resource-limited countries. These MPP licenses do not apply to high-income countries. Although the pool initially targeted HIV drugs only, it began to cover Hepatitis C and tuberculosis in 2015, further expanded its mandate to include all small molecule drugs on the World Health Organization (WHO)'s essential medicine list, and it became part of the WHO's COVID-19 Technology Access Pool (C-TAP) on May 29, 2020.[3]

An illustrative example suggests that the MPP accelerates generic entry and new drug product development. A new compound, dolutegravir (DTG), was first approved in the US in August 2013 and was added to the MPP in March 2014. Over a hundred patents on DTG were

[3] Source: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/covid-19-technology-access-pool.

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 biomedical patent pool can affect static efficiency (i.e., deadweight loss) and dynamic efficiency (i.e., innovation incentives) through different channels. It can improve static welfare by addressing three problems: (1) transaction costs stemming from multiple royalty negotiations with multiple patent owners; (2) hold-up problems where one failed royalty negotiation can prevent licensing and distribution of a generic cocktail; and (3) double-markup problems where downstream firms can also exert market power. The impact of a pool on dynamic efficiency is less clear. A pool can spur new drug product innovation from branded or generic firms by reducing licensing and litigation costs, increasing royalty revenue from underinvested markets for branded firms which pool patents, and enabling the development of new generic products to meet the demand in poor countries. However, a pool can stifle innovation if licenses have price-fixing terms and restrict licensees in product development. Hence, the effect of a patent pool on innovation is ambiguous and depends on its design, underscoring the need for empirical analysis.

This paper examines the impact of the MPP on static and dynamic welfare: how the MPP affects generic shares in developing countries and the spillover effect to R&D. To examine how the MPP affects generic drug diffusion, I use the arguably exogenous variation of when a drug is included in the pool for generic licensing for a given territory. A new dataset is constructed with drug sales in developing countries and with the generic share of 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, and are not often changed at the drug-country level. Critically, I show that the timing is not determined by changes in demand-side factors such as HIV prevalence and death rates. Adding a drug in the MPP for a country is found to increase generic 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, robustness tests, Bacon decomposition, new methods to test and model pre-trends, and interviews that all indicate that the timing of MPP entry is orthogonal to my outcomes of interest.

To further understand MPP-related changes of R&D on HIV drugs, all US-registered global clinical trials and drug product approvals by the two largest global approval agencies are

collected. With pro-competitive MPP license terms that emphasize diffusion-oriented innovation, I find increases in follow-on clinical trials that improve the use or bundling of a compound. Once an MPP compound enters the pool, more trials are initiated and more firms participate in drug trials that include the compound. In particular, firms outside the pool increase late-stage trials for 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.

This paper contributes to two strands of literature. First, I extend research on innovation and the economy by studying an institutional innovation designed to balance intellectual property protection and access to medicines. Prior studies find that innovation increases with market size (Acemoglu and Linn, 2004; Dubois *et al*., 2015) but changes ambiguously with patents (Williams, 2013; Sampat and Williams, 2019). 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, there is limited understanding on how to sustainably scale up drug diffusion and innovation for diseases primarily affecting low-income countries. 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 the first evaluation of whether a novel 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. Theory papers emphasize the importance of pooling complements (Shapiro, 2001; Lerner and Tirole, 2004) and discuss the complications for patent pools with both complementary and substitutable patents (Lerner and Tirole, 2015; Rey and Tirole, 2019). Even patent pools consisting of complements may have adverse effects (Reisinger and Tarantino, 2019). 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. The MPP is designed to include all patents for a pre-set licensing territory and thus does not have patent-level selection in inclusion. In addition, most empirical studies on patent pools are either

historical (Lampe and Moser, 2013, 2015) or on modern software pools (Lerner *et al*., 2007; Bekkers *et al*., 2017) that face challenges in data and measurement that limit implications for other sectors.[4] I overcome these hurdles by using rich institutional details from life sciences.

In addition, this paper complements the recent study by Galasso and Schankerman (2021) that focuses on MPP's impact on drug diffusion through licensing (see also Martinelli et al., 2021). Galasso and Schankerman (2021) focuses on diffusion using proprietary data, and estimates a 5 to 10 fold increase in licensing stemming from the MPP. In comparison, my paper offers a systematic evaluation of MPP by examining the theoretically ambiguous effects on innovation (Rey and Tirole, 2019) and its relationship with generic drug diffusion on a larger sample of low-income countries. Previous studies have not investigated the effects of the MPP on upstream innovation. My paper is also distinctive in that it finds positive spillover effects of the MPP on upstream R&D measures. This is an important empirical finding in the patent pool literature, as a patent pool can potentially result in negative innovation outcomes theoretically and demonstrated in empirical work on other patent pools (Lampe and Moser, 2013, 2015).

Finally, the Covid-19 pandemic has caused many challenges in the global supply chain, and the MPP has mitigated some of these issues. In particular, since becoming a key implementing partner of the Covid-19 Technology Access Pool (C-TAP), the MPP has made substantial contributions in facilitating licensing of Covid-19 related treatments and technology. For example, by the end of 2021, the MPP has made voluntary licensing agreements with Merck and Pfizer for Covid-19 treatments and investigational drug cocktail therapies. The MPP has also been essential in the establishment of technology transfer hubs in developing countries.[5] While a patent pool cannot solve all challenges in drug access and innovation, and cannot be applied in all contexts, my study on the MPP in its pre-pandemic activities provides early insights on one option to tackle problems associated with the current pandemic and possibly future ones.

The paper proceeds as follows. Section 2 lays out the background. Section 3 describes the data. Sections 4 and 5 present empirical strategies and results for diffusion and innovation analyses. Section 6 concludes. An online appendix contains additional results and information.

2. Background and Conceptual Framework

[4] The MPP is closer to traditional, historical patent pools (i.e., with a small number of patent owners, not much ambiguity of who holds patent rights), compared to modern software pools.
[5] A summary of the MPP's contribution to drug access in Covid-19: https://medicinespatentpool.org/covid-19

2.1 HIV and Drug Cocktails

As one of the most significant infectious diseases in history, AIDS/HIV has killed more than 35 million people and infected over 70 million people globally since the 1980s. Today, AIDS remains a leading global cause of death, with almost two-thirds of the people living with HIV residing in Africa. Once a person is infected, HIV cannot be eliminated and can progress to AIDS that 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 fatal to a chronic disease. The HAART typically uses a cocktail of antiretrovirals from multiple drug classes based on the mechanisms of action that target HIV at different stages of its life cycle. A patient who cannot maintain medication adherence and develops resistance to a drug will be resistant to all drugs within the same class, and a patient may 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 single-pill cocktails and new compounds can improve current treatment. The cocktail features also apply to therapies for cancer and Covid-19.

2.2 Patent Pools and the Medicines Patent Pool (MPP)

There is no universal design for patent pools. First used in 1856 to reduce litigations in the sewing machine industry, a typical patent pool involves patent holders sharing rights for joint licensing with members or firms outside of the pool, with licensing rules varying across pools. Patent pools were seen as exempt from regulatory scrutiny in the early twentieth century but almost disappeared after a 1945 US Supreme Court decision on cartel behavior.[6] A pool can be dissolved by courts or it expires when all pool patents expire. Although not historically used in the medical sector, the prevalence and lack of cures for many infectious diseases and extensive patents provide a testing ground for the MPP to reduce intellectual property (IP) issues in health.

The MPP aims to reduce coordination failure in the global medical supply chain, to spur generic access of patented drugs in developing markets, and to avoid infringement or compulsory

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

licensing.[7] The MPP negotiates with branded firms (i.e., patent holders) for drug licenses that enable generic firms to develop new treatments, including fixed-dose cocktails and pediatric formulations (Figure 2). Any improvements in production or formulation by licensees can be non-exclusively granted back to the original patent holders. Generic firms can license all territory patents on the set of drugs they need from the pool. Royalty rates are typically set at no more than 5% of revenue.[8] The MPP receives quarterly drug development updates from licensees and encourages competition among generic firms that can bring down prices and increase access.

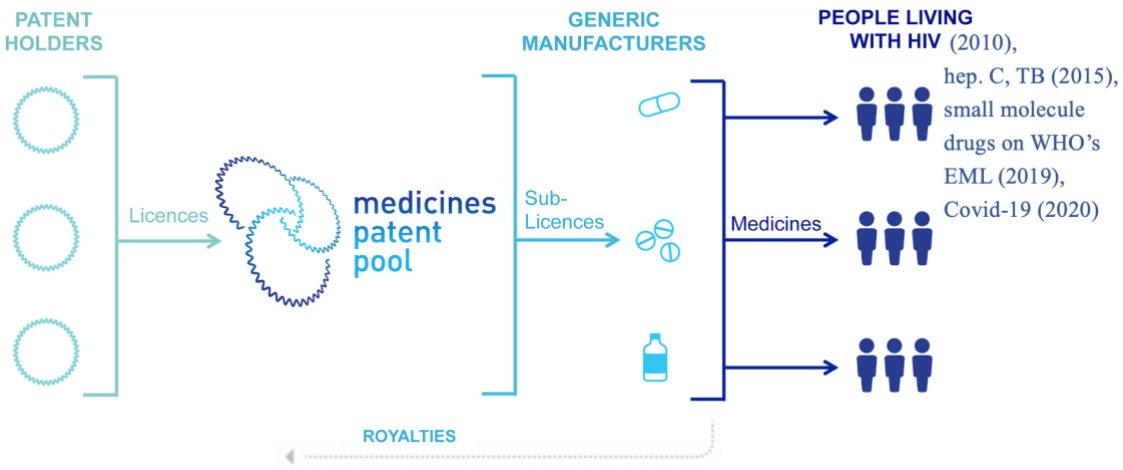
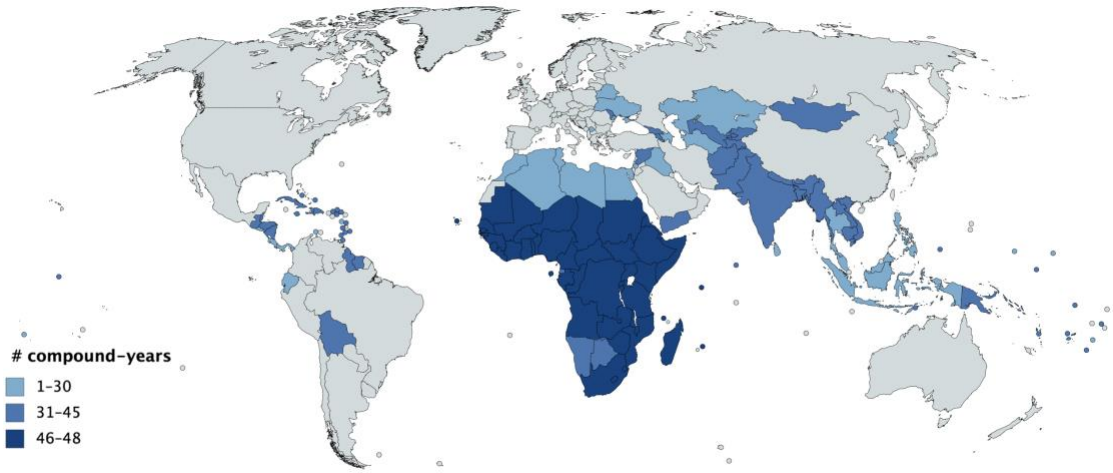


Figure 2: Licensing Structure for the Medicines Patent Pool

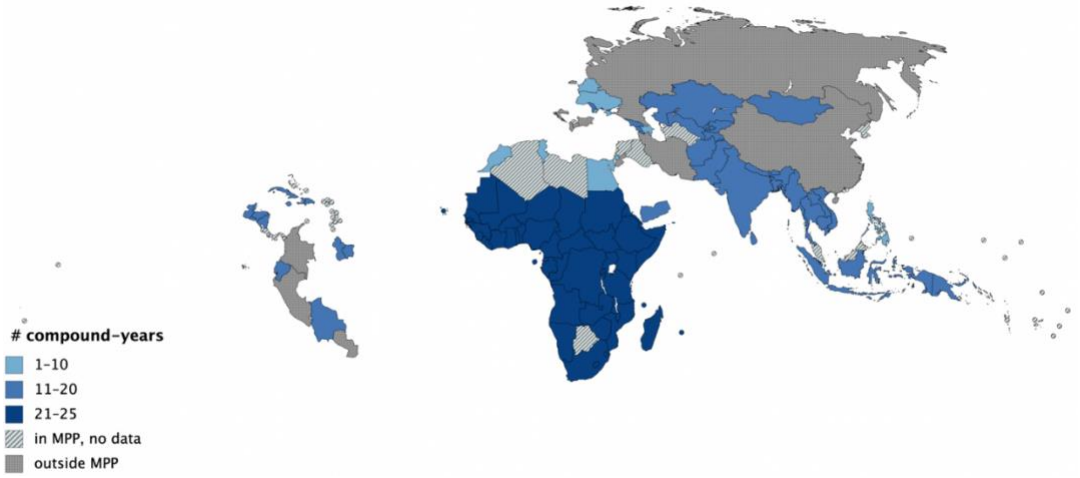
Notes: The figure is edited from MPP official material. The pool works as the intermediary between branded drug firms and qualified generic licensees. Royalties are normally capped at 5% of revenue and are often free.

By 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 joined the pool.[9] Figure 3 shows the MPP sales territories; Appendix C reports a summary of MPP license terms. Generic drug industries are heterogeneous across developing countries, with major firms based in India, China, Brazil, and South Africa; sub-Saharan African countries lack local production and mainly rely on imports. To assure branded firms that the MPP aims to increase generic access in resource-limited countries, licenses cannot be used for drug sales in high-income countries.

[7] With compulsory licensing, a government allows producing a patented product or process without the consent of the patent owner.
[8] The 5% implicit cap is lower than the average US rate (5-8%, author's calculation based on BioSciDB).
[9] As of early 2019, nine patent holders have pooled thousands of patents on 17 drugs. Excluded from the analysis are those that are not for HIV, pediatric-only licenses, and non-sue agreements.



