Ecosystem Evolution and Bottleneck Shifts: Evidence from The Evolution of the Anti-HIV Drug Ecosystem

Elena Plaksenkova∗ and Olivier Chatain†

Abstract

How do bottlenecks – the loci of value creation and value capture in business ecosystems – evolve over time? How can firms shape this evolution? To answer these questions, we trace the evolution of the anti-HIV drug industry – where the standard treatment is a combination of multiple drugs belonging to two distinct components – between 1997 and 2018. We examine firms’ strategies in terms of the entry into complementary component, developing exclusive complements, and attempts to challenge the existing bottlenecks by offering an alternative pathway to value creation. Using a hand-coded dataset of clinical trials of anti-HIV drugs we find that while firms with inferior offerings attempt to solve value constraining bottleneck, stronger firms seek, instead, to decrease competition and make their offering a value capture, or strategic, bottleneck, by strategically timing innovation and using exclusive complements. Once the strategic bottleneck emerges, its owners develop bundles with exclusive complements to maintain the bottleneck. However, these strategies may backfire as losing firms in the focal component switch their innovative effort to the complementary component and try to shift the bottleneck to the latter by making the original bottleneck component irrelevant. These findings add more nuanced predictions in terms of how firms react to value creation bottlenecks and offer some of the endogenous drivers of bottleneck evolution.

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∗Management and Human Resources Department, Fisher College of Business, The Ohio State University, 2100 Neil Ave, Columbus, OH 43210, USA. E-mail: plaksenkova.1@osu.edu.
†Strategy and Business Policy Department, HEC Paris, 1, rue de la Libération, 78350 Jouy-en-Josas, France. E-mail: chatain@hec.fr.
1 INTRODUCTION

Bottlenecks are a key feature of business ecosystems (Adner, 2017; Jacobides, Cennamo, and Gawer, 2018; Kapoor, 2018) by the virtue of being the “points of value creation and value capture” (Baldwin, 2018). Bottlenecks’ resolution or, alternatively, their persistence significantly affect the potential for value creation (Adner and Kapoor, 2010; Hannah and Eisenhardt, 2018; Kapoor and Furr, 2015) and differences in the abilities of ecosystem participants to capture value (Jacobides and Tae, 2015). While there is evidence that bottlenecks can evolve within an ecosystem (Baldwin, 2018; Hannah and Eisenhardt, 2018), we need to have a more profound understanding of possible trajectories of bottleneck evolution, and how the latter can affect and, in turn, be affected, by firm strategies.

Extant literature has so far approached the question of bottleneck evolution from two perspectives. The first stream of literature focuses on the role of a bottleneck as a technical constraint to the ecosystem’s total value creation, and examines how firms may attempt to resolve this constraint (Adner and Kapoor, 2010; Ethiraj, 2007; Kapoor, 2013; Kapoor and Furr, 2015), and how firms react to it (Hannah and Eisenhardt, 2018; Kapoor and Agarwal, 2017). The second stream of literature views bottlenecks as a consequence of competitive scarcity that enables firms to capture a larger share of value created, and explores how firms may try to maintain their bottleneck position (Jacobides and MacDuffie, 2013; Jacobides and Tae, 2015; Miller and Toh, 2020).

As a result, three lacunae stand out. First, given the two distinct patterns of bottleneck evolution emerging from the literature we need to understand how they interact and how they can be reconciled. Baldwin (2018) suggests that the resolution of the technical constraint may result in a value capture bottleneck provided the solution to the technical constraint is unique and protected by property rights. We ask the question whether other trajectories of bottleneck evolution are possible, especially given that bottlenecks can sometimes shift across ecosystem components (Hannah and Eisenhardt, 2018). Second, we need a systematic account of the implications of this evolution for the firms’ strategies – particularly given sometimes opposite recommendations emerging from the two literature streams as to resolution or maintenance of the bottleneck. Third, the question
remains as to how firms may shape the bottleneck evolution. While recognizing that firms may act upon a bottleneck once it arises, the literature typically considers bottleneck emergence and shifts as determined by exogenous shocks (such as emergence of new technology, property rights expiry, etc.). As a result, we need to learn more about how firms may strategize on and around bottlenecks, and how these strategies can affect the trajectory of bottleneck evolution.

In this paper we thus seek to address these three gaps: What are the possible trajectories of bottleneck evolution in an ecosystem? How does bottleneck evolution shape the strategies that firms adopt to compete in an ecosystem? How can firms influence this evolution and shift the ecosystem to a more favorable bottleneck state? We focus on ecosystem-level strategies: entry into complementary component, developing exclusive complements, and attempts to challenge the existing bottleneck.

To answer these questions we develop a taxonomy of bottlenecks combining the mechanisms from the two literature streams (the extent of technical constraint and competitive scarcity, respectively), and then use it to trace the evolution of anti-HIV drug ecosystem between 1997-2018. A standard treatment for HIV represents a combination of multiple drugs belonging to two distinct components. We use the fact that one of these components has historically featured severe side effects – a significant obstacle for the treatment prescription and adherence – which can be interpreted as a technical constraint on a value creation. Over time this component featured variance in terms of the number of approved drugs allowing us to explore the effect of both technical constraint and competitive scarcity.

Given the complexity of the firm interactions in an ecosystem, and that of the context, we use an abductive approach. We start by identifying the trajectories of bottleneck evolution in the anti-HIV drug ecosystem along the two dimensions – the extent of technical constraint and competitive scarcity – based on medical guidelines. We then use a rich hand-coded dataset of clinical trials on anti-HIV drugs complemented with the information on drug quality and ownership to examine firms’ strategies along the bottleneck evolution. We conclude by testing the key insights with a regression analysis.
We find that firms’ strategies depend both on the extent of technical constraint and the scarcity of competitive solutions, as well as on the relative quality of the firm’s offering in its focal component. For instance, when ecosystem features technical constraint it is mostly new entrants or lower-quality incumbents who seek to find solutions to resolve it while high-performing incumbents try to enhance their positions by entering into complementary component. Conversely, high-performing incumbents may strategically postpone investing in constraint component until after the constraint is resolved in order to maintain their favorable position.

Our findings also suggest that firms might, in turn, affect the bottleneck evolution. We find that firms may leverage their portfolio to come up with exclusive bundles of complements to shift the ecosystem towards the state with higher scarcity resulting in a value capture bottleneck. Furthermore, we show that the firms owning such value capture bottleneck can strategically time their innovative effort in the bottleneck component, and develop exclusive complements to maintain the ecosystem in this favorable bottleneck state. Since a bundle of products is necessary to create value firms with superior products in both focal and complementary components are able to develop “inter-temporal” property rights over the bottleneck by the virtue of having strong property rights over only one part of this bundle. However, these strategies may backfire as losing firms in the focal component switch their innovative effort to the complementary component and try to shift the bottleneck to the latter by making the original bottleneck component irrelevant.

Our paper offers several contributions to the ecosystem literature. First, we provide a comprehensive framework to characterize bottlenecks that reconciles the two divergent views in the extant literature: bottleneck as a constraint on value creation vs. bottleneck as an opportunity for value capture. Second, we endogenize bottleneck evolution by showing how both exogenous technology evolution and endogenous firms’ actions shape this evolution. In particular, we show how firms can use integration with complements to shift and maintain the ecosystem in the state with value capture bottleneck, and how losing firms, in turn, seek way to invent around the bottleneck by changing the technology of value creation. Third, we further the knowledge on competitive interactions and rivalry in the context of ecosystems by examining the role of within-component
heterogeneity in shaping firms’ strategies. This complements the extant literature that explores the effect of between-component competition (Jacobides and Tae, 2015) on firm’s actions, such as reactions of complementors to platform innovation (Kapoor and Agarwal, 2017), platform’s entry into complementors’ space (Miller and Toh, 2020; Zhu, 2019; Zhu and Liu, 2018), and comple mentors responses to the platform’s exertion of power (Wang and Miller, 2020; Wen and Zhu, 2019).

The paper proceeds as follows. Section 2 provides theoretical background on ecosystem bottlenecks and outlines our proposed taxonomy. Section 3 gives an overview of the anti-HIV drug context. Section 4 provides the description of the data and the measures that we use in our analysis. Sections 5 and 6 contain the results of our analyses on the ecosystem evolution and firms’s strategies, respectively. Section 7 provides the results of the regression analysis, and in Section 8 we discuss the results and provide conclusions.

2 Theory

2.1 Ecosystems and bottlenecks

The concept of business ecosystem, originally introduced by Moore (1993), has started to take prominence in strategy research in the recent years (Adner, 2006; Adner and Kapoor, 2010). An ecosystem can be defined as a set of actors whose products and services comprise a bundle that provides value to the customer (Adner, 2017; Hannah and Eisenhardt, 2018; Jacobides, Cennamo, and Gawer, 2018). The key features of an ecosystem include the existence of non-generic complementarities between the offerings of its participants and a lack of hierarchical control (Jacobides et al., 2018). The former necessitates strategic decisions regarding which complements an ecosystem participant wants to be compatible with. The latter implies limited power that an ecosystem

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1This definition is similar to that by Hannah and Eisenhardt (2018). It is consistent with Adner (2006, 2017) where an ecosystem is defined as centered around a specific innovation or a product – “the alignment structure of the multilateral set of partners that need to interact in order for a focal value proposition to materialize” (Adner, 2017). By acknowledging that there may competition among multiple firms who can produce the focal product (innovation) and among those who can produce complements, our definition allows to incorporate the concept of competitive scarcity from the industry architecture literature (Jacobides, Knudsen, and Augier, 2006).
participant has over the complements and makes ecosystem a distinct governance mode, different from hierarchy or vertical supply chains (Miller and Toh, 2020). Together, these features requires firms to carefully balance the total value creation by an ecosystem and individual firm’s value capture (Brandenburger and Nalebuff, 1997). A crucial construct to understand these decisions are ecosystem bottlenecks.

The literature has two ways to look at the bottlenecks. The value creation perspective defines bottleneck as a part of an ecosystem constraining value creation (e.g., Adner and Kapoor, 2010; Hannah and Eisenhardt, 2018). This type of bottlenecks is sometimes referred to as technical bottlenecks (Adner and Kapoor, 2016; Baldwin, 2018), which reflects their nature: they arise due to the technology evolution when a certain component (or components) of an ecosystem is lagging behind other components (Ethiraj, 2007; Adner and Kapoor, 2010), or, in the extreme case, is not available at all (Kapoor and Furr, 2015). This view of bottlenecks suggests that ecosystem participants must actively seek to resolve the bottleneck by investing in the constraint component (Ethiraj, 2007; Hannah and Eisenhardt, 2018), adopting collaborative governance modes with the firms in the constraint component (Kapoor and Lee, 2013; Kapoor, 2013), or subsidizing the entry into the constraint components (Gawer and Henderson, 2007).

