

A Balanced Trade Context for HIV Patent Pool

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Abstract

Background: Reluctance of the multinational pharmaceutical companies to join the Medicines Patent Pool plan for HIV drugs (antiretrovirals-ARVs) might undermine its desirable objective of scaling up long-term, extended access to novel, affordable and appropriate ARV formulations in resource-limited settings.

Methods: This paper makes an analysis of conflicting issues and calls for a trade context facilitating a reverse of multinational drug manufacturers' reluctance to join patent pool. To this aim, partnerships between multinational companies are urged first to make cutting edge brand fixed-dose combination (FDC) ARVs promptly available, and secondly, to allow patent pool agreements to be negotiated immediately afterwards. This context rejects clauses that exclude middle-income countries from sharing in the patent pool.

Expected results: The suggested trade context can help speed up the participation of originator pharmaceutical companies in the Medicines Patent Pool, while allowing them to maintain competitiveness, take advantage of incoming joint venture opportunities and circumvent the need for additional incentives. This context potentially tackles in an appropriate way the directions of evolution in emerging markets, while bringing benefits to resource-limited populations, multinational drug corporations and manufacturers from middle-income countries.

Conclusions: This study mixes analysis of health needs and of changing dimensions both in legislation and the pharmaceutical industry, with a political economy focus that considers the interests and capacities of key participants in global HIV treatment. So compounded, this study offers practical suggestions to stimulate the current debate.

Key words: HIV patent pool, resource-limited populations, antiretroviral medicines, trade context, manufacturers from middle-income countries, multinationals.

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Shaping needs

4.8 billion people live in the developing countries: 43 percent of them rely on less than US\$ 2 a day. Communicable diseases disproportionately affect these populations [1,2]. Drug treatments for these diseases may be very expensive, or toxic, or difficult to administer, or ineffective if microbial resistance spreads. With regard to HIV infection, only 5 million infected people (out of 15 million in need) were receiving specific medicines (antiretrovirals-ARVs) in the low- and middle-income countries in 2009, while Sub-Saharan Africa accounts for three-quarters of these figures and HIV resistance against first-line ARVs involves about

20% of patients in three years time from the beginning of treatments [3, 4]. Thus, appropriately formulated novel medicines that are safe, affordable and effective are needed.

As the current patent system generates incentives for new drug development in profitable markets only, where originator firms can recoup their research and development (R&D) expenses through sales at monopoly high prices, it does not work for the poor end users in resource-limited countries.

Nonetheless, increasing pressure is registered nowadays for strategies able to promote pharmaceutical innovation and

ensure long-term access to treatments by the poorest populations [2, 5]. The resolutions of 61st World Health Organization (WHO)'s World Health Assembly included patent pools as part of the whole Global Strategy on Public Health, Innovation and Intellectual Property aimed to increase access to medicines, stimulate R&D related to diseases that disproportionately affect the developing world, and delink R&D costs from the end product prices [1].

A patent pool is created when a number of patents by different owners are pooled and made available on a non-exclusive basis to third parties (for instance, the generic drug manufacturers).

Major commitment to putting the patent pool idea into effect, by initially focusing on ARVs, is shown by UNITAID in its reference field as an international facility to provide long-term funding to increase access to drugs and diagnostics for HIV, malaria and tuberculosis (TB) [6]. As of November 1, 2010, the "Medicines Patent Pool" has transitioned out of UNITAID, and is functioning as a separate legal entity, though UNITAID continues to support it and is funding its operations under a five-year Memorandum of Understanding [7].

From public health and political economy perspectives, a key issue is how to design a suitable trade context for making the patent pool for ARVs both politically feasible and effective in achieving its goals. This paper contributes to debate and discussion of these issues.

A Troublesome Matter for Multinational Manufacturers

The patent pool plan invites patent holders to offer the intellectual property (IP) related to their inventions to the Medicines Patent Pool [7, 8]. Any company that wants to use the IP to produce or develop ARVs can seek a license from the pool against the payment of royalties, and may then produce the medicines for use in developing countries (conditional upon meeting agreed quality standards). The plan relies on a voluntary mechanism, meaning its success will depend on the willingness of originator pharmaceutical companies to participate and commit their IP to the pool. Quantified benefits are expected to encompass, through greatly increased competition, substantially lower prices for second and third-line patent pool generated fixed-dose combination (FDC) ARVs¹.

