Pharmaceutical Patents, Developing Countries and HIV/AIDS Research

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Abstract

Patents are one of the reasons why many patients from developing countries lack access to AIDS treatments. The usual justification for implementing patent systems in the third world economies is based on the increased incentives to innovate that patents should provide. In this paper, we argue that, for various reasons, developing countries' patent systems are unlikely to be a crucial determinant of access to innovation against AIDS. On the other hand, however, patents could act as a complement to public funds dedicated to buying back treatments and future vaccines from pharmaceutical firms.

Résumé

Les brevets d'invention sont une des raisons pour lesquelles les patients des pays en voie de développement n'ont pas accès aux traitements contre le sida. La justification traditionnellement donnée à la mise en place de systèmes de brevets dans ces pays réside dans les incitations à innover accrues des firmes pharmaceutiques. Dans cet article, nous discutons la pertinence de cet argument et concluons qu'en réalité, les brevets d'inventions délivrés par les pays en développement ne sont probablement pas suffisants pour accélérer la recherche contre le sida. En revanche, ils pourraient s'avérer un complément à la mise

en place de fonds publics destinés à racheter aux firmes pharmaceutiques les traitements et les futurs vaccins.

Introduction

The debate on whether developing countries should enforce pharmaceutical patents protecting treatments of deadly and widespread diseases such as AIDS confronts two distinct, opposing arguments. Governmental and non-governmental organisations argue that patents entail a significant increase in the price of medicines, thus restricting treatments to a minority of wealthy patients. On the other hand, pharmaceutical firms, as well as the United States'representatives, stress that these patents are needed to encourage research in areas that are already under-explored, such as the HIV/AIDS viral strains affecting developing countries.

This debate starkly reflects the dynamic trade-off between the static deadweight loss generated by the patent-induced monopoly and its incentive-enhancing effect on research. Ever since Nordhaus and Scherer wrote their seminal papers in the 70s, economists have tried to come up with an evaluation of the direction and extent of this trade-off.

For developed countries, it has often been pointed out that suppressing pharmaceutical patents would entail long-term, dynamic losses in terms of new medicines, which would be less than compensated by the downward pressure on drug prices [1]. Hence, despite having been initially very reluctant, most industrialised countries, such as the United Kingdom (in 1949), France (in 1959), Germany (in 1968), Italy and Sweden (in 1970), Japan (in 1976), have introduced patent protection for pharmaceutical innovations. Several trends, such as an increasing patent life or the application of patents to human genes, also seem to indicate that in the United States at least, this protection has even been strengthened.

But how should economists consider the implementation of the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement in disease-ridden, low-income, developing countries? This paper analyses the likely impacts of developing countries'patent systems in the case of the HIV/AIDS treatments. Patents are indeed likely to be crucial in the price-fixing strategies of pharmaceutical firms: for instance, a copy of the antiretroviral treatment Stavudine was retailed at a price of US$0.6 in India compared with a US$4.9 gross price in the

United States. If patents were to impose comparably high prices in developing countries, the cost in terms of access to treatments would be huge, since most patients could not afford such medical expenses, partly because of low individual incomes, partly because of the absence of any health care insurance system. Indeed, if all AIDS patients in Sub-Saharan Africa were to be treated through a combined therapy (using Crixivan™, AZT and 3TC) priced on the American standard, the resulting health expenses would by far exceed the total Gross Domestic Product (GDP) of these countries [2]. Current anecdotal evidence stresses that patents can result in large price increases for AIDS treatment. In South Africa, for instance, a daily treatment of the patent-protected Fluconazole (against AIDS-induced meningitis) is currently priced at US$17.84, twice as much as the daily local average wage [3]. More generally, countries that have built ambitious generic programs to provide treatments to their patients seem to fare much better than countries that bowed to the demands of patent protection from pharmaceutical firms and the United States.

To balance these static deadweight losses, stronger patents in developing economies should entail dynamic gains in the form of higher investments in research against AIDS. This paper discusses the intuitions and empirical evidence gathered so far on this matter.

