The Impact of Weakened Patent Rights on Innovation: Evidence from HIV's Drug Development*

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Abstract

Starting in 1997, countries such as South Africa and Brazil attempted to procure low-cost HIV drugs via compulsory licensing, triggering a dispute between these countries and pharmaceutical companies. Does the threat of compulsory licensing alter pharmaceutical companies' willingness to invest in drug development for diseases affecting developing countries? The bad publicity received by pharmaceutical companies, driven by the increasing awareness of the HIV epidemic, forced the end of the disputes, resulting in lower HIV drug prices. Using the synthetic control method and pharmaceutical pipeline data, we examine the impact of the compulsory licensing threat on HIV drug development. Our findings reveal a substantial negative effect on HIV drug development, suggesting that policies designed to improve access to existing medicines may inadvertently reduce the creation of future treatments. This presents policymakers with a tradeoff, with potentially profound implications for global health outcomes and the design of international intellectual property regimes.

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1 Introduction

Pharmaceutical companies invest billions of dollars in researching and developing new drugs. They rely on patent protection to recoup these research and development (R&D) costs, since chemical molecules are easily replicated once they reach the market. Patents provide legal protection against imitators, enabling supra-competitive pricing that gives pharmaceutical firms ex ante incentives to make costly investments. However, charging high prices for drugs that have already been developed is ex post inefficient, as patients who need treatment may be unable to afford it, potentially resulting in preventable deaths. Therefore, commitment to respecting intellectual property rights is central to patent-driven innovation. This framework, however, becomes problematic during public health emergencies, when countries may impose compulsory licenses—mandates requiring patent holders to grant production licenses to other entities—to override patents and make existing drugs available at lower cost. A prominent example is South Africa's "Medicines and Related Substances Control Act" of 1997 (henceforth, MRSCA), enacted to address the country's HIV/AIDS crisis (Rigamonti et al., 2005).

Although compulsory licensing can save lives in the short term, it can also limit an innovator's ability to profit from an invention. This weakening of intellectual property (IP) rights that may discourage pharmaceutical firms from developing new drugs that may save lives in the future. Because of this trade-off, the literature has given arguments both in favor and against the use of compulsory licensing to tackle public health crises (e.g., see McMillan 2003; Anderson Jr 2010). However, evidence to date on the impact of weakened patent rights on the development of new drug therapies to inform this debate remains scarce.

We analyze and quantify the impact of weakened intellectual property rights on innovation by studying the case of HIV drugs. The 1995 TRIPS agreement harmonized patent protection across countries while establishing conditions under which countries may use compulsory licensing (Article 31). Following the TRIPS agreement, many countries either threatened to impose or implemented compulsory licenses. The first major instance was South Africa's MRSCA, which enabled the country to procure patented antiretroviral drugs at reduced costs for distribution below retail prices. Subsequently, Brazil, Zimbabwe, and more than a dozen other countries issued compulsory licenses to obtain

low-cost HIV/AIDS drugs (Hoen et al., 2011).[1] Although pharmaceutical companies initially fought these patent overrides through lawsuits, they ultimately abandoned their legal challenges following a public relations disaster, leading to lower drug prices.[2]

The main empirical challenge lies in finding a control group for the HIV drug industry. To overcome this difficulty, we use the synthetic-control methodology (Abadie and Gardeazabal, 2003; Abadie et al., 2010, 2015). This framework constructs a synthetic industry that "looks like" the HIV industry before the event under examination. The evolution of the outcome of interest in this control industry after the event provides a counterfactual scenario against which we can compare the actual evolution of the HIV industry.

To measure the impact of weakened IP rights on the development of drug therapies, we use the timing of MRSCA as a shock to the strength of patent rights. This shock is the "treatment event" that was specific to HIV drugs, and use it as the basis of our identification strategy. In our analysis, we use several datasets to measure the number of drugs in development for every disease at every moment of time during the period 1991-2007 as well as a number of time-varying covariates that predict drug development.

Our main finding is that the weakening of patent rights in the HIV drug therapy industry caused a large reduction in the number of therapies under development. Over the mid-1997–2006 period, the number of drugs in development decreased on average by 138, which is approximately 47% of the baseline level of outcome in July 1997 (i.e., when the "South African Medicines and Related Substances Control Act" was passed). We use an alternative outcome variable in order to measure the effects among drug therapies that are closer to completion. The number of drug therapies undergoing phase II or III clinical trials decreased on average by 42 in the post-intervention period, which is approximately 61% of the baseline level of outcome.

This result holds under a series of placebo studies and robustness exercises described in Abadie and Gardeazabal (2003) and Abadie et al. (2010, 2015). We test the credibility of our estimates by reassigning the treatment to industries other than the HIV industry and periods other than July 1997. The in-space placebo study results suggest that the

[1] Compulsory licensing has been used by other countries to address other health crises. In 2006, Italy imposed a compulsory license on Finasteride, a drug treating benign prostatic hyperplasia. In 2007, Thailand imposed a compulsory license on Clopidogrel Bisulfate, a heart disease drug.

[2] See "Drug Makers Drop South Africa Suit Over AIDS Medicine," *The New York Times*, 2001.

likelihood of obtaining estimates as large as our main results is 0.035 (0.031 when the number of drugs in phase II or III is used as the outcome variable), suggesting that our results are unlikely to have been obtained by chance. The in-time placebo study results suggest negligible effects when the treatment period is reassigned to periods before the weakening of patent rights.

We also discuss the potential confounding of the simultaneous emergence of highly effective combination antiretroviral therapies (HAART) in the mid-1990s, which transformed HIV into a manageable chronic condition and may have reduced commercial incentives for innovation. However, several patterns suggest this cannot fully explain our findings. First, we observe an abrupt 47% monthly drop in HIV candidates immediately after South Africa's July 1997 compulsory licensing threat, whereas pipeline growth remained steady until that point, even years after the emergence of HAART. Second, placebo tests show no comparable pipeline contractions for other diseases or dates, indicating the decline is uniquely associated with the licensing event. Third, even late-stage Phase II/III candidates declined 61% after mid-1997, whereas a cocktail explanation would predict stronger effects on early-stage programs.

