Global Drug Diffusion and Innovation with the Medicines Patent Pool

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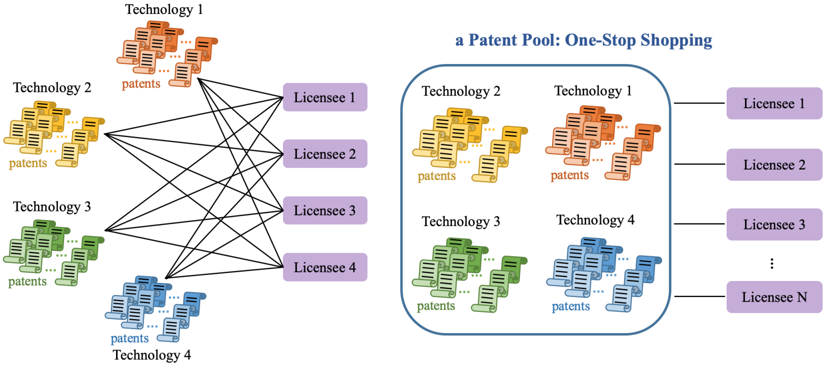
Patent Protection *vs.* Access to Medicines

- Patents lead to high drug prices; then rising patent litigations
- More severe in developing countries and with drug bundling
- Branded-drug firms lack incentives to invest and sell in low- and middle-income countries (LMIC)
- Limited impact from policy interventions (not enough)

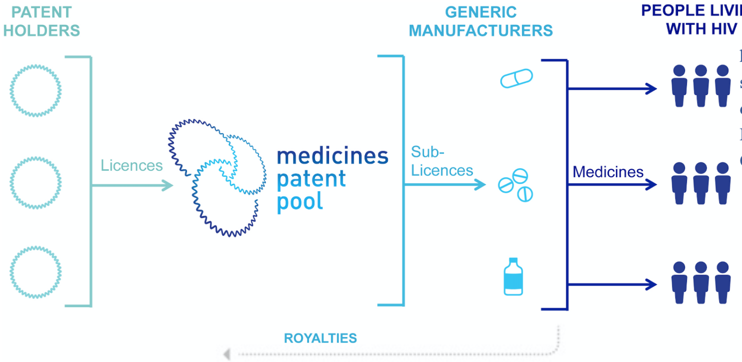
Research Question: Big Picture

Can a patent pool spur global drug diffusion & innovation?



This Paper: the Medicines Patent Pool (MPP)

- Founded & funded by Unitaid in 2010.7, Geneva, Switzerland
- MPP aims to reduce coordination failures and benefit all players



(2010), hep. C, TB (2015), small molecule drugs on WHO's EML (2019), Covid-19 (2020)

Patent Pools: Theoretical Impacts

- Increase consumer welfare by reducing
  - Transaction costs: numerous searches and negotiations
  - Hold-up problem: one failed negotiation can deter innovation
  - Double markups: monopoly power in the vertical chain

- Effects on R&D investments depends on the net of
  - (+) reduce litigation costs and downstream infringement
  - (+) attract funds for contribution in access to medicine
  - (+) facilitate specialization in comparative advantages
  - (-) risks of price-fixing by pool participants
  - (-) restrictive licensing terms on product sales/development

Research Questions

Does the MPP spur global drug diffusion & innovation?

- Does the MPP spur affordable generic access in LMIC?
- How do firms react to the MPP in R&D inputs & outputs?
- What are the welfare gains compared to counterfactuals?

Goal: evaluate whether this novel institution can balance *diffusion* and *innovation* in a *cost-effective* manner.

Preview of Results

- MPP spurs generic access to HIV drugs in LMIC
  - Increases % generic utilization for a drug by 7 p.p.
- Firms react to MPP with more R&D inputs & outputs
  - In clinical trials, firm participation, and product approvals
- Welfare analysis: gains in consumer & producer surpluses
  - Consumer: $ 0.7-1.3 billion; producer: up to $181 million

Literature Review & Contribution

- **Innovation and the Economy, esp. in Health Care**

(Finkelstein 2004; Chaudhuri et al. 2006; Williams 2013; Kyle & Qian 2014; Cockburn et al. 2016; Duggan et al. 2016; Song et al. 2017; Sampat & Williams 2019)

- **Patent Pools on Competition and Innovation**

(Lerner & Tirole 2004, 2015; Lemley & Shapiro 2005; Chiao et al. 2007; Lerner et al. 2007; Lampe & Moser 2013, 2015; Bekkers et al. 2017; Rey & Tirole 2019)

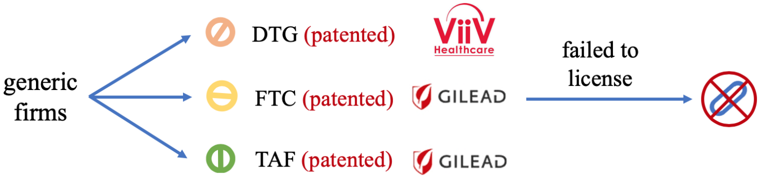
- Recent paper: Galasso & Schankerman (2021) focuses on diffusion: MPP increases drug licensing

- First empirical analysis on a biomedical patent pool; novel data on diffusion & innovation; implications to policy & future institutions