By contrast, the industry architecture (IA) literature has examined bottlenecks from the value capture angle. This research stream defines a bottleneck as an ecosystem component “that is in most scarce supply” and thus allows the firms producing such component to appropriate a higher share of value (Jacobides, Knudsen, and Augier, 2006). Bottlenecks in the IA literature arise due to competitive asymmetry between components: the one having less competition becomes the bottleneck and manages to capture more value as its constituents have higher bargaining power over the constituents in a more competitive component (Jacobides et al., 2006). These bottlenecks are

2 The industry architecture (IA) literature builds on the seminal contribution by Teece (1986) on Profiting from Innovation (PFI), as well as on the modular design literature (Baldwin and Clark, 2000). While industry architecture and business ecosystems literature streams developed relatively independent of each other they examine similar kind of settings albeit using different terminology (“industry” or “industry sector” in the IA literature versus “ecosystem” in strategy literature). Because they focus on different questions pertaining to the ecosystem – value creation in strategy literature as opposed to value capture in the IA literature – we believe that there is great value in bridging the gap between these two literatures. Specifically, we believe that we can gain new insights in the competition within a business ecosystem by reconciling the assumptions from these two literatures.
considered the “points of value capture” (Baldwin, 2018) as opposed to value creation (technical) bottlenecks, and firms who find themselves in a bottleneck component should maintain its “bottleneckness” by, for instance, investing in setting standards (Jacobides and Tae, 2015; Toh and Miller, 2017), being a gate-keeper for quality control (Jacobides et al., 2016), and protecting property rights (Baldwin, 2018).

2.2 Bottleneck evolution

The two perspectives also focus on different patterns of bottleneck evolution. Value creation focuses on how the presence of absence of technical constraint affects firms’ performance (Adner and Kapoor, 2010; Kapoor and Furr, 2015); how firms can make the ecosystem move towards bottleneck resolution (Ethiraj, 2007; Hannah and Eisenhardt, 2018; Kapoor, 2013; Kapoor and Lee, 2013), and how firms in the complementary component react to such transitions (Hannah and Eisenhardt, 2018; Kapoor and Agarwal, 2017). Value capture view is mostly interested in the evolution around scarcity of an ecosystem component: the consequences of a component becoming more or less scarce (Jacobides, Knudsen, and Augier, 2006; Jacobides and MacDuffie, 2013), and how firms attempt to preserve the scarcity of their component (Jacobides et al., 2016; Jacobides and Tae, 2015).

Yet there is evidence that suggests that both dimensions – technical constraint and competitive scarcity – can be simultaneously involved in the bottleneck evolution. For instance, the need to solve technical constraints on the personal computer industry induced the OEMs to allow more competition in their component, subsequently reducing competitive scarcity and curtailing the opportunities for value capture (Jacobides et al., 2016; Jacobides and Tae, 2015). Conversely, Hannah and Eisenhardt (2018) show that technological evolution may result in a new and scarce technology creating a value capture bottleneck for the given firm.

To the extent of our knowledge, the major attempt to link these two perspectives is the work by Baldwin (2018). Following Baldwin (2018), if a technical constraint in an ecosystem can be resolved in a unique way with some form of property rights protection, then a value capture bottleneck will emerge, which is called a strategic bottleneck. If property rights weaken, or if there
are alternative solutions to the technical constraint then there can be no competitive scarcity, and no strategic bottleneck can emerge.

Yet, despite this important contribution, several questions remain. First, the possibility of strategic bottleneck is assumed to be a consequence of exogenously determined property rights/technological evolution – thereby ignoring the possibility of firms strategizing to maintain their hold on the value capture bottleneck. Second, the absence of strategic bottleneck is assumed to be final, though we could think of firms trying to increase competitive scarcity. Third, the possibility of inventing around the bottleneck – the attempt to shift the bottleneck – is not considered in these trajectories. To address these questions and to explore possible bottleneck evolution trajectories we propose to explicitly articulate the two mechanisms of bottleneck emergence – technical constraint and competitive scarcity – and analyze what different combinations imply for ecosystem participants’ strategies.

2.3 Proposed bottleneck taxonomy

We propose to combine the mechanisms underlying bottleneck emergence from the two perspectives to develop a more comprehensive framework. The value creation perspective posits that the presence of a technical constraint is what defines the bottleneck existence: “a component in a complex system whose performance significantly limits the performance of the system as a whole” and whose “hindrance to performance derives from physical properties of the system” (Baldwin, 2018). The value capture perspective uses the competitive intensity to characterize bottleneck existence: bottleneck is a part of a system that is “in most scarce supply” (Jacobides et al., 2006). In other words, what matters in this view is the number of competitive solutions present in the component compared to other components. Using these two dimensions – the presence of technical constraint in the component and the number of competitive solutions in the component – we can have a two-by-two matrix for bottleneck taxonomy (Figure 1).

We can see now how the two views overlap, and where they may diverge. According to value creation perspective, an ecosystem has a bottleneck if it is in quadrants I and II whereas ecosystems corresponding to quadrants III and IV will be considered as devoid of bottlenecks. In terms
of evolution, it focuses on the movement from the left-hand side to the right-hand side of the matrix while being generally indifferent to the level of solutions scarcity, treating quadrant III (no bottleneck) and IV as similar.³

Value capture view would consider that an ecosystem has a bottleneck if it corresponds to quadrants I and IV where the component is in scarce supply. It mainly focuses on the transition between the upper and the lower half of the matrix while assuming the ecosystem structure as fixed and absent of significant technological shifts (i.e., treating quadrants I and IV as similar). Note that quadrant IV corresponds to the the notion of strategic bottleneck in Baldwin (2018) – a unique solution to a technical bottleneck which can be controlled by an agent. Conversely, quadrant III is absent any bottleneck reflecting a situation of a large number of high-quality solutions.

The use of this matrix allows to map more efficiently the evolution of bottleneck depending on the state of technical constraint and the number of competitive solutions. It may also help us further qualify predictions of the two literature streams regarding firm strategies by taking into account both dimensions. For instance, how would the presence of absence of a technical constraint affect the firms’ strategies when there are few solutions? Would firms behave in a different way towards technical constraint depending on whether there are many or few solutions?

2.4 Firms’ ecosystem strategies

We propose to use the bottleneck taxonomy to examine firms’ strategies in an ecosystem to understand how these strategies are contingent on the state of the bottleneck in the ecosystem and, in turn, how these strategies affect bottleneck evolution. Since we are interested in interdependencies between firms’ strategies and bottleneck evolution we look at strategies that have the potential to affect the state of bottleneck, i.e., the strategies that are at the ecosystem level rather than within component (Hannah and Eisenhardt, 2018; Miller and Toh, 2020). In this paper we focus on three distinct strategic choices.

First, we explore the direction of innovative effort: whether firms choose to invest in the focal component.

³A notable exception is Hannah and Eisenhardt (2018) who highlight the situation when only one firm has the access to the novel winning technology.
(constraint) component or complementary component. Focus of the innovative effort and its evolution over time has been a key subject of interest in the value creation literature (Adner and Kapoor, 2010; Hannah and Eisenhardt, 2018), as well as its dependence on technical constraint resolution (Ethiraj, 2007). Value creation literature suggests that firms will tend to direct their innovative effort to resolve technical constraint (Adner and Kapoor, 2010; Ethiraj, 2007; Hannah and Eisenhardt, 2018). On the other hand, there is evidence that powerful firms in the focal component may invest in complementary component to leverage their position (Miller and Toh, 2020; Zhu and Liu, 2018).

Second, we examine whether firms attempt to shift, or circumvent, the bottleneck component. We know from the literature that bottlenecks may migrate across components (Adner and Kapoor, 2010; Baldwin, 2018; Hannah and Eisenhardt, 2018), yet since the literature typically treats these shifts as results of exogenous technological shocks we know less about how firms may attempt to spur such evolution. Our goal here is to understand who and when attempts to challenge the existing bottleneck and shift it to another component.

If firms are present in both focal and complementary components they may choose to leverage their portfolio and limit complements available to their competitors. This is why the third strategic
choice we are looking at is the *exclusivity* strategies. Platforms often seek to enforce exclusivity from complementors, for instance having a video game available only on a certain console (Cen-namo and Santalo, 2013; McIntyre and Srinivasan, 2017). Ecosystem participants having presence in the focal and complementary components may sometimes preclude other firms from accessing their complements, especially when competition intensifies (Hannah and Eisenhardt, 2018).

To conclude, there are two approaches in the literature to look at the bottleneck: value creation perspective that views bottlenecks as a technical constraint on the value creation that needs to be resolved, and value capture perspective that views bottlenecks as competitive scarcity enabling value capture that needs to be maintained. While there is work linking these views (Baldwin, 2018) we argue that a more comprehensive framework explicitly including the two underlying mechanisms from both literatures is needed to understand bottleneck evolution in an ecosystem. We further argue that incorporating the two mechanisms will help us better understand firms strategies at the ecosystem level – direction of innovative effort, challenging the bottleneck, and developing exclusive complements – specifically, when and how these strategies are employed. As a result, we seek to endogenize bottleneck evolution in an ecosystem. We will now proceed to describe the anti-HIV ecosystem and relate it to the bottleneck taxonomy matrix.

3 **ANTI-HIV TREATMENT CONTEXT**

To explore bottleneck emergence and shifts we examine the evolution of the anti-HIV drugs context. It is particularly amenable to our research because anti-HIV treatment represents a combination of several drugs, generally referred to as a “cocktail”, rather than a single drug. Specifically, an anti-HIV drug combination consists of two distinct components (as identified by medical guidelines).

The HIV virus was discovered in 1983, and the first anti-HIV drug was approved in 1987. While early anti-HIV drugs provided a temporary improvement for the patients, the virus quickly developed resistance to the treatment, and many patients experienced a relapse of the disease. The major breakthrough that has shaped the HIV market until this day came in 1996. A combination
treatment of at least three drugs from two different drug classes was found to be more effective than a single drug, because different mechanisms of action are better at keeping the virus at bay, and even if the virus develops resistance to one drug the remaining two drugs will still be active (Gulick et al., 1997).

This landmark trial established the anti-HIV treatment template: the so-called two-drug “treatment backbone” plus the “third drug” (see Figure 2). Treatment backbone consists of two antiretroviral drugs belonging to a certain drug class (NRTI), while the third drug is chosen among several drug classes. For the sake of clarity and to avoid the use of medical jargon we will refer to the treatment “backbone” as the base component, and to the third drug as the add-on component. As of 2018 (the end of our sample) there were 8 base drugs and 23 add-on drugs that have been approved throughout 1997-2018, with another 11 base drugs and 34 add-on drug that made it to phase II clinical trials stage.

Therefore, an anti-HIV drug combination can be viewed as an ecosystem consisting of two components – base and add-on – displaying unique complementarities (Jacobides et al. 2018) as each component on its own is far less valuable than the combination. Furthermore, these complementarities are non-generic since a combination of drugs must be tested in a clinical trial to enable doctors to prescribe it (even if the constituent drugs have been approved). Given the number of possible combinations and the cost of trial firms have to be selective when choosing complementary drugs in their trials. Finally, while the firms can affect the “menu” of combinations available for prescription, it is ultimately the doctor and the patient who combine the complementary drugs, resulting in firm having limited control which is typical of an ecosystem as opposed to a supply chain or a hierarchy (Jacobides et al. 2018).