Our results empirically document the fundamental trade-off inherent in using compulsory licensing to address public health crises. While such policies can provide immediate access to life-saving treatments, our findings suggest they may substantially discourage future drug development, potentially reducing the availability of new therapies that could save even more lives over the long term. This evidence reveals a critical tension between short-term access and long-term innovation that policymakers must carefully weigh when designing intellectual property regimes for global health emergencies.

Literature Review

The literature has documented that weak intellectual property regimes and price controls delay new drug entry, particularly in middle and low-income countries. Danzon et al. (2005) find longer entry delays in markets with lower prices across 25 major markets in the 1990s, while Cockburn et al. (2016) and Kyle (2006, 2007) provide evidence that new drugs launch with greater delays in countries with price controls and weak property rights. Studies of the implementation of TRIPs in India show that stronger patent protection affects markets. Chaudhuri et al. (2006) find that stronger IP right cause a static welfare loss, while Duggan et al. (2016) find only small effects on quantities and firm entry, and

Mohapatra and Chatterjee (2015) show that price controls for malaria drugs induce firm exit and welfare losses.

Some authors have documented the use of compulsory licensing after TRIPS. Harris (2010) discusses whether TRIPS has been successful regarding compulsory licensing use, while Beall and Kuhn (2012) document 24 compulsory licensing instances between 1995-2011, with 16 involving HIV/AIDS drugs and 11 cases where mere threats induced companies to reduce prices voluntarily. Theoretical work by Ramani and Urias (2015), Bond and Saggi (2017) and Bond and Samuelson (2019) examines price negotiation under compulsory licensing threats, while our empirical finding of abrupt pipeline collapse aligns with predictions from Bond and Saggi (2014) and Bond and Saggi (2018) that such threats can induce firms to reduce incentives to invest in some markets.

The innovation effects of compulsory licensing vary significantly across industries. Studies outside pharmaceuticals often find positive effects: Watzinger et al. (2017) show that Bell Labs' compulsory licensing encouraged innovation, Moser and Voena (2012) find 20% increases in U.S. chemical invention, and Baten et al. (2017) demonstrate increased downstream patenting in German chemicals post-WWI. However, pharmaceutical evidence is mixed. While Chien (2003) concludes that compulsory licensing does not decrease innovation incentives based on six episodes, Scherer and Watal (2002) argue the opposite, and Stavropoulou and Valletti (2015) find non-monotonic relationships between compulsory licensing costs and R&D investment.

Our findings connect to the broader literature on market size and innovation, as compulsory licensing threats effectively reduce expected returns. Acemoglu and Linn (2004) show that a 1% increase in potential market size leads to a 4% growth in new drug entry, with limited research toward small markets. Dubois et al. (2015) estimate that $2.5 billion in additional revenue supports one new chemical entity, highlighting pharmaceutical innovation's sensitivity to expected returns. Kyle and McGahan (2012) find that stronger TRIPS protection increased R&D in wealthy countries but had no effect on drugs targeting diseases in poor countries, possibly reflecting hesitancy where compulsory licensing threats are higher. Related work by Gallini (2017) discusses patents' role in antibiotic innovation, Sampat and Williams (2019) find that gene patents had no effect on follow-on innovation, Budish et al. (2015) show that shorter patent protection decreases innovation incentives, and Finkelstein (2004) demonstrate how short-term vaccination policies

can have long-term R&D effects. Stern (2017) provides additional evidence that regulatory uncertainty delays pioneer inventors more than followers. The contrast between our substantial HIV R&D reduction and positive effects in other industries underscores that compulsory licensing impacts depend on industry structure, market size, and global innovation networks.

2 Industry Background

The worldwide revenue of the pharmaceutical industry in 2018 was about 1.2 trillion dollars.[3] The total cost of developing a new drug is estimated to be about 2.5 billion dollars, which includes the cost of discovering new molecular targets, paying for clinical trials to test efficacy and safety of new drugs, and the cost of complying with the requirements imposed by regulatory agencies (DiMasi et al., 2016). The process of bringing a new drug to the market also takes a long time (about 10 years) and involves a great deal of uncertainty (less than 10% success rate from discovery to reaching the market). Once a drug has been developed, a generic manufacturer can copy the drug and produce it cheaply, which is why pharmaceutical firms rely on patent protection to appropriate rents from a successful new drug.

In 1994, the World Trade Organization (WTO) established the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which came into force in 1995. The goal of this agreement was to homogenize intellectual property laws among WTO members, requiring patent protection, with a duration of 20 years from the date of the filing of the patent application, in all of the relevant technology fields. One salient aspect of this harmonization was the recognition of pharmaceutical patents—before the TRIPS agreement, many countries did not grant patents for pharmaceutical products—which would presumably increase investment in developing countries. Some became concerned with the consequences of strengthening patent protection. They argued that TRIPS could lead to higher drug prices and less access to drugs for life-threatening conditions. This debate was particularly important in sub-Saharan countries where HIV/AIDS had became a global epidemic (Hoen et al., 2011). Table 3 shows the number of HIV/AIDS cases by region in 1998.

[3] http://www.statista.com/statistics/263102

In February 1998, several pharmaceutical companies sued the government of South Africa over amendments to its legislation that would increase the availability of affordable drugs (namely, its "South African Medicines and Related Substances Control Act" of 1997). According to the drug companies, the amendments comprised a violation of the TRIPS Agreement. Also, in 1998, Brazil threatened companies with compulsory licenses in order to bring drug prices down, which triggered a complaint by the U.S. against TRIPS's compulsory license provisions. These events showcased the flexibilities contained in the TRIPS Agreement, specifically, the possibility for each country to determine the conditions required to issue a compulsory license (Article 31 TRIPS). The conflict between these countries and drug companies generated public outrage, and the backlash prompted drug companies to withdraw their cases. In 2001, the Doha Declaration on TRIPS and Public Health clarified that the TRIPS Agreement should protect public health and promote access to affordable drugs (Feldman, 2009).