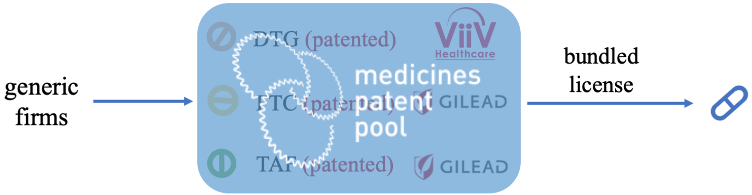
Outline

Conceptual Framework (1/2): Generic Firms' Perspective

- For generic firms that want to license a cocktail regimen



- Licensing the same set with the Medicines Patent Pool

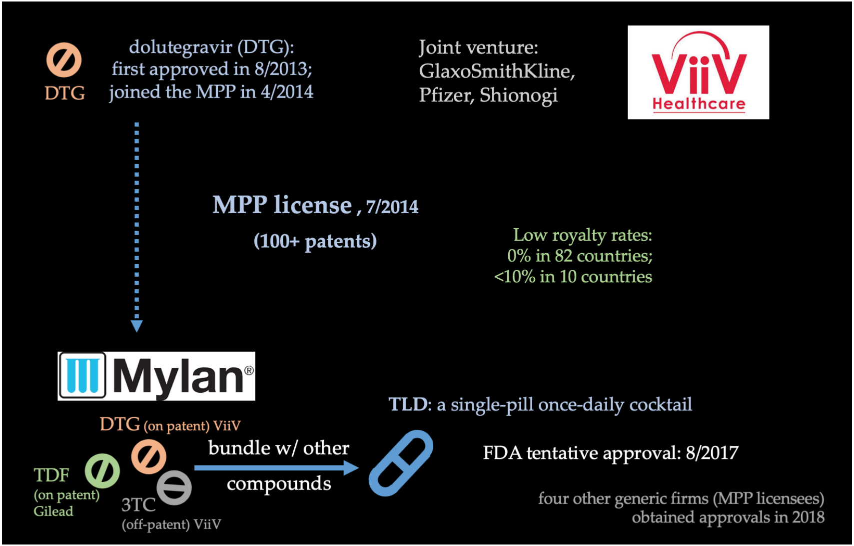


Note: Also apply to cases when a subset of compounds are patented within a regimen.

Conceptual Framework (2/2): Cross-Firm Motives

- Downstream generic firms: profit & low-cost licensing
  - Increase licensed sales in developing countries
- For research-oriented upstream firms outside the pool
  - Increase diffusion-oriented innovation upstream
- Branded firms in the MPP: profit, costs, & social image
  - Gain sales in market with large volume and elastic demand
  - Lower administrative costs in licensing & legal costs
  - Possibility to license back follow-on innovation

MPP illustrative Example: New Cocktails Created & Sold

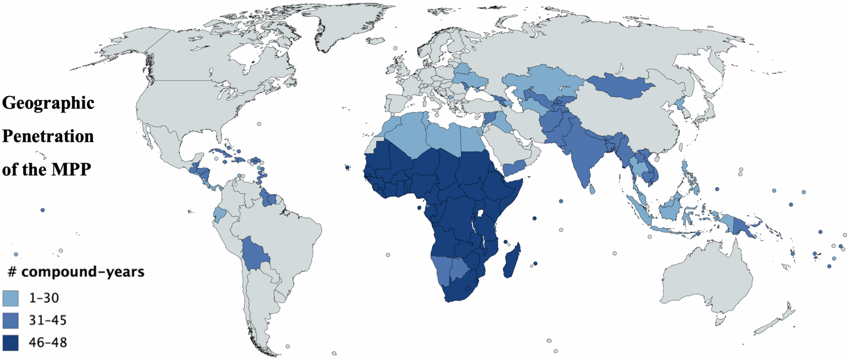


Background: MPP Geographical Coverage

- 10 HIV compounds are available for *effective* licensing, 2018
  - Comparable in/out: sales, avg. approval time, drug classes

MPP compounds

- Generic firms worldwide can license drug bundles from the MPP to sell in territories defined in licensing contracts



Data: HIV Drug Sales, R&D Inputs & Outputs

- The complete HIV drug portfolio data: FDA & AIDSinfo
  - patent status in LMIC: MedsPaL & DrugPatentWatch
  - US drug patent data: Drug Bank via FDA Orange Book
- 40% of total HIV drug procurement in LMIC, 2007-2017
  - price & quality reporting by Global Fund-supported programs
- Country-year characteristics: HIV prevalence & age-adjusted death rates, population, income, institutional factors, 2007-2017
  - from World Bank & Institute for Health Metrics & Evaluation
- R&D inputs: global clinical trials with HIV drugs, 2000-2017
  - global trials from US-registry & identifiers from AIDS*info*
- R&D outputs: all drug approvals for HIV treatment, 2005-2018
  - Drugs@FDA (tentative) approvals & WHO pre-qualification

more details: diffusion data | more details: innovation data

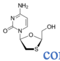
Outline

Diffusion Analysis: Overview

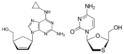
1. Does the *Medicines Patent Pool* spur generic diffusion?

- Diffusion analysis: difference-in-differences & event studies
  - Sample: 103 countries, 29 drugs with 18 compounds map
- Outcome variables: generic efficiency & product variety
  - % generic drug orders $= \dfrac{\#\textit{purchases from generic firms}}{\#\textit{ all purchases for the drug}}$
  - % generic quantity ordered (% generic weighted by US adult dosing)
  - # distinct products purchased for a drug (-streng-dose-firm level)

drugs



3TC (single compound)



ABC+3TC (multi-compound drug cocktail)

products (drug-strength-dosage form by firm)

3TC 300mg tablet by Cipla 

3TC 150mg tablet by Mylan 

3TC 10mg/mL oral solution by Aurobindo 

MPP on Drug Diffusion: Method

- Difference-in-Differences method: drug-country-year level

$$y_{dct} = \delta_{dc} + \delta_t + \underbrace{\beta \, MPP^{lic}_{dct}}_{=1 \text{ if } dc \text{ in pool at } t} + \tilde{\gamma} X_{ct} + \eta X_{dct} + \varepsilon_{dct}$$

- y_{dct}: % generic orders, % generic quantity ordered, #products
- X_{ct}: country-year controls: HIV prevalence & death rates, log(pop.), income, institutional factors (government effectiveness, regulatory quality, rule of law, control of corruption, voice & accountability, political stability & absence of violence)
- X_{dct}: whether a drug is effectively patented in a country-year
- $\delta_{dc} + \delta_t$: fixed effects for drug-country pairs and years
- Two-way cluster standard errors at the country & drug levels

