HIV drug policies and South markets: settling controversies

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Despite progress, antiretroviral therapy coverage in low- and middle-income countries remains poor: only 31% of HIV-infected people in need were receiving treatment in 2007. Obstacles include weak healthcare systems, a critical shortage of human resources and a lack of sustainable, long-term funding. Considering that health spending is still less than US$10 per person per year in most African countries, these obstacles act as key barriers in preventing poor people from obtaining life-saving drugs. Under this backcloth, out-of-reach prices still prevent HIV-infected people in most income-constrained countries from accessing brand antiretroviral drugs (ARVs). In the meantime, evolutionary strategies by governments and generic companies in emerging South markets look like they would place a risk of failure on the ARVs pricing policies of the multinational brand corporations. This article explores an attuned model to allow the brand and generic manufacturers to appropriately tackle evolutionary trends in the emerging markets, while securing the poorest expanded access to fairly priced ARVs, either for the present or the future. The potential of the model was investigated by examining: the current brand and generic company roles; the forecasts from government and drug trading directions of India, China, USA, Canada, Brazil and Thailand; the foreseeable implications of multiplying South–South partnerships; and the impact of the UNITAID–Clinton Foundation coalition. The highlighted model aims to reliably provide – through a combination of incentives, the WHO's brokerage, fairly used differential pricing and the World Trade Organization's flexibilities – several opportunities to the brand and generic enterprises, while cutting prices and promoting equitable access to ARVs.

Keywords: antiretroviral drug pricing policies, brand and generic manufacturers, emerging South markets, equitable access

future medicine part of fsg

Despite progress, antiretroviral therapy coverage in low- and middle-income countries remains poor: only 31% of HIV-infected people in need were receiving treatment in 2007 [101]. Obstacles include weak healthcare systems, a critical shortage of human resources and a lack of sustainable, long-term funding [101]. At the end of 2007, the annual gap between the required and available financial resources to achieve universal access goals was estimated to be US$8.1 billion; to meet targets, available funding must rise up to approximately US$35 billion by 2010 and up to US$41 billion by 2015 [101]. Considering that health spending is still less than US$10 per person per year in most African countries, these obstacles play as key barriers in preventing poor people from obtaining life-saving drugs.

Under this backcloth, out-of-reach prices still prevent HIV-infected people in most income-constrained countries from accessing brand antiretroviral drugs (ARVs) [102]. This adds to hindrances bound up with the enforcement of Trade-Related Aspects of Intellectual Property Rights (TRIPS) inside the World Trade Organization (WTO) (**Box 1**): patent protection, by eliminating generic competition, has skyrocketed drug prices [103]. At the same time, TRIPS-plus measures do hamper the development of any new generic antiretroviral formulation containing drugs under exacerbated data exclusivity (**Box 2**) [1].

This is a worrying situation, despite the fact that the TRIPS encompass flexibilities (including voluntary licenses [VLs] and compulsory licenses [CLs]) to help equitably access low-priced drugs: without price reductions, the cost of second-line ARVs (presently, two- to nine-times more expensive than first-line drugs) could account for as much as 90% of funding used for ARV treatment by 2012 (**Box 1**) [2,3,104].

In the meantime, evolutionary strategies by governments and generic companies in emerging South markets look like they would place a risk of failure on the pricing policies of the multinational brand corporations for the ARVs.

This article explores an attuned model to allow the brand and generic manufacturers to appropriately tackle evolutionary trends in the

Box 1. TRIPS regulatory terms for patent status of drugs.

Patent

- A 20-year warranty securing the inventor exclusive rights on the overall drug production and marketing aspects. When countries signed up to the WTO they agreed to protect the patent rights of corporations selling drugs within their boundaries.

TRIPS

- WTO Agreement (1994) to the safeguard of Intellectual Property Rights around the world.
- It protects companies by stopping anyone from copying their products for at least 20 years.

Drugs invented before 1995

- No need for patent protection by a WTO member State if drugs were not patented before 1995 (i.e., before TRIPS came into force).