In a first section, we acknowledge the role played by patents in the pharmaceutical industry. Still, we argue that the introduction/strengthening of the patent systems in developing countries is unlikely to be a necessary component of innovation if AIDS is considered as a "global" disease. Indeed, the bulk of market revenues is and will be made in industrialised countries. Therefore, innovation incentives in AIDS research would only be marginally affected by a strengthening of patent protection in developing economies.

In contrast, research incentives for those innovations concerning local diseases, such as the HIV strains affecting developing countries, may well be sensitive to the scope and effectiveness of patents (section II). Still, they are probably far from sufficient to ensure the socially desirable rate of innovation. Yet, patents could act as a complementary mechanism to other policy initiatives (for instance, to strengthen the credibility of funding programs for vaccine development).

We are therefore drawn to the conclusion that patents alone are very unlikely to provide much incentive to pharmaceutical firms while their social costs in terms of higher drug prices are certainly not marginal. On the other hand, patents could increase the effectiveness of other innovation programs like research and procurement funds. Such programs should however seek to reduce the adverse consequences of the patent systems.

I
PATENTS AND THE RESEARCH AGAINST "GLOBAL" DISEASES

Ever since they came into existence in 18th century industrialised countries, patents have stirred a controversial, if lively, debate on whether that reward system was effective and/or necessary. Note that, contrary to what is currently happening in the context of the TRIPS agreement, the discussion was not so much focused on the static dead-weight losses imposed on the economy, as to whether patents were really performing the function they were supposed to. Some of these arguments still carry great weight for today's economists.

Patents, imitation and innovation incentives

A patent is supposed to deter imitation, thus providing the innovator with a monopoly for a period of 10 to 20 years (depending on the lag between the patent grant and the market introduction of the innovation). The short-term distortion entailed by patent monopolies can only be justified by the boost given to research incentives. Theoretically, the optimal length of a patent is that which equals the marginal benefit of greater protection (in terms of innovation performance) with its marginal costs (in terms of deadweight losses). This basic principle falls prey to several criticisms, however:

– first, firms resort to other strategies than patent enforcement to protect their innovations. The study by Levin *et al.* [4] and its recent follow-up by Combe & Pfister [5] demonstrate that very often, patents are evaluated as less effective than alternative appropriation schemes, such as lead-time or secrecy. In that case, what is the point of maintaining costly and administrative patent systems?

– second, the patent system can act as a barrier to innovation: from a theoretical standpoint, they discourage cooperation and can be used to block rivals doing research in related fields (see Lerner [6] and Austin [7] for evidence of this sort in the biotechnology industry, and Shapiro [8] for a discussion on overlapping patent rights in high technology industries);

– third, effective patents can lead to an overall excessive level of Research and Development (R&D) as firms try to outpace each other to reach the patent office first [9]. Several theoretical models recommend that some of the rents earned by the patent owner be redistributed to rival companies in order to prevent excessive investment from emerging;

– finally, the patent mechanism bears sense only for those innovations that are generated through private (as opposed to public) R&D expenditures. Otherwise, the cost of public innovations would be imposed twice on the consumers, first through tax mechanisms, then through monopoly pricing. Note though that the United States have introduced patent protection for government-funded research institutions, as a way to promote cooperation between public and private organizations.

Let us take each of the above criticisms and see whether they are of any relevance to the pharmaceutical industry and to AIDS research in particular.

Consider first the "patents-are-ineffective" line. All empirical studies stress the economic importance of patents in the pharmaceutical industry. Corporate respondents to patent surveys judge them as more effective than any other appropriation tool at their disposal. This relative effectiveness stems from the ease with which pharmaceutical imitations can be detected: indeed, pharmaceutical research deals mainly with which compound to use against a given disease and how to use it, rather than how to produce that compound. Thus, once a chemical entity is discovered, a patent allows the innovator to have a market exclusivity on the new molecule and its therapeutic applications, regardless of the industrial process of production[1]. Copy-cat drugs or treatments, based on chemical compositions or molecules under patent protection, are therefore easy to detect. The intense lobbying by pharmaceutical firms to extend patents' geographical reach and duration is also a proof of the industry's commitment towards patent protection. Finally, the stock market value of biotechnology firms often increases when patents that are judged to be relevant for future developments are granted, while that of pharmaceutical firms routinely declines when their patents on blockbuster drugs expire [10].