(a) MPP overall effective sales territory



(b) MPP representation in the diffusion data

Figure 3: Geographic Penetration of the MPP: (a) Overall and (b) in the Diffusion Data

Notes: Color groups represent the compound-year weighted intensity of MPP impact by 2017. Panel (a) includes all compound countries covered in the MPP sales territory, and panel (b) accounts for MPP compounds and countries included in my sample. Not all MPP-related compounds appear in the data, as many newer drugs need a few years to pass the registration, production, and distribution process.

2.3 Conceptual Considerations

Theoretical work shows that the static welfare effect of a patent pool depends on the relationship between patents in the pool (Lerner and Tirole, 2004): pools with complements will lead to lower license fees and are welfare enhancing, but pools with substitutes are anti-competitive with collusive behaviors. In reality, substitution and complementarity patterns can be far more complex. First, consumers may buy a combination of products when prices are low, but only one product when prices are high, meaning patents are complements at low prices and substitutes at high prices (Lerner and Tirole, 2004; Rey and Tirole, 2019). Second, because firms

often develop cocktails composed of existing compounds, compounds within a drug class compete once a class is selected to complete a regimen (substitution), but compounds within the same cocktail complement each other (complementarity), and different cocktails compete (substitution). When a pool works as a price capping device (limits collusion, e.g., MPP's implicit royalty cap), regardless of the relationship between patents, incentives are maintained to price low, and thus the static welfare of a pool are always weakly positive (Rey and Tirole, 2019).

The impact of a pool on innovation is even more complex (Lerner and Tirole, 2004; Rey and Tirole, 2019). Innovation is more likely to increase in pro-competitive pools when the complementary effects dominate. This is because insiders increase innovation in anticipation of pool formation, while outside pool innovation may increase when firms can develop a new product that can be easily used in combination with others. These effects differ across drugs: a pool can lead to more innovation for products that combine well with the existing products in the pool, but less so for new products that may compete with the existing pool products. In a pool with substitutes, by contrast, innovation by outsiders may be reduced in the face of higher licensing fees. Beyond these simplified cases, the impact of pools on innovation is ambiguous and depends on the nature of strategic interactions, for example if incumbent producers lower prices to deter entry or if the firms engage in tacit collusion. It is also hard to draw a simple conclusion on the impact of pools on innovation given the complex substitution and complementarity patterns, especially as the same pair of drugs may be complements within one treatment regimen but substitutes across competing treatment regimens. Overall, my empirical results on R&D are consistent with the literature and are discussed in detail in section 5.

Below, I further discuss how three types of firms interact with the MPP with different incentives: generic firms, branded firms in the pool, and institutions outside the pool. Generic firms can use the MPP to overcome IP-related barriers (e.g., patents and exclusivities).[10] High royalties of patented compounds may deter generic firms from licensing, and thus they will exit the market or infringe patents and face costly litigations. If a generic firm has two compounds but needs a third, patented compound to develop a new single-pill cocktail, this process can be held-up by the branded firm. In addition, downstream firms may be unwilling to negotiate with

[10] Exclusivities also hinder drug diffusion and R&D (Gaessler and Wagner, 2019). Most MPP licenses also include transfer of know-how but not market exclusivities. For firms that sell in countries without granted patents, there can be pending patents. Licensing is always a safe option with limited information.

branded firms to license patents on multiple new compounds for sales in different countries. The royalty negotiation process can be costly for branded and generic firms. A generic firm that pays multiple royalties can use its downstream market power in the absence of generic competitors. The MPP makes licensing easier, reduces royalty rates, and avoids patent litigations.

At the same time, branded firms in the MPP can benefit from simplified licensing and the royalty negotiation process, use the pool to monitor licensee compliance, and choose to license back patentable improvements developed by the licensees.[11] Many branded firms are proactive in advancing drug access in developing countries, but shy away from the difficulties of setting up sales networks in those countries. In fact, branded firms can gain more profit from low-income markets by generic licensing instead of selling directly.[12] As a result, branded firms may increase R&D in technically feasible trials that adapt to the needs of developing country markets. However, branded firms may charge a low royalty rate to generic firms and lose out from IP sharing without prior evidence on MPP license compliance. A pool with price caps on royalty rates can be pro-competitive even with substitutable technologies, but how firms would behave is ambiguous in theory and requires empirical work (Rey and Tirole, 2019).

In addition, a patent pool can generate spillover effects to upstream R&D-oriented firms outside the pool. MPP employees regularly present in 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 results enter commercialization phase (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). Furthermore, follow-on innovation by pool outsiders can complement branded firms' R&D by discovering new or better uses 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.

3. Data

3.1 Data on HIV Drugs and MPP Licensing Contracts

[11] A licensor can use licensee-developed patentable technology through an agreement or reverse licensing.
[12] Gilead planned to license to the MPP the blockbuster drug sofosbuvir, but the initial MPP mandate does not cover hepatitis C. According to the MPP, Gilead has to set up an access program for generic licensing of sofosbuvir in developing countries. See also Harvard Business School cases (# 9-510-029; 9-515-025).

I first collected data on all HIV drugs approved by the US Food and Drug Administration (FDA), including both standalone compounds and multi-compound drug cocktails. I obtained the data from the FDA and AIDS*info*.gov—a US government agency providing information on HIV/AIDS. I converted branded names to generic names to standardize the coding, as the same drug can have different branded trade names in different countries.[13] I then collected details about the MPP from its official website and from licensing contracts. The timing of a compound-country being included in the MPP is documented in the original contract and amendments.

Table A1 displays key information on all HIV compounds approved by 2018. There are six drug classes for HIV therapy, including 30 distinct compounds (27 compounds by 2017) owned by 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 till the end of 2018.

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

HIV drug purchase records are 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).[14] The implementation relies on within-country and international partners in government, non-profit, and private sectors, 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. The raw data report the transaction date, the quantity of drugs purchased in various strengths and dosage forms, prices, selling firm, and destination country. I aggregate the raw data from purchasing records to create a country-drug-year level unbalanced panel dataset.

To measure the diffusion of generic HIV drugs, the share of generic drug purchases in each drug-country-year is calculated. As a direct measure of generic diffusion and widely used as a generic efficiency measure in practice, higher generic share is a sufficient but not necessary

[13] All HIV drugs are approved in the US, the most lucrative market. Similarly, all clinical trials on new drug development (for US drug approval or academic publications) must be registered in the US.
[14] Source: Global Fund publication, 2016, available at https://tinyurl.com/y4dgwy3w.

condition for lower prices, as the latter can be achieved by non-market strategies such as price ceilings and donations from branded firms. Generic share is an assumption-free measure that captures normalized generic utilization level. Specifically, I divided the number of purchases from generic firms by the total number of purchases for a drug within a country-year.[15] Each drug-purchase is then converted into a standardized quantity in units of per US patient-day to calculate the share of generic drug quantity purchased at the drug-country-year level. Then, the number of distinct drug products—as a drug-strength-dosage form-firm combination—is calculated at the drug-country-year level as a proxy for within-drug market competitiveness. During the sample period, the average shares of generic purchases and generic quantities are 84.3% and 85.6%, respectively (Table 1 Panel A).

HIV drug-country-specific international patent data are obtained from two sources. First, I used data from the MPP's own patent database, MedsPaL, which was created in collaboration with regional patent offices. This dataset provides the patent status by country of selected drugs using public data. Second, I acquired data on all available international patents on HIV drugs from the Drug Patent Watch database, following Galasso and Schankerman (2014). A drug is effectively patented if there are any active patents for that drug in the country-year.[16]

Country-year level control variables are collected from two sources. First, the World Bank provided data on population, GDP per capita, and the widely-used institutional factors Worldwide Governance Indicators (WGI), 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, HIV prevalence and age-adjusted death rates are obtained from the Global Burden of Disease Study Life Tables from the Institute for Health Metrics and Evaluation and curated by Our World in Data from Oxford University.

Table 1: Summary Statistics of Main Outcome Variables

Variables	Unit of obs.	Obs.	Mean	Std. Dev.	Min	Max

[15] Last accessed in 8/2018. Price and quantity calculation requires more assumptions in converting drugs of same ingredients but different strengths that are not directly comparable. The conversion to a per-unit price relies on US adult dosing in the absence of LMIC country-specific data; quantity-adjustments are thus calculated to show robustness after the assumption-free share measure (Appendix A). Generic shares are the desirable reduced-form outcomes given the lack of all transaction data, right truncation, and inconsistent shipping cost inclusion. Robustness results also show direct price and quantity analyses.

[16] Due to data availability reasons, I cannot distinguish which types of patents are in effect for each drug in each of the 103 countries. Empirical results suggest that this control does not affect the main results.

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
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

Panel C: summary of compounds covered in each sample

MPP compounds: 2011: evg, ftc, tdf, cobi (joined as "the quad" cocktail); 2013: atv; 2014: dtg, taf; 2015: lpv,r (joined as a bundle); 2017: bic (10 available for effective licensing; 6 from Gilead: the "quad", taf, evg, among which 4 joined the pool one year before FDA approval: bic, cobi, evg, taf)

Diffusion sample: 3tc, abc, atv, d4t, ddi, drv, efv, etr, ftc, idv, lpv, nfv, nvp, r, ral, sqv, tdf, zdv (18 out of 27 compounds approved by the end of 2017; 23 compounds are in the raw data, 5 are dropped with <20 observations in data: dtg, enf, fpv, mvc, tpv); 29 drugs (standalone/cocktails) are covered.
Innovation sample – clinical trials: 3tc, abc, atv, cobi, d4t, ddi, drv, dtg, efv, enf, etr, evg, fpv, ftc, idv, lpv , mvc, nfv, nvp, r, ral, rpv, sqv, taf, tdf, tpv, zdv (trials for *all* 30 compounds approved by 2018; including 4 approved in 2012-2017 and 3 compounds approved in 2018: bic, dor, iba)
Innovation sample – drug approvals: 27 compounds – all above except three approved only in 2018

Notes: "Comp." is short for compound. Panel A is for drug-country-year and compound-country-year level variables (2007-2017). Panel B1 is for compound-year level variables from HIV clinical trials (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 (2005-2018). For panel C, acronyms are used for readability and conciseness (Table A1 reports the full information). Three 2018-approved compounds are excluded in the drug approval sample as they only appear one time at the end of the panel; in contrast, the clinical trials data are available years before approval given the R&D life cycle of drugs.

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

R&D inputs are measured by clinical trials at the compound-year level from 2000–2017. I obtained clinical trials data from ClinicalTrials.gov, the US registry of global trials and a widely used source. The registry was first released in 2000 and is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). I obtained identifiers provided by AIDS*info* of trials related to each FDA-approved HIV drug and pre-approval investigational drug. AIDS*info,* another NLM service, offers access to the latest federally approved HIV/AIDS medical information. I converted all branded drug names to their generic counterparts to unify the coding. About 10 new trials involving a HIV compound are initiated in a year, among which 4.4 trials are by branded firms in the MPP—2.4 trials in-house and two collaborated with firms outside the pool (Table 1 Panel B1). About 21 firms are engaged in these trials each compound-year, with a similar distribution pattern.

R&D outputs are measured by HIV drug product approvals (branded and generic) from 2005–2018 by FDA and WHO, the two largest agencies whose approvals can expedite related registration in many developing countries. The FDA approves HIV drugs via either the regular channel or the international program. I extracted all regularly-approved HIV drug products from Drugs@FDA; I obtained international program approvals via the US President's Emergency Plan for AIDS Relief (PEPFAR).[17] The two channels maintain the same safety, efficacy, and quality standards; the PEPFAR provides expedited reviews of generic drugs. The WHO pre-qualification program is the other main channel through which firms can fast register an approved, quality-assured drug in many low-income countries. There are 0.7 approvals per drug-year and 2.3 approvals per compound-year (Table 1 Panel B2), among which most approvals are for cocktails.

US patent data are obtained from DrugBank, a database widely used in peer-reviewed research. The US patent status is closely tied with a drug's owner perceived value, given that the US is the largest drug market. The data provider obtained compound-specific patent records from the FDA's Orange Book and further undertook a manual curation process. I recorded the US patent status based on the effective patent period for each compound (i.e., before the last granted patent expires), and I then assigned drug-year level patent status accordingly.

[17] Source: https://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm. PEPFAR is for non-US marketed drugs and began in 2004. The Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement's grace period for Indian generic firms ended in 2005.

4. Patent Pool and Generic Diffusion of HIV Drugs

4.1 Empirical Strategy

To estimate the causal impact of the MPP on generic drug diffusion, I first define a drug "as it is"—either a standalone compound or a fixed-dose single-pill drug cocktail. Pool inclusion timing is coded based on compound-level inclusion into the pool, as a compound is the lowest-level unit for standalone and cocktail drugs alike. I exploit variation in the timing of compound-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 purchases 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.[18] 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).[19]

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. The event study framework assesses the validity of the common trends assumption that the trend in the control group (drug-country-years outside the MPP) is a valid counterfactual for the treated

[18] The institutional factors are the six worldwide governance indicators described in the data section. I also use country-year fixed effects instead of observable controls as a specification test (robust).
[19] Estimated standard errors are smaller using other clustering methods at the country or country-drug level.

group (drug-country-years in the MPP). Differential trends of outcome variables between the treated and control groups in the pre-treatment period would suggest endogeneity in drug-country inclusion or, potentially, correlation with other shocks. In addition, the event study measures the dynamic responses of outcomes to policies—whether the effects fade away or build over time. The MPP impacts could 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:

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

Here, β_j represents the difference between treated and control outcomes j years relative to the MPP inclusion. 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, evidence suggests that drugs in and outside the pool appear similar in quality (e.g., approval year, initial sales). The US approval dates are similar for drugs in and outside the pool (Table A1); six compounds are listed in the top 100 drugs by global sales in 2012, and three of the six compounds are in the MPP (Table D3). The set of drugs entering the pool is affected by firm attitudes towards licensing and randomness in negotiation outcomes, both of which are likely to be orthogonal to unobservables affecting generic shares of drugs across LMIC. In fact, 6 out of the 10 effective compounds were contributed by Gilead during my sample period, all they have owned, and the additions are either in blocks or at the earliest time possible (esp. for pre-approved drugs). Although the MPP may check the WHO *Essential Medicine List* on marketed drugs, many pre-approval drugs are added to speed up access.[20] Two other compounds are owned by AbbVie, which also contributed all their available HIV drugs. Table B4 shows similar results on subsets of drugs by pharmacological, regulatory, ownership and cohort features.