So compounded, the pool could help overcome inadequacies limiting the roles currently played by the brand and generic

manufacturers in availability and supply of ARVs in resource-limited countries [9]. Generic, mainly Indian, companies are supplying Sub-Saharan Africa with most of these drugs at prices below those charged by brand enterprises, and until now almost exclusively provided FDCs. Brand companies have supplied almost all newer second/third-line ARVs, stipulated voluntary licenses-VLs² with generic firms, and pursued differential pricing.

Note that the ability of Indian firms to provide these ARVs is due to the fact that India delayed introduction of pharmaceutical patents until 2005 [10]. This means that most of the first-line drugs demanded throughout the developing world (and recommended by the WHO) are not patented in India. Indeed, the fact that the drugs principally in demand were unencumbered by patents in India was a crucial factor in facilitating the massive scaling up of ARV treatment since the early 2000s.

The coincidental connection between the drugs demanded and the drugs that Indian firms could supply is changing however [11, 13]. Newer drugs are subject to patent protection in India and other supplier countries, which will make the supply heavily dependent on brand-name firms' willingness to supply drugs at low cost or via VLs. There is good reason to believe that, in the absence of generic competition, the sources of supply are unstable. After all, VLs only account for a small fraction of current procurement, while non-enforcement policies have only been implemented selectively and at full discretion of the brand enterprises. Eventually, differential prices of brand products remain (with isolated exceptions) higher than the ones of corresponding generics: frequently, such prices have only been achieved after the threat of compulsory licenses-CLs², or have sometimes failed to meet the promised country coverage due to delayed drug registration in entitled countries. Taking these realities into account, suited cutting edge ARVs for negotiations with the brand-name pharmaceutical sector were selected and put in the November 2009 UNITAID Patent Pool Implementation Plan [6].

2 World Health Organization's TRIPS (Trade-Related Aspects of Intellectual Property Rights) flexibilities: http://www.wto.org/English/tratop_e/trips_e/intel2_e.htm

Voluntary License - Agreement with the patent's owner for manufacturing and marketing. Notwithstanding royalty rates imposition on generic firms, these licenses only imply straightforward agreements between companies; they do not require changes in national legislation, while including non-exclusivity, openings towards technology transfer, access to owner's data for branded drugs as well as permission for export.

Compulsory License - When a poor country government allows to manufacture domestically or to import copies of patented drugs at prices much cheaper than those imposed by the patent holder and without his consent. Both importing and exporting countries need to have enabling legislation in place (a corresponding CL for export has to be issued by the exporting country). Prior negotiation with the patent owner for VL first is required except for situations including extreme health crisis and not-for-profit government use. Royalties to the patent owner are encompassed by CL rules.

1 FDC ARVs are multiple antiretroviral drugs combined into a single pill. They may combine different classes of ARVs or contain only a single class. These combinations allow people living with HIV to reduce the risk of developing virus resistance to treatments, while making life easier and increasing adherence by reducing the number of pills to be taken each day.

The Medicines Patent Pool plan is generating concern among the originator pharmaceutical companies. They are reluctant to join the plan owing to fears that patent pooling could result in slashed profits of the brand-name industry in middle-income countries where a significant percentage of the population can afford out-of-pocket spending (about 300 million people in India, at least 800 million in China). Inherently, the originator companies suspect that patent pooling could result in an unbalanced surge of innovation, development and research activities undertaken by the middle-income countries' (mainly India, China, Brazil, South-Africa, Thailand) manufacturers, in cutting edge generic FDC ARVs flooding the wealthy markets, in lost opportunities for VL agreements, as well as in a threat to their overall leadership [13, 14]. Issues also involve the geographical scope of the licenses, specifically who will have access to the middle-income country markets; the measures to prevent products from entering high-income markets; the bonus for patent owners (such as regulatory incentives, funding sources, or alternate methods of calculating royalties) to include many of the middle-income countries in the pool licenses [6].