Second, may patents deter inter-firm cooperation and slow down rival research projects? Economists are rather divided on this point. As Bessen and Maskin [11] point out, a firm that owns a patent may not be willing to license its innovation to a competitor as competition may significantly erode its innovation rent. The problem is compounded by what Heller and Eisenberg [12] term the "anti-commons tragedy": there are other already granted patents that will be needed to do research in the patented area, and the negotiation and transaction costs might deter any potential licensee. Hence, several economists

1. An innovator can patent different production methods to obtain the molecule and benefit from patent protection on the different therapeutic applications, if these are claimed in the original patent application (molecule).

have stressed that antitrust provisions regarding inter-firm cooperation and patent pools might have to be relaxed in order to diminish obstacles to patent licensing [13, 14].

On the other hand, however, the absence of patent protection can be an obstacle to cooperation: indeed, secrets remain hard to commercialise and the protection of intellectual assets reduces the risk of misappropriation by the partner. Empirical evidence tends to indicate that patents actually help firms to cooperate one with the other [15].

Consider for instance the patent issued to Human Genome Science (HGS) concerning the gene CCR5 (that controls how AIDS begins infecting its victim). This patent gives its owner a sweeping control over who gets to use the gene in commercial development of a new class of AIDS drugs. However, HGS plans to make the gene widely available to other drug companies in exchange for fees and future royalties (and to academic researchers at no cost). It should also be noted that the absence of patent protection might have prevented HGS from disclosing its knowledge altogether, thus incurring large R&D wastes as duplicative investment would have lingered on. Given the high cost of research and the relatively unpredictable results it could yield, patent-induced disclosure could be a great economic and social improvement over secrecy.

On the other hand, however, it was a Maryland university that found the AIDS-related chemical property of gene CCR5, after a broad patent had been granted to HGS for having discovered the gene itself (regardless of its use). Their research was in no way inspired by the HGS patent which was disclosed to the public only after the Maryland university found their results. Hence, the economic and technologic role played by the HGS patent has been very minor so far, and some argue that HGS did not deserve a patent so broad as to foreclose any research in this area. Yet, given that many a gene could turn out to have no function leading to marketable applications, HGS should reap a reward for its research on these "useless" genes too.

Now, take the "excessive R&D" argument. Pharmaceutical firms are often very secretive about their R&D investments on individual projects, so it is hard to evaluate whether they may be driven too high by the prospect of patent grants. Note though that Cockburn and Henderson [16] find no evidence of cross correlations in R&D project-level investments so that an increase in one's research investment has no impact on project competitors (contrary to the "excessive R&D" argument that predicts a positive relationship).

More generally, this type of argument may not be relevant for HIV/AIDS research. Indeed, patent race models usually assume that only one competitor

can win and be granted a patent. Yet, pharmaceutical patents rarely narrow the prospects of further patent on inventions (as the case of "me too drugs" patents tends to demonstrate). For instance, ten patented anti-retroviral drugs (ARVs) using nucleoside or nucleotide reverse-transcript inhibitors are currently available. Three non-nucleoside reverse transcripts inhibitors and six different protease inhibitors have also earned patent protection [17]. Further, each one of these drugs fights the HIV virus in a slightly different way. Since combining several different drugs yields more favourable results than using any single drug alone (HAART, highly active antiretroviral therapy for instance), and because genetic mutation enables the virus to develop into resistant strains, differentiated classes of drugs are particularly needed. The same logic applies to the research prospects in vaccines. The probable need for vaccines adapted to different strains – at least 11 genetic subtypes of HIV virus have been identified to date – will translate into a significant number of patenting opportunities.

Finally, innovation in public health matters is not only driven by patents. The public sector has been an irrefutably important element of pharmaceutical innovations [18][2]. As an illustration, around 70% of the drugs considered as having a therapeutic gain in the United States are produced with governmental support. Indeed, publicly funded research in that country has led to major drug discoveries for various diseases such as tuberculosis, cancer, and infectious illnesses. In the case of HIV/AIDS, publicly funded research has led to the discovery of an important number of therapeutic advances: AZT, 3TC, Saquinavir, Abacavir, Staduvine, Zerit™, Didanosine, Lamivudine, Nevirapine [21][3]. For instance, Didanosine [ddI] was originally synthesized by NIH scientists, and the United States holds the key use patent for ddI (Patent No. 4861759), which

2. In general, as confirmed by different studies, public sector involvement in pharmaceutical innovation has been more significant in determining private sector productivity than in any other industry (except defence) in the United States. Quantitative estimates suggest that the rate of return to publicly funded research (through different funding mechanisms such as tax-credits, subsidies, direct funding, cooperative R&D, etc.) as measured by its effect on the private sector, may be as high as 30% [19, 20].