Focusing on the evolution of the anti-HIV treatment context since 1997 – right after the treatment template “base plus add-on” was established – over the years the base component exhibited

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4As of now there are five drug classes among which the third drug is selected: NNRTI (non-nucleoside reverse transcriptase inhibitors), PI (protease inhibitors), FI (fusion inhibitors) and EI (entry inhibitors), IN (integrase strand transfer inhibitors), and CCR5 antagonists. In earlier years an NRTI drug (the “backbone”) could also be selected, but in late 2000s this practice became rare. Combinations including PI drugs can also include a fourth drug acting as a booster for the efficacy of the main drug, however, we do not focus our attention on the booster drug as it can be considered an adjuvant drug rather than the main drug of interest in a combination.
significant variation in terms of constraint over the overall value creation and in terms of the number of options, making it the focal component of the bottleneck taxonomy matrix.

First, base drugs were historically more toxic compared to add-on drugs and had more severe side effects. Because anti-HIV treatment has to last for the whole patient lifetime base drugs toxicity presented a problem for patients’ adherence to treatment and quality of life. Base component can thus be considered as imposing a technical constraint as, on the one hand, it was an indispensable part of the treatment due to its high efficacy, but, on the other hand, it hindered the performance of the combination as a whole in terms of safety (because of higher toxicity) and, indirectly, efficacy (potential lower adherence to the treatment).

Second, base component displayed significant variance in terms of the number of competitive solutions, as opposed to the add-on component which didn’t see much variance in the number of firms or products. Taken together, these features allow us to explore different combinations of having technical constraint (base drug toxicity) and competitive scarcity (variance in the number of competitive solutions) corresponding to different quadrants of the theoretical matrix. We will now proceed to discuss our data, sample, and the measurement of the key theoretical constructs.

4 DATA AND METHODS

4.1 Data and Sample

We explore firms’ strategies in an ecosystem by examining the design of clinical trials on anti-HIV drugs conducted by the firms. Clinical trials are the key input to the medical guidelines recommendations, and as such they clearly shape the anti-HIV ecosystem by affecting the type and
number of combinations that are recommended. Clinical trials have traditionally been viewed as a strategic investment given the cost and the effort required. Taking into account the cost of trial and the number of potential combinations of anti-HIV drugs firms have to select the combinations that they believe would be most beneficial to them. We can therefore consider the choices of drugs to be tested in a clinical trial as firms’ strategic choices that have the chance to shape the ecosystem. We look at phase II and III trials as earlier phases focus on the safety of an individual drug rather than comparing its performance, in combination with other drugs, to that of its competitors. Because phase II and III trials examine drugs’ comparative performance versus extant solutions these trials are also the ones that can truly affect medical guidelines recommendations.

We use the database of the clinicaltrials.gov website provided by the US National Library of Medicine. The website was created in 1997, and was made public in early 2000. Clinical trial sponsors (firms, universities, research centers, hospitals, NGOs, etc.) submit information on clinical trials they intend to conduct to this website, and provide updated information until the study completion. While the website is US-based the firms and nonprofit actors typically publish their trials conducted in other countries as well.

We searched clinicaltrials.gov database for phase II, II/III and III trials with “HIV” as the condition, and cross-checked with National HIV Curriculum website from AETC that lists the key trials per each HIV drug. This resulted in 1348 phase II-III clinical trials, which we then manually checked in order to code the drug combination(s) that are being tested, and the key parameters of interest. Following this check we further removed the trials which were conducted in HIV-infected patients but focused on the treatment of HIV complications or associated diseases, trials focusing on specific patient demographic (such as pregnant women), and trials conducted by actors other than firms. We limited our sample to the trials that started after 1997, which is when the “base plus add-on” standard of treatment emerged. The final dataset contains 381 trials which corresponds to 552 trial-combinations as many trials had more than one treatment group.

Using each trial’s description provided by the database we identified the main drug of interest in the trial – the drug whose efficacy or safety is ostensibly being tested – and the complementary
drugs used in the combinations tested. Information in the trial descriptions allowed us to isolate the combinations tested in the treatment group(s) as opposed to control group combinations. Where the information was limited we supplemented the search by the publications related to the trial, or trial protocols available on the firms’ website. Many trials had more that one combination of interest being tested, and each combination was coded separately. We also used the information on the trial start date and trial sponsor (the firms that is the key decision maker in the trial).

This provided us, on the one hand, with a detailed data at the level of trial-combination, and, on the other hand, with a universe of relevant anti-HIV drugs in both components. We then collected the data to characterize these drugs using the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents in the US developed by the Department of Health and Human Services (DHHS). These guidelines are developed by medical experts based on the results of clinical trials, and are updated at least once a year to reflect the new scientific knowledge. The first guidelines came out in 1998, which closely matches the time when the base plus add-on template emerged. These guidelines, among other things, provide a list of recommended combinations of base drugs and add-on drugs, and further distinguish between preferred and second-best options, based on the current medical evidence. Informal interviews with medical specialists confirmed that these guidelines are quickly disseminated throughout the medical community, and guide doctors’ and patients’ choices. Using the guidelines, we determined the component where each drug belonged (base or add-on), and the relative standing of the drug within its component in each year of our sample.

Finally, we identify the owner firm for each drug for each year of our sample using AdisInsight database, supplemented by the information from trial publications, information on the web, and Drugs@FDA database to determine drug ownership history. Based on this information we could

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5DHHS guidelines are valid for the US, however, since they are based on clinical trials results we can view them as a proxy for the overall scientific knowledge available at the given time. The US is also the largest market for biopharmaceutical firms (often representing up to 50% of a drug’s revenue) which allows us to plausibly argue that firms are likely to take into account the combinations considered superior by the US doctors. We also checked WHO guidelines, however, those are mostly targeted towards developing countries and tend to feature older drug combinations which not frequently used in North America and Europe. We cross-checked DHSS guidelines with those by the French Ministry for Health (which feature a similar level of detail and are available since 2002), and we found them largely aligned.
reconstruct HIV drug portfolios for each trial sponsor in each year in our sample. This allowed us to code the key parameters of interest, which we describe in the next section.

4.2 Key parameters of interest

We examine three strategic choices which we measure in the following way:

*Direction of innovative effort:* we look at whether firms chose to invest in the base or in the add-on component. Using manually coded trial information we look at whether the focal drug of the trial belongs to the base or the add-on component.\(^6\)

*Challenging bottleneck:* in the anti-HIV drugs context circumventing the bottleneck involves firms testing combinations that do not feature drugs from the base component, instead using only add-on drugs. The problem with such combinations is the often insufficient efficacy of add-on drugs to keep the HIV virus at bay (recall that it was the high efficacy of base drugs that made them an indispensable part of the treatment and hereby a technical constraint); however, as more potent add-on drugs came to market there was hope for a successful combination without base drugs. Based on the information on each drug’s class we code “no-base” combinations.

*Developing exclusive complements:* we use two different measures. First, we look at whether base firms conducting a trial on an add-on drug tests it together with their own base drugs; and – using the information on drug ownership – whether it owns all drugs in a tested combination.

Second, we look at the use of integrated pills – pills containing several anti-HIV drugs. Originally the standard HIV drug combination comprised multiple pills, with a separate pill for each drug. This placed a significant burden on patients in terms of adherence and convenience. To make the administration of a drug cocktail more convenient firms started to develop single pills containing two or more drugs. The trend started with developing single pills containing both base drugs, and later firms started developing single pills containing all three drugs – base drugs and an add-on drug – in one pill. On the one hand, developing a single pill improves the convenience of drug administration to the patients and can have medical benefits in terms of improved adherence to

\(^6\)In some cases the trial was looking at combination as a whole rather than on a specific drug. In those cases we compared treatment and control groups to infer the variation and thus the most likely focal drug of the trial.
treatment. On the other hand, it can be viewed as a way to restrict access to one’s drugs and reduce the chances to create value by competitor and an ultimate form of exclusivity. We used the fact that trial protocols specify whether the drugs used in the trial are standalone pills or integrated into a single pill, and this information is available in the trial description in clinicaltrials.gov database.

Furthermore, as we are interested in the patterns of the firms’ behavior we explore firm heterogeneity in our sample. In particular, we look at two aspects: the focal component of the firm and the relative quality of the firm’s offering within the focal component.

*Firm’s focal component:* we code each trial sponsor as base or add-on firm using the information on drug portfolios. Historically, some of the firms who started in the base component eventually entered the add-on component, but firms who originally started in the add-on component did not enter base component. We thus code the firm as the base firm if in the year of the trial start it had at least one base drug in phase II or III development; otherwise we code the firm as a pure add-on firm.\(^7\)

*Relative quality of the firm’s offering within its focal component:* we use the information from the medical guidelines on the preferred and second-best drugs which we combine with the information on drug portfolios. Preferred drugs, as the name implies, are the drugs that have been shown to offer superior efficacy and/or safety based on reliable and sufficient scientific data from clinical trials. Drugs can be recommended as alternative options when the data is not considered sufficient (for instance, small-scale clinical trials as opposed to larger ones), or because they can nevertheless be a viable option for patients for whom preferred options are not compatible due to side effects. For instance, one of the preferred base drugs has significant side effects on kidneys, therefore patients with pre-existing kidney complications would use another drug despite the overall inferior efficacy-safety profile. This allows us, on the one hand, to have an objective measure of drug quality and, on the other hand, observe heterogeneity within each component (as opposed to winner-take-all market).

If at least one of the firm’s base drugs in the year prior to the trial start was included among

\(^7\)If a base firm discontinued the production of all of its base drugs and only kept producing add-on drugs (which happened to two firms in our sample) we changed the coding to a pure add-on firm.
preferred options in the medical guidelines, we code it as a high-base owner, while the base firms not having any of their products included in the preferred set are coded as low-base owners. Similarly, we split add-on only firms into high-add-on and low-add-on owners. We focus on the firm’s relative quality within its focal component, i.e., if a base firm developed an add-on that was included in the preferred options in the guidelines we still code it based on its position within the base component.

We will now examine how anti-HIV market evolution maps into the four quadrants of the bottleneck taxonomy matrix (Section 5), and then proceed to analyze the strategic choices of the firms in Section 6.

5 Trajectory of the Anti-HIV Drugs Ecosystem

We start by mapping the two dimensions of the theoretical matrix in the anti-HIV context to trace the context evolution trajectory across matrix quadrants. We will first briefly describe how we constructed the matrix dimensions in our context, and then proceed to describing the evolution of bottleneck states. We will outline the key events that happened in the base component relative to the extent of technical constraint and the set of competitive solutions, and the key players.

5.1 Measures of matrix dimensions

Our theoretical framework uses two dimensions to understand the existence and the type of bottlenecks in an ecosystem: the presence of a technical constraint and the number of competitive solutions. We map these two dimensions in the anti-HIV drug context, specifically, in the base component. To develop these measures we use the information from the HIV guidelines.