Second, drug-specific MPP sales territories typically vary by branded firm and always include sub-Saharan Africa and Djibouti; additional inclusion of countries partly depends on income groups, prior voluntary licensing status, and exercises in public relations.[21] When

[20] The WHO list includes all approved HIV drugs except three pre-2000 withdrawals and are all of high market values. The MPP broadly target any HIV drugs in early years to demonstrate the business model.
[21] Based on discussions with MPP employees in Switzerland. A firm may follow the World Bank "low-income" definition or use its own cut-off value for income. A firm once included one island country (with a long name) into the MPP territory but listed two country names to boast public relations. Another firm

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 vary by firms' attitudes and administrative efficiencies. For example, MPP approached both Gilead and Janssen in 2010. Gilead used generic licensing years before the MPP was established, joined in 2011, and has gradually put all HIV drugs into the pool, including two investigational drugs in clinical trials. In contrast, Janssen has never officially joined the MPP.[22] 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, institutional factors, and fixed effects at drug-country and year levels. As shown in Table B1, none of the key observables are significant predictors of the timing, and the goodness of fit barely increases when adding observables to the regression.[23] 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-

unintentionally left a sub-Saharan African country outside the MPP territory and added it once been reminded. These factors are orthogonal to changes in my outcomes of interest.

[22] Janssen agreed on a covenant not to sue without commitment in technology transfer or licensing, unsure whether the MPP model would work [interview with Frank Daelemans].

[23] Figure B1 depicts trends of HIV death rates and prevalence (no spikes). Civil society advocacy and compulsory licensing threats for the inclusion of additional countries into the MPP are typically outside my sample periods and can affect the control group, making it harder to estimate an MPP impact.

country-year (y_{act}) aggregated data, with fixed effects at the compound-country and year levels. It's worth noting that while it is natural to expect that the inclusion of a compound in the MPP can increase generic drug diffusion, it is not obvious whether such inclusion has a statistically positive and economically meaningful impact, and how the effect size varies across measures. Finally, despite extensive evidence for the lack of common shocks, there may still be aspects of firms' pool participation decisions that are related to unobservables affecting diffusion. This is a potential limitation of the identification strategy, though I provide evidence later that any bias from selection is likely to be small.

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 2). Column (1) controls for fixed effects at drug-country and year levels; columns (2)–(3) add controls at country-year and drug-country-year levels, respectively.[24] Coefficient estimates are stable across columns. The results indicate that adding a drug-country to the MPP increases the share of generic purchases of this drug in the country by about seven percentage points (Panel A) – a substantial increase given the already high generic coverage in developing countries (84% on average during my sample period). Columns (4)–(6) report results using the share of generic quantities purchased as outcomes. Estimates are similar in magnitude and precision to those in columns (1)–(3), and are stable across specifications. Estimates on the number of drug products purchased are positive, although statistically insignificant (columns 7-9). This result suggests that generic share increases mainly in existing products, and does not yet lead to a substantially more diversified purchase set. This is consistent with the idea that countries do not purchase all products on the market, but can still benefit from competition-induced price reductions in the choice set. The lack of power prevents more specific conclusions.

The results are robust to using alternative measures of the MPP variable: the share of MPP compounds over total number of compounds for a drug in a country-year (Table 2 Panel B). The results are qualitatively similar to the indicator measure and slightly larger in magnitude. I mainly focus on the indicator measure below, as it captures the most salient changes at the extensive margin, and because of straightforward interpretation.

[24] 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.

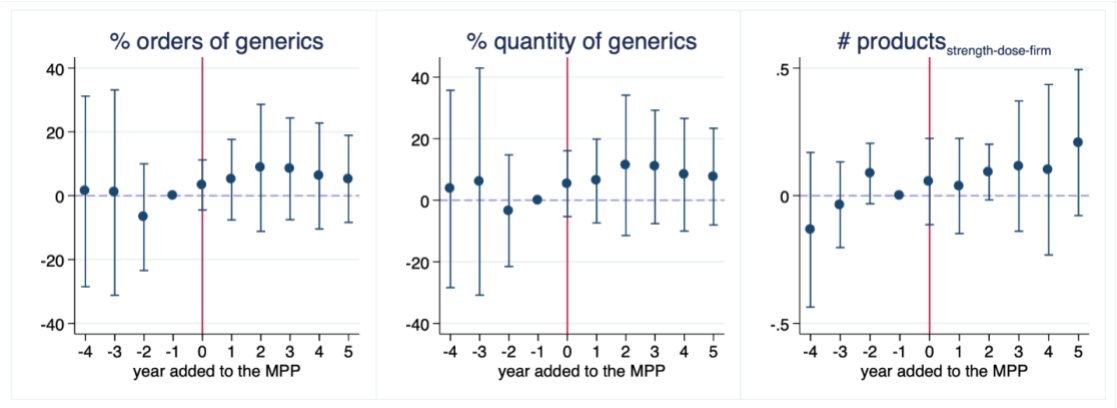
Table 2: MPP and Generic HIV Drug Diffusion in LMICs

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]	[0.0812]	[0.0800]	[0.0798]
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]	[0.0874]	[0.0850]	[0.0848]
drug-country & year FEs	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
Observations	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 & year FEs	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
Observations	6,485	6,485	6,485	6,485	6,485	6,485	6,485	6,485	6,485

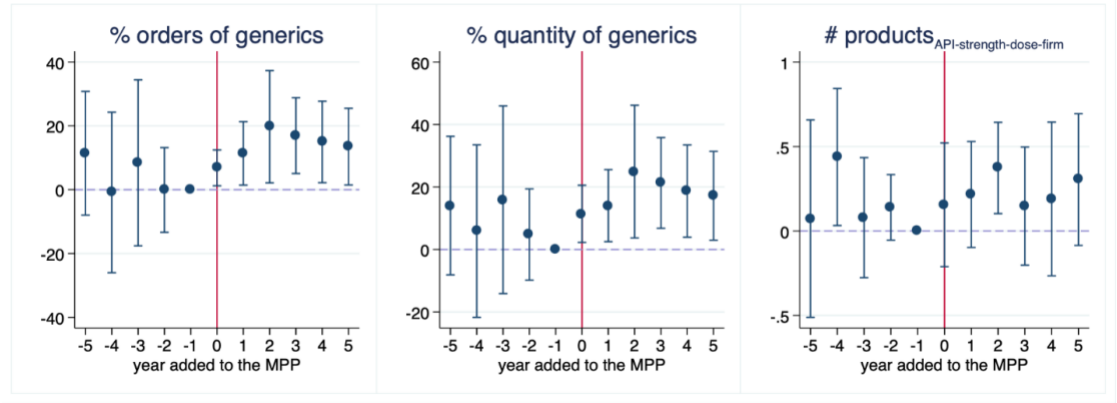
Notes: This table reports the results of estimating Equation (1). "Comp." is short for compound. Each cell reports the coefficient of interest from a separate regression. Coefficient estimates for the treatment variables $MPP_{d(a)ct}$ are reported across three measures across panels. The specification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

The event studies support the above results (Figure 4). No pre-trends exist that violate the identifying assumptions. The lack of pre-trends is particularly clear for the outcomes of generic share and quantity-adjusted generic share. The post-period trends for these outcomes rise from zero, consistent with the significantly positive average treatment effects estimated, despite the lack of power to estimate precisely the impact for each post-period. The effects gradually build and stabilize over time, consistent with time varying treatment effects that take time to establish, which are then bounded by 100%. The event study for product variety shows a similar pattern.

The compound-country-year analysis further supports my main results with more precise estimates, after converting drug cocktails into compounds (Table 2 Panel C). In the full sample, adding a compound in the pool increases generic shares (raw and quantity-adjusted) about 10% across specifications, and the estimates are 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 significant at conventional levels. Overall, there are no pre-trends from the event studies for the outcomes of interest (Figure 4). The post-period increases in the share of generic drug purchases and quantities are clear and significant.



(a) Drug-Country-Year Panel



(b) Compound-Country-Year Panel

Figure 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 whiskers correspond to 95% confidence intervals.

An alternative specification is tested that includes a full set of country-year level fixed effects (Table B2). 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 that occurred in a country-

year not captured by the feasible observable controls. For example, changing legislative culture towards drugs, the overall likelihood of compulsory licensing, and activist activities – old country-specific channels that widely existed before the MPP's establishment but still have limited impact. All of the coefficient estimates are very similar in magnitude and statistical significance to those in the preferred main specification.[25]

4.3 Heterogeneity, Robustness Checks, Sensitivity Tests, and Bacon Decomposition

To demonstrate robustness regarding country territories in the control group, a set of tests are reported using alternative definitions (Table B3). Some countries are more experienced in bringing generic drugs via traditional channels like patent invalidation and challenges that are independent to the MPP's establishment. Others (e.g., sub-Saharan Africa) are waived from patent enforcement but lack local production capacity and rely on international trade and other firms' incentives to sale in their territory. Although these concerns are addressed by the previous test, a subsample analysis further supports that the pool makes an impact even in areas with the most lenient access policies. The estimated impact is smaller (i.e., 5 percentage point) in MPP-common territories for all drugs (47 countries: sub-Saharan Africa and Djibouti) and larger (i.e., 7.5 percentage point) in the territories ever covered by any MPP drugs (92 countries).

A similar idea applies to a test including different drugs in the control group to strengthen the main results (Table B4). Column (1) focuses on the first ever 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 US but are still widely used in LMIC. Column (4) drops drugs approved before 1996, the year the oldest MPP compound was approved in the US. Column (5) keeps only drugs developed by branded firms inside the MPP. The results are robust in all cases and support that the estimates are not sensitive to control drug choices.

The estimated MPP impacts differ in subsamples that vary by patent status (Table B5). As discussed, the MPP's impact is expected to be stronger in countries in which a drug is

[25] I also test a specification with a set of drug-year fixed effects. The MPP estimates are insignificant and smaller in magnitudes. The lack of power with three sets of fixed effects is expected as compounds enter the pool for 47-92 countries at a time (e.g., Table B3) and drug-year fixed effects absorb treatment effects.

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. The results match the prediction that across specifications and measures, the share of generic drug orders increases more in countries where a MPP compound was effectively patented. The MPP estimates are similar when using quantity-adjusted generic share 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 novel institution to increase generic utilization. Additional analyses are provided using calculated price and quantity measures (Table B6).[26] For completeness and to account for outliers, I report the results from responses in both log(prices) and log(quantities) for each of overall sales, generic sales, and branded sales. The overall price reductions are mostly driven by price reductions in generic drugs (35%), and the corresponding generic quantity supplied rises by 71% (i.e., more patient-years served). The results are statistically significant at the 1 percent level. This robustness check is consistent with the main result that the MPP effectively increased sales of generic drugs.

In addition, I investigate heterogeneous treatment analysis using new methods developed (De Chaisemartin and d'Haultfoeuille, 2020; Goodman-Bacon, 2021). In this setting, as in many other cases, the MPP treatment is staggered over time in a multi-treatment group DD setting. Drug-country pairs that enter the MPP later (earlier) serve as control groups for those that enter the pool earlier (later), and drug-country pairs that never joined the pool during the sample period can serve as control groups. The Bacon decomposition helps disentangle how much of the estimated effect results from timing and these different control groups ("Timing" groups) as compared to a simple, "clean" control group where drug-country pairs are not in the MPP over the entire sample period ("Never vs. Timing"). Most of the estimated treatment effects (88-90%) in the diffusion analysis stem from a comparison of treated unit with classic control units (Table B12, Figure B8), with treatment magnitudes similar to the average treatment effect estimates.

Furthermore, Roth's (2022) approach is implemented to investigate how well-powered the event study test is in my context by calculating the size of the potential biases. Table B13 reports the largest potential biases I cannot detect for key outcomes under 50% and 80% power. The largest potential biases are much smaller than the estimated effects using conventional

[26] In the main analysis, generic shares are used as main outcomes for reasons mentioned in section 3.2.

clustering (as in Cockburn et al., 2016) but are sizable using two-way clustering that tend to inflate the standard errors (Abadie et al., 2017). I then explicitly model differential pre-trends à la Greenstone and Hanna (2014) and Dobkin et al. (2018) with differential linear pre-trends for treated and control units and re-estimate both the treatment effects and the parameterized event studies (Table B14). Regarding biases, the average treatment effect estimates are very close to the benchmark and even sometimes larger, mitigating concerns of biases from under-powered pre-trends. Regarding efficiency, my sensitivity analyses results show sufficient evidence that the effects are significant under various clustering methods. Overall, pre-trends are not a concern to the diffusion results, as the results remain robust when directly accounting for pre-trends.

In sum, the MPP is estimated to increases generic access in LMIC, and the direct impact is robust to alternative specifications, measures, and subsamples consisting of different control groups. However, it is *ex ante* unclear how firms react to the MPP indirectly in upstream R&D.

5. Patent Pool and Innovation in HIV Drugs

5.1 Drug Innovation Process: Clinical Trials and Drug Approvals

R&D inputs are measured using all trials initiated in 2000–2017 that include HIV drug compounds. Before a new drug is marketed by a branded firm, it typically undergoes three phases of trials. Phase I usually tests drug safety in multiple doses on healthy volunteers. Phase II tests drugs on patients with the targeted disease to assess efficacy and side effects. Phase III studies a drug's efficacy and safety on a large scale *versus* a control drug. Phase IV involves post-market surveillance to monitor drug use and long-term effects. Follow-on trials of drugs that were already approved can skip phase I-II.[27] After Phase III, 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.[28] Generic drugs typically enter the market after the expiration of patents and market exclusivity, with exceptions.[29] Generic firms are not required to conduct trials as long as they provide sufficient evidence on the generic drug's bioequivalence to the reference drug.

[27] With toxic drugs, HIV trials often replace healthy volunteers with patients, reduce three phases to two, and use surrogate endpoints (e.g., viral load) instead of mortality. A trial can take several months to years. About 10% of HIV trials do not record phases, when phases are not applicable or for behavioral trials.
[28] Drugs for life-threatening diseases are eligible for fast review (i.e., a decision within six months). The FDA posted a few examples: https://www.fda.gov/forpatients/illness/hivaids/treatment/ucm118915.htm.
[29] 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.