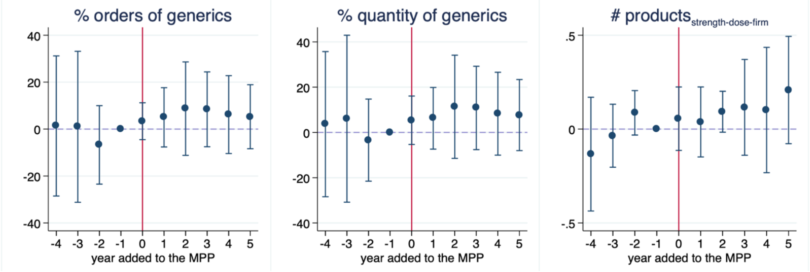
Threats to Identification & Justifications

- *Identification*: common trends (event study) & lack of common shocks (DGP)
- Which drugs are included in the pool, and how?
  - Perceived values, negotiation outcomes, voluntary contribution
- Which countries are covered in sales territory for a drug?
  - LMIC, HIV prevalence, public relations, prior voluntary licenses
  - Drug-region-year level variation & I use % generic measures
- How is the timing of drug-country inclusion determined?
  - Partly depends on scientific discovery & negotiation time
  - Cannot be predicted by country-year level observables

identification: timing reg.

MPP increases generic diffusion at drug-country-year level

Dept. Vars.	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	% generic orders (#)			% generic quantities (patient-year)			# products (strength-dose-firm)		
MPP_{dct}	6.888** (3.178)	7.223** (2.933)	7.226** (2.932)	6.653** (3.035)	7.003** (2.802)	7.010** (2.796)	0.0739 (0.113)	0.0719 (0.104)	0.0717 (0.104)
drug-country FE	Y	Y	Y	Y	Y	Y	Y	Y	Y
year FE	Y	Y	Y	Y	Y	Y	Y	Y	Y
X_{ct} control		Y	Y		Y	Y		Y	Y
X_{dct} control			Y			Y			Y
LHS mean	84.3	84.3	84.3	85.6	85.6	85.6	1.7	1.7	1.7
Observations	7,084	7,084	7,084	7,084	7,084	7,084	7,084	7,084	7,084



Other Specifications & Robustness

- Use country-year fixed effects instead of observables
- Sensitivity analysis on country inclusion: robust
- Sensitivity analysis on drug comparisons: robust
- Subsample: in countries where a drug is not patented
- Debundle drugs at compound-level and re-analyze: robust
- Reduced form analyses on price/quantity channels
- DiD treatment heterogeneity: Bacon decomposition (De Chaisemartin and d'Haultfoeuille, 2020; Goodman-Bacon, 2021)

results: alternative specification | sensitivity results: countries | sensitivity results: drugs
subsample: patent status | robust results: debundle | robust results: P, Q | Bacon decomp. D

Outline

Drug Innovation: R&D Inputs & Outputs

2. Does the *Medicines Patent Pool* foster innovation?

- Firms' R&D decisions: from pipeline to market
- R&D inputs in clinical trials: Phases I-IV (waived for generics)
- R&D outputs in drug approvals: fast review for HIV drugs

MPP on Drug Innovation: Method

- Exploit variation in the timing of when a compound enters the MPP

- Difference-in-differences model: at compound-year level

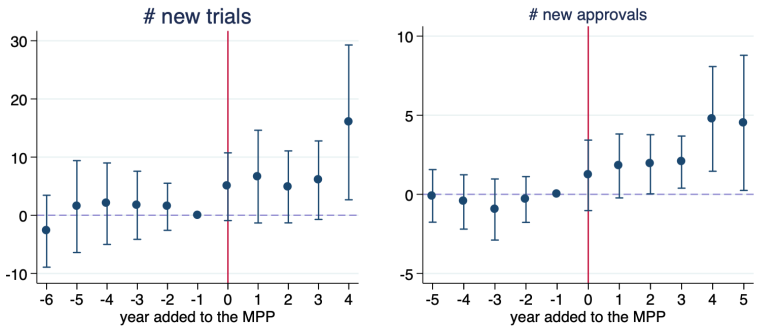
$$y_{at} = \delta_a + \delta_t + \underbrace{\beta\, MPP_{at}}_{=1 \textit{ if a in pool at t}} + \gamma X_{at} + \varepsilon_{at}$$

- y_{at}: # new clinical trials, # firms in trials, # new approvals
- X_{at}: compound-year control on 1st FDA approval, US patents
- $\delta_a + \delta_t$: compound FE and year FE, cluster at compound level
- Stratify outcomes by MPP-affiliation, phases, funders, etc.
- Timing is uncertain in theory (Rey & Tirole, 2019), data & interview

more on innovation identification

MPP increases follow-on innovation: inputs & outputs

- R&D inputs (clinical trials) & outputs (approvals) increase



MPP increases trials, but more for outsiders than insiders

- $MPP_{insiders} = MPP_{branded\ firms}$; outsiders = other entities
  - Majority of the outsider firms are public/academic institutions