Pharmaceutical companies addressed the threat of compulsory licenses by selling their drugs at discounted prices (e.g., by issuing voluntary licenses). As a consequence, the price of HIV/AIDS treatment decreased considerably after the Doha Declaration of 2001. For instance, Brazil used the threat of compulsory licenses to negotiate lower prices of AIDS drugs with Merck in 2001 and 2003, and with Abbott Laboratories in 2005. In 2004, Indonesia issued compulsory licenses on the production of the HIV/AIDS drugs Lamivudine and Nevirapine. In 2006, Thailand issued compulsory licensing for the HIV/AIDS drug Efavirenz and two other drugs. In 2007, Brazil issued a compulsory license for Efavirenz (which allowed imports of generic drugs from India) after a price-negotiation disagreement with Merck. In 2007, Indonesia renewed the compulsory licenses on Lamivudine and Nevirapine and added a compulsory license on Efavirenz. In fact, since 2001, more than 15 countries have issued compulsory licenses to procure low-cost HIV/AIDS drugs (Hoen et al., 2011).

3 Data

Our analysis makes use of a combination of datasets. First, we make use of Pharmaprojects from Pharma Intelligence, which is widely used in the innovation literature (e.g., Kyle 2006). This database is a comprehensive and reliable source of information. The data

is collected from public sources such as press releases, reports by regulatory agencies, conference proceedings, medical literature, as well as pharmaceutical firms and researchers. The data contains information on pharmaceutical firms' pipelines, including if/when a development project enters the discovery stage, phase I, II, or III, if/when it is approved by the FDA, and if/when and where the drug is being commercialized. Importantly for our purposes, Pharmaprojects tracks these development milestones for each drug project with associated diseases that it intends to treat. The raw data covers the 1983–2017 period, which has enough observations to reproduce the preintervention drug development in the synthetic control analysis. If a drug is developed for more than one target disease, the list of diseases is documented with the records of the drug. We transform the raw dataset, which is at the drug level, to the disease level. For our empirical analysis, we construct disease–year–month level measures of the number of drugs in development for every disease at every moment of time so as to capture the firms' R&D effort.

Second, we construct disease–year level measures of the number of deaths caused by a disease based on the World Health Organization Mortality Database so as to capture the market size of each drug therapy industry (i.e., the potential number of patients who could benefit from curing the disease). The information in the database contains the cause of death and the number of deaths by year, sex, and age group. The International Classification of Diseases, a diagnostic tool for epidemiology, is used to record the cause of death. The WHO Mortality database contains datasets associated with each of the four subsequent revisions of the ICD, from ICD-7 through ICD-10. We use the datasets for the 9th and 10th revisions of the ICD that cover the estimation periods.

Making use of these mortality data requires matching the disease definitions in the WHO Mortality Database and Pharmaprojects. We first assign likely ICD codes corresponding to each disease in Pharmaprojects using medical dictionaries, online ICD browsing tools by the WHO, and data documentation files. We then combine the two databases using identified ICD codes and aggregate the death statistics to construct our measure. In this process and the synthetic control analysis, we consider the top 100 diseases in Pharmaprojects in terms of the number of drugs developed for each disease. These 100 diseases account for about 70% of the drugs in the pipelines, which is fairly representative to support the robustness of our analysis.

Among the top 100 diseases, 11 diseases that are not medical conditions causing deaths

(i.e., no mortality data had been reported for assigned ICD codes) or do not have corresponding ICD codes are excluded from the analysis. Dropping these 11 diseases leave us with 89 diseases (88 control industries and HIV/AIDS therapy industry). Among these 89 diseases, unspecified cancer has the largest number of drugs developed, 8,743 in total, and sepsis has the smallest number of drugs developed, 213 in total.

Third, we use disease–year level information both on the number of patent applications and granted patents with subject matter relevant to each disease in Pharmaprojects. The patent data were collected from Google Patents and the United States Patent and Trademark Office.

Lastly, we use disease–year level information on the number of academic publications relevant to that disease. Similarly to the patent data, we use the disease definitions in Pharmaprojects. The data were collected from PubMed, which contains citations and abstracts of biomedical literature from MEDLINE, life science journals, and online books. For each disease, we retrieve how many research articles are published each year between 1950 and 2019.

4 Empirical Framework and Results

4.1 Empirical Framework

The objective of our empirical analysis is to quantify how weakened patent rights impact the firms' research pipelines. We do this by comparing the number of HIV therapies under development relative to those of a control industry both before and after the weakening of patent rights in July 1997 (i.e., the timing of the "South African Medicines and Related Substances Control Act").

To make this comparison, we construct a synthetic "HIV drug therapy" industry, which was not affected by the threat of compulsory licenses, making use of the framework proposed in Abadie and Gardeazabal (2003) and Abadie et al. (2010, 2015). In practice, we construct a synthetic HIV drug therapy industry by computing a weighted average of other industries unaffected by the threat of compulsory licensing at time T^*. Given a set of J control drug therapy industries, we seek a vector of non-negative weights, $\mathbf{W} = (w_1, \ldots, w_J)'$,

which sum up to one and where w_j represents the weight placed on control industry j. Each vector $\mathbf{W}$ leads to a different synthetic HIV drug therapy industry, so we choose the vector $\mathbf{W}$ that minimizes the differences between the synthetic and actual HIV drug therapy industries in the period before the threat of compulsory licensing.

More specifically, let $\mathbf{X}_{HIV} = (\mathbf{Z}'_{HIV}, Y_{HIV,1}, \ldots, Y_{HIV,T^*-1})'$ be a $(k \times 1)$ vector of both covariates ($\mathbf{Z}_{HIV}$) and pre-intervention outcomes ($Y_{HIV,1}, \ldots, Y_{HIV,T^*-1}$) for the HIV drug therapy industry and let $\mathbf{X}_{controls}$ be a $(k \times J)$ matrix containing the same variables but for all J control drug therapy industries. We choose the vector of weights given by

$$\mathbf{W}^* = \arg\min_{\mathbf{W}} (\mathbf{X}_{HIV} - \mathbf{X}_{controls}\mathbf{W})'\mathbf{V}(\mathbf{X}_{HIV} - \mathbf{X}_{controls}\mathbf{W})$$

subject to $\sum_j w_j = 1$, where $\mathbf{V}$ is a diagonal matrix with non-negative components. Note that $\mathbf{W}^*$ minimizes differences between the actual and synthetic HIV drug therapy industry both in covariates and outcomes in the pre-intervention period.