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

5.2.1 Empirical Strategy

The identification argument is similar to that discussed in the diffusion part (section 4.1). As a diffusion-oriented pool, the MPP is not designed to change R&D except via encouraging incremental R&D to make better use of existing compounds, e.g., new formulations and single-pill cocktails that suit the LMIC market. The timing of new compound additions is uncertain at the aggregate level. 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. The focus is on reactions from firms outside the MPP and I do not claim causality for MPP insiders, as it is not feasible to disentangle planned and reactive behaviors.

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:[30]

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

Here, y_{at} is an outcome at the compound-year (at) level, including the number of new trials, the 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 in the MPP. Each regression contains fixed effects for compound (δ_a) and year (δ_t). X_{at} controls for compound-year level observed differences, such as whether compound a was FDA-approved and whether the compound is US-patented in year t. Standard errors are clustered at the compound level.

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 denotes the difference between treated and control units j years relative to pool addition. The event window is set as 6 years before and 4 years after the event for reasonable sample sizes.

[30] 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 pool design are inconsistent with common shocks that would bias the results. One concern is that the MPP may target and obtain compounds that are likely to generate follow-on innovation. In practice, the MPP has fewer than 20 employees, focuses on drug access rather than R&D, and is not likely to have superior data on 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 validated by FDA approval and US patents. Most compounds in the pool are approved and have been marketed for years.[31] 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).[32] Empirically, the data and my interviews suggest that branded firms are not making sophisticated compound-level decisions. For example, Gilead contributed all the six HIV compounds it owned to the MPP by 2018. The first four entered in 2011 shortly after the pool approached Gilead, and the other two were added at the earliest possible.[33] Another firm almost contributed all its drugs but did not due to a CEO change.[34] Hence, experience indicates that compound-level unobserved factors that make R&D more attractive do not necessarily increase the likelihood of a compound entering the pool. As the first pool on drug access in LMIC, most of the negotiations with branded firms are diffusion-oriented.

5.2.2 Do Firms Invest More in Compounds that entered the MPP?

I find that firms respond to MPP compound addition with more follow-on clinical trials (Table 3 Panel A). Column (1) indicates that the number of new trials on drugs including a given compound increases by 9.9 trials after MPP compound addition, close to the mean annual trial rate for a compound during the sample period. The initial estimate is significant at the 5% level but loses statistical significance once controlling for observables. Nevertheless, the coefficient

[31] The results are similar when excluding two Gilead investigational drugs entering the MPP pre-approval.
[32] 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.
[33] The first four compounds (a cocktail) entered in 2011 are approved by US FDA in 2001, 2003, 2012 (for 2), respectively. The fact that Gilead did not distinguish compounds by age, class, and other factors reduces the concern of endogenous timing for R&D and supports the key focus on diffusion.
[34] According to the MPP administrators, the timing of inclusion for other firms is mostly affected by firm leadership and administrative efficiency. Also see related discussion and anecdotes in section 4.1.

magnitude remains close to the original estimate. FDA approval has a significantly positive association with follow-on trials, while patent status does not have a significant impact. Results in column (4) indicate that branded firms inside the MPP collectively choose to initiate 1.6 more trials with MPP-related compounds, significant at the 10% level. Similarly, column (8) indicates that MPP outsiders collectively increase trials that include MPP-related compounds, significant at the 10% level. 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 (Table 3 Panel B). Coefficient estimates are positive but not statistically 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 trials initiated per firm. The per-firm trial rate is about 0.9, 0.4, and 0.3 among insiders, outsiders, and mixed firms, respectively. The cross-column estimates are less stable among MPP insiders than outsiders, as branded firms react strongly to FDA approvals—when drugs can be marketed; instead, 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 from the pool creates incentives for follow-on innovation given the lower costs, while the per-firm trial is smaller, as outsiders are typically smaller firms. Overall, the results suggest that firms, on the margin, react positively to the MPP in terms of follow-on trials.

Table 3: 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 Equation (3) at the compound-year level. Each cell reports a result from a separate regression. $MPP_{insiders}$: all trial participants are branded firms contributed to the MPP, $MPP_{outsiders}$ are

trials by firms outside the MPP, and MPP_{mix} denotes trials that are collaborated on by MPP insiders and outsiders. Robust standard errors are clustered at the compound level. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

The event studies support the estimates above (Figure 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 a few 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, despite not significantly 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. Innovation tends to take longer to react than diffusion after pool inclusion, as preparing research, obtaining funding, and recruiting patient subjects in clinical trials often take longer than licensing and dissemination of existing products. There are also some heterogeneities across outcomes. As Figure 5 shows, trials initiated by insiders rise faster post-inclusion than those initiated by outsiders, as insiders have better access to information about the inclusion of drugs in the MPP. 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, indicating that increases in post-MPP trials from MPP outsiders are primarily driven by more firm participation.

The R&D results are consistent with the theoretical literature (Shapiro, 2001; Lerner and Tirole, 2004; Rey and Tirole, 2019). Note that the drugs in the MPP are primarily complements (e.g., compounds used in cocktails), even though they can sometimes be substitutes. Firms developing drugs that can be used in conjunction with MPP-included compounds now have a stronger incentive to innovate, since demand for these new drugs will be higher (due to complementarity), and this dominates the negative effect of increased competition from MPP substitutes. Since many of the innovation activities are follow-on trials to expand the use of a compound, MPP insiders may not want to increase such innovation by as much (since their rents from the new patents are lower, with MPP inclusion), but outsiders do as they can earn much larger rents from the patents. Instead, MPP insiders can shift time and resources into developing new cocktails or new compounds that can further complement existing drugs (see sections 5.2.3-5.2.4) and rely on outsiders to exert comparative advantage in follow-on innovations (e.g., new formulations, off-label use, new patient population).

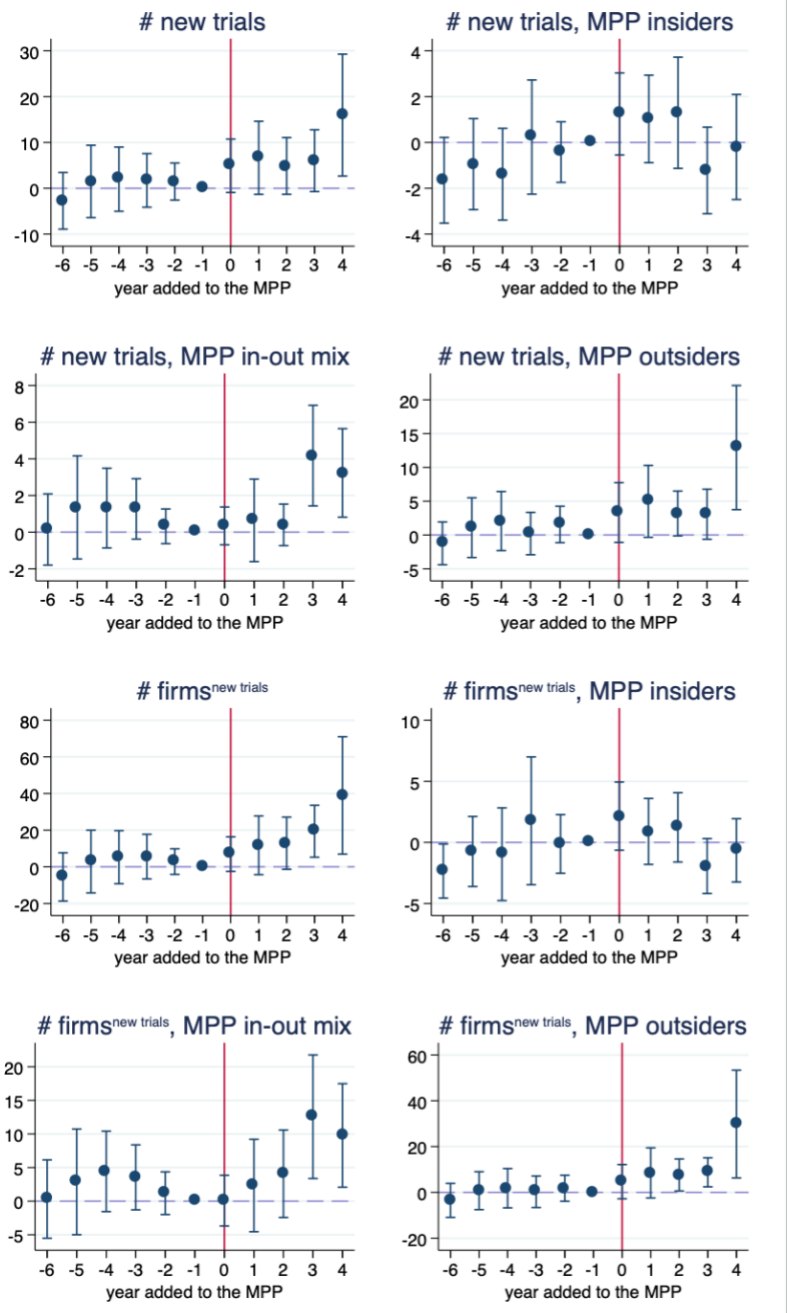


Figure 5: Event Studies for Innovation Analysis: New Clinical Trials and Firms Participated

Notes: The dots are point estimates of differences in outcomes between treated and control groups 6 years before and 4 years after MPP inclusion. The whiskers correspond to 95% confidence intervals.

5.2.3 Heterogeneous Effects on R&D Reallocation and by Funding Status

Across phases, firms respond to the MPP by starting more late-stage trials (Table 4). One would not expect the MPP 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 for 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 phase I-II. The increases in new trials and firm participation for phase III trials are significant at the 1% level. Event studies in Figure B2 justify the results for phase III trials except for fully in-house trials by MPP insiders. Notably, MPP insiders reduce phase IV post-market trials by about 0.4 per compound-year, with about 0.5 fewer firms participating, significant at the 5% and 1% levels, 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 support this point.

Table 4: 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). 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 trial participants are branded firms contributed to the MPP, $MPP_{outsiders}$ are trials by firms outside the MPP, and MPP_{mix} denotes trials that are collaborated on by MPP insiders and outsiders. Panels A to D report results by trial phase; phase IV is post-market surveillance. Controls variables include FDA approval status, patent status, and fixed effects for compounds and years. Robust standard errors are clustered at the compound level. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Firms' responses to the MPP vary by funding source, where firms with public-sector funding react more strongly with follow-on clinical trials (Table B7). Most firms outside the MPP are academic or public institutions. The increases are particularly strong among trials that

are not fully funded by industry and in phase III that involve multiple compounds. In contrast, privately funded trials reallocated phase IV trials to pre-market development trials; this reduction is more than offset by increases in publicly funded phase IV trials. There are no pre-trends in the event studies for all cases except a pre-period shift in insider phase III trials (Figure B4).

These results extend prior findings in the literature. First, Finkelstein (2004) finds that demand-oriented policies can spur technically feasible, follow-on clinical trials by 2.5-fold. My findings indicate that a demand-oriented public-private partnered institution can generate about 40% of that effect (1-fold) in a broader setting with LMIC drug market. Second, the magnitude of my upstream estimates lies well below the 5 to 10-fold increase in MPP licensing estimated by Galasso and Schankerman (2021), consistent with a smaller upstream spillover effect. Finally, Williams (2013) and Sampat and Williams (2019) find that private gene data restriction hinders follow-on R&D and patents do not necessarily so. My results complement their finding that more openness from private IP can foster follow-on innovation for small molecule drugs in LMIC.

5.2.4 Do Firms Invest More in New Compound Development?

Because trials on new compounds did not have unified names (i.e., generic names) pre-approval, in previous sections I focus on trials with compounds approved by 2018. Meanwhile, it is also important to understand the interaction of MPP compound addition and firms' R&D activities in developing new compounds that can further complement existing drugs. To account for the fact that most of these pre-approved compounds do not have a unified name, HIV investigational trials are aggregated to the drug class-year level for this analysis. First, the trend in trials on investigational HIV drugs suggests no reduction in overall incentives in developing new drugs (Figure B5). Second, Table B8 confirm the hypothesis that the MPP weakly increases overall R&D activity in investigational drugs. In addition, phase-specific event studies (Figure B6) justify that MPP insiders and industry-funded trials are increasing particularly for phase III trials. This result indicates that MPP insiders and industry trial funders invest more in new compounds that can further complement existing drugs.

5.3 R&D Results in New Drug Approvals

In this market, generic firms often introduce new drug cocktails by bundling compounds owned by different originators and offering more versions in strength and dosage forms. The

same empirical strategy is applied to new outcomes (i.e., new drug product approvals). More follow-on drug products are approved with compounds that entered the pool earlier relative to those that entered the pool later or outside the pool. This increase includes generic approvals of new cocktails and more firms gaining generic approvals of drug products with pooled compounds. The MPP-induced rise in generic approvals is consistent with the regulatory standard that generic firms are exempted from new trials for priorly approved drugs. The estimates are larger when converting drugs to the compound level, when the estimates capture the follow-on drug product approvals involving a compound in either standalone or cocktail form. Alternative models are implemented, including count data models and cox proportional hazard models, yielding similar results. Appendix F provides more detailed results.

5.4 Other Results

In addition, Table B12 and Figure B8 report Bacon decomposition results on treatment heterogeneity for the innovation analyses in both clinical trials and drug approvals. Similar to those in the diffusion analysis, most of the estimated treatment effects (81-84%) stem from a comparison of treated compound-years with classic control units ("Never vs. Timing"), with treatment magnitudes slightly larger than the finally weighted average treatment effect estimates. The "within" variation from observables mitigates the treatment effects but with small weights.

Following Roth (2022), the largest calculated potential bias is of a magnitude much smaller than the estimated effects in my event studies (i.e., a pre-trend of such size is likely to generate at least one statistically significant pre-period event study coefficient). If a linear trend indeed exists (although not detectable), my actual estimates are still substantially larger (4.5-8.5 times for main innovation outcomes) than the size of the calculated largest potential biases. For example, I estimate an increase of 9.9 new trials and 20.8 participating firms per compound year after MPP, and the calculated potential biases with 50% power are 1.1 trials and 2.4 firms, respectively (with 80% power: 1.7 and 3.6) – i.e., much smaller than the estimates (Table B13).