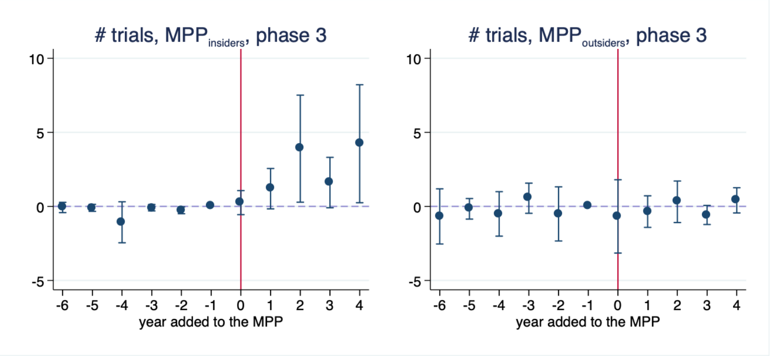
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dept. Vars.	# trials		# trials: $MPP_{insiders}$		# trials: MPP_{mix}		# trials: $MPP_{outsiders}$	
MPP_{at}	9.925**	8.093	2.098**	1.625*	1.672	1.100	6.155**	5.368*
	(4.534)	(4.831)	(0.883)	(0.859)	(1.025)	(1.051)	(2.848)	(3.084)
LHS mean	10.08	10.08	2.367	2.367	1.915	1.915	5.794	5.794
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

event studies: new trials
R and D reallocation: cross-phase

- The pattern of result is similar for # firms involved
- Compare magnitude with literature: Finkelstein (2004)
  - Demand-side policy can induce 2.5-fold increases in trials

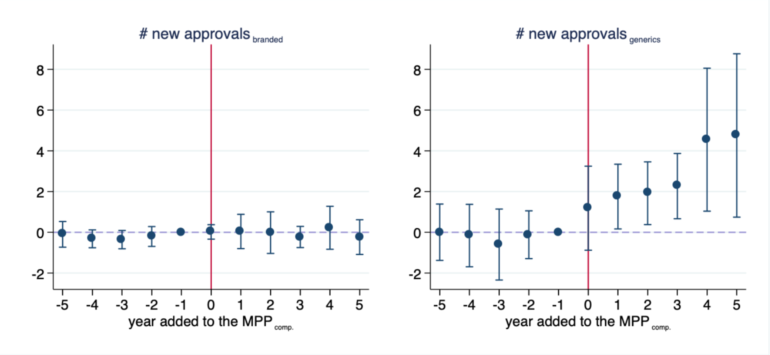
Branded firms invest more in new compound development

- New compound development: pre-approval investigational trials
  - Explore new drugs, e.g., vaccines, gene therapy, cell therapy
  - Drug class-year unit; when a drug class is 1^{st} added to the pool
  - R&D input mainly increases in phase 3 by MPP insiders



MPP increases new (generic) HIV drug product approvals

- Generic firms' comparative advantage: multi-firm bundling
  - 1^{st}-ever drug cocktail and the status quo details
- Increases in R&D outputs: new drug product approvals
  - Generic versions of: existing drugs, new combination/formulations



drug approvals: DID results

Results Summary: MPP & Innovation

- Increases in **R&D inputs**: new trials & firm participation
  - Pool outsiders increase trials on pooled compounds
  - Pool insiders invest more in new compound development
  - *Post-market trials* are shifted from pool insiders to outsiders
- Increases in **R&D outputs**: mainly generic product approvals
- Others: duration analysis: shorter branded-to-generic time with MPP compounds; sensitivity analysis with count data models

  histograms | duration analysis | sensitivity: count data model | Bacon decomp. I
- Case studies: 1) a pediatric cocktail | 2) the TDF family | 3) TLD revisit

Outline

Welfare/Cost-Benefit Analysis: Overview

3. Is the *Medicines Patent Pool* cost-effective?

- MPP directly affects supply; counterfactuals: no/full MPP
- Demand side: nested discrete choice model (nest = drug class)
  - Treatment regimen depends on resistance and side effects
- Supply-side: oligopoly w/ a competitive fringe (infeasible to model)
  - MPP reduces costs in 2 cases: MC pricing & oligopoly

demand structure estimating demand estimating supply

Counterfactual Welfare Simulations

- Counterfactuals w/o the MPP annualized details C.F. w/ full MPP

welfare estimates ($ million)	MC pricing flat MC	Bertrand-Nash Oligopoly single-prod. firm	Bertrand-Nash Oligopoly multi-prod. firm
$\widehat{CS}_0$	\$7,355m	\$8,055m	\$8,026m
CS	\$8,748m	\$8,748m	\$8,748m
$\Delta\$: CS_0$	\$1,393m	\$693m	\$722m
$\Delta\%: CS_0$	18.9%	8.6%	9.0%
$\widehat{PS}_0$	0	\$3,998m	\$4,195m
PS	0	\$4,180m	\$4,310m
$\Delta\$: \mathrm{PS}_0$	0	\$181m	\$115m
$\Delta\%: \mathrm{PS}_0$	0	4.5%	2.7%

Note: MPP operating costs are \$33m during the same period, by 2017 ($\leq$\$5m/year).

Outline

Conclusion: MPP (Pre COVID-19)

- The MPP effectively spurs generic drug diffusion in LMIC
- Firms react to the MPP with more R&D inputs & outputs
- The MPP is a cost-effective institution in achieving its goal

external validity pool design Appendix TOC

Discussion: MPP During COVID-19

"Commitments to share knowledge, intellectual property and data
The COVID-19 Technology Access Pool (C-TAP) will compile, in one place, pledges of commitment made under the Solidarity Call to Action to voluntarily share COVID-19 health technology related knowledge, intellectual property and data. The Pool will draw on relevant data from existing mechanisms, such as the Medicines Patent Pool and the UN Technology Bank-hosted Technology Access Partnership…"

Implementing partners

medicines patent pool | OPEN COVID PLEDGE | TECH ACCESS PARTNERSHIP | Unitaid Innovation in Global Health