With estimates for $\mathbf{W}^*$ in hand, we can then compute the outcomes for the synthetic HIV drug therapy industry using $\mathbf{Y}_{synth} = \mathbf{Y}_{controls}\mathbf{W}^*$, where $\mathbf{Y}_{controls}$ is a $(T \times J)$ vector containing the outcome variables for all J control industries for all T periods in the data (i.e., including both pre- and post-intervention periods).

In our specifications, the observed covariates for each disease–year–month combination include the number of patent applications and granted patents related to therapies of the disease, the number of research publications related to therapies of the disease, and the number of deaths caused by the disease, which is our measure of the potential number of patients who could benefit from a cure to the disease. Our main outcome variable is the number of drug therapies in development, which is also measured at the disease–year–month level. We use the lagged values of the outcome variable and matching covariates listed above in running the synthetic control analysis.

In the analysis, we separately apply the synthetic control method to the number of all drug therapies in development and the number of drugs in phase II or III clinical trials. We use the two kinds of outcome variables to examine whether the results are heterogeneous depending on how the degree of drug development. Drug therapies with favorable results in earlier development stages might be less likely to be canceled.

All drug therapies in development		Drug therapies in phase II or III	
Drug therapy industry	Synthetic weight	Drug therapy industry	Synthetic weight
Cancer, breast	0.568	Cancer, breast	0.508
Cancer, unspecified	0.249	Hypertension, unspecified	0.193
Hypertension, unspecified	0.120	Cancer, colorectal	0.179
Infection, unspecified	0.053	Asthma	0.121
Ischemia, cerebral	0.011		

Table 1: Industry weights in the synthetic HIV drug therapy industry

4.2 Constructing a Synthetic HIV Drug Therapy Industry

As explained above, we construct the synthetic HIV drug therapy industry as a weighted average of other industries chosen to resemble the values of covariates and outcomes of the HIV drug therapy industry before the threat of compulsory licensing. Table 1 presents the weights of each drug therapy industry in the synthetic HIV drug therapy industry, $\mathbf{W}^*$. The weights reported in the left panel of Table 1 indicate that the number of all drug therapies in development for HIV before the intervention is best reproduced by a combination of the drug therapy industries for breast cancer, unspecified cancer, unspecified hypertension, unspecified infection, and cerebral ischemia. The weights reported in the right panel of Table 1 indicate that the number of drug therapies for HIV in phase II or III is best reproduced by a combination of the drug therapy industries for breast cancer, unspecified hypertension, colorectal cancer, and asthma. All other drug therapy industries in the donor pool are assigned zero weights. Breast cancer receives the highest weight in both synthetic controls, 0.568 and 0.508.

Table 2 compares the preintervention characteristics of the actual HIV drug therapy industry to those of the synthetic HIV drug therapy industry (obtained by $\mathbf{X}_{synth} = \mathbf{X}_{controls}\hat{\mathbf{W}}^*$), and also to those of an average of the 88 drug therapy industries in the donor pool. The results in Table 2 suggest that the synthetic HIV drug therapy industry provides a better comparison unit for the HIV drug therapy industry than the average of other industries in our donor pool. The synthetic HIV drug therapy industry is very similar to the actual HIV drug therapy industry in terms of lagged outcome values. The number of drugs under development prior to the weakening of patent rights is much lower in the

	Actual HIV drug therapy industry	Synthetic HIV drug therapy industry		Average of 88 control industries
Number of all drugs in development	239.26	239.60		59.00
Number of drugs in phase II or III	44.67		44.76	13.22
Log(number of deaths)	10.99	11.91	12.12	10.71
Number of publications	6.17	3.00	3.58	2.98
Number of patents filed	48.00	22.49	20.84	19.83
Number of patents granted	35.57	12.33	11.48	9.53

Note: The number of drugs is averaged for January 1991–June 1997. The log of the number of deaths caused by each disease, number of publications, number of patents filed, and number of patents granted related to each disease are averaged for 1991–1997. The number of publications is divided by 1,000 in the estimation.

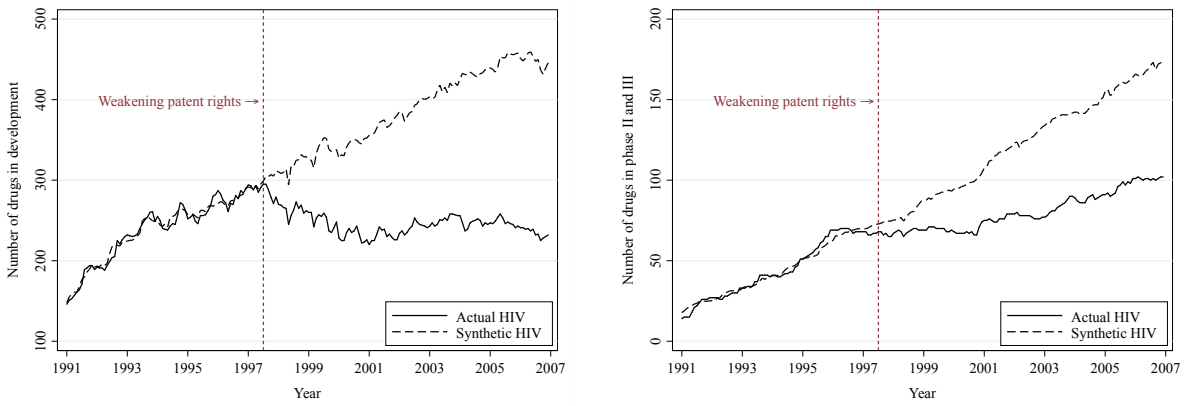
Table 2: Predictor means before weakening of patent rights

average of 88 control industries than in the HIV drug therapy industry. Although the synthetic HIV drug therapy industry loses its fit in the other predictors, it still matches the actual HIV drug therapy industry closer than the average of 88 control industries, except for the number of deaths.