Reportedly, the originator companies would possibly agree to be paid a royalty on their patents, but relinquish control over drug manufacturing, distribution and pricing in the countries to which the pool applies, limiting their revenues [15]. In short, apart from the fact that the pool would set a negative precedent for their core business, these companies are reluctant to give up their patent rights via the patent pool to the advantage of competing industries in the middle-income countries.

Meanwhile, though the US National Institutes of Health (NIH) recently licensed to the Medicines Patent Pool a royalty-free patent for third-line HIV drug darunavir (DRV), this is not enough to allow a generic low-cost version to be produced since other major manufacturers own different DRV patents [16]

Likely, the brand-name companies' fears also take into account the economic and balance of power trends in the Asia-Pacific region, where China's and India's trade/business paces appear fast [9, 17]. These insights look understandable now that Southern industries highly skilled in innovation, manufacturing and marketing are increasingly involved in South-South drug commercialization partnerships and in North-South R&D outsourcing ventures [9, 18-20]. While this environment means that trade competition between wealthy and middle-income countries is around the corner, it relies on moves (from WHO, World Intellectual Property Organization-WIPO, US President's Emergency Plan for AIDS Relief-PEPFAR, European Union-EU) and on mounting circumstances, such as enforced CLs by middle-income countries, Patent Offices' resistance to "evergreening" drug patent applications³, which reinforce each other and recommend the originator companies improve their

policies to avoid their privileges being put in jeopardy [1, 2, 9, 13, 17, 21-31]. These changes add to the cost-saving ARVs bulk purchasing agreements achieved by Clinton HIV/AIDS Initiative (CHAI)-UNITAID/Global Fund coalitions with the generic manufacturers; the in progress setting of country-owned plants for generic ARV, malarial and TB drugs in Sub-Saharan Africa; and the multiplying free trade areas set up by the developing countries to enhance trade with one another [13, 17, 20, 32, 33].

Taken together, these realities translate as backing to the core interests of leading generic manufacturers and could result, should the originators refuse to join the patent pool, in CLs charged with constraining royalty clauses and tighter room for negotiations.

Overall, the conflicting matters reported here can actually prevent the multinational manufacturers from participating in the Medicines Patent Pool plan and may well support urgency for a new trade context formulated to reverse their reluctance to join. To this aim, partnerships between originator companies are needed first to make cutting edge brand fixed-dose combination (FDC) ARVs promptly available, and secondly, to allow patent pool agreements to be negotiated straight afterwards. Clauses that exclude middle-income countries from sharing in the patent pool must be rejected.

Partnerships for Cutting Edge Fixed-Dose Brand HIV Drug Combinations

Partnerships between originator companies are required in order to produce innovatory second/third-line brand FDC ARVs and then to allow patent pool agreements to be negotiated immediately afterwards. This would allow the brand-name manufacturers to keep R&D standards and marketing power, while profiting by additional joint venture opportunities, circumventing the need for further incentives to join the patent pool, and avoiding risks of CLs. Without counting, from an ethical perspective, the gain in prestige and corporate social responsibility for making up-to-date, adherence-enhancing drug formulations available while meeting pressures from the global health community.

The suggestion above looks ready to be implemented. Deals between originator companies have, indeed, been struck as far as joint manufacturing and production of second/third-line brand FDC ARVs are concerned: for instance, the GlaxoSmithKline-Pfizer tie-up to merge HIV businesses into the new company ViiV Healthcare; and the Bristol Myers Squibb-Gilead venture for efavirenz (EFV)/emtricitabine (FTC)/tenofovir (TDF) FDC ATRIPLA® [13, 34]. These ventures would expectedly create additional partnerships now that a heat-stable 100 mg tablet version of Abbott ritonavir-RTV (which is the only sanctioned booster protease inhibitor-PI drug to be taken in conjunction with other PIs to enhance effectiveness) has been approved by both the European Medicines Agency (EMA) and the US Food and Drug Administration [35]. The expectations for additional

³ Most common in the pharmaceutical industry, "evergreening" patent application refers to the strategy of getting multiple patents that cover different aspects of the same product, usually by obtaining patents on improved versions of existing medicines.

brand partnerships would make even more sense by considering that several new ARVs and a novel booster drug are currently in the brand industry pipelines, while Tibotec is working with Gilead to produce a rilpivirine (RPV)/TDF/FTC once-daily FDC tablet up to competing with Bristol Myers Squibb-Gilead FDC ATRIPLA® (**Table 1**) [36].