1995–2005 'mailbox' drugs

- Refers to drugs invented in the period 1995–2005 (including second-line ARVs) for which WTO members that did not recognize drug patents before 1995 were offered diversified time limits to become TRIPS compliant. Transitional countries have to hold patent applications on these drugs in a so-called mailbox and secure patent applicants exclusive marketing rights for 5 years once the drug was in the mailbox and registration was made by the national drug regulatory authority.

Post-2005 drugs

- All WTO members, with exception of the LDCs, are requested to be TRIPS compliant.

Dates for LDCs

- LDCs had to become TRIPS compliant by 2006 but, if national legislation was consistently amended, they are exempt from accepting patent protections and TRIPS enforcement until 2016. Aside from this flexibility, even LDCs have to issue compulsory licenses (see below) for importing copies of drugs already patented in pre-TRIPS domestic law.

Doha Declaration, 14 November 2001

- Stated that each WTO member has the right to use TRIPS-encompassed flexibilities (which include compulsory and voluntary licenses) to secure universal access to drugs in the face of a public-health need.

Compulsory licensing

- When the government of a poor country allows the domestic manufacture or import of 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 compulsory licensing [CL] for export has to be issued by the exporting country). Prior negotiation with the patent owner for voluntary license first is required, unless for situations including extreme health crisis and not-for-profit government use. Payment of a royalty to the patent owner is encompassed by CL rules.

Voluntary licensing

- Agreement negotiated 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 nonexclusivity, openings towards technology transfer, access to owner's data for branded drugs and permission for export.

Decision, 30 August, 2003

- Allows non-manufacturing countries to issue a CL to import a generic version of a particular medicine based on a CL for export issued by the exporting country government. Declaration by the non-manufacturing country of insufficiency in manufacturing the specific drug is required. WTO amendment approved on 6 December 2005 made the Decision permanent, based on two-thirds of WTO members ratifying it by December 2007. On 23 October 2007, the deadline was postponed to the end of 2009.

Data exclusivity

- Data protection against unfair commercial use only (but 5- and 8-year protection have been requested by the USA and Europe, respectively).

ARV: Antiretroviral drug; LDC: Least-developed country; TRIPS: Trade-Related Aspects of Intellectual Property Rights; WTO: World Trade Organization.

emerging markets, while securing the poorest expanded access to fairly priced ARVs (including second and third lines) either for the present or the future.

The potential of the model was investigated by examining:

- Current brand and generic company roles
- Forecasts from government and drug trading directions of India, China, the USA, Canada, Brazil and Thailand
- Foreseeable implications of multiplying South–South partnerships
- Impact of the UNITAID–Clinton Foundation coalition

Box 2. Exacerbated data exclusivity.

The term exacerbated data exclusivity refers to a practice that temporarily bars registration files of an originator from being used to register the generic copy of a brand-name medicine. As long as it is within a fixed time period (5 years in the USA and 8 years in the Europe), Drug Regulatory Authorities are prevented from registering such generic equivalents unless the generic producer has independently carried out the required safety and efficacy tests, or bilateral agreements encompassing VL use (**Box 1**) have been undertaken.

Data exclusivity impacts by barring CL use (**Box 1**) until the expiry of data exclusivity itself and, mainly, by securing research-based companies a monopoly period in countries agreeing to data exclusivity even when a medicine is not patented in the specified country.

This practice goes beyond the WTO's request for data protection against unfair commercial use only (**Box 1**).

CL: Compulsory license; VL: Voluntary license; WTO: World Trade Organization.

The present: brand & generic company roles

Brand and generic companies are playing different roles in increasing the availability of ARVs in the resource-constrained countries [4,5]. Generic companies (sometimes through government CLs) are supplying sub-Saharan Africa with most of these drugs at prices below those charged by brand enterprises, and, until now, almost exclusively provided fixed-dose combinations (FDCs) (**Box 3**) [102]. Brand companies have supplied almost all second-line ARVs, stipulated VLs with generic firms, pursued differential pricing, and are not strictly enforcing patents in some countries. These realities suggest that a combination of tools, including CLs, a lack of product patents over older drugs, VLs and nonenforcement of patents have pushed the generic production of patented drugs.