3. D4T - one of the components of a dual therapy shown to slow the progression of the AIDS virus which Bristol-Myers Squibb (BMS) sells under the brand name Zerit™ - was synthesized by the Michigan Cancer Foundation in 1966 with the support of public funds. Its use to treat AIDS was discovered by Yale University, which holds a patent on D4T [21]. See also www.cptech.org/ip/health/aids/gov-role.html documents on Public Sector involvement on AIDS drugs.

has been exclusively licensed to Bristol-Myers Squibb (BMS) through the National Technical Information Service (NTIS)[4].

Thus, our discussion has highlighted four distinct points on whether and how patents can affect pharmaceutical research:

– patents are an important incentive to innovate in that industry;

– the insights developed by the theoretical literature on how strong patents can block pharmaceutical research disproportionately exceed the empirical evidence that has been gathered on that subject;

– it is very unlikely that stronger patent protection might result in excessive R&D investments in AIDS research for firms often pursue complementary rather than substitute objectives (as in the case for HAART);

– finally, the strong role of state intervention in this industry testifies that even in industrialised countries with strong patent systems, some sort of public support is needed to reconcile private incentives to innovate with social needs.

Developing countries'patent systems and innovation

In addition to the above arguments, the effectiveness of a pharmaceutical patent system for developing economies remains very uncertain too, for at least two reasons.

First, the incentive to innovate is mainly driven by those markets with a strong, creditworthy demand, and most developing countries are unlikely to fit in this group. Indeed, because of their low purchasing power, developing countries account for less than 20% of the global drug market, and Africa itself represents only 1.1% of the global sales of pharmaceuticals [23]. Thus, regardless of patent protection, these markets are unlikely to be of great importance in determining the level and direction of R&D spending. For instance, a recent study based on IMS data and the World Bank reports that countries with Gross Domestic Product (GDP) per capita lower than US$2500 together contributed less than one half of one percent to global spending on ARV drugs in 1999 [24]. Therefore, patent protection on antiretroviral drugs in developing countries should not greatly affect the research path for antiretroviral drugs primarily developed to be marketed in industrialised countries, even less so since

4. The recent case of the anti-retroviral AZT (Zidovudine) also illustrates the case of public involvement in HIV/AIDS treatments. Indeed, Zidovudine was initially synthesized through a National Cancer Institute (NIC) grant at the Michigan Cancer Foundation, and therefore several patent suits have challenged Glaxo, as NIH scientists claim they were the first to identify anti-HIV activity and clinical efficacy of AZT [22].

relatively strong patent laws in industrialised countries preceded the implementation of the TRIPS agreement in developing countries. Likewise, given the low level of South/North parallel imports, generics sold in developing countries should not affect prices in Northern markets, and neither should they reduce the incentives to innovate by pharmaceutical giants.

Second, many developing countries' local firms lack the technological capital to compete with industrialised companies, so that imitation does not represent a significant threat to the innovators' profits. Unsurprisingly, patent protection has been sought by pharmaceutical firms firstly in countries showing increasing imitative capabilities and some pharmaceutical expertise such as Chile, Turkey and Mexico (1991), Thailand, Taiwan, Romania, Russia and Ukraine (1992), and Brazil (1996).

Furthermore, as suggested by some recent studies by Harvard University and UNAIDS on the patent status of ARV drugs, patents are not systematically applied for in developing countries. Hence, very few patents for ARVs are reported in those African countries providing legal opportunities for patent protection, one exception being South Africa which has granted patents on most ARVs [25].