These insights look intriguing in light of the breakthrough FDC ARVs recently brought out by the middle-income country (mainly Indian) generic manufacturers. Most of these generic formulations are reported in **Table 2**, wherein we can notice 1) that patent pools for first-line FDC ARVs are no longer needed in the developing countries, 2) that a number of FDC or co-packaged ARVs (not available yet from brand companies) are rolled out only by the generic manufacturers [32, 37]. Among these, TDF/lamivudine (3TC)+ atazanavir (ATV)+heat stable RTV (by Mylan/Matrix) and TDF/FTC/EFV (by Matrix, Emcure and Cipla) deserve special mention as a forerunner formulation and copy of the blockbuster brand FDC ATRIPLA®, respectively.

The instances just cited would urge Bristol Myers Squibb-Gilead to enter patent pool as far as their FDC ATRIPLA® is concerned. Again, they would strongly advise Abbott, Bristol Myers Squibb and Gilead to soon partner and manufacture a ATV/heat stable RTV/TDF/FTC FDC to resist the forerunner Mylan/Matrix formulation (wherein 3TC and FTC are interchangeable).

Overall, these moves would allow the originators to maintain competitiveness as far as purchasing agreements with CHAI-UNITAID/Global Fund coalitions to supply the under-served markets with new FDC ARVs are concerned.

Aside from the quoted cases, the entire issue here seems enough to advise the brand corporations to straightaway enter into partnership and roll out cutting edge FDC ARVs, provided the requirements below are carried into effect:

- once-daily (alternatively, twice-daily) combinations.
- partnerships not exceeding two (three max) patent owners.
- formulations suitable for hot climate, poorly electric power equipped countries.
- alignment with DHHS, EACS and WHO ARV treatment guidelines [38-40].

As per the insights above, cutting edge FDCs should include at least those listed in **Table 3**. Among them, once-daily either RPV/TDF/FTC (Gilead-Tibotec) or elvitegravir (ELV)/cobicistat (GS-9350)/TDF/FTC (Gilead) play as expected options in the near future.

TABLE 1 New ARV drugs in development

Nucleoside reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Integrase inhibitors and a new "booster"	Maturation inhibitors, CCR5 antagonists, and monoclonal antibodies
<p>Apricitabine (Avexa): Phase 3 study (stopped early for analysis). Side effects include nausea, diarrhea, nasal and chest congestion, and increases in tryglicerides.</p> <p>Amdoxovir (RFS Pharma): Phase 2. Studied doses are 300 or 500 mg taken by mouth twice-daily. Reports of eye problems or visual disturbances have been noted, and resolved upon discontinuation of the medication.</p> <p>Elvucitabine (Achillion Pharmaceuticals): Phase 2. Studied doses are 5 or 10 mg by mouth once-daily. This drug shows activity against B hepatitis. Apricitabine, Amdoxovir, and Elvucitabine may have activity against HIV strains that are resistant to other NRTIs.</p> <p>Racivir (Pharmasset, Inc.): Phase 2 studies. Standard dose yet to be determined (likely once-daily). The drug shows activity against B hepatitis.</p>	<p>Rilpivirine (Tibotec): Phase 3 studies. It seems to be active against HIV strains that are resistant to other NNRTIs. Standard dose yet to be determined (likely once-daily). Tibotec is working with Gilead using their TDF/FTC FDC drug Truvada® to roll-out a once-daily fixed dose tablet.</p> <p>DEA806 (Ardea): Phase 2. It has been shown to be active against EFV-resistant HIV strains.</p> <p>2248761, or IDX899 (ViiV Healthcare-Glaxo): Phase 2. Less susceptible to resistance when compared to EFV and nevirapine (NVP).</p>	<p>Elvitegravir (Gilead): Phase 3 integrase inhibitor. This drug needs to be "boosted" for it to be effective (RTV, as Abbott Norvir®, was used in earlier studies). It is currently studied with a new "booster" drug called cobicistat (GS-9350), also being developed by Gilead and currently in two Phase 2 studies, one comparing a once-daily "Quad" regimen (four-in-one drug combo with GS-9350, elvitegravir, and TDF/FTC FDC Truvada®) with once-daily, EFV/TDF/FTC FDC Atripla®.</p> <p>S/GSK1349572 (ViiV Healthcare-Shionogi): Phase 2 study integrase inhibitor as once-daily unboosted drug. Limited cross-resistance to raltegravir (RAL) and elvitegravir is expected</p>	<p>MPC-4326 Bevirimat (Myriad Pharmaceuticals, Inc.): Phase 2 study twice-daily taken maturation inhibitor.</p> <p>MPC-9055 Vivecon (Myriad Pharmaceuticals, Inc.): Phase 2 maturation inhibitor.</p> <p>Vicriviroc (Schering-Plough/Merck): Phase 2 CCR5 antagonist for once-daily use. Respiratory infection is one of the most common side effects. Vicriviroc seems active against HIV strains that are resistant to other entry inhibitors, like enfuvirtide (Fuzeon®).</p> <p>PRO-140 (Progenics) and Ibalizumab (Tanox): Phase 2 entry inhibitors. Both are monoclonal antibodies that bind to CCR5 receptors on CD4 cells, preventing HIV from entering the cell. Both are administered intravenously every two weeks.</p>