Finally, a few case studies are provided to support the R&D analysis (Appendix E). Results from this part suggest that firms react to the MPP with higher R&D inputs and outputs. 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 are driven by approvals of generic versions of existing drugs and new formulations.

6. Conclusion

I find that the MPP increases the diffusion of affordable generic versions of 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 weakly increases R&D in follow-on clinical trials and drug product approvals. Branded firms inside the pool 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 underdeveloped LMIC markets.

Although the focus is on the MPP's initial work on HIV drug cocktails, the general focus on infectious diseases and pool expansion deserve future work. The inclusion of hepatitis C and tuberculosis in 2015, the expanded mandate to WHO's small molecule essential drugs in 2018, and the partnership in the Covid-19 Technology Access Pool expose the MPP to challenges and opportunities. As many diseases have originated in LMIC and later become prevalent in the US, it is beneficial to develop global institutions for drug diffusion and innovation. Amid the current pandemic and rising anti-microbial resistance, institutions such as the MPP offer new options.[35]

The MPP also provides insights from a mechanism design perspective. As a non-profit pool with for-profit patent holders, the public-private partnership makes it natural to consider diffusion and innovation in coordinated manners. Different from software pools, the lowest MPP licensing unit is at the compound level, including all relevant territory patents in the licenses, eliminating concerns on selection in patents. Furthermore, the MPP segments the market to lower licensing costs for sales in LMIC but not in high-income territories, allowing branded firms to maintain prior strategies in lucrative markets and to broaden licensed sales in LMIC.

There are some limitations given the context of the MPP. The pool design is taken as given and cannot be extrapolated if the design changes drastically. With substantial internal validity of the MPP on infectious diseases in LMIC, more research is needed to evaluate pools with more complex products in developed countries. Furthermore, since a patent pool is designed to reduce multiple market frictions, it is difficult to quantify the magnitude of each mechanism.

[35] The new challenges also highlight value of various institutions in the supply chain, for example, pooled procurement institutions can supplement IP licensing for older, off-patent drugs (Wang and Zahur, 2021).

Finally, given the practical challenges to account for all unobservables that can affect outcomes and firms' decision in pool participation, future research is needed to overcome this limitation.

This paper has implications for policy and firm strategies. Institutional innovation can align public and private interests to improve welfare. Branded firms can use a patent pool to collaboratively expand market in LMIC and reduce costs. Such technology diffusion involves licensing designs that allow for broad use of patents and the preservation of licensor's rights in preferred territory, which are particularly valuable for diseases with heavy global burdens.

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Online Appendix: Not for Publication

Global Drug Diffusion and Innovation with the Medicines Patent Pool

Online Appendix Table of Content

Appendix A: Data Construction

A.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.[1] 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 facilitates data merging across different datasets. I also drop 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 level, I focus on generic names (international names of compounds within a drug), given that 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 are then 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 collect standard U.S. adult daily doses from FDA, AIDS*info*, and WHO, and I report the information in Appendix III (the medical appendix) Table A2.[2]

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 – the stock keeping unit (SKU). I then calculate the total strength supplied in a transaction by multiplying strength per SKU with the number of SKUs 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. Finally, 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 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.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

[1] 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.

[2] 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.

clinical sites.[3] Each clinical trial has a unique identifier (i.e., an NCT number) and a set of data recorded and updated periodically.[4] 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 participating in a compound-year by computing the total number of firms collaborating 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 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.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.[5] To pinpoint all approvals for HIV drugs, I convert the "active ingredients" variable all to lower-case and perform a text match, keeping the records 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 antiretroviral compounds. Following the same logic, I then clean the WHO pre-qualification program—the other largest drug approval and qualification agency.[6] The list is comprehensive and relatively clean. The other steps follow the same logic and process 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.

[3] 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).

[4] A descriptive webpage with data element definitions and mandatory information disclosure requirement in trials is available at: https://prsinfo.clinicaltrials.gov/definitions.html.

[5] 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.

[6] Available at https://extranet.who.int/prequal/content/prequalified-lists/medicines.

Table A1: Approved Active Pharmaceutical Ingredients (Compounds) Treating HIV
(generic names marked with * are compounds no longer recommended in the US)

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]
	didanosine *	ddI	Bristol-Myers Squibb	1991.10.09	
	emtricitabine	FTC	Gilead Sciences, Inc.	2003.07.02	2011.07.11
	lamivudine	3TC	ViiV Healthcare	1995.11.17	
	stavudine *	d4T	Bristol-Myers Squibb	1994.06.24	
	tenofovir alafenamide	TAF	Gilead Sciences, Inc.	2015.11.05	2014.07.22
	tenofovir disoproxil fumarate	TDF	Gilead Sciences, Inc.	2001.10.26	2011.07.11
	zidovudine	ZDV	ViiV Healthcare	1987.03.19	
NNRTIs	doravirine	DOR	Merck & Co., Inc.	2018.08.30	
	efavirenz	EFV	Bristol-Myers Squibb	1998.09.17	
	etravirine	ETR	Janssen	2008.01.18	
	nevirapine	NVP	Boehringer Ingelheim	1996.06.21	
	rilpivirine	RPV	Janssen	2011.05.20	
PIs	atazanavir	ATV	Bristol-Myers Squibb	2003.06.20	2013.12.11
	darunavir	DRV	Janssen	2006.06.23	
	fosamprenavir	FPV	ViiV Healthcare	2003.10.20	
	indinavir *	IDV	Merck & Co., Inc.	1996.03.13	
	nelfinavir *	NFV	Agouron (ViiV)	1997.03.14	
	lopinavir	LPV	AbbVie Inc.	2000.09.15	2014.11.24[ped]; 2015.12.17[adult]
	ritonavir	r	AbbVie Inc.	1996.03.01	2014.11.24[ped]; 2015.12.17[adult]
	saquinavir	SQV	Hoffman-La Roche	1995.12.06	
	tipranavir	TPV	Boehringer Ingelheim	2005.06.22	
FIs	enfuvirtide	ENF	Hoffman-La Roche	2003.03.13	
EIs	Ibalizumab	IBA	TaiMed Biologics	2018.03.06	
	maraviroc	MVC	ViiV Healthcare	2007.08.06	
IIs	bictegravir	BIC	Gilead Sciences, Inc.	2018.02.07	2017.09.26
	dolutegravir	DTG	ViiV Healthcare	2013.08.12	2014.03.31[ped. & adult]
	elvitegravir	EVG	Gilead Sciences, Inc.	2012.08.27	2011.07.11
	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) The table shows all drugs approved but not all in the diffusion sample (Table D2). E.g., IBA, the only monoclonal antibody, does not show up in any sales data. (2) I excluded 3 compounds withdrawn from the market pre-2000 (i.e., APV, ddC, DLV). EVG and COBI were first approved as part of a cocktail; standalone compounds were approved on 9/24/2014. Standalone TAF was approved on 2016.11.10 after cocktail approval on 2015.11.05. (3) MPP licenses for ABC and RAL restrict to pediatric formulation. I treat DRV as not in the pool, although NIH put its part of related patents but not those owned by Janssen, resulting in no technology transfer nor sub-licensing so far. (4) drug classes are groups by mechanisms of action (details in Table D1). (5) 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 territories for adult and pediatric products. (6) Agouron is a Pfizer subsidy since 1999 and Pfizer is part of ViiV Healthcare (joint venture with GlaxoSmithKline and Shionogi).

Appendix B: Figures and Tables

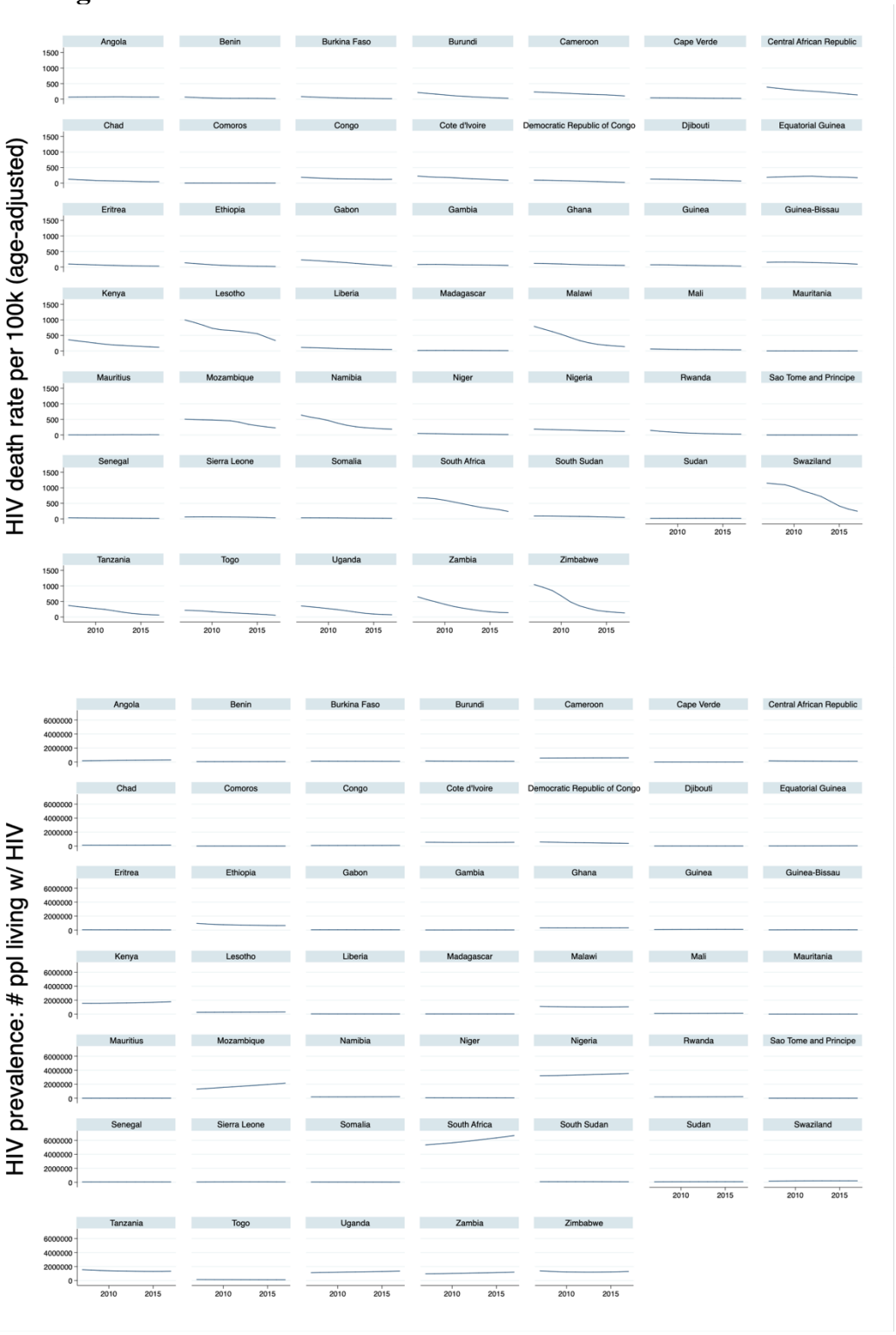


Figure B1: HIV death rate and prevalence, across MPP common territories

Notes: This figure visualizes age-adjusted HIV death rates (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 my sample period.

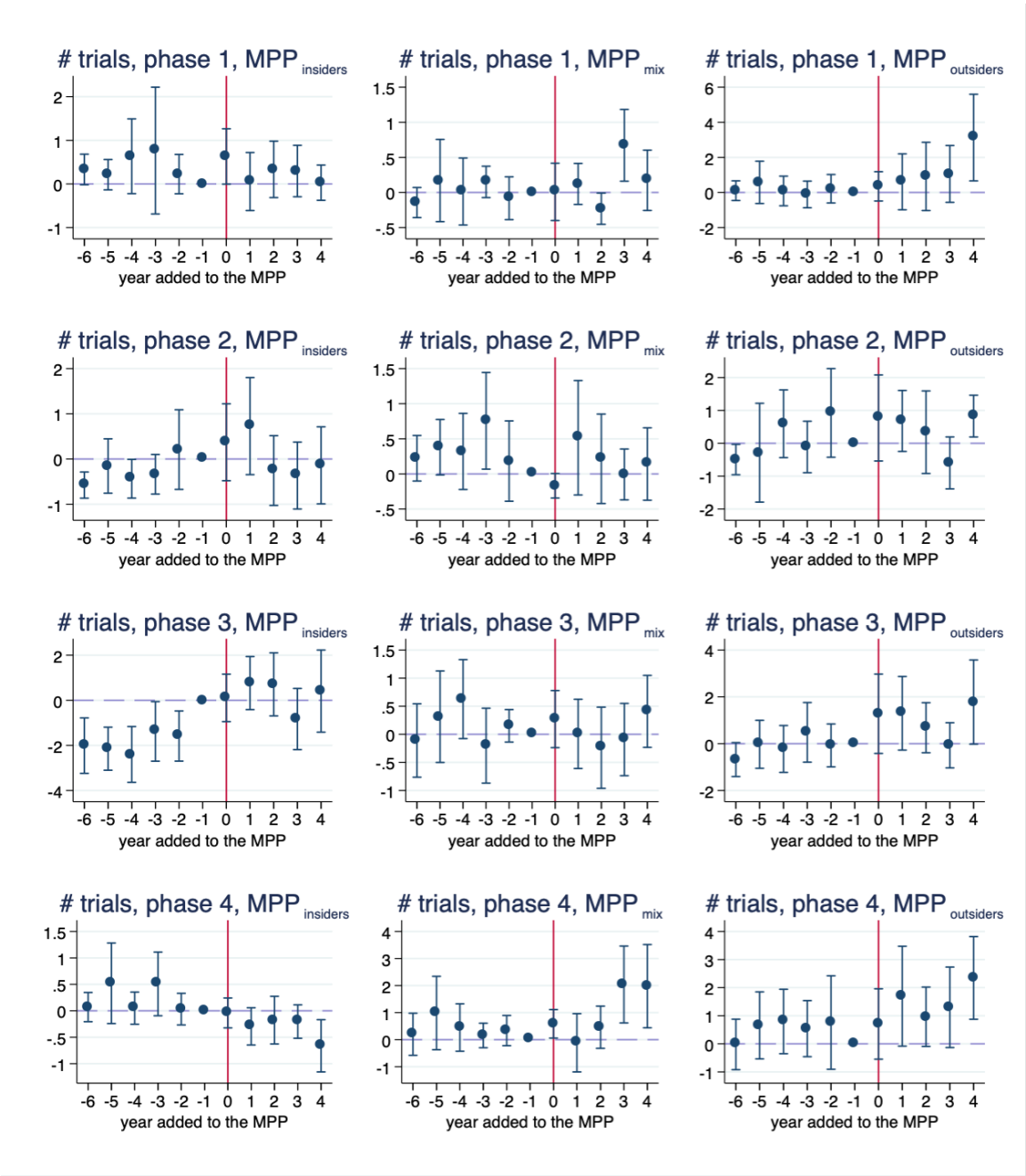


Figure B2: Event Studies for Innovation Analysis: Clinical Trials, by Firm and Phase