II
PATENTS AND THE RESEARCH AGAINST "LOCAL" DISEASES

Some diseases that were eradicated from industrialised countries decades ago still plague southern countries: according to the World Health Organization, 100% of the cases of malaria and tetanus and 99.9% of the cases of polio, syphilis and leprosy are found in low income countries. Besides, some diseases are common to industrialized and developing countries but present region-specific traits. Hence, the AIDS virus affecting the USA and Europe is not of the same type as that affecting South America and Africa. Finally, treating one particular disease in a given country may need existing treatments to be adapted to local conditions (for climatic reasons, for instance). What role may developing countries' patent systems play in this context?

Patents and innovation on tropical diseases

Relative to their effects on R&D for global diseases, patents might stimulate a stronger additional investment on diseases for which incentives are currently

weak, such as those specific to poor countries [26]. If the regional strains of HIV/AIDS affecting poor countries can be considered as tropical diseases, and consequently as neglected diseases, a strengthening of patent protection might potentially lead to increased R&D investment in this area.

Lanjouw and Cockburn [27] explored how R&D investment on neglected diseases evolved during the years surrounding the conclusion of bilateral and multilateral agreements on intellectual property rights. With much effort, a 10 to 15% increase in the number of patents on neglected diseases is discernible between 1985 and 1990, *i.e.* those years which correspond to the beginning of international efforts to ensure a better enforcement of patents in developing countries. Yet, the number of granted patents on tropical diseases remains very marginal (0.5% of the pharmaceutical patents). According to the US National Institutes of Health, a similar trend is observed for scientific articles related to tropical diseases (they represent 1.5% of the total) and for public funding (2% of which was devoted to research on tropical diseases in 1985 against 3.7% in 1995). Along with patents, other dimensions of profit incentives remain prime movers of R&D investment. For instance, there are more patents and scientific articles for those diseases likely to affect the third world upper class (like malaria and unlike leprosy).

One proposed interpretation of these trends is that the building-up of international (mainly American) efforts to promote patents in the third world encouraged more "tropical" research towards the end of the 80s, while the levelling-off corresponds to the period when opposition against patent laws began mounting. In any case, given that these reforms remain highly reversible, pharmaceutical firms are probably not too keen to invest in research areas where property rights and profitability remain so uncertain. At the other extreme, the slight increase in research output at the end of the eighties may rather be due to a small burst of technological opportunities in this scientific area, making research less costly and/or more productive. At the same time, it is worth noting that Indian pharmaceutical firms have also turned out to be more innovative, as the proportion of their patents (over all Indian patents) in Europe and in the USA increased from 15 to 25% between 1980 and 1998.

In any case, even though patent laws may influence research on tropical diseases, investment will not take off if the market demand remains uncreditworthy. One estimation puts the number of new "tropical compounds" developed between 1975 and 1997 at 13 out of a total of approximately 1400. In other

words, less than 1% of the total pharmaceutical innovations (new chemical entities) reported in the last twenty years represent new medical solutions for tropical diseases. For instance, less than 0.2% of world pharmaceutical investment is spent on diarrhoea, pneumonia and tuberculosis [28]. Moreover, while 50% of global health R&D in 1992 was undertaken by private industry, less than 5% of that was spent on diseases considered specific to less developed countries [29]. Likewise, a recent paper by Trouiller *et al.* [30] concludes that only 16 of the 1393 new chemical entities marketed between 1975 and 1999 in the United States and Europe targeted tropical diseases and tuberculosis; all were developed with public-sector involvement.

As far as AIDS is concerned, a disproportionate amount of investment is devoted to treatments as opposed to vaccine research, that if successful would offer an effective and cheaper tool for HIV prevention. But lack of investment in this area does not exclusively stem from the low levels of market incentives:

- searching for a treatment is less risky and less costly than pursuing future vaccines, which represents a scientific challenge and whose clinical tests are likely to be very costly too. Indeed, daunting scientific obstacles remain to date in HIV vaccine development: unknown correlates of immune protection, high variability and mutation of genetic clades, undemonstrated effectiveness in reducing transmission in large populations, etc. [31];

– for firms marketing drugs entering into HAART combinations, vaccine research falls prey to the "replacement effect" [32]. Indeed, treatments are more beneficial in terms of profits, given that they have to be administered for the whole life of a patient. The introduction of a vaccine may reduce this important flow of profits. Therefore, research against AIDS remains disproportionately focused on treatments (US$2 billion a year, against US$300 million on vaccines according to the World Bank);

– as stated by industry representatives, the threats of compulsory licensing (article 31 of the TRIPS agreement) and marginal-cost pricing following public debate on patents and access to ARV drugs, might lead to a reduced commitment to further private overall investment in R&D that would affect the discovery of both new drugs and vaccines for HIV/AIDS.