TABLE 2 FDC ARVs produced by generic (mainly Indian) manufacturers

<p>ZDV/3TC: adult formulations by Aspen, Aurobindo, Cipla, Emcure, Hetero, Matrix, Ranbaxy and Strides. The Clinton Foundation has negotiated reduced prices with Cipla, Aurobindo, Hetero and Matrix. Paediatric formulations by Matrix and Aurobindo.</p> <p>ZDV/3TC/ABC: adult formulations by Aurobindo (co-pack), Cipla, Hetero, Matrix and Ranbaxy. Paediatric formulations by Matrix.</p> <p>ZDV/3TC/NVP: adult formulations by Aspen (co-pack), Apotex, Aurobindo, Cipla, Hetero, Matrix, Emcure, Ranbaxy and Strides. The Clinton Foundation has negotiated reduced prices with Aurobindo, Cipla, Hetero, and Matrix. Paediatric formulations by Matrix, Ranbaxy and Government Pharmaceutical Organization (GPO). <i>Not available from originator companies.</i></p> <p>D4T/3TC/NVP: the Clinton Foundation has negotiated with Aurobindo, Matrix, Cipla and Hetero reduced prices for adult formulations. Adult formulation also made by Emcure and Ranbaxy. Paediatric formulations by Cipla and GPO (reduced prices in Clinton's consortium for versions by Cipla). <i>Not available from originator companies.</i></p> <p>ABC/3TC: adult formulations by Aurobindo (reduced price in Clinton's consortium) and Cipla. Paediatric formulations by Matrix and Aurobindo (reduced prices in Clinton's consortium).</p>	<p>D4T/3TC: adult formulations by Aurobindo, Cipla, Hetero, Matrix, Ranbaxy, Emcure, and Strides. Paediatric formulations by Cipla and Emcure. <i>Not available from originator companies.</i> Reduced prices in Clinton's consortium for versions by Aurobindo, Cipla and Matrix.</p> <p>Heat stable LPV/RTV: adult formulations by Aurobindo, Emcure, Hetero, Cipla and Matrix (reduced price for Aurobindo, Cipla, Hetero and Matrix versions in the Clinton Foundation's consortium). Paediatric formulations by Aurobindo and Matrix. N.B.: generic soft gel capsule LPV/RTV is currently produced by Cipla (no paediatric formulations).</p> <p>D4T/3TC+EFV: adult formulations by Cipla, Emcure, Strides and Ranbaxy. No paediatric formulations. Reduced prices for Cipla and Strides versions in the Clinton Foundation's consortium. <i>Not available from originator companies.</i></p> <p>ZDV/3TC+EFV: adult formulations by Aurobindo, Cipla, Emcure, Ranbaxy and Strides. No paediatric formulations. <i>Not available from originator companies.</i></p> <p>TDF/FTC: adult formulations by Aurobindo, Cipla, Emcure, Hetero and Matrix (reduced price for Matrix and Aurobindo versions in the Clinton Foundation's consortium). Not for paediatric use.</p>	<p>TDF/3TC: adult formulation by Matrix and Hetero (reduced price in the Clinton Foundation's consortium), plus Cipla. Not for paediatric use. <i>Not available from originator companies.</i></p> <p>TDF/FTC/EFV: adult formulation by Matrix (reduced price in the Clinton Foundation's consortium), Emcure and Cipla. Not for paediatric use.</p> <p>TDF/3TC+EFV: adult formulation by Cipla. Not for paediatric use. <i>Not available from originator companies.</i></p> <p>TDF/3TC/EFV: adult formulation by Matrix (reduced price in the Clinton Foundation's consortium) and Cipla. Not for paediatric use. <i>Not available from originator companies.</i></p> <p>TDF/3TC+ATV+heat stable RTV: by Mylan/Matrix (reduced price in the Clinton Foundation's consortium). <i>Not available from originator companies.</i></p> <p>ZDV = zidovudine, 3TC = lamivudine, ABC = abacavir, NVP = nevirapine, D4T = stavudine, LPV/RTV=lopinavir/ritonavir, EFV=efavirenz, TDF=tenofovir, FTC=emtricitabine, ATV = atazanavir / = FDC + = co-pack Information sources available in the reference list [32, 37].</p>
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TABLE 3 FDC ARVs doable for rolling out through brand company partnerships