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

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Outline

Appendix Table of Content

Outline

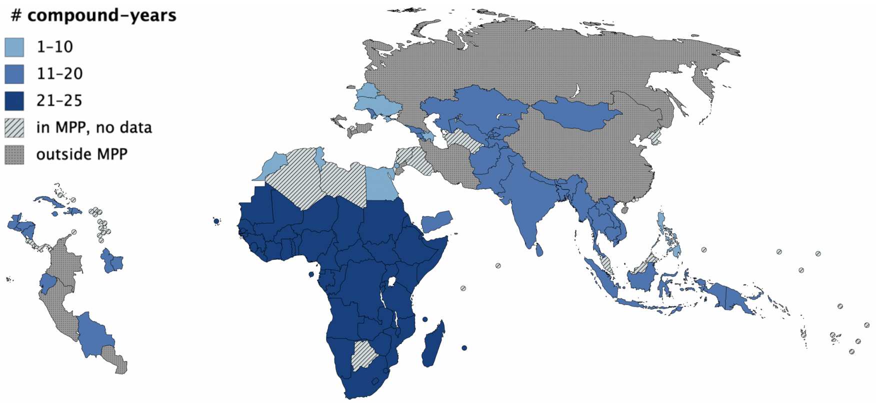
MPP compounds comparison

- Comparison: sales, approval time, drug class, owners
  - Global top 200 drug sales 2012: 6 for HIV - 3 in MPP & 3 out
  - Average "age" of drugs are similar in & outside MPP (t-test)
  - Among all 6 drug classes for HIV: 4 for MPP drugs (outside: 4)
  - Among branded firms owns HIV drugs: 4 effectively in & 4 out

MPP overview

Outline

Diffusion Sample: MPP Geographic Coverage



◂ diffusion: overview

Diagnostic Regression

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

◂ diffusion ID: timing

Diffusion Analysis: alternative specifications

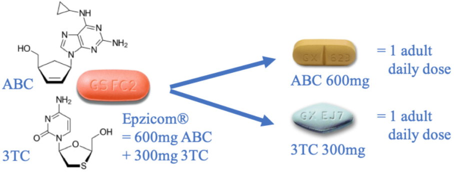
- Use country-year FEs instead of observable controls

Dept. Vars.	(1) % generic orders	(2)	(3) % generic quantities	(4)	(5) # products	(6)
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)
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

- Robust and almost identical to main results diffusion: robustness

Robustness 1: compound-country-year analysis

- Debundle drugs at compound-level and re-analyze: robust
  - Cluster at the country level: allow cross-compound correlation



Dept. Vars.	(1) % generic orders (#)	(2)	(3)	(4) % generic quantities (patient-year)	(5)	(6)	(7) # products (strength-dose-firm)	(8)	(9)
MPP_{act}	9.576***	9.977***	10.12***	10.09***	10.42***	10.55***	0.156	0.140	0.132
	[3.088]	[3.050]	[3.076]	[3.227]	[3.204]	[3.226]	[0.115]	[0.114]	[0.110]
comp.-country FE	Y	Y	Y	Y	Y	Y	Y	Y	Y
year FE	Y	Y	Y	Y	Y	Y	Y	Y	Y
X_{ct} control		Y	Y		Y	Y		Y	Y
X_{act} control			Y			Y			Y
LHS mean	79.8	79.8	79.8	82.1	82.1	82.1	2.5	2.5	2.5
Observations	6,485	6,485	6,485	6,485	6,485	6,485	6,485	6,485	6,485

◂ diffusion: robustness

Robustness 2: subsample analysis

- Subsample: in countries where a drug is not patented
  - Smaller magnitude (=> main channel: reduces licensing costs)

	(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)
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*
	[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

◂ diffusion: robustness

Robustness 3: price and quantity channels

- Reduced form analysis of price and quantity regressions
  - Can't define a compound-country-year level counterpart

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

◂ diffusion: robustness

DID treatment effect heterogeneity

- Bacon Decomposition results in the diffusion sample (De Chaisemartin and d'Haultfoeuille, 2020; Goodman-Bacon, 2021)

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

◂ diffusion: robustness

Sensitivity Analysis 1: Countries

- Sensitivity analysis on territory inclusion: robust
  - MPP common territories: sub-Saharan Africa + Djibouti
  - Territories ever in MPP: countries in some drug's 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
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)
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

diffusion: robustness

Sensitivity Analysis 2: Drugs

- Sensitivity analysis on drug comparisons: robust
  - (1) only 1^{st} MPP drug addition and drugs in the same class; (2) drop drug classes without MPP inclusion; (3) drop drugs with US not recommended compounds; (4) drop drugs approved before 1996; (5) only drugs owned by MPP insiders

Outcome: % generic Q	(1) drug class in 1st pool addition	(2) drop one drug class	(3) drop U.S. not-recommended	(4) drugs approved since 1996	(5) drugs by MPP insider firms
MPP_{dct}	10.32***	6.520**	7.234**	6.620**	7.145**
	(3.366)	(2.874)	(2.838)	(2.823)	(2.727)
LHS mean	95.44	84.11	85.25	84.64	88.13
# Obs.	4,463	5,828	6,316	5,786	6,127

diffusion: robustness

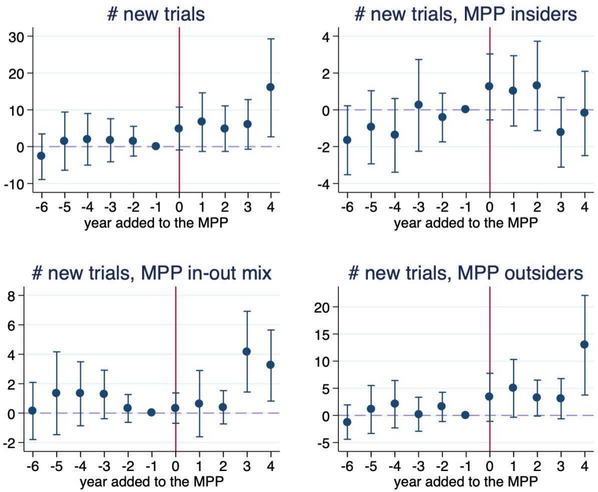
Outline

Identification Assumptions & Justifications

- *Identification*: common trends (event study) & lack of common shocks (DGP)
- Are compounds in MPP of higher values? w/ compound FE
  - Control for: US FDA approval status & US patent status
- Are firms strategically timing compound-level MPP entry?
  - Ambiguous in theory (Rey & Tirole, 2019); No, from data & interview