Figures in the pipeline of clinical stages of vaccines for sub-clades A, C, D, E, etc. also suggest a polarized strategy by private firms. First, investment in vaccine development remains still far from that in HIV/AIDS treatments. Second, research is concentrated on the B sub-clade, the one prevalent in

rich countries. Indeed, among the 60 phase I/II trials conducted since 1987, approximately 30 concern different HIV candidate vaccines for the sub-clade B in the United States and Europe.

Nonetheless, private and public research strategies are beginning to target the local needs of developing countries. Two clinical trials currently conducted in Thailand (and in the United States) target those clades affecting the local population. A first candidate vaccine against HIV (a gp120 product from VaxGen) has entered phase III efficacy evaluation and uses clades B/E depending on the transmission mode of the virus[5]. Even if most of the clinical testing against non-B strains done so far primarily targets strains of the virus that affect middle-income countries such as Brazil and Thailand, phase I and II trials are currently being implemented in Africa [33][6]. These are based on the so-called "canary pox", which is one of the first candidate HIV vaccines that has induced cross-clade functional CTL (cytotoxic T lymphocytes) responses. This testing should determine the extent to which Ugandan volunteers have CTL active against the subtypes of HIV prevalent in the region, sub-types A and D. It will also explore immunogenicity across clades, or subtypes, of HIV, thus answering questions about the possibility of designing a global vaccine[7]. Likewise, the above-mentioned Thai clinical trials are expected to be soon extended to Africa and tests on a hybrid vaccine candidate for sub-clades A/G conceived by the United States should be initiated in Côte d'Ivoire. These clinical experiments may indicate that vaccine development on traditionally neglected sub-clades is now increasing, thanks to stronger public-financing. Indeed, budgetary constraints have often prevented local governments from supporting clinical testing for regional clades. The lack of medical infrastructure in much of the less developed economies remains an important obstacle to the implementation of clinical trials there.

5. Testing began in Thailand in 1999 and involved 2,500 recovering injected drug users (IDU) in Bangkok. The interim efficacy analysis of the US and Thai trials is still underway. There are plans to initiate a second phase III trial in several countries, including Thailand, the Caribbean and South American countries, using a prime-boost strategy including two different subtype B products: a canarypox-HIV recombinant vector (Aventis Pasteur) followed by gp120 (VaxGen).

6. Aventis Pasteur in collaboration with WRAIR has initiated trials on clades E; phase I/II trials are under way in Thailand in combination with protein boosts [33].

7. This vaccine research strategy parallels that of the Agence Nationale de Recherches sur le Sida (ANRS) in France (lipopeptide program) in partnership with Aventis-Pasteur. Again, this program attempts to circumvent the problem of clades diversity by inducing cross-clade functional CTL responses.

How to strengthen incentives in AIDS research?

It seems clear that strengthening the developing countries'patent system is not, by itself, sufficient to accelerate AIDS research and development, as the number of vaccine candidates currently in the pipeline may suggest for instance. The main barriers are the non-profitability of these markets, the limited information concerning the exact market demand, as well as strong uncertainty about the appropriation of innovations ("the time inconsistency problem"; [34, 35]). In the case of vaccines, extremely high uncertainty about the best research avenues to explore among the scientific community, even for the development of vaccines on strain B, accentuates the reluctance of the private sector to invest in this domain. Since patents in poor countries are not sufficient to build the required investment, implementation of complementary incentives and funding are necessary.