4.3 Results

Figure 1a displays the number of drugs in development for the HIV drug therapy industry and its synthetic counterpart during 1991–2006. The synthetic HIV drug therapy industry closely reproduces the number of drugs in development for the HIV drug therapy industry during the entire preintervention period. The close fit for the predictors presented in Table 2 and the close fit for the preintervention drug development trajectory shown in Figure 1a suggest that the synthetic HIV drug therapy industry approximates the number of drugs that would have been developed to treat HIV in the second half of 1997–2006 in the absence of the threat of compulsory licensing.

Our estimate of the effect of weakened patent rights on drug development for HIV is given by the difference between the actual HIV drug therapy industry and its synthetic version, as visualized in Figure 1a. The solid line visualizes the evolution of the actual



(a) All drugs in development

(b) Drugs in phase II or III clinical trials

Figure 1: Trends in drug development: actual HIV drug therapy industry vs. synthetic HIV drug therapy industry

HIV drug therapy industry (i.e., $\mathbf{Y}_{HIV}$), whereas the dashed line visualizes that of its synthetic counterpart (i.e., $\mathbf{Y}_{synth} = \mathbf{Y}_{controls}\hat{\mathbf{W}}^*$). The dashed vertical line indicates the period that the HIV drug therapy industry was exposed to a weakening of patent rights (i.e., July 1997) via a threat of compulsory licensing. After such measure is taken, the two lines diverge noticeably. While drug development in the synthetic HIV drug therapy industry continued to increase at a pace similar to that of the preintervention period, the actual HIV drug therapy industry experienced a substantial decline in drug development. The difference between the two lines increases over time toward the end of the estimation period. At the end of the estimation period, the number of drugs in development for the HIV industry is about 92% (=(232-445.735)/232) lower than that for its synthetic version. Over the entire mid-1997–2006 period, the number of drugs in development decreases by about 138 per month on average. This is approximately 47% of the baseline level of outcome in July 1997. Thus, our results suggest a substantial negative effect of weakened patent rights on HIV drug development.

As an alternative outcome variable that would allow us to measure the effects among drug therapies that are closer to completion, we use the number of drug therapies in development that are undergoing phase II or phase III clinical trials. As those drugs have already achieved the earlier stages of development, firms might have less incentive to discontinue them. Figure 1b displays the number of drugs in phase II or III for the HIV drug therapy industry and its synthetic version during 1991-2006. The close fit for

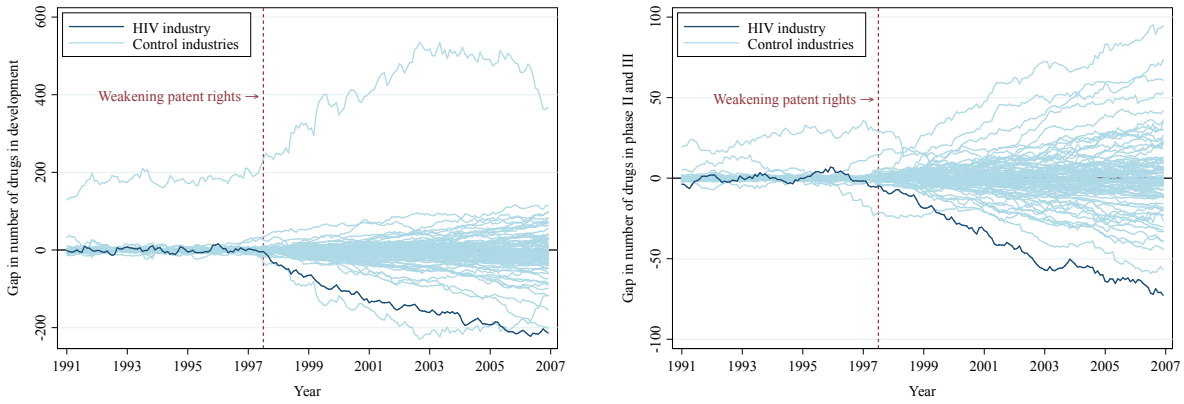
the preintervention characteristics in Table 2 and the close fit for the preintervention drug development trajectory in Figure 1b suggest that the synthetic HIV drug therapy industry provides a close approximation to the number of HIV drugs that would have been undergone phase II or III clinical trials during mid-1997–2006 in the absence of the threat of compulsory licensing. After July 1997, the two lines shown in Figure 1b diverge noticeably, and the difference between the two lines increases in time. At the end of the estimation period, the number of HIV drugs in phase II or III is about 71% (=(102-174.697)/102) lower than that for its synthetic version. Over the entire mid-1997–2006 period, the number of drugs in phase II or III decreases by about 42 per month on average. This is approximately 61% of the baseline level of outcome in July 1997. The magnitude of the negative effect is smaller for drug therapies in the later stage of development (71% vs. 92%). Combined with the discussion of the number of drug therapies in development above, our results suggest a negative effect of weakened patent rights via a threat of compulsory licensing on the incentives to develop new drug therapies.

5 Placebo Studies and Robustness Checks

To evaluate the significance and credibility of our estimates, we conduct placebo studies where the treatment of interest is reassigned to industries other than HIV and its timing was a period other than July 1997. We also replicate our analysis modifying the donor pool to assess sensitivity.