*Technical constraint*: base component has historically been the component with a higher toxicity which led to severe side effects that reduced patients’ quality of life and increased the possibility of not adhering to the treatment (which, in turn, can provoke the resurgence of the virus). Resolving this constraint would mean a discovery of bases with at least similar efficacy, but higher safety, devoid of the most debilitating side effects of the existing bases. In late 1990s - early 2000s sev-
eral new base drugs emerged promising better safety compared to existing drugs. The medical guidelines of October 2004 included the most promising of these new drugs – *tenofovir* – in the preferred options, simultaneously “demoting” some of the older drugs to alternative options only. The aforementioned *tenofovir* went on to become the major base drug as it kept consistently showing a better safety profile with a similar, or better, efficacy compared to other base drugs. We thus consider that before 2005 base component featured high extent of technical constraint, while starting from 2005 the technical constraint was largely resolved as a much safer drug became accepted as the standard of treatment. Our assertion is confirmed by the usage of the new base in clinical trials: pre-2005 clinical trials featured different bases, while after 2005 there is a steady trend of using *tenofovir* base.

*Number of competitive solutions*: we measure the number of competitive solutions as the number of bases recommended by the medical guidelines that were valid for the given year. The base consists of two drugs from a specific drug class (see Figure 2), which can be combined in different ways, and the medical guidelines provide a set of recommended ways to combine base drugs. To avoid confusion we will refer to “base drugs” when we talk about individual drugs, and to “base” when we talk about combinations of two base drugs. Given the importance of medical guidelines in the doctors’ prescribing behavior and the fact that they are based on the up-to-date scientific evidence we can reasonably assume that the recommended base options constitute a viable competitive set, while other possible combinations are far less likely to be used.⁸

In addition, one ought to consider the cases when base drugs became generic: while this doesn’t affect the number of possible bases in terms of the molecule, it clearly affects the number of firms competing in the market corresponding to the situation of property rights loss (Baldwin (2018)). In our context several base drugs lost patent protection in late 2000s, however, by the time it

⁸We look at the number of base drug *combinations* rather than counting individual base drugs because it gives a more accurate picture of mix-and-match opportunities available to the doctors. For instance, imagine a situation with two firms – A and B – each producing two base drugs. Compare a scenario where only firm A drugs taken together and firm B drugs taken together are recommended – meaning only two combinations available – versus a scenario where any combination of firms A and B drugs are recommended (meaning six possible combinations). While the number of recommended drugs stays the same across both scenarios – four drugs – the latter scenario allows to mix-and-match drugs while the former offers firms opportunities for exclusivity strategies.
happened they were not in a competitive set any more.\footnote{Based on our discussion with medical specialists, as there has been a lot of innovation in anti-HIV treatment and newer drugs usually had better safety and/or efficacy, the use of generic drugs in developed countries has largely been limited. Since the firms in our sample are based in North America or Europe, and derive most of their profits from these two regions, we can reasonably assume that if the drug in question is no longer recommended by the guidelines, its loss of patent protection would not change the composition of these firms’ competitive set.} One exception to this is the aforementioned tenofovir – the drug that resolved technical constraint on the base component and became one of the preferred base options – which lost patent protection in 2017, implying that post-2017 we can expect an increase in the number of competitive solutions.

5.2 Anti-HIV ecosystem evolution

Figure 3 maps the two dimensions of the matrix – technical constraint and the number of solutions in the competitive set – in the anti-HIV drugs context across years. The number of bases within the competitive set ranges from two bases at the minimum to eleven bases at the maximum, with the year 2005 serving as a watershed for the technical constraint resolution.\footnote{Comparing to the add-on component, there was little fluctuation in terms of recommended add-ons – the number generally varied between 7 and 9 over the years. There was a “spike” in the number of add-ons drugs in 2000-2002 due to some add-on drugs being recommended for use both with and without an adjuvant booster drug. This supports our assertion that base component should be the focus for the changes in bottleneck states.} Note that Figure 3 shows base number \textit{as of the prior year} to reflect the knowledge available to the firms and to allow us to compare it to firms’ trial activity. We can identify several periods in terms of constraint–competitive scarcity combinations, and see how the anti-HIV treatment ecosystem evolved across the matrix quadrants. At this point we merely document the evolution of base component, and its winner and losers, without examining firms’ strategies. Figure 4 provides a visual mapping of the key information about each period onto the bottleneck matrix.

\textit{Period 1: 1997-1999.} The ecosystem starts with having a technical constraint in the base component and a moderate number of competitive solutions, corresponding to quadrant I (or the border between quadrants I and II). This is the period right after the template of “base plus add-on” emerged, with older, toxic bases available. There are three major incumbents in the base components: GlaxoSmithKline (we will refer to the firm as GSK/ViiV as in 2009 GSK transferred its anti-HIV assets to ViiV Healthcare, a joint venture where GSK owned a majority stake), Bristol-Myers Squibb (BMS for short), and Roche.
Period 2: 2000-2004. The number of bases within the competitive set increases as several new bases were launched in the market and included in the recommended set – but the preferred set is still formed by the older bases, and the technical constraint still unresolved. Notably, a new firm – Gilead Sciences (Gilead for short) – enters with its base drugs, one of which is a future winner.

Period 3: 2005-2007. The technical constraint can be considered as resolved due to the sufficient evidence around the new bases, reflected by their inclusion in the preferred set. This is also a period of the highest number of competitive bases, with eleven solutions possible, up from the six in the previous period. The key driver of this abrupt increase in the competitive base number is the mix-and-match possibilities among base drugs. Recall that the base consists, in fact, of two base drugs. By this time a distinction emerges between a primary (which is the most potent) and a secondary base drug, simplifying the mix-and-match possibilities. Inclusion of Gilead’s new secondary drug into the recommended set virtually doubled viable base solutions as most primary base drugs were compatible.

Period 4: 2008-2010. The number of base solutions drops dramatically, thus starting the era of the coveted matrix quadrant: technical constraint resolved while competition is scarce. The drop in base solutions is driven by two reasons. First, some of the older base drugs are no longer
recommended due to high toxicity and overall inferiority to the new base drugs. Second, mix-and-match opportunities become curtailed by the widespread adoption of integrated pills – pills containing both base drugs, which offered higher convenience to the patients. In this period the guidelines started to recommend the use of integrated pills, rather than separate one, in a way to improve patients’ adherence to treatment. This, in turn, limited the number of viable competitive solutions because an integrated base pill has to include both a primary and a secondary drug, and firms tended to develop an integrated pills only with its own base drugs, and not with another firm’s drugs. Only two firms – Gilead and GSK/ViiV – had both drugs in their respective portfolios, and developed integrated pills, while the third incumbent – BMS – still had to mix-and-match.

Period 5: 2011 (2013) - 2016. The number of competitive bases further decreases. By 2011 there are only three recommended base options: two by GSK/ViiV and one by Gilead, while bases belonging to BMS are no longer in the recommended set. Furthermore, only one base – by Gilead, containing the aforementioned tenofovir – is the preferred option, while GSK/ViiV bases are the alternative ones. Starting from 2013 this further reduces to only two bases in the competitive set – preferred one by Gilead, and alternative by GSK/ViiV. This period approximates the coveted “strategic bottleneck” case (Baldwin, 2018) as there is a a leading solution (Gilead’s tenofovir as the strategic bottleneck) and a partial substitute from GSK/ViiV’s.11

Period 6: 2017-2018. We distinguish the last couple of years as a separate period as the patent on the winning tenofovir base expired in 2017, which should spur generic drugs entry and increase competition in the base component shifting the ecosystem back into quadrant III. In addition, the base of GSK/ViiV was once again included in the preferred set, when it was used in combination with its highly potent add-on, and thus became a closer substitute of the leading solution. Yet, as we will show later, Gilead adopted a number of strategies that helped it maintain the ecosystem in quadrant IV.

11By this point older base drugs have lost patent protection, however, since they are no longer recommended (and most of them are explicitly outlined as inferior in the guidelines) this does not truly affect competitive situation in developed countries. Because pharmaceutical companies derive an overwhelming majority of their revenues from the latter as opposed to developing countries we do not consider the launch of generic versions of the older base drugs as increasing competitive variety.
We further checked whether this evolution – based on the medical guidelines recommendations which we expect to be an accurate reflection of the scientific knowledge available during the period – is reflected in the actual use of bases in clinical trials. In Appendix A we looked at the distribution of bases used in the add-on trials for each year, and it was well-aligned with the guidelines.

To summarize, we observe several distinct periods with respect to the technical constraint in the base component, and the number of competitive base solutions, summarized in Figure 4. The anti-HIV ecosystem starts with having a technical constraint in the base component and a moderate number of competitive solutions, which increases over time. As more base solutions become available the ecosystem shifts to high number - no technical constraint scenario (quadrant III). This is a scenario that presents few opportunities for the firms to capture a higher share of value (Baldwin, 2018). Then, the ecosystem starts to shift towards resolved constraint - low competitive variety (quadrant IV), eventually ending with one leading base and its imperfect substitute – the situation which provides an opportunity to create a strategic bottleneck. There is, however, a looming threat of swinging back to quadrant III due to the loss of property rights (patent expiry) on the leading base.

The implication is that the evolution of bottleneck might be more complicated than what we could infer from the extant literature, and there appears to be a lot of action once technical constraint is resolved: there can be a lot of fluidity between quadrants III and IV, which has direct implications on the firms’ ability to capture value. Furthermore, the patterns that we observe also hint that the evolution of bottlenecks might be shaped by both exogenous (such as a discovery of a better drug) and endogenous factors (for instance, leveraging portfolio, or strategically timing innovative effort). We will now explore how firms strategized to build the strategic bottleneck, solidify, and challenge the existing bottleneck within the ecosystem.

6 FIRM STRATEGIES TO SHAPE ECOSYSTEM TRAJECTORY

In this section we will examine how firms’ strategies in an ecosystem are determined by the state of bottleneck and by their competitive positioning within their component. We will also see how
these strategies, in turn, affect the evolution of bottlenecks. We focus on three key strategies that firms employed: direction of innovative effort (base vs. add-on component), challenging existing bottleneck strategies (exploring combinations eschewing base), and exclusivity strategies (unique bundles with one’s own base). We primarily focus on the actions of base component firms, although we do provide a comparative view on what add-on firms did. For each of the strategies we will start with presenting the evidence of firms’ actions over the time periods identified in the previous section, then proceed with our interpretation of the patterns observed and the implications for the ecosystem literature. We will conclude the section with regression analysis testing the key insights from the exploratory analysis.

6.1 **Direction of innovative effort – entry into complementary component**

First, we examine how the focus of the firms’ innovative effort changed as the ecosystem evolved across the matrix quadrants. Specifically, we explore how the innovative effort shifted between the base and the add-on component.
Figure 5 shows the number of trial-combinations in each year depending on whether the trial focused on a base or an add-on drug, by firm type. The top left panel (Figure 5a) shows the split between base and add-on trials for base firms owning high-quality bases, while the top right panel (Figure 5b) shows the trial of base firms who do not. Among the latter we further distinguish between incumbents – firms having at least one base drug authorized for use in the market – and new entrants that have no authorized drug. This allows us to compare the behavior of “demoted” firms (incumbents) versus those aspiring to establish their position in the market. The two bottom panels replicate the analysis for pure add-on firms to ensure consistency.

Focusing on base firms, we see that in the earlier period a significant portion of trials focused on base drugs, driven by both incumbent high-quality base owners (Figure 5a) and new entrants (Figure 5b). The goals of the trials are, however, slightly different: incumbents are mainly trying to prove their bases versus incumbent competitors, while new entrants are trying to develop new bases (most of these trials are by the future leader Gilead who at the time had no authorized anti-HIV drugs and was a new entrant).