<p>NAIVE PATIENTS</p> <p>Once-daily:</p> <ul style="list-style-type: none"> - DRV/heat stable RTV (Abbott-Tibotec) - ATV/heat stable RTV (Abbott-Bristol Myers Squibb) - LPV/heat stable RTV/TDF/FTC (Abbott-Gilead) - ATV/heat stable RTV/TDF/FTC (Abbott-Bristol Myers Squibb-Gilead) - DRV/heat stable RTV/TDF/FTC (Abbott-Gilead-Tibotec) - RAL^o/TDF/FTC (Gilead-Merck) <p>Alternative choices:</p> <ul style="list-style-type: none"> - once-daily SQV/heat stable RTV (Abbott-Roche) - once-daily SQV/heat stable RTV/TDF/FTC (Abbott-Gilead-Roche) - twice-daily LPV/heat stable RTV/ZDV/3TC (Abbott-GlaxoSmithKline) - once-daily FSV/heat stable RTV (Abbott-GlaxoSmithKline) - once-daily FSV/heat stable RTV/TDF/FTC (Abbott-GlaxoSmithKline-Gilead) <p>Once-daily RPV/TDF/FTC (Gilead-Tibotec) and ELV/cobicistat/TDF/FTC (Gilead) as expected options in the near future</p>	<p>EXPERIENCED PATIENTS</p> <p>Once-daily:</p> <ul style="list-style-type: none"> - ETV/DRV/heat stable RTV (Abbott-Tibotec) - ETV/LPV/heat stable RTV (Abbott-Tibotec) - ETV/TDF/FTC/DRV/heat stable RTV (Abbott-Gilead-Tibotec) - ETV/RAL^o/DRV/heat stable RTV (Abbott-Merck-Tibotec) - ETV/RAL^o/LPV/heat stable RTV (Abbott-Merck-Tibotec) <p>Twice-daily:</p> <ul style="list-style-type: none"> - ETV//DRV/heat stable RTV (Abbott-Tibotec) - ETV/LPV/heat stable RTV (Abbott-Tibotec) - RAL/DRV/heat stable RTV (Abbott-Merck-Tibotec) - ETV/RAL/DRV/heat stable RTV (Abbott-Merck-Tibotec) - ETV/RAL/LPV/heat stable RTV (Abbott-Merck-Tibotec) - ETV/MRV/DRV/heat stable RTV (Abbott-Pfizer-Tibotec) - ETV/MRV/LPV/heat stable RTV (Abbott-Pfizer-Tibotec) <p>Alternative choices:</p> <ul style="list-style-type: none"> - once-daily ETV/SQV/heat stable RTV (Abbott-Roche-Tibotec) - twice-daily ETV/SQV/heat stable RTV (Abbott-Roche-Tibotec)
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^o = final results pending about once-daily RAL.