5.1 In-Space Placebo Study

One can raise the question of whether our results visualized in Figure 1a and Figure 1b quantify the true effect of weakened patent rights on drug development or are driven merely by chance. To answer this question, we conduct an in-space placebo study by iteratively applying the synthetic control method to drug therapy industries that did not experience the threat of compulsory licensing. In each iteration, we reassign the intervention to one of the 88 drug therapy industries, shifting the HIV drug therapy industry to the donor pool. Then we compute the estimated effect associated with each industry, which is the difference between the drug development for the actual HIV drug therapy industry and



(a) All drugs in development

(b) Drugs in phase II or III clinical trials

Figure 2: Estimated effect for the HIV drug therapy industry and placebo effects for 88 industries in the donor pool

its synthetic version. This gives us a distribution of placebo estimates that enables us to examine how often we would obtain estimates of the magnitude of our main results if the intervention is randomly assigned. If the estimated effects are unusually large compared to the distribution of placebo estimates, then the results are considered significant.

Figure 2a displays the results of this in-space placebo study, where the outcome variable is the number of all drugs in development. The light blue-colored lines represent the estimated effects associated with the 88 drug therapy industries in the donor pool. The navy-colored line is the estimated effect associated with the HIV drug therapy industry. Drug development in the synthetic HIV drug therapy industry resembles the actual evolution during the preintervention period (i.e., the placebo gaps are close to zero), and it starts to diverge from the actual trajectory after the intervention (i.e., placebo gaps differ from zero), reflecting the results discussed above. As shown in Figure 2a, the estimated effect for the HIV drug therapy industry after July 1997 is substantially larger in absolute value relative to the distribution of the estimated effects for the industries in the donor pool. The likelihood of obtaining estimates as large as our main results is 0.035 if a treated industry is randomly chosen. It suggests that our results for the HIV drug therapy industry are unlikely to have been obtained by chance.

Similarly, Figure 2b presents the in-space placebo study results for the alternative outcome variable, the number of drugs undergoing phase II or III. As the figure indicates, the

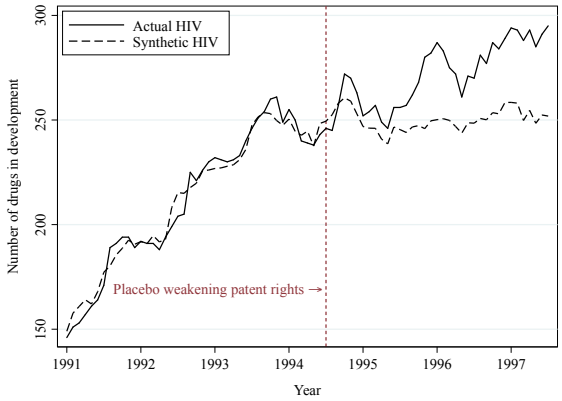
estimated effect for the HIV drug therapy industry is larger relative to the distribution of placebo effects. It suggests that if we choose a treated industry at random, the chances of obtaining the estimated effect as large as the one in our main results is 0.031.

In Figure 2a, the plot with the worst fit in the preintervention period lying above all the other lines is for unspecified cancer. The plot below the one for the HIV drug therapy industry in the mid-1998 to mid-2005 period is for unspecified hypertension. The third and fourth-lowest plots are for unspecified infection and cerebral ischemia. In Figure 2b, the plot below the one for the HIV drug therapy industry during the 1996 to mid-1999 period is for unspecified cancer. The second-lowest plot from mid-2001 is for Alzheimer's disease. The plot for unspecified hypertension has the worst fit in the preintervention period.

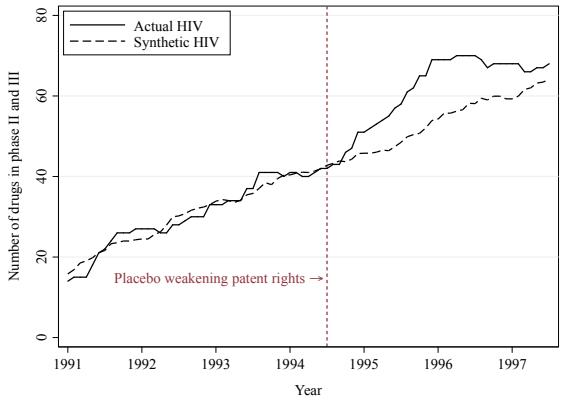
5.2 In-Time Placebo Study

We perform an in-time placebo study as an alternative way to evaluate the credibility of our main results. Here, we reassign the hypothetical treatment to a period before the weakening of patent rights actually happened. If the estimated placebo effects are negligible, it supports that our main estimates were not driven by chance and capture the true effect of our interest. Contrariwise, large placebo estimates undermine the credibility of our main results. To conduct this in-time placebo study, we estimate the model where the treatment is reassigned to periods 1, 2, and 3 years earlier than the intervention period in our main analysis (i.e., July 1996, July 1995, and July 1994, respectively).

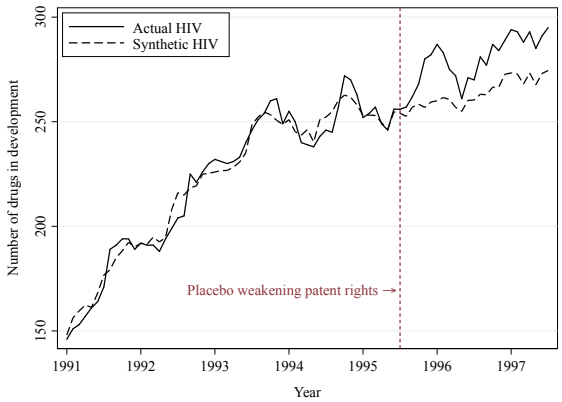
Figure 3 presents the result of this in-time placebo study. The panels (a), (c), and (e) on the left side are obtained by using the number of drugs in development as the outcome variable, whereas the panels (b), (d), and (e) on the right side are obtained by using the number of drugs in phase II or III clinical trial. The two panels in the first row use July 1994 as a hypothetical treatment period. The ones in the second and third rows use July 1995 and July 1996, respectively. In all cases, the drug development trajectory of the synthetic HIV drug therapy industry closely reproduces that of its synthetic counterpart for the preintervention period. The placebo effects are negligible or smaller relative to the estimated effects in our main results. This suggests that our main results in Figure 1a and Figure 1b reflect the effect of weakened patent rights and are not driven by chance.