As the ecosystem shifts closer towards resolving the bottleneck (years 2000-2004) and features increased competition we start seeing more divergence between the incumbents and new entrants. While new entrants are still conducting trials in the base component in the quest to find a better base, incumbents – especially those owning superior bases – start to shift their efforts towards the add-on component and develop add-on drugs (for instance, Bristol-Myers Squibb, or BMS, had two drugs in late-stage clinical development, and GSK/ViiV had three during this period).

When the owners of superior bases conduct a base trial they focus on establishing their existing bases, in particular by conducting trials on integrated base pills. Recall that a base, in fact, contains two drugs. An integrated base pill includes both of these drugs instead of having two separate pills. GSK/ViiV was the first to develop two integrated pills combining each of its two primary base drugs with its secondary drug. Gilead followed suit integrating the future bottleneck base

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12 We look at the number of trial-combinations to account for the trial size and intentions. We repeated the analysis at the trial level and found similar results.
13 Clinical trial protocols have to specify whether the clinical trial uses separate drugs or an integrated drug, which allowed us to identify such trials.
tenofovir with its secondary drug, while add-on producers increasingly started to adopt integrated base pills in lieu of two separate ones.

As the technical constraint gets resolved (post-2005), the shift of base incumbents towards the add-on component becomes even more pronounced: during 2005-2010 there are only a couple of base-focused trials that were conducted by the incumbent firms (and these were the trials on the existing drugs in a specific patient population – children and adolescents – rather than developing a new base). New entrants are still trying to keep on searching for the new base, but by period 4 (2008-2010) these efforts are ceased as a clear winner – Gilead’s tenofovir – has emerged.

Starting from period 4, when the technical constraint is resolved and the competitive set starts shrinking, with only two firms – Gilead and GSK/ViiV – having bases that are a part of the preferred set, it is clear that base firms shift their efforts to the add-on component. As Gilead’s bottleneck becomes more entrenched (moving into period 5) we once again see a divergence between the owners of superior bases and inferior bases. While losing base firms are highly active in the
add-on component the winning base owner – Gilead – while also doing add-on trials directs a lot of effort into base trials once again (Figure 5a). These trials involve a new version of Gilead’s tenofovir which has a somewhat better efficacy and, importantly, much better safety profile.

**How do we interpret these patterns?**

On the one hand, the pattern in the years preceding 2011 seems overall consistent with the idea of value creation bottleneck: firms first attempt to resolve it, but once it is resolved the innovative effort shifts to another component (e.g., Ethiraj, 2007; Hannah and Eisenhardt, 2018), which is what we see happening once tenofovir “won the battle”. On the other hand, this pattern is mainly exhibited by the firms lacking a superior base, while the owners of superior bases appear to be focused less on finding solution to the constraint and more on improving their competitive positions. Importantly, some of these strategies – such as the development of integrated pills – appear to be aimed at keeping competitive set more limited.

Recall the sharp increase and later abrupt drop in the number of competitive base solutions (Figure 3). One of the key reasons for the reduction in mix-and-match opportunities was the existence of integrated base pills. Medical guidelines of 2004 suggested that such pills might simplify the treatment regimen for patients, while at the end of 2006 the guidelines suggest that integrated pills help improve treatment adherence, and from that point onwards explicitly list integrated pills, where available, in the recommended list.\(^1\)

Another noteworthy consequence of integrated pills development is that this leaves the third major base producer, BMS, who does not own a secondary drug, unable to mimic its two rivals. In 2010 the bases owned by BMS were no longer in the competitive set, and in in 2012 they were explicitly outlined as not recommended. While these drugs had problems in terms of side effects, one may speculate whether the inability to have an integrated pill contributed to BMS struggle. For instance, in the years before 2010 its newer, potentially more promising, base was always listed among the alternative, not preferred, options due to the insufficient data. Seeing that both base and add-on producers started to increasingly adopt integrated pills in the clinical trials since 2004, we

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\(^{14}\) As these guidelines were released late in 2006 we assume that firms did not have enough time to react to them before January 2007, and thus consider these guidelines from the year 2008.
may speculate that the inability to create an integrated pill with a secondary drug might have been a contributing factor to the reluctance of add-on producers to use it in their trials. Overall, this illustrates how firms’ strategies can shape the bottleneck state of the ecosystem and highlights how strong incumbents may leverage their portfolios to reduce competition.

Once a strategic bottleneck has emerged (post-2011) we see that losing base firms fully switch to the add-on component. Our interpretation is that since it is clear that the winning base cannot be unseated, the options are either to exit the market altogether (which smaller firms did) or to re-focus on complementary component (where they already had a foot). By contrast, the winning firm maintains a balance between the efforts in the add-on and base components, which runs contrary to the typical prediction that firms invest to resolve the constraint. We interpret the winner’s motivation as, on the one hand, the opportunity to leverage its dominant position in the base component by entering add-on component (similarly to how platforms sometimes leverage their position to promote in-house complements). On the other hand, the winner still needs to maintain its bottleneck, for instance, to protect it from the looming threat of property rights loss (in this context, patent expiry).

There is some anecdotal evidence to support our interpretation of the winner maintaining the bottleneck. Several lawsuits from patient associations accused Gilead of purposefully delaying the development of a potentially better base drug (which was launched in 2015) in order to capture value with its tenofovir-related combinations, and to match the eventual expiration of tenofovir patent in 2017.\textsuperscript{15, 16} The lawsuits cited the fact that Gilead had a newer version of its original base in development back in early 2000s, but in 2005 the firm notified the regulators of suspending its clinical development, and resumed it only in 2010 when it finally applied for patent. While it is difficult to gauge the factors behind Gilead’s timing to develop a newer version of its winning base, the evidence suggests that even after the technical constraint resolution firms may have incentives to invest in the component to maintain the bottleneck and protect against property rights erosion.

\textsuperscript{15}Rowland C. December 5, 2019. Gilead delayed safer HIV drug to extend monopoly profits, advocates allege. \textit{Washington Post}.
\textsuperscript{16}Sagonowsky E. May 14, 2019. Gilead tries—and fails—to dodge lawsuit claiming it delayed safer HIV meds | FiercePharma. \textit{FiercePharma}.
What does this tell us about ecosystem evolution?

From this we can gain two theoretical insights. First, while the extant literature views innovative effort mainly as a function of the technical constraint existence, our findings underscore the importance of taking value capture considerations in concert with value creation ones: following value creation view there is no need to invest in the component once the technical constraints is resolved, however, the investment can be key to maintaining the strategic bottleneck. Second, innovative effort also depends on the relative standing of the firm’s product within the component as our findings show divergence between the firms who own a high-quality base and those who do not: for instance, even when technical constraint is present the former are more focused on improving their positions and venturing into complementary component whereas the latter are searching how to resolve the constraint.

6.2 Strategies to challenge the bottleneck: combinations without base

Out of 552 trial-combinations in our sample there were 102 combinations that did not include base.\(^\text{17}\) Figure 3 maps trial-combinations that do not contain base over time distinguishing between firm types, in a manner similar to Figure 5. It shows that there were two waves of search for no-base combinations, which were led by different type of firms. The first wave occurred at the peak of the number of competitive bases in 2005-2009 (ecosystem in quadrant III) and was primarily led by add-on producers, both incumbents and new entrants. Base owners were not much involved in this wave – what we see as significant activity in 2008 is, in fact, a single outlier trial conducted by Gilead which tested 15 different combinations of its new add-on drug with other add-ons.

The second wave started in 2012, when the ecosystem was in quadrant IV with Gilead owning the strategic bottleneck. Unlike the first wave this one is led by new entrants into add-on component and losing base incumbents. The latter are particularly active as they account for more than 50% of no-base trials. Particularly prominent are the trials by GSK/ViiV whose bases were “demoted”

\(^\text{17}\)Based on our conversations with medical specialists we included combinations with secondary base drugs, but not primary base drugs, in this category as well. The reason is that it is primary base drugs that have higher toxicity and present a problem, while secondary base drugs are well tolerated, and it is the efficacy of primary base drugs that makes them indispensable in the first place. Including combinations with secondary base drugs results in only 8 more trial-combinations, and does not change temporal patterns.
to alternative options by the guidelines of November 2008. To date GSK/ViiV has launched three no-base combinations pills. Two of them combine an add-on by GSK/ViiV with another add-on drug by Janssen, and one combines two GSK/ViiV drugs. The most recent medical guidelines now include the latter in the preferred options for the HIV treatment start, and also recommend two of the three combinations as the preferred options for patients who want to switch.

While the first wave seems to be equal, if not larger, than the second wave, the importance of no-base combinations appears to increase as the ecosystem shifts into quadrant IV. Looking closely at the trials, in the period with high number of bases the trials featuring no-base combination were much smaller in size compared to their counterparts in the scarcity period: 94 patients enrolled vs. 261 patients enrolled, the difference is statistically significant (by contrast, the difference is much smaller when comparing standard trials – it is 268 vs. 332 patients). The implication is that when the competitive base solutions are more numerous, there is search for shifting the bottleneck, but this search efforts become much stronger when the strategic bottleneck emerges.
How do we interpret this?

The marginal interest of high-quality base owners during the period with many base solutions could be explained by such combinations being only partial substitutes (trials in patients who are already pre-treated and might have severe side effects as opposed to trials in first-time patients), and leveraging one’s portfolio when it is not clear whether a strategic bottleneck is possible (we are in quadrant III of the matrix). Naturally, once a strategic bottleneck is established, the winner has incentives to maintain this bottleneck, not circumvent it.

What is particularly interesting is that losing base firms become the key players in the no-base trials, even more so than pure add-on producers. One interpretation could be that by the virtue of losing in the base component they have to switch to the add-on component, and they have high incentives to develop high-quality add-ons as otherwise they will not be able to capture value. This, in turn, may lead them to develop such good add-ons that they no longer require a base.

The implication is that having a strategic bottleneck, can backfire as the losing firms have high incentives (and since they are incumbents they also have capabilities) to make the bottleneck irrelevant. In our context, while GSK/ViiV no-base combinations’ sales are currently far below those of the latest combinations by Gilead (0.4 bn USD vs. 4.7 bn USD in 2019) the former are, nevertheless, considered to pose a serious threat to Gilead’s dominance, in particular as the results of the ongoing trials appear promising. For instance, the newly approved GSK/ViiV drug requires once-a-month instead of once-a-day intake, which is an attractive option for patients in terms of scheduling and protecting their privacy.

Another interesting pattern is that add-on incumbents do not seek to venture into no-base combinations once the strategic bottleneck emerges, even though one could plausibly argue that their incentives should be similar to those of losing base firms. Our interpretation is that the winning base owner keeps on collaborating with add-on producers (even while developing its own add-ons), enabling them to continue capturing value and upholding status quo, while losing base firms may suffer from the “dethronement effect” (Ferrier, Smith, and Grimm, 1999). Alternatively, this could be explained by add-on producers free-riding on base firms’ efforts. Losing base firms, who may
not be well-established in the add-on component have, at the margin, higher incentives to circumvent the strategic bottleneck. Since a no-base combination still require another add-on they are willing to use the add-ons of the successful add-on incumbents, but due to higher incentives they are willing to bear the cost of effort.