ZDV = zidovudine, 3TC = lamivudine, LPV/RTV = lopinavir/ritonavir, TDF = tenofovir, FTC = emtricitabine, ATV = atazanavir, MRV = maraviroc,

RAL = raltegravir, ETV = etravirine, ELV = elvitegravir, RPV = rilpivirine, DRV = darunavir, SQV = saquinavir, FSV = fosamprenavir

Non-Exclusion of Middle-Income Countries from the patent pool

In this context, clauses that exclude middle-income countries (World Bank defined) from sharing in the patent pool should be rejected. Indeed, the inclusion or exclusion of middle-income countries is a key issue that merits further discussion. Given the large and growing markets in such countries, the originator firms are reluctant to participate in a patent pool that allows generic drugs derived from the patent pool's molecules to be sold in such countries. These firms want middle-income countries to be excluded in order to retain exclusive rights in such countries. Yet if the originator firms get their way and middle-income countries are excluded, it is difficult to see how the patent pool can be successful. One reason for this is that, while middle-income countries are home to almost all leading generic industries, many of them have high levels of HIV prevalence and thus high demand for cutting edge ARVs. The exclusion of middle-income countries would, therefore, exclude their own population from the patent pool market. Worse, this would severely affect the low-income countries as these are lacking in manufacturers qualified to meet home market needs with quality assured medicines. Excluding India, would mean excluding Africa given that Indian ARV manufacturers have substantially covered the African market needs [12]. So, it is odd to create a mechanism for scaling up treatment that, by design, would fail to address the treatment needs of the millions of people with HIV in the low- and middle-income countries.

A second reason for the importance of middle-income countries has to do with market structure. It is imperative that generic companies have an incentive to participate, to conduct R&D on molecules in the pool and develop appropriate formulations of generic FDCs to supply developing countries, and then sell them at low prices through UNITAID (and other organizations that pool procurement, such as the Clinton Foundation). The incentives to do so are a function of the size of the potential markets, i.e. the volume of sales that could make an exceptionally low-margin activity seem worthwhile, and if middle-income countries are excluded the patent pool may fail to promise enough demand to make it worthwhile for generic firms to participate [41]. This is a key – and perhaps irresolvable – conflict, and in designing the patent pool it is important that the price paid for originator firms' participation not be so high as to make the patent pool ineffective.

Another important issue regards whether or not patent pool-originated generic ARVs can be sold in the high-income country markets. Here we see the same trade-offs: originator firms

will not want to contribute important molecules if doing so will reduce their sales in core, developed country markets; generic firms may not find participation worthwhile if they cannot sell products in markets with larger volumes. One possibility is to align the prices of these generic formulations with the corresponding brand ones in wealthy markets, so that generic firms cannot undercut originators in these markets. The loss of market share this could imply for the brand companies would be offset by retained leadership, royalty revenues from patent pool negotiations with generic firms, profitable new joint venture opportunities, and the avoidance of major threats to their profits. Of course, this solution risks introducing a perverse set of incentives for generic firms, encouraging them to dedicate finite resources and production capacity to selling drugs at high prices in already-served high-income markets rather than focus on serving low-income markets. Thus, it may make the most amount of sense – economically and politically – to allow generic firms to export to middle-income countries but prohibit them from exporting to high-income countries.

Expected Benefits

The trade context explored here can help speed up the participation of originator pharmaceutical companies in the Medicines Patent Pool plan and make it politically feasible and effective in achieving its goals. This context seems to be equipped to uphold fairly balanced needs/market-driven dynamics for health in the drug trading policies facing generic and brand competitors. Additionally, it potentially tackles in an appropriate way the directions of evolution in emerging markets, while bringing benefits to the resource-limited populations, the multinational drug corporations and the pharmaceutical manufacturers from middle-income countries [9, 42].

Conclusions

This study mixes analysis of health needs and of changing dimensions in both legislation and the pharmaceutical industry, with a political economy focus that considers the interests and capacities of key entities involved in global HIV treatment. This approach could compensate for a limitation of the study related to its attempt to analyze the future while the patent pool story is still unfolding. So compounded, this study presents feasible proposals in the current debate, without pretending to definitely address or overcome the conflicting issues.

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Competing interests

The author declares that there are no competing interests.

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