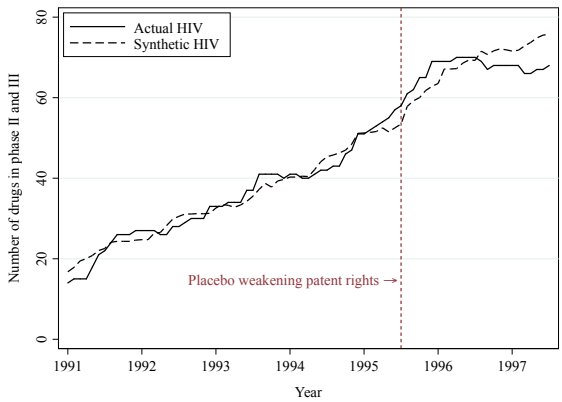
(a) All drugs in development, July 1994



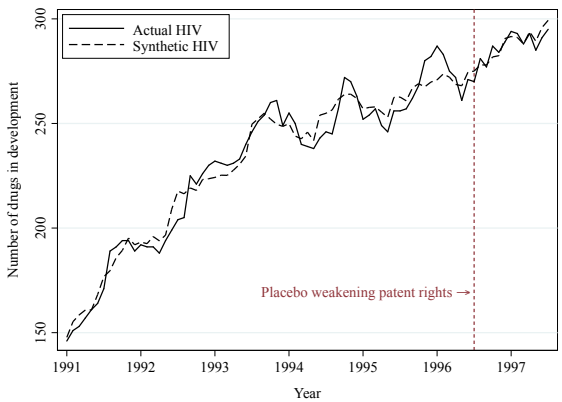
(b) Drugs in phase II or III, July 1994



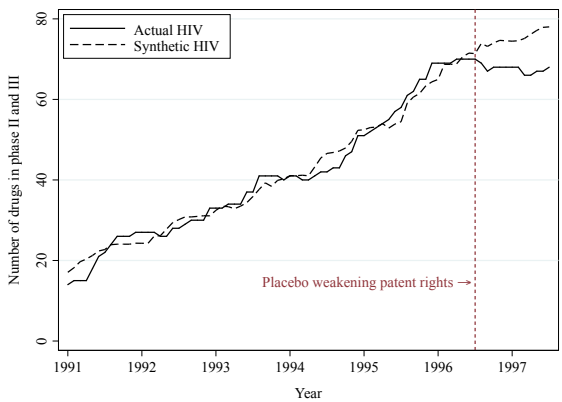
(c) All drugs in development, July 1995



(d) Drugs in phase II or III, July 1995



(e) All drugs in development, July 1996



(f) Drugs in phase II or III, July 1996

Figure 3: In-time placebo study

(a) All drugs in development

(b) Drugs in phase II or III clinical trials

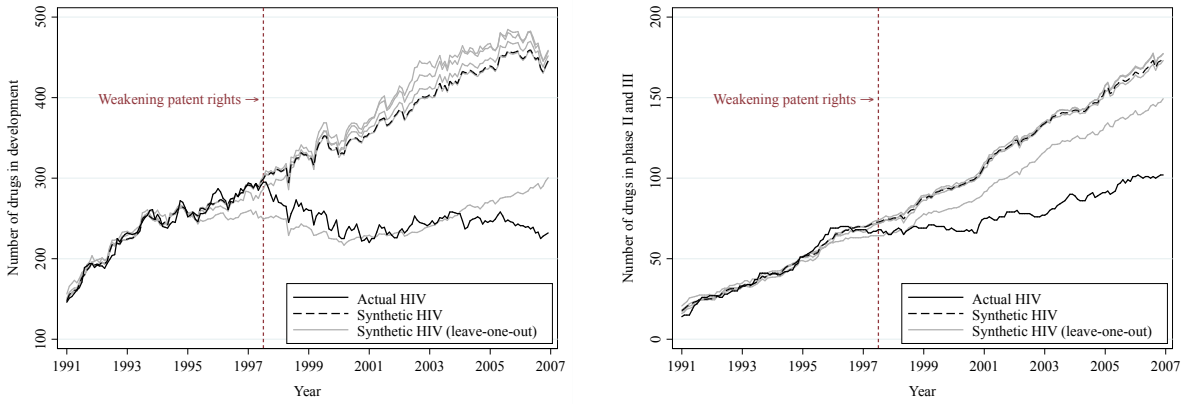
Figure 4: Trends in drug development: actual breast cancer therapy industry vs. synthetic breast cancer therapy industry

5.3 Placebo Study using Breast Cancer Therapy Industry

To test whether the estimated effects in our main results are driven by factors other than the weakening of patent rights, we apply the synthetic control method to a drug therapy industry that was not subject to the event of interest. This placebo study compares drug development in an industry similar to the HIV drug therapy industry but unrelated to compulsory licensing to its synthetic counterpart.

For this placebo study, we use the breast cancer drug therapy industry, which receives the largest weight in constructing the synthetic HIV drug therapy industry as presented in Table 1. We construct a synthetic breast cancer therapy industry as a weighted average of 87 other industries (excluding the HIV drug therapy industry from the donor pool) that most closely resembles the preintervention values of covariates and outcomes of the actual breast cancer therapy industry. The estimates are given by the gap between the drug development trends of the actual and synthetic breast cancer drug therapy industries.

Figure 4a shows the evolution of the number of drugs in development for the actual breast cancer therapy industry (solid line) and that of the synthetic version (dashed line). The weighted average of non-HIV drug therapy industries reproduces the preintervention drug development for the breast cancer therapy industry.



(a) All drugs in development

(b) Drugs in phase II or III clinical trials

Figure 5: Leave-one-out distribution of the synthetic HIV drug industry

5.4 Sensitivity to Donor Pool

We conduct a leave-one-out robustness test to check whether our main results are sensitive to changes in the synthetic weights. Recall that the synthetic HIV drug therapy industry is estimated as a weighted average of breast cancer, unspecified cancer, unspecified hypertension, unspecified infection, and cerebral ischemia when our outcome variable is the number of drugs in development. The synthetic HIV drug therapy industry is estimated as a weighted average of breast cancer, unspecified hypertension, colorectal cancer, and asthma when our outcome variable is the number of drugs in phase II or III clinical trials.