**What does this tell us about ecosystem evolution?**

The extant literature generally takes the ecosystem structure as exogenously given: value capture view focuses on value split given the existing ecosystem structure, and value creation literature, while while recognizing and examining the changes in ecosystem structure, still treats these changes mainly as a consequence of exogenous technological shocks. Our analysis suggests that shifts of bottleneck to another component can be due to both exogenous technological shocks and endogenous factors, such as firms strategizing to circumvent the bottleneck. Specifically, our findings suggest that it is the losing firms from the bottleneck component who could be best positioned and motivated to challenge the strategic bottleneck.

### 6.3 Exclusivity strategies by bundling with one’s own base

Being present in both base and add-on component gives firms an opportunity to bundle the newly developed add-on drugs to their own base. We explore two types of exclusivity strategies: bundling via an exclusive trial and bundling via an integrated pill.

#### 6.3.1 Exclusivity strategies: bundling via trial

One way of bundling could be for a base firm to conduct add-on trials with its own bases. Recall that a combination must be tested in a clinical trial to be on the prescription “menu” and to have an opportunity to be included in the medical guidelines. Testing add-ons exclusively with one’s own base might help the firm to prop its base. While other firms may still later test the add-on in question with their bases the firm owning both components of the treatment has an opportunity to create a larger body of clinical evidence at an earlier point in time and, potentially, to establish a larger base of prescribers.

We thus examine whether base firms gave preference to their own bases when doing trials
on add-on drugs. Figure 4 shows the relative engagement of base firms in bundling depending on whether a firm owns a high-quality base (blue-colored bars) or does not (red-colored bars). Specifically, (1) the light-colored bars show the total add-on trials (trial-combinations) by year, (2) the darker bars show how many out of these are trial-combinations where firms bundled with their own base, and, finally, (3) the darkest-colored bars show how many of the latter are the cases where the firm owns all drugs in a tested combination.\textsuperscript{18} The main difference between (2) and (3) is that a base firm might test an add-on that it doesn’t own (for instance, it wants to show that a certain add-on works well with its base); also a base firm may use one base drugs of its own combined with a second base drug own by a different company (for instance, BMS did not have a secondary base drug, and post-2005 would have to use the one owned either by GSK/ViiV or by Gilead).

Two key observations stand out. The first one is related to the timing. We can see that there were two waves when firms tried to bundle: the earliest period, when technical constraint was not resolved (quadrant I, and to some extent II, of the matrix), and then the later period, when technical constraint was resolved and competitive variety was being reduced (quadrant IV of the matrix). Overall, it appears that firms tend to bundle more when there are fewer competitive solutions available.

The second observation is related to the type of the actor who engages in bundling. Figure 4 shows that it is mostly the owners of high-quality bases who engage in bundling. In the second wave (quadrant IV) while losing firms in the base component do engage in bundling, they do so to a far lesser extent compared to the winning firm. This is supported by our additional analysis when we checked whether the firm used its own bases for \textit{all} combinations in a given trial – a more stringent test. We had very similar results, except for the losing base firms in the second wave – who tend to conduct trials of its add-on drugs with both their own base and the winning base – while for the winning firms the results were virtually the same. We further checked for the presence of a general trend towards bundling with certain bases by looking at whether add-on

\textsuperscript{18}The analysis of bundling is at trial-combination level, which means that the firm might still test other combination in the same trial with a different base. We conducted a more stringent test – whether all focal combinations tested in a given trial featured firm’s own base(s). The results were very similar, the only slight difference occurred in the years 2010-2012 for the firms not owning the superior base, which we discuss later in the section.
producers tended to bundle with a unique base. Appendix B provides the details. We found that while add-on producers do appear to shift more to using only the winning Gilead’s *tenofovir* base in their trials, they still conduct a fair share of multi-base trials, in a stark contrast with the behavior of the winner Gilead who at some point conducted all of its trials uniquely with its own bases.

6.3.2 *Exclusivity strategies: bundling via integrated pills*

Conducting trials with one’s own base is an indicator of exclusivity strategies, yet it still allows other firms to do their own trials and combine the add-ons with other bases. This opportunity disappears if the firm develops an add-on as a part of a single pill with its base. If there is no standalone add-on pill available then the firm can develop a truly exclusive bundle with its own base and preclude other firms from using that add-on in combination with another base.

The first such pill was launched in 2006, and starting from 2009 – when Gilead was firmly established as the bottleneck base owner – such integrated pills became more and more common as they provided even higher convenience and supported patient adherence. We have 45 trial-
combinations out of the total 552 in our sample using these pills. This trend is primarily driven by the winning base firm Gilead who after the first successful integrated pill collaboration worked on other integrated pills developing its fully-owned combinations as well as collaborating with add-on firms (Gilead’s trials represent around 80% of the effort on the integrated pills). The losing base incumbent – GSK/ViiV – who at this point has fully switched to the add-on component – was less active in this regard, though it did develop a few integrated pills of its own. Add-on producers also appear less active, with a handful of trials conducted by Janssen (as a part of the collaboration with Gilead), and Merck who, anticipating patent expiry of the bottleneck base in 2017 sought to develop an integrated pill with its add-on.

**How do we interpret this?**

Our analysis suggests that firms owning high-quality bases tended to pursue exclusivity through bundling in the periods of competitive scarcity, and especially once the strategic bottleneck emerged. We interpret the initial wave of bundling through trials as base firms trying to leverage complementary component to establish their position. However, with the arrival of newer bases in 2000s and the eventual increase in base solutions variety it may not have been clear which base will end up being a better one, and it could have been risky to tie an add-on to one’s own base, which is why we see a significant increase in bundling post-2008, when the ecosystem shifted to quadrant IV.

What is particularly interesting is how actively the winning base firm Gilead pursued the development of exclusive complements, especially through the development of integrated pills without standalone options, once its base became a strategic bottleneck. One explanation is that Gilead sought to leverage its leading position in the base component. Another explanation is that developing add-ons exclusively available with Gilead’s drugs allowed it to prolong its *de facto* property rights over the strategic bottleneck. Recall that the patent on Gilead’s winning base *tenofovir* was expected to expire in 2017. New integrated pills meant new patents with further expiry dates, and since by this point patients developed a preference for integrated pills the implication was that they may be less likely to switch to a generic version of Gilead’s base which will entail taking two separate pills. Furthermore, as Gilead’s add-on drugs were developed *only* as a part of an integrated
pill this meant even they would not be available for use with another base even if patients agreed to use separate pills. In other words, developing integrated pills allowed Gilead to maintain quasi-property rights over its winning base and prevent the ecosystem from shifting to quadrant III, away from strategic bottleneck.

**What do we learn about ecosystem evolution?**

The key insight is that firm’s presence in both the focal and complementary components, and making complements exclusive to its focal product allows to protect against property rights erosion. As long as the bundle is exclusive the firm needs only maintain strong property rights over one part of the bundle. In case of Gilead, developing add-ons available only as a part of an integrated pill with Gilead’s own bottleneck base bestowed quasi-property rights over the bottleneck even after the patent expiry. Developing exclusive bundles can be seen as a way to create inter-temporal property rights. The latter are conditional, though on the firm having high-quality products in both components.

The implication is that the entry into complementary component may not only be a way to leverage a firm’s bottleneck position in the new component (Gawer and Henderson, 2007; Zhu and Liu, 2018), but also a way to maintain and reinforce the bottleneck position, and prevent the ecosystem from shifting to a state with more competitive solutions. It can also be a way to survive the migration of a bottleneck to another component while still keeping a strong position.

7 **Regression analysis**

Informed by the insights in the previous section, we test the heterogeneity in firms’ strategies based on the firm type in a regression analysis. We use three dependent variables, one for each strategic choice. For *direction of innovative effort* we use *AddonTrial* equal to 1 if the focal drug of the trial is add-on, and 0 otherwise. For *challenging bottleneck* we use *NoBaseCombo* equal to 1 if the trial-combination does not feature base drugs. For *exclusive complements* we use *UniqueBase* equal to 1 if the trial only uses base drugs belonging to one base firm. This allows us to use add-on producers as a baseline category, rather than comparing base producers only. Since it is highly
unlikely that a base firm will test its add-on uniquely with another base firm’s drugs we believe that this variable reflects well firms’ exclusivity strategies. For UniqueBase we limit the sample to add-on trials only to avoid the bias when the focus of the trial is a base drug.

The two key independent variables are High-Base Owner and Low-Base Owner, with pure add-on producers as the baseline category. We control for the firm having a high-quality add-on, conducting trial on first-time treated patients, and for all drugs of the combination being launched in the market. The level of analysis is trial-combination. We use logistic regression, weighting observations by the number of combinations per trial to account for multi-combination trials, with errors clustered at trial sponsor level. We do a logistic regression for each quadrant of the bottleneck matrix, and we further refine the analysis of the last quadrant by looking at how firms’ behavior changed as Gilead’s strategic bottleneck becomes more established (post-2011 and post-2013). Given space limitations a detailed description of the variables and the results of logistic regressions are relegated to Appendix C, while here we focus on average marginal effects.

Table 1 shows average marginal effects of the key variables of interest on each of the three dependent variables across the periods. The first row indicates the state of bottleneck in each period as to the level of technical constraint and competitive scarcity. The top panel provides average marginal effects on the likelihood of conducting a trial on an add-on drug as opposed to a base drug. Initially, base owners are more likely to do a base trial rather than an add-on trial. As the ecosystem moves into the state with more competitive solutions base firms without a superior base are highly unlikely to do an add-on trial, whereas the owners of superior bases become more similar in that regard to pure add-on producers (average ME goes from $-0.3$ to $-0.16$, and loses significance). As competition grows scarce the situation is flipped as the owners of superior bases are more likely to do a base trial rather than add-on (average ME is back at $-0.3$). Owners of inferior bases become more similar to add-on producers as we get into the “scarcest” competitive situation: we can see the negative marginal effect becoming smaller and losing significance, in the post-2013 time period average ME is up to $-0.14$, and not significantly different from zero. These

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19 High standard errors for low-base owners are mostly due to a small number of trials conducted.
results confirm our insights that firms owning superior bases enter complementary component even before the technical constraint is resolved, but later invests again in the former constraint component to maintain its position, whereas firms owning inferior bases switch to complementary component.

The middle panel shows the results of the same analysis with *NoBaseCombo* as the dependent variable. Because there were very few trials on combinations without base before 2005 we combine the two earlier periods together (first column). In earlier periods base firms are similarly unwilling to explore no-base combination. Once the technical constraint is resolved base firms with superior bases are clearly not interested in pursuing such combinations (average ME increases to $-0.21$, and in later periods high-base ownership perfectly predicts failure to develop no-base combinations) while low-base owners and pure add-on producers appear to have a similar likelihood of pursuing such combinations. In later period (post-2013) we see that firms with inferior bases become the most likely to explore no-base combinations. In fact, comparing pre-2013 and post-2013 sub-periods we see that pre-2013 having high-quality add-on appeared to best explain the likelihood of exploring a no-base combination, but post-2013, even accounting for the ownership of high-quality add-ons, the firms with inferior bases are more likely that add-on producers to explore no-base combinations (average ME of $0.23$). This confirms our insights that as strategic bottleneck becomes more established it is the losing firms in the bottleneck component that are most likely to attempt shifting it to a different component.