◂ method: innovation

Event Studies: # new trials



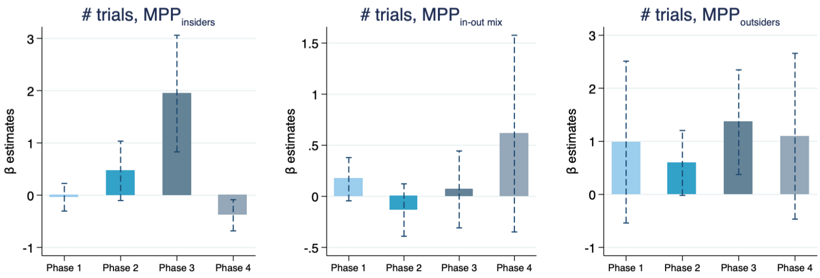
innovation results: baseline

Firms further reallocate clinical trials across phases

- R&D reallocation cross-phase: esp/ phases 3 & 4 follow-on trials
  - 1: safety; 2: efficacy; 3: effectiveness; 4: post-market surveillance

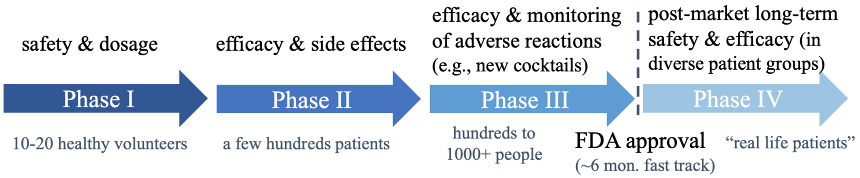
▸ trial phases desc. ▸ phase 3 follow-on trials: events ▸ phase 4 follow-on trials: events

- Large heterogeneity across phases and firm types ◂ back
  - Follow-on trials on ph.3 trials mainly increases from outsiders
  - Post-market (ph.4) trials shifted from pool-insiders to outsiders



Overview of the Drug Approval Process

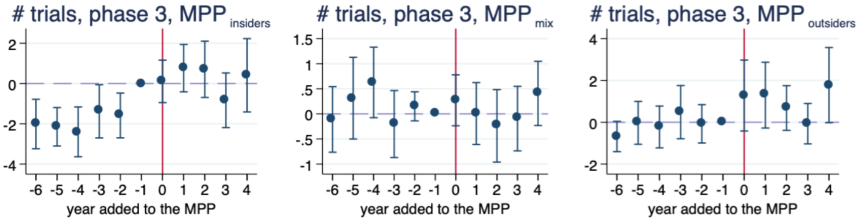
- Clinical trials from pipeline to market
- Increase ph.3 trials to push more products to the market



RnD reallocation

R&D input: phase 3 follow-on trials

- Phase 3: the large scale pre-approval human trial
  - Last stage before FDA review drugs for marketing
- MPP insiders increase ph.3 follow-on trials (new cocktails)



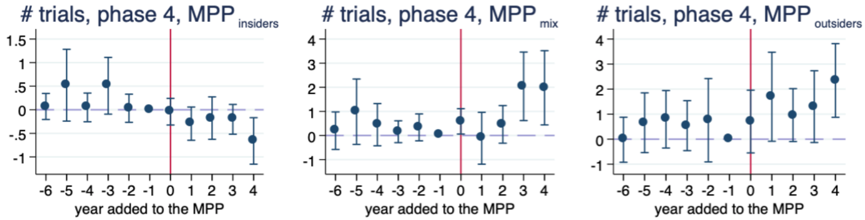
RnD reallocation

R&D input: phase 4 follow-on trials

- Phase 4: post-market surveillance trials monitoring safety

Often mandatory to monitor the long-term impact for life-saving drugs

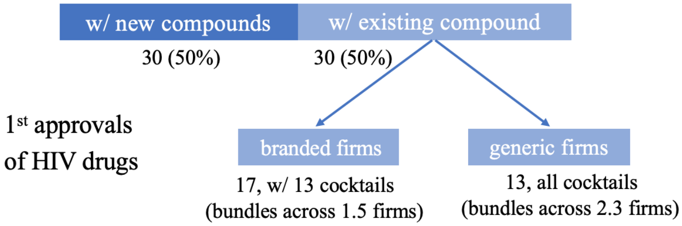
- MPP insiders reduce ph.4 trials & outsiders increase ph.4 trials



RnD reallocation

R&D outputs: an overview of HIV drug approvals

- All approvals: branded & generic (innovation & imitation)
- Generic firms' comparative advantage: multi-firm bundling
  - From the 1^{st}-ever drug cocktail to the status quo



RnD outputs

HIV Drug Approvals: DID results

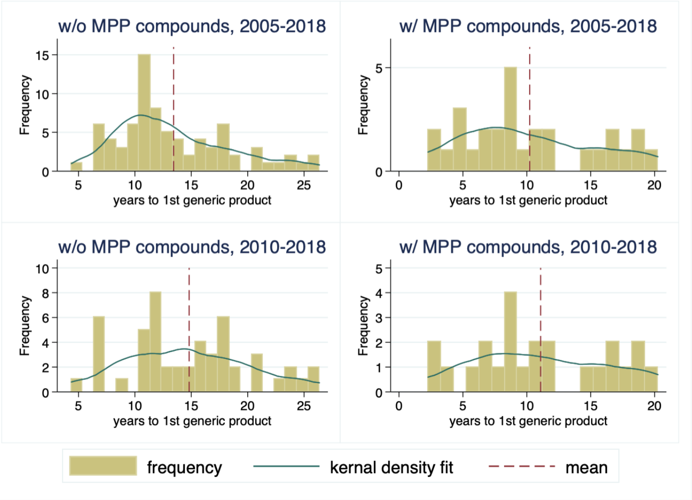
- Compound-year level # new drug product approvals