Policy options to encourage R&D efforts can take different forms [36, 37]. Incentives to innovate can be enhanced from the supply side ("push" policy), and from the demand side ("pull" policy):

– push mechanisms such as subsidies for research input, R&D tax credits or grants to researchers, aim to reduce the costs of investment by providing direct funding for research. Other push instruments may focus on facilitating regulatory processes for the new pharmaceuticals (such as the fast regulatory approval of ARVs) [18]. Nevertheless, the effectiveness of these instruments to spur HIV/AIDS research for poor countries would be limited since market failure is not explained by the costs or the supply of R&D *per-se*;

– programs to increase investment must therefore seek to build market prospects in these research fields. By improving the likelihood of a return on investments, pull incentives reward the actual output of R&D efforts, such as vaccine development for HIV strains in poor countries.

Pull programs such as purchase pre-commitment may constitute a good alternative because of their attractive features over the traditional push-type incentive [34, 35]. Indeed, a pull system avoids the traditional moral hazard and information asymmetry problems that plague the push. To the extent that researchers overestimate the probabilities of discovering, and since monitoring of R&D efforts is difficult to implement, subsidies suffer from not delineating innovation outcomes. By rewarding actual outputs of R&D, pull instruments stimulate researchers to self-select the most promising projects, and therefore

to focus more precisely on developing marketable innovations (rather than other goals such as scientific publications, etc.). On the other hand, the diffusion of innovations will be ensured as the purchasing agencies should distribute the treatments/vaccines across affected countries.

Nonetheless, such an approach does present some shortcomings. In particular, sponsors are likely to downplay the value of the new treatments in order to favour a better deal. In order to reduce uncertainty, and therefore achieve a higher return on investments, private firms need clear and transparent rules concerning the property rights to prevail on innovations as well as the rules governing their exploitation. Patents could thus serve as a property right mechanism ensuring firms that they could still revert to a monopoly-based pricing strategy in the case of governmental proposals being judged unfair. Thus, patents can enhance the creditworthiness of purchasing mechanisms and ensure a better reward for innovators without imposing heavy deadweight losses on the patients.

Thus, patents have not been discarded from recent regulatory proposals. Some of these suggest, for instance, that international funding organizations should seek to acquire a patent-pool on essential medicines, which would then be put in the public domain under an international drug procurement policy [38,2]. This fund could be managed by UN agencies and payments to patent holders would be in the form of a fixed yearly lump-sum transfer that would guarantee innovators a net present value roughly equal to R&D costs and positively related to the social value of the innovation and the global share of patients in the licensed areas.

More specifically, Kremer [39] suggests that a patent buy-out program might be implemented through an auction system to determine the private value of patents and the sums that should be paid by the government. Finally, Lanjouw [24] argues for the international recognition of a discriminatory patent protection, depending on whether the drug targets global or neglected diseases.

Conclusion

There is hardly any doubt that patents are needed to promote pharmaceutical innovations and, although some concerns have recently been raised about whether strong patents might block pharmaceutical research rather than enhance it, they have so far proved to be very effective in industrialised countries. The dire state of pharmaceutical research on AIDS treatments and vaccines for developing countries might support the argument that these economies lack an effective,

well-enforced and credible patent system that could direct pharmaceutical firms'research towards their needs.

However, there are several reasons why reforms aimed at strengthening patent protection may turn out to be rather ineffective at promoting research into AIDS. First, regardless of patent protection, developing countries represent a minor market since low average income makes the strong potential demand largely unsolvable. Secondly, in many developing countries, there is no capability of developing copies of patented medicines, therefore strengthening patent laws would not have a great impact on the innovator's profit. Thirdly, in accordance with these two arguments, there is no convincing evidence so far that the TRIPS agreement has led to an increase in R&D investment in tropical disease. Fourthly, there are at least two other reasons than property right why vaccines remain under-developed in the case of AIDS: they are technically more costly and challenging, and the profits associated with them remain low compared to the revenues raised through the daily AIDS treatments.

We finally argue that patents can find a positive role in strengthening the creditworthiness of purchasing funds into which governmental organisations would pay in exchange for a license for the patented drug or vaccine. While treatments and vaccines would be sold to patients at low marginal cost price, the incentive to innovate relies on the pledge of the government to buy such drugs at pre-negotiated prices. In this context, patents would greatly reduce the risk of opportunism by governments and be a spur to innovation: indeed, knowing that they would retain the property of their inventions, pharmaceutical firms would be more willing to invest in HIV/AIDS research.

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