The last panel of Table 1 shows the results for *UniqueBase* dependent variable. It confirms our intuition that when competition is scarce firms are more likely to pursue exclusivity. As we go into later periods the increasing average marginal effect of high-base ownership (from $0.2$ to $0.5$) confirms our insights about firms with superior bases developing exclusive complements. Firms without superior base drugs are generally not keen on developing exclusive complements, but given that they started to conduct add-on trials only in the later period, we should focus on what happens once we are in low technical constraint – scarce competition period. We see that initially

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20Large standard errors for high-base owners are likely due to the fact that they have few trials on add-on drugs in that period.
they were also pursuing exclusivity, albeit to a much lesser degree than superior base owners, but post-2013 the average marginal effect flips to negative (−.26), which is in line with our insights that they “gave up” on trying to prop their base with exclusive add-ons.

Table 1: Average Marginal Effects of base firm types (standard errors in parentheses)

<table>
<thead>
<tr>
<th>Technical constraint</th>
<th>High</th>
<th>High</th>
<th>Low</th>
<th>Low</th>
<th>Low</th>
<th>Low</th>
<th>Low</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competitive solutions</td>
<td>Scarce</td>
<td>Many</td>
<td>Scarce</td>
<td>Many</td>
<td>Scarce</td>
<td>Many</td>
<td>Scarce</td>
<td>Many</td>
</tr>
<tr>
<td>Post-2011</td>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Post-2013</td>
<td></td>
<td></td>
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<tr>
<td>DV=Add-onTrial</td>
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<td></td>
</tr>
<tr>
<td>High-Base Owner</td>
<td>−0.31</td>
<td>−0.16</td>
<td>−0.11</td>
<td>−0.3</td>
<td>−0.33</td>
<td>−0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Base Owner</td>
<td>−0.21</td>
<td>−0.49</td>
<td>−0.65</td>
<td>−0.32</td>
<td>−0.24</td>
<td>−0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DV=NoBaseCombo</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-Base Owner</td>
<td>−0.09</td>
<td>−0.21</td>
<td>−0.28</td>
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<td></td>
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<td></td>
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<tr>
<td>Low-Base Owner</td>
<td>−0.14</td>
<td>−0.008</td>
<td>0.081</td>
<td>0.01</td>
<td>0.23</td>
<td>−0.09</td>
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<tr>
<td>High-Add-on Owner</td>
<td>0.005</td>
<td>−0.01</td>
<td>0.2</td>
<td>0.12</td>
<td>0.06</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DV=UniqueBundle</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>High-Base Owner</td>
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<td>0.03</td>
<td>0.22</td>
<td>0.42</td>
<td>0.5</td>
<td>0.47</td>
<td>0.38</td>
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</tr>
<tr>
<td>Low-Base Owner</td>
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<td>0.04</td>
<td>−0.12</td>
<td>−0.005</td>
<td>−0.04</td>
<td>−0.26</td>
<td>0.18</td>
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<tr>
<td>High-Add-on Owner</td>
<td>0.37</td>
<td>−0.11</td>
<td>0.09</td>
<td>0.1</td>
<td>0.2</td>
<td>0.31</td>
<td>−0.27</td>
<td></td>
</tr>
</tbody>
</table>

(1) We omit pre-2013 analysis for Add-onTrial dependent variable as convergence could not be achieved
(2) Variable omitted because HighQualityBasedOwner=1 predicted failure perfectly

8 DISCUSSION AND CONCLUSIONS

In this paper we develop a taxonomy of bottleneck types that allows to incorporate and reconcile value creation and value capture perspectives on ecosystem bottlenecks. We use two dimensions – the degree of technical constraint on value creation and the scarcity of competitive alternatives – to trace the evolution of bottlenecks in the anti-HIV drug industry and its interactions with firm strategies. Specifically, we examined how three types of ecosystem-level strategies – the focus of innovative effort, challenging existing bottlenecks, and exclusivity – depend on the state on the
ecosystem bottleneck. Figure 8 provides a visual summary by mapping the key insights related to each strategy on the bottleneck taxonomy matrix. The key insights from our analysis are that firms’ ecosystem strategies are contingent on both dimensions, and depend on the firm’s relative standing within its focal component. Figure 9 summarizes the key insights in the form of propositions.

Our first contribution to the literature on ecosystems is a comprehensive bottleneck taxonomy that helps bridge the gap between value creation (Adner and Kapoor, 2010; Ethiraj, 2007; Kapoor, 2018) and value capture (Jacobides et al., 2016; Jacobides and Tae, 2015) view of the bottlenecks. Our findings from the empirical context show that we need to distinguish between the two dimensions underpinning the bottleneck definition in each literature as different combinations of these dimensions lead to different strategies adopted by the firms. This underscores the importance of explicitly recognizing value creation and value capture incentives as separate mechanisms that drive firms’ strategies in an ecosystem (Chatain and Plaksenkova, 2020). For instance, while the extant literature predicts that firms will seek to resolve the technical constraint that the component imposes on an ecosystem our findings show that it depends on the competition in the focal compo-
Figure 9: Summary of propositions

<table>
<thead>
<tr>
<th>Technical constraint</th>
<th>Number of solutions</th>
<th>Direction of innovative effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Scarce</td>
<td>Superior firms are slightly more likely to develop complements exclusive to their focal product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Firms unlikely to invest in complementary component, especially superior firms</td>
</tr>
<tr>
<td>Yes</td>
<td>Many</td>
<td>Superior firms either invest to maintain their existing solutions to constraint or invest in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>complementary component</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior firms invest to find new solutions to constraint</td>
</tr>
<tr>
<td>No</td>
<td>Many</td>
<td>Superior firms are more likely to develop complements exclusive to their focal product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Firms in both focal and complementary components are not likely to develop exclusive complements</td>
</tr>
<tr>
<td>No</td>
<td>Scarce</td>
<td>Superior firms invest both in the complementary component and in the new solutions to the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>former constraint</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior firms invest in complementary component</td>
</tr>
</tbody>
</table>

A second contribution lies in unpacking how within-component firm heterogeneity affects firms’ reactions to the bottleneck evolution. The extant literature has generally explored heterogeneity at the component level. Value capture literature explicitly focuses on the role of between-component heterogeneity and how it affects value appropriation (e.g., Jacobides and MacDuffie, 2013; Jacobides and Tae, 2015). Value creation literature, while often looking at individual firm performance, generally assumes that the changes happen at the component level or at the ecosystem level, and affect actors in a similar way. While there is some work recognizing that the size of the effect from these changes may not be the same for all firms within a component (Hannah and Eisenhardt, 2018; Jacobides and Tae, 2015; Kapoor and Agarwal, 2017), the implicit assumption is that the direction of the effect is similar. By contrast, our findings suggest that shifts across
bottleneck states may have sometimes opposite impact depending on the firm’s relative standing within its component and thus induce very different patterns of strategies adopted. For instance, our findings highlight the differences in terms of exclusivity strategies between the winning and the losing firms within the same component, and provide a first glance at when and who among ecosystem participants will be most incentivized to attempt bottleneck shifts.

A third contribution is by recognizing both exogenous and endogenous antecedents to bottleneck emergence and shifts. While the extant literature treats ecosystem structure and bottleneck emergence as mostly determined by exogenous technological factors (e.g., Adner and Kapoor, 2010; Hannah and Eisenhardt, 2018) we show that firms exhibit strategic intent and have a certain degree of agency to leverage these technological shocks. We highlight how firms may use their portfolios to shift ecosystem to a state with less competition, or to maintain its property rights over the strategic bottleneck. We also show that challenging bottlenecks can be endogenously driven. Paradoxically, winning firms’ strategies to maintain their bottleneck position may, actually, backfire as they incentivize losing firm to try and circumvent the bottleneck, in the process creating an alternative pathway for value creation.

Finally, our analysis sheds light on the intricacies of bottleneck evolution in ecosystems and furthers the research on ecosystem evolution (Hannah and Eisenhardt, 2018; Kapoor and Agarwal, 2017; Ozcan and Hannah, 2020). To the extent of our knowledge, Baldwin (2018) is the only work that explicitly looks at how value creation bottlenecks may morph into strategic bottlenecks. We offer novel insights by highlighting that once a value creation bottleneck is resolved there can be multiple possible trajectories: firms can go back and forth regarding strategic bottleneck, and they may even try to set the ecosystem on an alternative trajectory by circumventing the bottleneck.

In conclusion, in this paper we seek to answer the question of how bottlenecks evolve in an ecosystem, and how this evolution affects and is shaped by the strategies of ecosystem participants. We use a rich case study of the anti-HIV drug industry development over twenty years to provide a comprehensive analysis of the firms’ strategies depending on their competitive position and on the state of the ecosystem bottleneck. Our study offers novel insights by highlighting pos-
isible trajectories of bottleneck evolution across the two key dimensions – the extent of technical constraint on value creation and the scarcity of competitive alternatives – and by proposing determinants of this evolution. We hope that this paper will pave the way for the future research to further our understanding of the mechanisms underpinning ecosystem evolution.

REFERENCES


APPENDIX A  THE USE OF BASES IN THE CLINICAL TRIALS

Having established the evolution in terms of technical constraint and variety based on the medical guidelines we now seek to confirm that this evolution is reflected in the actual use of bases in clinical trials. In other words, we check whether the real-life use confirms the evolution that we inferred from the experts’ opinion.

We do not attempt to claim causality here; we merely seek to check whether the use of bases in clinical trials is aligned with what we see in medical guidelines (i.e., whether medical guidelines information can truly be used as proxies for technical constraint and competitive variety). Figure 10 shows the distribution of bases used in add-on trials for each year (the number of trial-combinations that feature a given base in a given year). To avoid bias it looks only at the trials focusing on testing add-on drugs while excluding trials testing bases. It also looks at the combinations used for the patient treatment groups only to avoid the bias for older bases that might be used in the control group.

Figure 10 shows that in pre-2005 era there was much more variety in terms of different bases used. While 2005-2007 period – which corresponds to the highest variety as per guidelines – appears to favor three major bases (by GSK/ViiV and Gilead) that formed the recommended set in 2010 (though they were already the preferred options in 2005) – a large portion of trials during this period does not specify base at all. The base in these trials is referred to as “OBT” – “optimized background treatment” – which are usually trials testing add-on drugs in patients who are already pre-treated and who switch from their current add-on to a new one while keeping the base. The implication is that it can be any base. Note that after 2005 there is a sizable number of trials using Gilead’s tenofovir while almost no trials use older bases – which is aligned with the resolution of technical constraint.

Post-2008 era appears consistent with the evolution of the base number in the guidelines: the majority of the trials use one of the three major bases (and the share of trials without a specific base declines), and after 2013 most trials use just the winning base (Gilead’s tenofovir) and later its newer version.