Dept. Vars.	(1)	(2)	(3)	(4)	(5)	(6)
	# new approvals		# new approvals ^{generic}		# new approvals^{branded}	
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

- Branded firms react strongly with FDA approval, and generic firms react strongly w.r.t. the MPP net of FDA approval of a compound

◂ RnD outputs

Descriptive Analysis: "Time-to-1st Generic" Histograms



innovation results: summary

Duration Analysis: Time-to-Generic & the MPP

- Simple analysis of "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

◂ innovation results: summary

Alternative Method: Count Data Models

- Robustness results for the drug approval analyses

	(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

innovation results: summary

DID treatment effect heterogeneity: innovation

- Bacon Decomposition results in the innovation sample (De Chaisemartin and d'Haultfoeuille, 2020; Goodman-Bacon, 2021)

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		

◂ innovation results: summary

MPP Case 1: a Pediatric HIV Cocktail

- The lack of pediatric formulations reflect US demand: most US pregnant women are tested for HIV, and quick use of HIV drugs can prevent mother-to-children transmission
- The first pediatric granules formulation for LPV/r was developed by Mylan with MPP licenses and marketed in 2018 (for sales in developing countries); and more to come (NYT 11/29/2019)
- If needed, branded firms can be granted back low-cost non-exclusive licenses for patents on this new formulation

The New York Times

GLOBAL HEALTH

Nov. 29, 2019

New Strawberry-Flavored H.I.V. Drugs for Babies Are Offered at $1 a Day

Thousands of infants are doomed to early deaths each year, in part because pediatric medicines come in hard pills or bitter syrups that need refrigeration.

"… the more common ped. HIV treatment contains 40% alcohol and had a bitter metallic taste…" (4 syringes, twice a day)

innovation results: summary

MPP Case 2: the TDF family

- Case study: Gilead Sciences & TDF (prodrug of tenofovir)
- Gilead joined the MPP in 2011, put in drugs including TDF
- TAF (prodrug of TDF) enters MPP in 2014 (ph.3 starts in 2012, primary completion 2014, FDA approval 2015)
- Pipeline: tenofovir-based microbicides (ph.s 2+3 started in 2012, Gilead with partners; phase 1 finished in 2008)

innovation results: summary

MPP Case 3: TLD revisit (the illustrative example)

- TLD, the 3-compound daily cocktail 1st created by Mylan
- TLD = TDF (Gilead) + DTG + 3TC (ViiV), 2017 approval
- ViiV started a clinical trial in 2017 on DTG+3TC (Dovato)
- FDA approval in 2019; same dose combo as TLD sub-dose
- The first, once-daily, single-pill, **two**-compound regimen
    - Comparable to some three-compound regimen

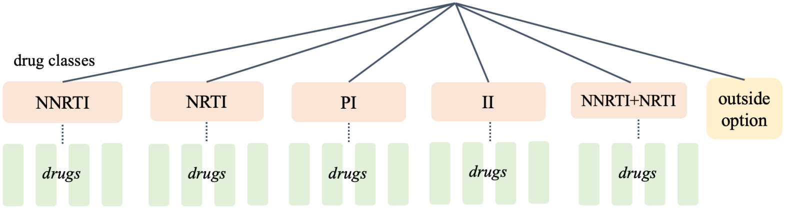
◂ innovation results: summary

Outline

Drug Cocktails in Discrete Choice Frameworks

- Intuition: market shares of drugs/drug cocktails reflect values
  - patient(-physician) i, drug j in group $g(j)$, country c, year t

$$u_{ijct} = \underbrace{X_{jct}\beta - \alpha p_{jct} + \xi_{jct}}_{\text{mean utility } \delta_{jct}} + \varsigma_{ig(j)ct} + (1-\sigma)\varepsilon_{ijct},\ \varepsilon_{ijct} \sim GEV$$



welfare analysis: overview

Estimating Demand

- Follow Berry (1994) and after some math. transformation
  - drugs j, j' under drug class g_j are more substitutable

$$\ln(s_j) - \ln(s_0) = \sigma \ln(s_{j|g}) + \underbrace{X_j\beta - \alpha p_j + \xi_j}_{\delta_j} - \underbrace{\delta_0}_{=0}$$

- s_j & s_0: market share for drug j and the outside option; $s_{j|g}$: share of drug j within its class g_j, market size: 20% pop. (robust to alter.)
- X_j include: #within-drug compounds, drug age (w.r.t. US approval), within-drug product variety, HIV death rate & prevalence, population, income, institutional factors, country & year FEs
- IVs for $s_{j|g}$ and p_j w/ demand shifters & BLP IVs: patent status, #competitors for j, #competiting product-firms in group g_j

▸ demand estimation results ◂ welfare analysis: overview

Estimating Supply: Two Cases

- Case 1: marginal cost pricing (flat MC) welfare analysis: overview

$$p_j = mc_j = X_j \gamma + \beta MPP_j + \omega_j$$

X_{jct}: $ln(population)$, $GDP\ pc$, $Patent_{dct}$, HIV death rate & prevalence, institutional factors, product variety, #manufacturers, country & year FEs

- Case 2: Oligopolistic Pricing - Bertrand-Nash Game

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

$$\Longrightarrow mc = p - \Delta^{-1} s = X\gamma + \beta MPP + \eta q + \omega, \ \Delta_{jk} \equiv -\frac{\partial s_k(p)}{\partial p_j}$$

Follow BLP (1995) logic; same X covariates as before; BLP IV for q_j: # competiting products within a drug class substitution matrix supply estimation results

- $\hat{\beta}$: -0.6 for MC pricing, about -1.9 for oligopolistic pricing ($/patient-day)

Demand Estimation Results

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

Notes: country FE, year FE, X_{dct} controls are always included.