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

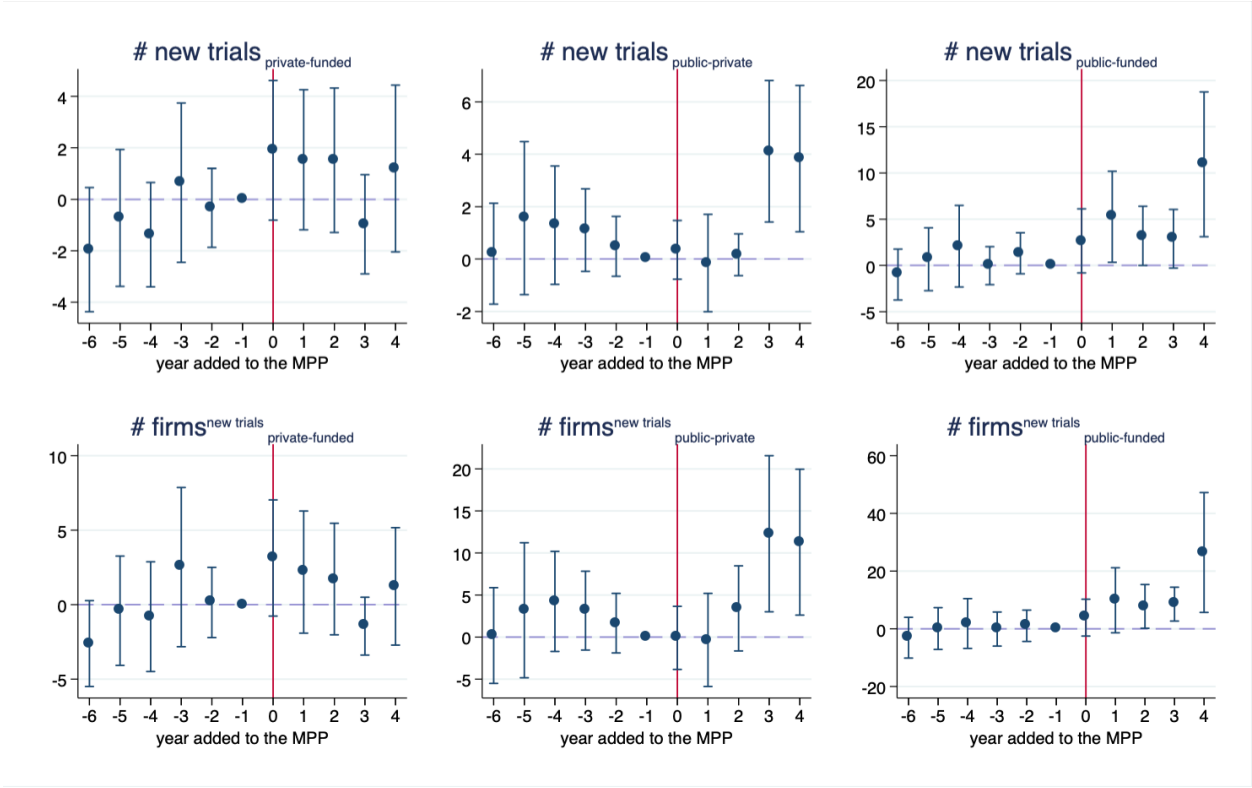


Figure B3: Event Studies for Innovation Analysis: Clinical Trials by Funding Type

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

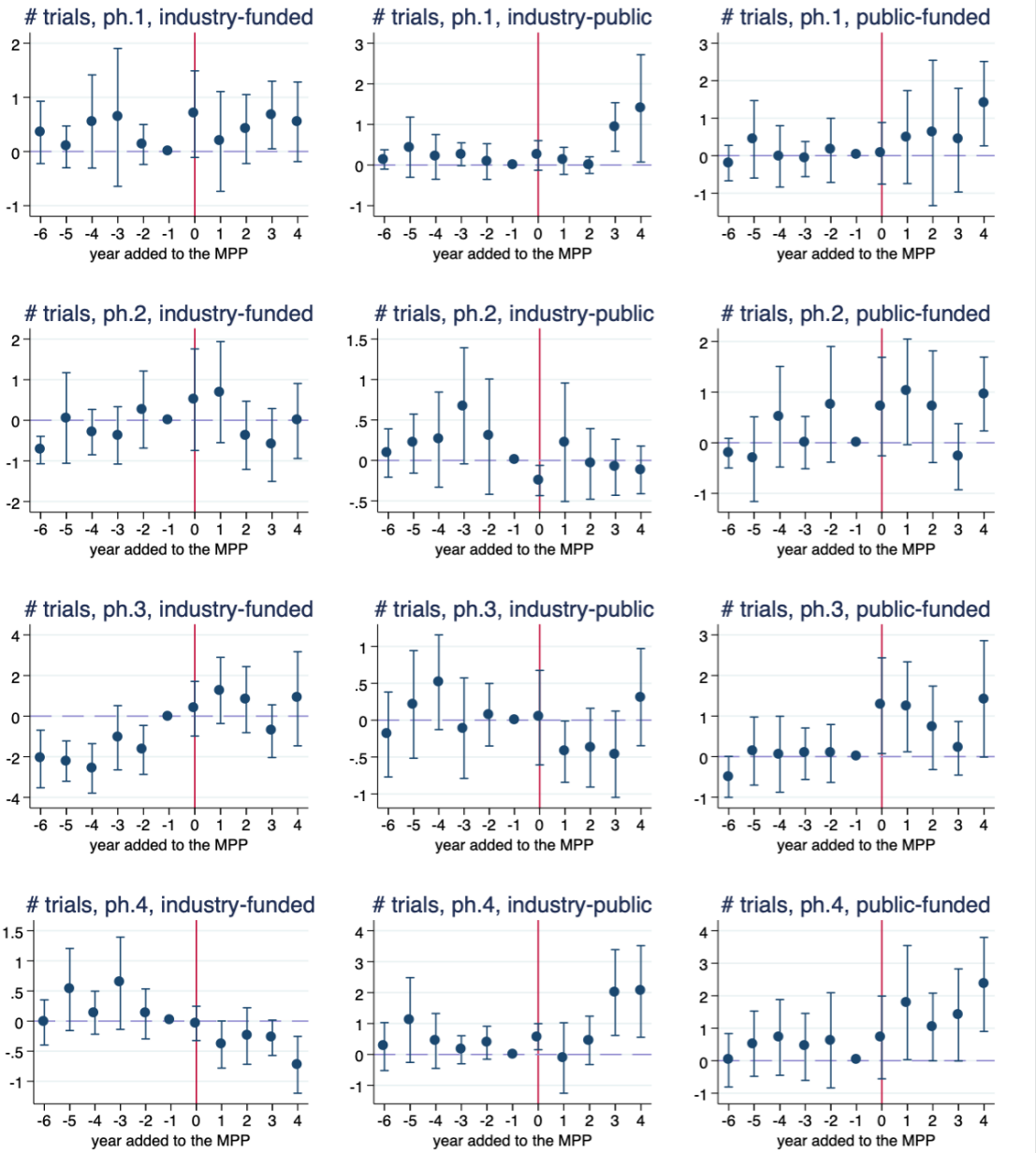
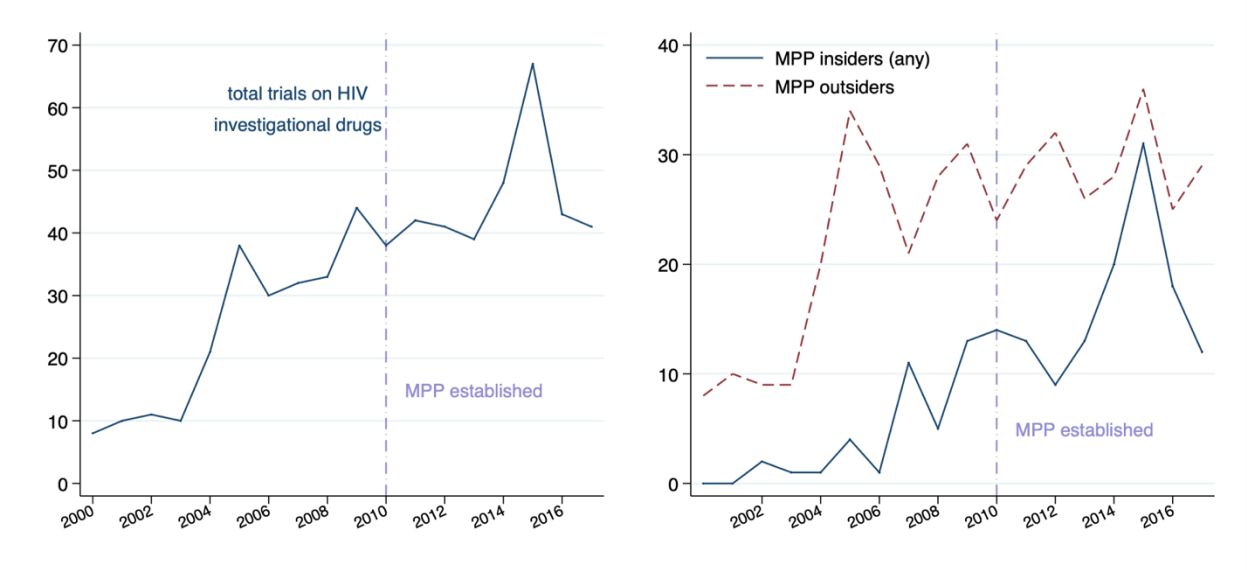
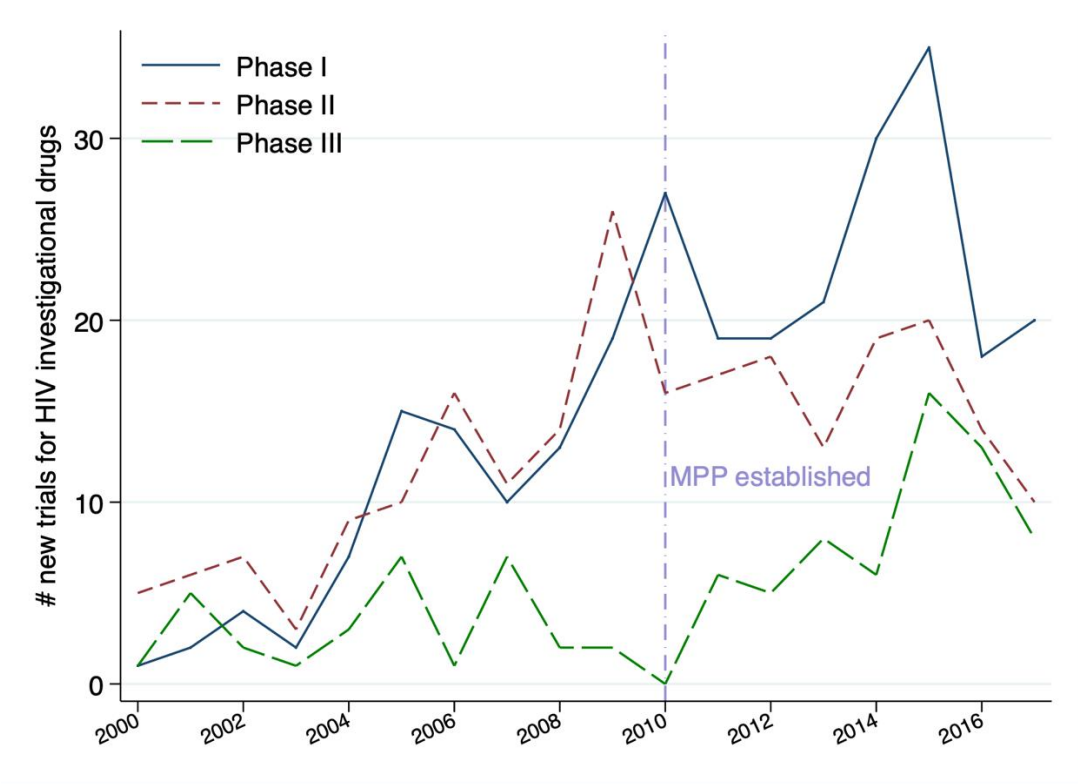


Figure B4: Event Studies for Innovation Analysis: Clinical Trials, by Funder and Phase

Notes: These figures report event-study coefficient estimates using Equation (4). The dots are point estimates of differences in outcomes between treated and control groups 6 years before and 4 years after MPP 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 B5: Descriptive Trends: # New Trials on HIV Investigational Drugs (pipeline)

Notes: This graph depicts 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 dashed line indicates the time when the MPP was established.