We repeated the analysis excluding trial-combinations that contain the base owned by the trial sponsor to account for base owners possibly choosing to use their own bases in the trials. For example, if Gilead tests two combinations of an add-on drug – one with its tenofovir and the other with GSK/ViiV base – we exclude the one with tenofovir while keeping the one with GSK/ViiV base. We obtained similar results.

Figure 10: Evolution of the variety in the use of bases in add-on trials
**APPENDIX B  BUNDLING WITH UNIQUE BASE: ADD-ON PRODUCERS**

To check whether there was a general trend towards bundling with certain bases we examine the behavior of add-on only producers as a baseline. Figure 11 maps the use of unique bases by add-on only firms: dark grey bars indicate trial-combinations in add-on trials featuring multiple bases, while other bars represent trial-combinations in trials where the add-on was tested with a unique base (blue-colored bars represent Gilead’s winning tenofovir-related bases, red bars are GSK/ViiV bases, and green-colored bars are BMS bases).

![Figure 11: Bundling with a unique base by add-on only firms](image)

**APPENDIX C  REGRESSION ANALYSIS**

Dependent variables:

- *AddonTrial* which is a binary variable set to 1 when the focal drug of the trial is an add-on drug, and 0 otherwise. For trials with multiple combinations, or when it was not evident from the trial’s description, we checked whether base of the focal combination was the same as the base of the comparator combination. If so, then we considered the trial being primarily on the add-on drug.

- *NoBasecombo* which is a binary variable set to 1 when the drug combination contains no base drugs. As explained in section 3 we cindlude combinations with secondary base drugs, but not primary base drugs, in this category as well, based on our conversation with medical specialists. The reason is that it is primary base drugs that have higher toxicity and present a problem, while secondary base drugs are well tolerated, and it is the efficacy of primary base drugs that makes them indispensable in the first place. Including combinations with secondary base drugs results in only 8 more trial-combinations, and does not change temporal patterns.
• *UniqueBase* which is a binary variable equal to 1 if the add-on trial uses the same base in all its focal combinations, and 0 otherwise. We correct for the cases when a base firm owns multiple bases and uses several of them in the trial, but not the bases owned by other firms.

Independent variables:

• *LowBaseOwner* is a binary variable equal to 1 if the firm owns at least one base that was recommended as *preferred* base in the guidelines in year $t-1$.

• *LowBaseOwner* is a binary variable equal to 1 if the firm owns at least one base, but doesn’t have any base that was included in the preferred recommendations.

Control variables:

• *NaivePatients* set to 1 is the trial includes patients who are naive (i.e., not pre-treated)

• *HighAddonOwner* is a binary variable equal to 1 if the firm owns at least one add-on drug that was recommended as *preferred* add-on in the guidelines in year $t-1$.

• *Combo_PostApproval* is equal to 1 if all drugs in the given combo are already marketed (irrespectively of the geography).

Tables 2, 3, and 4 provide the results of logistic regressions for each period. Note that in table 4 the sample is limited to the trials on add-on drugs to avoid potential bias when firms test a specific base. We use logistic regression, weighting observations by the number of combinations per trial, errors clustered at the sponsor level.

Table 2: Logistic regression, DV=AddonTrial (standard errors in parentheses)

<table>
<thead>
<tr>
<th>Technical constraint</th>
<th>Competitive solutions</th>
<th>High Base</th>
<th>High Base</th>
<th>Low Base</th>
<th>Low Base</th>
<th>Low Base</th>
<th>Low Base</th>
<th>Low Base</th>
<th>Low Base</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High BasesOwned</td>
<td>-1.983**</td>
<td>-1.579</td>
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<td>-2.871***</td>
<td>-2.674***</td>
<td>-2.470***</td>
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<tr>
<td></td>
<td>(0.840)</td>
<td>(1.168)</td>
<td>(1.476)</td>
<td>(0.877)</td>
<td>(0.807)</td>
<td>(0.934)</td>
<td></td>
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</tr>
<tr>
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<td>Low BasesOwned</td>
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<td>-4.824***</td>
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<td></td>
<td>(0.890)</td>
<td>(1.215)</td>
<td>(0.960)</td>
<td>(0.962)</td>
<td>(1.170)</td>
<td>(1.310)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudo $R^2$</td>
<td>0.21</td>
<td>0.32</td>
<td>0.41</td>
<td>0.12</td>
<td>0.11</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>99</td>
<td>113</td>
<td>97</td>
<td>243</td>
<td>157</td>
<td>105</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.1, **p < 0.05, ***p < 0.01.

(1) We omit pre-2013 analysis for Add-onTrial dependent variable as convergence could not be achieved.
Table 3: Logistic regression, DV=NoBaseCombo (standard errors in parentheses)

<table>
<thead>
<tr>
<th>Technical constraint</th>
<th>Competitive solutions</th>
<th>HighScare/Many</th>
<th>LowMany</th>
<th>LowScare</th>
<th>LowScarcest Post-2011</th>
<th>LowScarcest Post-2013</th>
<th>LowScarcest Pre-2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>HighBasesOwned</td>
<td></td>
<td>-1.629**</td>
<td>-1.764***</td>
<td>-1.977*</td>
<td>0.000(1)</td>
<td>0.000(1)</td>
<td>-0.725</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.733)</td>
<td>(0.545)</td>
<td>(1.071)</td>
<td>(.)</td>
<td>(.)</td>
<td>(0.846)</td>
</tr>
<tr>
<td>LowBasesOwned</td>
<td></td>
<td>-2.424**</td>
<td>-0.050</td>
<td>0.115</td>
<td>0.079</td>
<td>1.154*</td>
<td>-0.673</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.059)</td>
<td>(0.966)</td>
<td>(0.475)</td>
<td>(0.572)</td>
<td>(0.693)</td>
<td>(0.624)</td>
</tr>
<tr>
<td>HighAddonOwned</td>
<td></td>
<td>0.084</td>
<td>-0.124</td>
<td>1.162*</td>
<td>0.569</td>
<td>0.345</td>
<td>1.982***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.960)</td>
<td>(1.530)</td>
<td>(0.689)</td>
<td>(1.105)</td>
<td>(1.179)</td>
<td>(0.567)</td>
</tr>
<tr>
<td>NaivePatients</td>
<td></td>
<td>3.144***</td>
<td>1.368**</td>
<td>-0.346</td>
<td>-1.478***</td>
<td>-1.549***</td>
<td>0.274</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.057)</td>
<td>(0.590)</td>
<td>(0.325)</td>
<td>(0.256)</td>
<td>(0.466)</td>
<td>(0.662)</td>
</tr>
<tr>
<td>Combo_PostApproval</td>
<td></td>
<td>0.532</td>
<td>-0.367</td>
<td>-0.161</td>
<td>-0.097</td>
<td>-0.887</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.950)</td>
<td>(0.772)</td>
<td>(0.322)</td>
<td>(0.362)</td>
<td>(0.648)</td>
<td>(0.511)</td>
</tr>
<tr>
<td>_cons</td>
<td></td>
<td>-3.981***</td>
<td>-1.332**</td>
<td>-0.835</td>
<td>0.067</td>
<td>0.406</td>
<td>-1.670***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.328)</td>
<td>(0.549)</td>
<td>(0.513)</td>
<td>(0.690)</td>
<td>(0.642)</td>
<td>(0.422)</td>
</tr>
<tr>
<td>Pseudo R²</td>
<td>0.28</td>
<td>0.11</td>
<td>0.14</td>
<td>0.09</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>N</td>
<td>212</td>
<td>97</td>
<td>243</td>
<td>82</td>
<td>49</td>
<td>138</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.1, ** p < 0.05, *** p < 0.01
(1) Variable omitted because HighQualityBasedOwner=1 predicted failure perfectly

---

Table 4: Logistic regression, DV=UniqueBase, add-on trials only (standard errors in parentheses)

<table>
<thead>
<tr>
<th>Technical constraint</th>
<th>Competitive solutions</th>
<th>HighScarce</th>
<th>HighMany</th>
<th>LowMany</th>
<th>LowScarce</th>
<th>LowScarcest Post-2011</th>
<th>LowScarcest Post-2013</th>
<th>LowScarcest Pre-2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>HighBasesOwned</td>
<td></td>
<td>1.001</td>
<td>0.264</td>
<td>1.381**</td>
<td>1.968**</td>
<td>2.738***</td>
<td>3.055***</td>
<td>2.205***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.963)</td>
<td>(0.690)</td>
<td>(0.547)</td>
<td>(0.773)</td>
<td>(0.460)</td>
<td>(0.653)</td>
<td>(0.727)</td>
</tr>
<tr>
<td>LowBasesOwned</td>
<td></td>
<td>0.294</td>
<td>0.347</td>
<td>-0.919</td>
<td>-0.032</td>
<td>-0.252</td>
<td>-1.883***</td>
<td>1.193**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.822)</td>
<td>(0.780)</td>
<td>(1.017)</td>
<td>(0.544)</td>
<td>(0.406)</td>
<td>(0.826)</td>
<td>(0.475)</td>
</tr>
<tr>
<td>HighAddonOwned</td>
<td></td>
<td>1.972*</td>
<td>-1.058</td>
<td>0.627</td>
<td>0.549</td>
<td>1.180</td>
<td>2.323</td>
<td>-2.011*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.051)</td>
<td>(0.963)</td>
<td>(0.964)</td>
<td>(0.978)</td>
<td>(1.090)</td>
<td>(1.582)</td>
<td>(1.120)</td>
</tr>
<tr>
<td>NaivePatients</td>
<td></td>
<td>0.577</td>
<td>2.579***</td>
<td>0.000(1)</td>
<td>0.831***</td>
<td>1.101**</td>
<td>1.096*</td>
<td>1.558*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.631)</td>
<td>(0.714)</td>
<td>()</td>
<td>(0.274)</td>
<td>(0.537)</td>
<td>(0.571)</td>
<td>(0.835)</td>
</tr>
<tr>
<td>Combo_PostApproval</td>
<td></td>
<td>-2.075***</td>
<td>1.184</td>
<td>2.952***</td>
<td>-0.820**</td>
<td>-0.382</td>
<td>0.380</td>
<td>-0.745</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.685)</td>
<td>(1.064)</td>
<td>(1.006)</td>
<td>(0.409)</td>
<td>(0.624)</td>
<td>(0.426)</td>
<td>(0.702)</td>
</tr>
<tr>
<td>_cons</td>
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<td>-0.959</td>
<td>-2.957***</td>
<td>-1.173**</td>
<td>-1.396***</td>
<td>-1.570***</td>
<td>-2.000***</td>
<td>-2.177***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.826)</td>
<td>(0.770)</td>
<td>(0.582)</td>
<td>(0.396)</td>
<td>(0.560)</td>
<td>(0.948)</td>
<td>(0.766)</td>
</tr>
<tr>
<td>Pseudo R²</td>
<td>0.14</td>
<td>0.27</td>
<td>0.33</td>
<td>0.20</td>
<td>0.27</td>
<td>0.44</td>
<td>0.44</td>
<td>0.26</td>
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<tr>
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<td>200</td>
<td>116</td>
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<td>128</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.1, ** p < 0.05, *** p < 0.01
(1) Variable omitted because Naive=1 predicted failure perfectly.