estimating demand

Substitution Matrix & Price Elasticities

- Following Berry *et al.* (1995) and after some algebra

$$\Delta_{jk} = -\frac{\partial s_k}{\partial p_j} = \begin{cases} \alpha s_j \left(\frac{1}{1-\sigma} - \frac{\sigma}{1-\sigma} s_{j|g} - s_j\right) & j = k \\ -\alpha p_j \left(\frac{\sigma}{1-\sigma} s_{k|g} + s_k\right) & j \neq k, g_j = g_k, f_j = f_k \\ -\alpha s_j s_k & j \neq k, g_j \neq g_k, f_j = f_k \\ 0 & f_j \neq f_k \end{cases}$$

- Calculation simplified with the close-form expression

estimating supply

Supply Estimation Results

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

◂ estimating supply

Counterfactual 1: w/o the MPP, annualized

- Scenario: what if there is no MPP? Counterfactuals

welfare estimates ($ million/year)	MC pricing flat MC	Bertrand-Nash Oligopoly single-prod. firm	Bertrand-Nash Oligopoly multi-prod. firm
$\widehat{CS}_0$	$736m	$806m	$803m
CS	$875m	$875m	$875m
Δ$: CS_0	$139m	$69m	$72m
Δ%: CS_0	18.9%	8.6%	9.0%
$\widehat{PS}_0$	0	$571m	$599m
PS	0	$418m	$431m
Δ$: PS_0	0	$18m	$12m
Δ%: PS_0	0	4.5%	2.7%

Note: MPP operating costs are $33m during the same period, by 2017 (≤$5m/year).

Details on the Counterfactual Simulations

- Case 1 (MC pricing): set $\hat{\beta}_{mpp} = 0$, simulate p_0^{cf}, calculate $\hat{CS}_0$ in close-form and $\hat{PS}_0$ using the surplus triangle
- Case 2 (oligopoly): start w/ an initial guess of $\hat{p}_j$, calculate the objective function (fmincon) with relevant data & parameters and the counterfactual marginal cost (using C.F. MPP_j^{cf}) ◂ Counterfactuals

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

$$\widehat{mc}_j(\hat{q}_j) = \beta MPP_j^{cf} + X_j\gamma + \eta\hat{q}_j + \omega_j$$

$$\hat{\Delta}_{jk} = function\left\{\alpha, \sigma, \hat{s}_j, \hat{s}_k, \hat{s}_{j|g}, \hat{s}_{k|g}\right\}$$

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

Counterfactual 2: Fully-Expanded MPP

- Scenario: what if the MPP covers all developing countries in my sample (e.g., no cross-compound geo. differences) Counterfactuals

welfare estimates ($ million)	MC pricing flat MC	Bertrand-Nash Oligopoly single-prod. firm	Bertrand-Nash Oligopoly multi-prod. firm
$\widehat{CS}$	\$8,748m	\$8,748m	\$8,748m
$\widehat{CS}_1$	\$8,883m	\$8,822m	\$8,816m
$\Delta\$: \widehat{CS}_1$	136m	74m	69m
$\Delta\%: \widehat{CS}_1$	1.6%	0.8%	0.8%
$\widehat{PS}$	0	\$4,180m	\$4,310m
$\widehat{PS}_1$	0	\$4,321m	\$4,462m
$\Delta\$: \widehat{PS}_1$	0	\$141m	\$152m
$\Delta\%: \widehat{PS}_1$	0	3.4%	3.5%

Note: MPP operating costs are $33m during the same period, by 2017 (≤$5m/year).

Outline

Data: HIV Drug Diffusion in LMIC

- The complete HIV drug portfolio data: FDA & AIDSinfo
  - Generic names, abbreviations, drug classes, branded firms
  - Information on US adult daily doses using FDA labeling

- HIV drug public procurement data in LMIC, 2007-2017
  - Price & quality reporting by Global Fund-supported programs

- MPP inclusion time & territories: MPP licensing contracts
- International patent status: MedsPaL & DrugPatentWatch

- Country-year controls: HIV death rate & prevalence, population, income, six institutional factors (worldwide governance indicators)
  - World Bank and Institute for Health Metrics & Evaluation

data overview

Data: R&D Inputs & Outputs on HIV Drugs

- R&D inputs: clinical trials with HIV compounds, 2000-2017
  - Global clinical trials from the US-registry clinicaltrials.gov
  - Compound-level trial identifiers from AIDS*info*
- R&D outputs: HIV drug approvals, 2005-2018 (fast track, 2005+)
  - All FDA approvals and tentative approvals from Drugs@FDA
  - All WHO approvals from WHO pre-qualification program
- US drug patent data: Drug Bank via FDA Orange Book

data overview

Discussion: External Validity

- What can we learn beyond this case study of the MPP?
  - Combating HIV is important, yet it is still a special case
- External validity: beyond HIV and opportunistic infections
  - USPTO advocated patent pools for biotech, but no progress
  - CRISPR-Cas9 gene editing patent pools face many difficulties
  - MPP expands to cover all small molecule essential medicines
  - Business model innovation (Christensen et al., 2019).

"Prosperity paradox": "market-creating innovations"; "It's less about the actual product being sold, but more about the value networks and business model that innovators creates."

conclusion

Discussion: Pool Design

- Empirical evidence on patent pools is overall negative
  - Partly explained by the mechanism design features of pools
  - Measures matter: patent counts/citations vs. R&D activities
- Different from pools in ICT and the Eco-Patent Commons
  - No fragmented rights and clear value (closer to traditional pools)
  - Compound as the smallest licensing unit (not at patent level)
  - Highly skilled, passionate employees; active engagement

Esp. EcoPC: 1) lack of technology transfer; 2) firms are not specialized in energy/environment and file side-patents with limited values; 3) not much promotion of the EcoPC with unmotivated employees

conclusion