Figure B6: Event Studies: Clinical Trials for HIV Investigational Drugs, by Phase

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

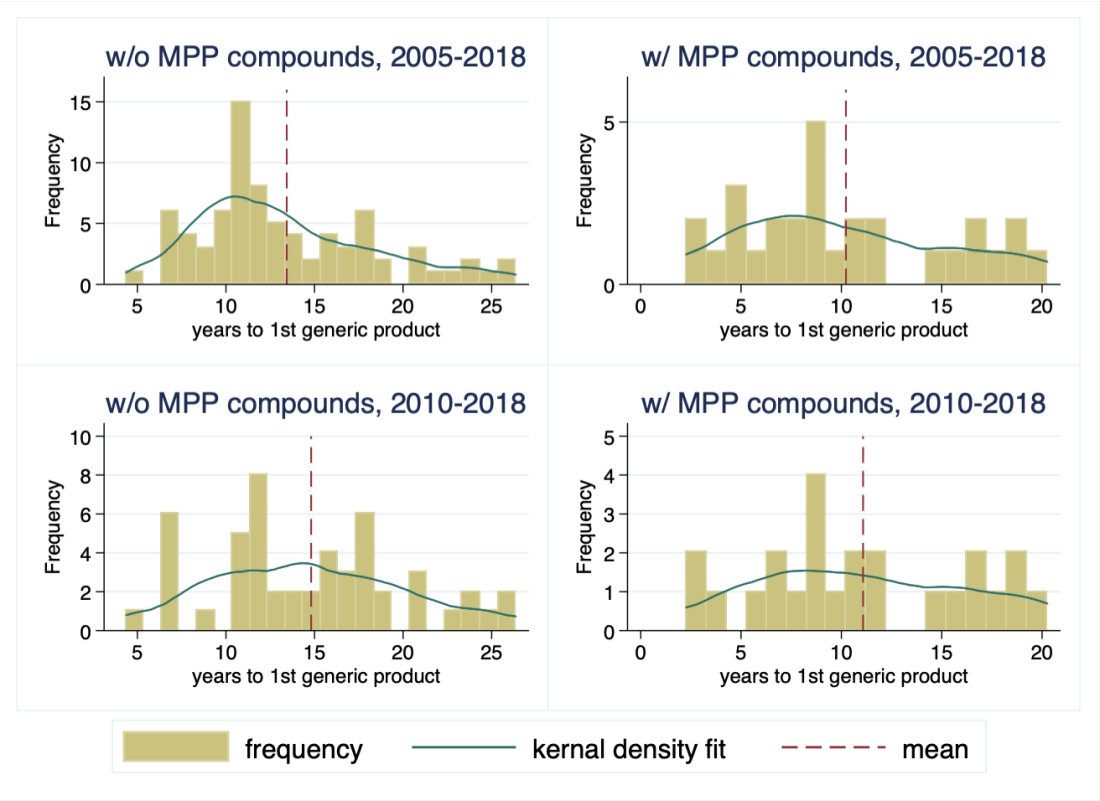
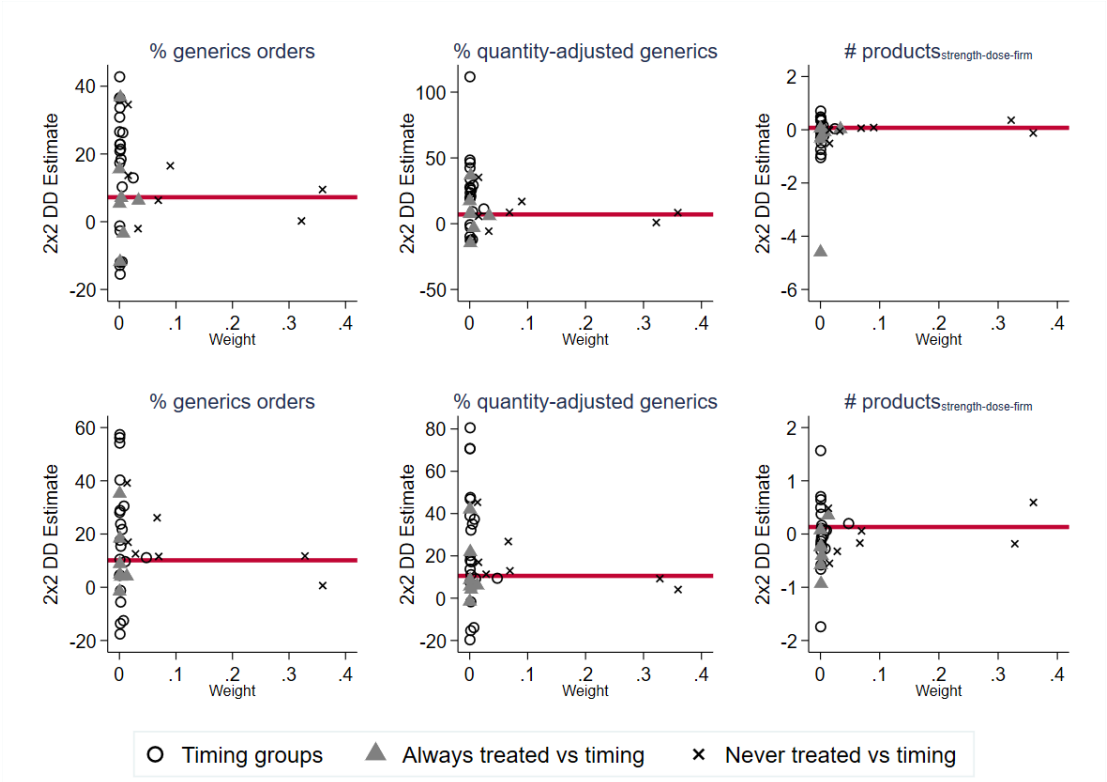
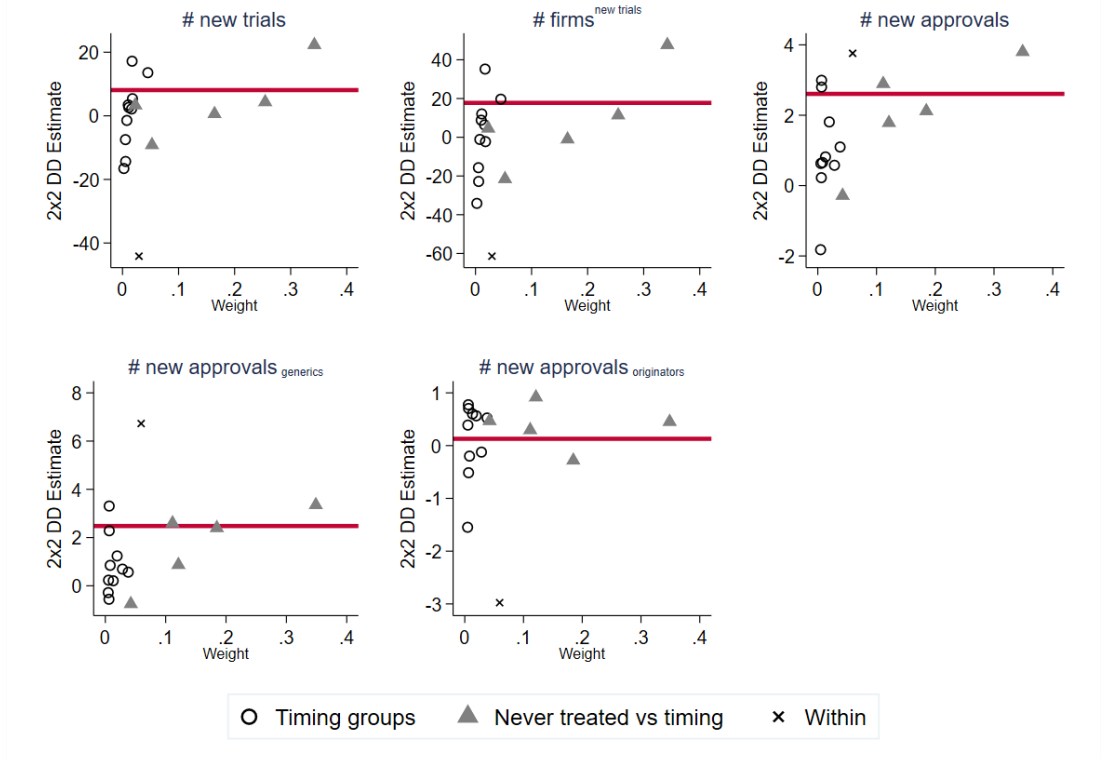


Figure B7: Histograms of Time-to-Generic by MPP Status

Notes: The figures show 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).



(a) Diffusion sample (upper: drug-country-year-level; lower: compound-country-year-level)



(b) Innovation sample: clinical trials & drug approvals

Figure B8: Bacon Decomposition for diffusion and innovation samples

Table B1: Regressing MPP Indicator on Observables

	(1) FE only	(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 the sample period. As shown above, none of the observables are significant predictors of when a drug-country pair is added to the MPP and is available for bundled licensing. In addition, 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 are reported in []. Two-way robust p-values: * $p<0.1$.

Table B2: 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's 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 is 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 two-way clustered 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 B3: 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 the 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 B4: Diffusion Analysis in Sample Drugs

Samples	(1) drug class in 1st pool addition	(2) drop one drug class	(3) drop drug no longer U.S. recommended	(4) drugs approved 1996+	(5) drugs by MPP insider firms	(6) by firms "all in" or "all out" MPP
Panel A: % generic orders as dependent variable						
MPP_{dct}	11.13***	7.030**	7.415**	6.848**	7.304**	8.087*
	(3.586)	(2.951)	(2.967)	(2.938)	(2.842)	(3.787)
	[3.471]	[2.773]	[2.687]	[2.705]	[2.706]	[3.633]
LHS mean	94.80	82.77	83.92	83.41	86.64	65.97
# Obs.	4,463	5,828	6,316	5,786	6,127	3,196
Panel B: % generic quantity ordered (patient year) as dependent variable						
MPP_{dct}	10.32***	6.520**	7.234**	6.620**	7.145**	7.258*
	(3.366)	(2.874)	(2.838)	(2.823)	(2.727)	(3.648)
	[3.335]	[2.781]	[2.693]	[2.702]	[2.709]	[3.973]
LHS mean	95.44	84.11	85.25	84.64	88.13	69.22
# Obs.	4,463	5,828	6,316	5,786	6,127	3,196

Notes: This table reports the results of estimating equation (1) in subsamples with different drugs in the control 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 two-way clustered 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 B5: 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 subsample diffusion analyses in countries where a drug (Panel A) or compound (Panel B) is ever or never patented during the sample period. Each cell reports the coefficient-of-interest from a separate regression. The specification controls effective patent status and country-year level observables. Fixed effects for drug(compound)-country pairs and years are always included. Robust standard errors reported in () are two-way clustered at the drug/compound 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 B6: Diffusion Analysis: Reduced-form Price and Quantity Regressions

	(1)	(2)	(3)	(4)	(5)	(6)
	log(Prices (Per Patient Year))			log(Quantity (Patient-Year Served))		
Dept. Vars.	Overall	Generic	Branded	Overall	Generic	Branded
MPP_{dct}	-0.355***	-0.350***	-0.0344	0.523***	0.707***	0.0797
	(0.103)	(0.0798)	(0.0653)	(0.171)	(0.152)	(0.323)
	[0.0489]	[0.0335]	[0.0887]	[0.126]	[0.149]	[0.352]
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	4.95	4.68	6.61	5.44	5.67	3.42
# Obs.	7,084	6,167	1,351	7,084	6,167	1,351

Notes: This table reports the results of estimating equation (1) using prices and quantities as outcomes. The problems and measurement issues with direct price and quantity regressions are discussed in section 3.2 and footnotes 18-19. 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 two-way clustered 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 B7: 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 with the balanced panel structure. 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. Control variables include FDA approval status, patent status, and fixed effects for compounds and years. Robust standard errors are clustered at the compound level (in parentheses). Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table B8: 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 at drug class-year level. The number of observations is always 91 with the balanced panel structure. There are seven drug classes in the analysis, of which six are drug classes with existing compounds approved and the further one captures 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 a trial is at least partly funded by industry. Control variables include FDA approval status, patent status, and fixed effects for compounds and years. Robust standard errors are clustered at the drug class level (in parentheses). Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table B9: 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 "#" counts 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, complete the list of first-approval information for all HIV drugs by the end of 2018.

Table B10: 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 analyzing 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 B11: 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 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 that always have zero approvals by the corresponding firm type create no variation, and are dropped to account for different focuses in actual investment areas.

Table B12: Treatment Heterogeneity: Bacon Decomposition Results

values/outcomes	coeff.	weight	coeff.	weight	coeff.	weight
Panel A: diffusion sample						
(drug-country-year)	% generic orders		% quantity-adj. generic		# prod. (within drug-country-year)	
Timing Groups	11.91	0.048	12.18	0.048	0.0001	0.048
Always vs timing	5.60	0.047	5.35	0.047	-0.04	0.047
Never vs Timing	6.79	0.901	6.66	0.901	0.09	0.901
Always vs never	50.92	0.001	38.31	0.001	-2.91	0.001
Within	76.23	0.003	82.28	0.003	0.10	0.003
(comp.-country-year)	% generic orders		% quantity-adj. generic		# prod. (within comp.-country-year)	
Timing Groups	11.30	0.088	12.67	0.088	0.10	0.088
Always vs timing	5.73	0.019	7.51	0.019	0.11	0.019
Never vs Timing	8.89	0.878	9.60	0.878	0.16	0.878
Always vs never	4.09	0.006	1.74	0.006	-0.17	0.006
Within	25.99	0.009	18.50	0.009	-1.92	0.009
Panel B: innovation sample *(compound-year level)*						
	# of new clinical trials		# firms in clinical trials		# drug product approvals	
Timing Groups	6.96	0.13	11.05	0.13	1.06	0.13
Never vs Timing	10.08	0.84	21.56	0.84	2.78	0.81
Within	-44.06	0.03	-61.29	0.03	3.77	0.06
	# approvals, generic		# approvals, branded			
Timing Groups	0.80	0.13	0.26	0.13		
Never vs Timing	2.44	0.81	0.34	0.81		
Within	6.74	0.06	-2.97	0.06		

Notes: The table reports Bacon decomposition (2021) results for main outcomes in the diffusion and innovation samples. The results are directly comparable to the benchmark results in Table 3 for diffusion and Tables 4 & 6 for innovation, and estimated using the same main specifications used in corresponding analyses. Figure B8 reports the corresponding visualization of Bacon decomposition results.