We iteratively estimate the effects for the HIV drug therapy industry, omitting one of the industries with a positive synthetic weight in Table 1 in each iteration. For example, we exclude breast cancer from the donor pool and run an estimation using the remaining 87 industries in constructing the synthetic HIV drug therapy industry. We repeat this for each of the five industries (four industries for the alternative drug development measure).

Figure 5a shows the leave-one-out estimates (gray lines) and our main estimates (solid and dashed black lines), where the number of drugs in development is used as our outcome variable. The leave-one-out synthetic controls for breast cancer, unspecified hypertension, unspecified infection, and cerebral ischemia give us slightly larger effects compared to the main results. This suggests that our main results are robust to the exclusion of any of these four control industries.

However, one thing to note in Figure 5a is that the main results would not be robust to the exclusion of the unspecified cancer therapy industry. Drug development for the synthetic HIV drug therapy industry that is reproduced as the weighted average of industries other than unspecified cancer does not show an increasing trend as it does in the main analysis. Rather, its evolution is similar to the actual drug development trajectory. The estimated effects are negligible and become negative only after the early 2000s.

Figure 5b displays the leave-one-out estimates (gray lines) and the estimates in our main results for the alternative measure of drug development, the number of drugs in phase II or III clinical trial (solid and dashed black lines). The leave-one-out synthetic control gives us the smallest estimate when the breast cancer drug therapy industry is excluded from the donor pool. The other leave-one-out synthetic controls for unspecified hypertension, colorectal cancer, and asthma show slightly smaller or larger effects of the weakening of patent rights compared to the main results. This suggests that the results for the number of drugs in later stages of development are fairly robust to the changes in the synthetic weights.

6 Discussion and Concluding Remarks

We provide evidence that the mere threat of compulsory licensing can dampen upstream pharmaceutical R&D. Exploiting South Africa's July 1997 announcement that it would invoke compulsory licenses on key HIV drugs, we implement a synthetic-control design and find an immediate 47% drop in the monthly count of new HIV-drug candidates. Placebo exercises in time and across therapeutic areas confirm that this collapse is not a general slowdown in drug discovery. We also argue that it is unlikely that contemporaneous scientific breakthroughs are responsible for all the effect. These empirical patterns relate to channels in the theoretical models of compulsory licensing (see, e.g., Bond and Saggi, 2014, 2018), where a credible compulsory licensing threat can induce firms to pull back from both licensing negotiations and local market entry.

A potential confounding factor in our analysis is the simultaneous emergence of highly effective combination antiretroviral therapies (HAART) in the mid-1990s. These "cocktails" transformed HIV from a fatal disease into a manageable chronic condition, leading

to a dramatic drop in mortality. This success may have reduced the urgency and commercial incentive for further innovation in HIV, especially compared to areas with unmet needs or higher potential returns. The repurposing of existing molecules into drug combinations led pharmaceutical firms to reallocate R&D resources toward optimizing dosing schedules, developing fixed-dose combinations, and improving formulations rather than pursuing entirely novel molecular entities (Ghosh, 2023).

Several empirical patterns, however, suggest that this scientific paradigm shift cannot fully account for the observed decline in HIV drug development. First, the timing evidence reveals an abrupt 47% monthly drop in HIV candidate counts immediately following South Africa's July 1997 compulsory licensing threat, whereas pipeline growth remained steady until that point—inconsistent with the gradual tapering one would expect from a cocktail-driven reorientation beginning in mid-1996. Second, extensive placebo tests demonstrate that no comparable pipeline contractions occurred for other diseases or at alternative dates, indicating the decline is uniquely associated with the licensing event rather than broader scientific trends. Third, and along these lines, Garfinkel and Hammoudeh (2024) present evidence suggesting that breakthroughs in pharmaceutical innovation have only a temporary negative effect on innovation by other firms (in concentrated industries). That we find persistent negative effects on innovation outcomes suggests that our findings are beyond the discovery of the effectiveness of HAART. Fourth, even late-stage Phase II/III candidates, which are less amenable to cocktail-based reformulation strategies, experienced a 61% decline after mid-1997, whereas a cocktail-driven explanation would predict more pronounced effects on early-stage discovery programs. Finally, other therapeutic areas experiencing paradigm-shifting breakthroughs, such as targeted oncology agents, did not exhibit similar immediate pipeline contractions. Nevertheless, our results must be taken with caution due to several factors: global R&D budget reallocations toward hepatitis C and oncology in the late 1990s (Di Marco et al., 2025), diminishing marginal returns from saturated HIV markets, and anticipation effects from expected future compulsory licensing actions might have influenced firm behavior prior to July 1997.

Our findings carry two main policy lessons. First, while compulsory licensing can improve short-run access and bargaining leverage for public health, it may impose a hidden cost by deterring the very innovation needed for next-generation therapies. Second, the design of access regimes should carefully balance price and licensing concessions against their upstream R&D externalities. In particular, combining temporary patent-buyout schemes

or prize funds with targeted compulsory licensing safeguards could mitigate rent erosion without sacrificing global innovation incentives.

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A Tables and Figures

Region of the World	Number of Cases	Percentage of the Infected Population
North America	860,000	2.81
Caribbean	310,000	1.01
Latin America	1,300,000	4.25
Western Europe	480,000	1.57
Eastern Europe & Central Asia	190,000	0.62
East Asia & Pacific	420,000	1.37
North Africa & Middle East	210,000	0.69
South & South-East Asia	5,800,000	18.97
Australia & New Zealand	12,200	0.04
sub-Saharan Africa	21,000,000	68.67
Total	30,582,200	100

Table 3: Adults and children living with HIV/AIDS in 1997.

Source: Report on the global HIV/AIDS epidemic, June 1998. Prepared by UNAIDS and WHO.