Table B13: Potential Bias under 50% and 80% Power, à la Roth (2022)

Diffusion	Drug-country-year level			Compound-country-year level		
Sample	% generic orders	% generic quantity	# products	% generic orders	% generic quantity	# products
β	7.226**	7.010**	0.0717	10.12***	10.55***	0.132
$\tilde{\gamma}_{0.5}$	9.896	10.663	0.082	4.756	5.423	0.110
$\tilde{\gamma}_{0.8}$	14.251	15.321	0.126	6.917	7.885	0.171
$\gamma_{0.5}$	3.034	3.243	0.067	1.816	1.962	0.065
$\gamma_{0.8}$	4.623	4.940	0.102	2.822	3.039	0.101

Innovation	Clinical trials results			Drug product approvals		
Sample	# new trials	# firms in trials	# trials III	# approvals	# generics	# branded
β	8.093	17.75*	3.374***	2.607**	2.478**	0.129
$\gamma_{0.5}$	1.161	2.448	0.397	0.393	0.325	0.128
$\gamma_{0.8}$	1.730	3.660	0.580	0.579	0.481	0.191

Notes: This table shows estimates of largest potential biases from under-powered pre-trends using Roth (2022). Biases are calculated under linear violations of parallel trends with slopes $\gamma_{0.5}$ and $\gamma_{0.8}$, against which conventional pre-tests have 50% or 80% power, respectively. For the diffusion sample: $\tilde{\gamma}_{0.5}$ and $\tilde{\gamma}_{0.8}$ report the largest sizes of slope from potential biases, when robust standard errors are two-way clustered at the drug (compound) and country levels. $\gamma_{0.5}$ and $\gamma_{0.8}$ as the largest potential biases where standard errors are clustered at the country-drug level (align with two-way fixed effect indices). For the innovation sample, robust standard errors are clustered at the compound levels. Robust p-values: *** p<0.01, ** p<0.05, * p<0.1.

Table B14: Estimation and Sensitivity Analyses on Diffusion Analyses with Linear Pre-trends

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	% generic orders (#)			% generic quantities (patient-year)			# products (strength-dose-firm)		
Panel A: drug-country-year panel, specification 1: linear pre-trend and treatment effects									
MPPdct	9.367	9.367**	9.367***	11.01	11.01***	11.01***	-0.00987	-0.00987	-0.00987
	(10.89)	(3.714)	(3.540)	(11.75)	(4.126)	(3.903)	(0.0985)	(0.0880)	(0.0895)
pre-trend	-1.011	-1.011	-1.011	-1.888	-1.888	-1.888	0.0385	0.0385	0.0385
	(5.646)	(1.815)	(1.982)	(5.912)	(1.958)	(2.098)	(0.0542)	(0.0405)	(0.0379)
specification 2: linear pre-trend and post period event study (in each period)									
MPP(t=0)	3.752	3.752*	3.752	3.423	3.423	3.423	-0.0311	-0.0311	-0.0311
	(5.143)	(2.258)	(2.422)	(4.454)	(2.479)	(2.641)	(0.0710)	(0.0634)	(0.0599)
MPP(t=1)	7.771	7.771***	7.771***	8.797	8.797***	8.797***	0.0186	0.0186	0.0186
	(9.226)	(2.418)	(2.249)	(9.522)	(2.549)	(2.356)	(0.0738)	(0.0714)	(0.0556)
MPP(t=2)	7.278	7.278***	7.278***	8.221	8.221***	8.221***	0.0475	0.0475	0.0475
	(7.119)	(2.040)	(2.103)	(7.367)	(2.187)	(2.128)	(0.123)	(0.0786)	(0.0734)
MPP(t=3)	4.752	4.752**	4.752*	5.275	5.275**	5.275**	0.0357	0.0357	0.0357
	(6.899)	(2.183)	(2.446)	(6.531)	(2.276)	(2.403)	(0.178)	(0.0840)	(0.0805)
MPP(t=4)	3.937	3.937*	3.937*	4.791	4.791**	4.791**	0.143	0.143*	0.143*
	(5.776)	(2.033)	(2.022)	(5.693)	(2.100)	(2.039)	(0.150)	(0.0767)	(0.0788)
pre-trend	0.725	0.725	0.725	0.271	0.271	0.271	0.0366	0.0366	0.0366
	(3.851)	(1.259)	(1.409)	(3.844)	(1.331)	(1.446)	(0.0472)	(0.0292)	(0.0301)
specification 3: linear pre-trend and post period event study (in three time groups)									
MPP(t=0)	3.807	3.807*	3.807	3.466	3.466	3.466	-0.0372	-0.0372	-0.0372
	(5.279)	(2.263)	(2.429)	(4.568)	(2.487)	(2.647)	(0.0696)	(0.0630)	(0.0598)
MPP (t=1–2)	7.614	7.614***	7.614***	8.596	8.596***	8.596***	0.0254	0.0254	0.0254
	(8.469)	(2.193)	(2.124)	(8.744)	(2.338)	(2.201)	(0.0841)	(0.0633)	(0.0508)
MPP (t=3–4)	4.346	4.346**	4.346**	5.045	5.045**	5.045**	0.0905	0.0905	0.0905
	(6.374)	(2.052)	(2.157)	(6.157)	(2.128)	(2.146)	(0.159)	(0.0705)	(0.0706)
pre-trend	0.727	0.727	0.727	0.275	0.275	0.275	0.0368	0.0368	0.0368
	(3.831)	(1.256)	(1.409)	(3.822)	(1.328)	(1.445)	(0.0467)	(0.0292)	(0.0300)
cluster s.e. by:	two-way: drug, country	drug-country	country	two-way: drug, country	drug-country	country	two-way: drug, country	drug-country	country
Panel B: compound-country-year panel (key estimates from specifications 1 & 2 are reported)									
MPPdct	16.83***	16.83***	16.83***	18.81***	18.81***	18.81***	0.201	0.201**	0.201*
	(4.940)	(2.754)	(3.551)	(5.761)	(3.112)	(4.007)	(0.196)	(0.0914)	(0.111)
MPP(t=0)	-1.409	-1.409	-1.409	-4.193	-4.193**	-4.193	-0.0800	-0.0800	-0.0800
	(2.729)	(1.734)	(2.229)	(3.328)	(2.047)	(2.706)	(0.144)	(0.0870)	(0.100)
MPP(t=1)	-0.926	-0.926	-0.926	-0.0950	-0.0950	-0.0950	0.264	0.264***	0.264**
	(2.322)	(1.770)	(2.324)	(2.546)	(2.081)	(2.882)	(0.178)	(0.100)	(0.129)
MPP(t=2)	3.267	3.267	3.267	3.239	3.239	3.239	0.491***	0.491***	0.491***
	(2.758)	(2.018)	(2.557)	(3.125)	(2.252)	(2.993)	(0.163)	(0.107)	(0.112)
MPP(t=3)	11.06**	11.06***	11.06***	12.15**	12.15***	12.15***	0.546**	0.546***	0.546***
	(4.854)	(2.261)	(2.966)	(5.310)	(2.397)	(3.177)	(0.231)	(0.125)	(0.141)
MPP(t=4)	3.576	3.576*	3.576	3.417	3.417*	3.417	0.400*	0.400***	0.400**
	(3.410)	(1.937)	(2.264)	(3.280)	(2.037)	(2.393)	(0.224)	(0.135)	(0.153)
MPP(t=5)	5.687	5.687**	5.687**	5.687	5.687**	5.687**	0.522**	0.522***	0.522***
	(3.270)	(2.331)	(2.620)	(3.362)	(2.456)	(2.743)	(0.211)	(0.142)	(0.149)

Notes: This table reports alternative estimation of diffusion with linear pre-trends, à la Greenstone and Hanna (2014) and Dobkin et al. (2018). Cross-column results are sensitivity analyses that cluster standard errors at different levels.

Appendix C: Legal Appendix

Table C1: Key MPP license contract terms

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 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 economies/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 MPP official website product page (https://medicinespatentpool.org/what-we-do/global-licence-overview/licences-in-the-mpp/), collected from each compound's profile and corrected a few case with raw information from the MPP sub-licensing contracts. Last updated: 12/31/2018.

Appendix D: 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 a 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 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 exists. 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 D1: 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 D2: 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 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 weighting over 60 kg (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 D3: 2017 and 2012 top selling HIV drugs and MPP status

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

Table D3.1: 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 D3.2: 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 E: Case Studies on R&D

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 LMIC 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 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).[7] Gilead then started phase II trials of tenofovir alafenamide fumarate (i.e., TAF, a prodrug of TDF) in 12/2011, collected primary results in October 2012, and started phase III trials in 12/2012. 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.[8]

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.

[7] 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.

[8] 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. 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.

Appendix F: R&D Results in New Drug Approvals

F.1 Innovation and Imitation: Overview and Exploratory Analysis

HIV drug approvals are used to analyze R&D outputs next. All FDA and WHO approvals of a new product at the drug-strength-dosage form-firm level are examined. These approvals are obtained by either branded or generic firms and include tentative generic approvals that only allow for sales in LMIC. At the drug level, a drug innovation is either an original approval of a new compound or the first approval of a cocktail, 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 a different firm. At the drug product level (i.e., drug-strength-dosage form), a product innovation is the first approval of a drug in a formulation (strength-dosage form) by the first applicant, while product imitations include follow-on approvals of the same drug product by other firms. Not all approvals are US-marketable, but all of them reflect the qualification of approved products.

Although branded drug makers are leaders in new compound development, generic firms develop many new cocktails and products. Among the 30 first approvals of drugs with already-approved compounds, 27 are new drug cocktails (Table B9). Among these 27, 13 new cocktails were first created by generic firms, with the constituent 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, through intra-firm bundling or cross licensing between two firms. This pattern shows an important role that generic firms play in innovation and their comparative advantage in cross-firm bundling. The pattern is similar at the drug product level, where generic firms capture a higher share of new products approved when strength and dosage forms are considered.

The relationship between MPP and "time to first generic" is analyzed in a sample includes cases where a drug product is first approved generically for a given drug-strength-dose after all of its underlying compounds are approved (i.e., it is technically feasible to produce a drug generically). Histograms (Figure B7) show that the average "time to first generic" product is shorter for drugs with MPP compounds. Table B10 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 suggestive evidence that the MPP is associated with faster generic approvals.

F.2 Does the Patent Pool Induce More Follow-on Drug Product Approvals?

The empirical strategy is identical to that used in the clinical trials analysis except the outcomes are now the number of new approvals at the drug and compound levels. Firms appear to 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 (Table F1), including generic approvals of new cocktails (innovation) and more firms gain generic approvals of existing drugs with pool-covered compounds (imitation). The MPP-induced increase in new drug product approvals is about 0.5 more approvals per year in pool-related drugs and is robust across specifications (Panel A columns 1-2). The

increased product approvals are driven by generic firms, which create new cocktails and existing products at lower costs. This is consistent with the regulatory standards that exempt generic firms from new trials when the underlying compounds were previously approved. The estimates are more precise statistically when the MPP treatment is measured as a percentage to capture changes in the extensive and intensive margins (Panel B).

Table F1: Innovation Analysis - Drug Approvals

	(1)	(2)	(3)	(4)	(5)	(6)
Dept. Vars.	# new approvals		# new approvals ^{generic}		# 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 Equation (3). Each adjacent two columns share the same dependent variable in different specifications. Panels A and B differ in how the treatment variable is defined: as an indicator or percentage. 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 estimates become larger (Table F1 Panel C). This result is expected as now the MPP effect captures the follow-on drug product approvals involving a compound in either standalone or cocktail form. These results are consistent with the hypothesis that follow-on approvals with pooled compounds are often developed as cocktails instead of as simple compound-level imitations, suggesting higher social values derived through competition among new and existing cocktails. All the results are robust to count data model using negative binominal (Table B11).

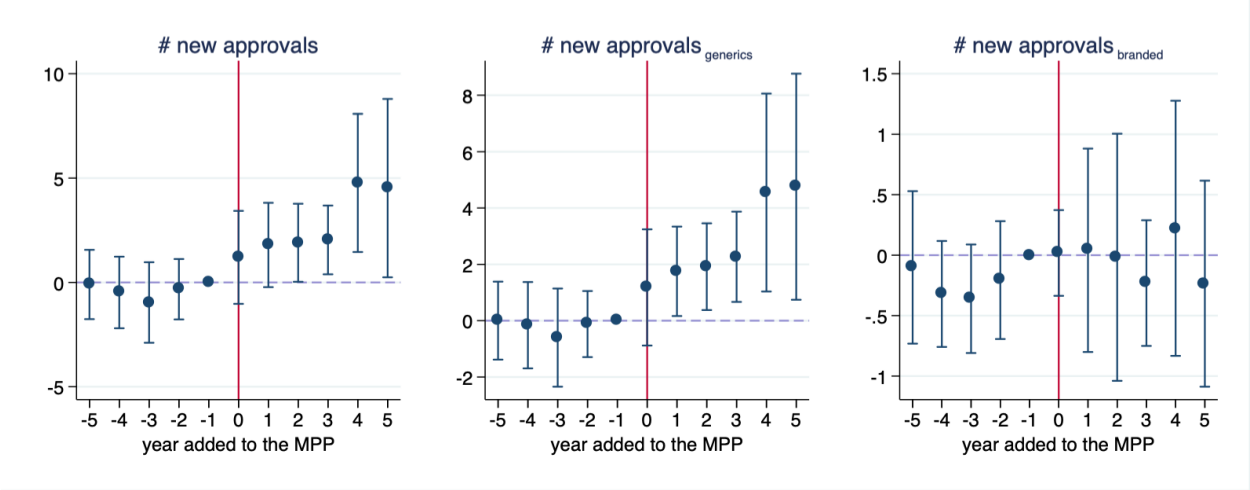


Figure F1: Event Studies for Innovation Analysis: New Drug Product Approvals

Notes: The dots are point estimates of differences in outcomes between treated and control groups. Unit: compound-year level. The whiskers correspond to 95% confidence intervals.

Event studies support the drug approval analyses (Figure F1). 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 graphs cross-column within panel, most of the new drug or compound-level approvals are driven by follow-on generic product approvals, suggesting large imitation-based responses. New branded approvals do not substantially change in these figures once controlling for initial approvals. Across panels, event study responses are larger when cocktails are de-bundled into compounds. Overall, the responses in innovation suggest that firms outside the pool are responsive to the increased expected return to technologically feasible products when barriers to entry are reduced. Within the set of innovation outcomes, clinical trials rise larger and faster than drug approvals, because the former can be initiated without FDA oversight, while the approval also involved FDA review and can take longer.