Unfortunately, newer drugs are subject to patent protection in India and other supplier countries, CLs have resulted in pressure, sometimes retaliation, from brand industries and governments in wealthy countries and VLs only account for a small fraction of current procurement, while nonenforcement policies have only been implemented selectively and at full discretion of the brand enterprises. Eventually, differential prices of brand products will remain (with isolated exceptions) higher than the ones of corresponding generics: quite often they have only been achieved after CL threat, or have sometimes failed to meet the promised country coverage due to delayed drug registration in entitled countries [102].

Forecasts from country policies

India & China's ways forward

China applied TRIPS in 2002, while India did so on the 1 January 2005. Overall, industrial plants of both countries supply most of the home needs, while exporting high volumes of drugs to the underserved markets. Chinese and Indian firms are becoming increasingly involved with multinational industries in manufacturing and R&D partnerships, including nanotechnology, robotics and bioinformatics and genomics [5]. It seems that China and India are enmeshed in overlapping interests with research-based corporations to support their forays into the world is major markets. In the meantime, the number of patent applications from China and India filed at the US Patent Office has been rising rapidly [5]. Furthermore, China and, to a lesser extent, India, are the major suppliers of active pharmaceutical ingredients (APIs) for ARVs to the developed and developing world [5]. This provides both countries with power in influencing the ARV drug price evolution. Indeed, as APIs do represent the largest components of direct manufacturing costs (55–99%), significant decreases in the price of ARVs will depend on a concomitant decrease in the cost of the APIs [6].

India's cornerstone policy

In line with WTO obligations, India recently granted the brand companies Pfizer (NY, USA) and Tibotec (Mechelen, Belgium) patents for the new HIV entry-blocking drug maraviroc and the new non-nucleoside reverse transcriptase inhibitor etravirine, respectively [105–107]. This adds to the patent granted for Merck's (NJ, USA) integrase inhibitor raltegravir [102]. At the same time, Section 3 (d) of the Indian Patent Act has denied patentability to "a new form of a known substance" unless it results in "enhancement of the known efficacy of the substance" [105]. In fact, India's Patent Office is considering Abbott's (IL, USA) patent application for heat-stable lopinavir/r (LPV/r), but, consistent with the Patent Section described above, could possibly reject it. If this was the end result, the Indian firms Matrix (Andhra Pradesh, India), Aurobindo (Andhra Pradesh), Cipla (Mumbai, India) and Emcure (Pune, India) would

Box 3. Fixed-dose antiretroviral drug combinations by generic companies.

- AZT/3TC: adult formulations by Aspen, Aurobindo, Cipla, Emcure, Hetero, Matrix, Ranbaxy and Strides. The Clinton Foundation has negotiated reduced prices with Cipla and Matrix. Pediatric formulation by Matrix.
- AZT/3TC/ABC: adult formulations by Aurobindo (co-pack), Cipla, Hetero, Matrix, and Ranbaxy. No pediatric formulations.
- AZT/3TC/NVP: adult formulations by Aspen (co-pack), Apotex, Aurobindo, Cipla, Hetero, Matrix, Emcure, Ranbaxy. The Clinton Foundation has negotiated reduced prices with Aurobindo, Hetero, Cipla and Matrix. Pediatric formulations by Matrix, Government Pharmaceutical Organization (GPO) and Ranbaxy. Not available from originator companies.
- D4T/3TC/NVP: the Clinton Foundation has negotiated with Aurobindo, Hetero, Matrix, Cipla and Ranbaxy reduced prices for adult formulations. Adult formulation also made by Emcure and Strides. Pediatric formulations by Cipla, Hetero, GPO, Emcure and Ranbaxy (reduced prices in Clinton's consortium for versions by Cipla and Ranbaxy). Not available from originator companies.
- ABC/3TC: adult formulation by Cipla. Pediatric formulations by Matrix and Aurobindo (reduced prices in Clinton's consortium)
- D4T/3TC: adult formulations by Aurobindo, Cipla, Hetero, Matrix, Ranbaxy, Emcure and Strides. Pediatric formulations by Cipla, Emcure and Ranbaxy. Not available from originator companies. Reduced prices in Clinton's consortium for versions by Aurobindo, Cipla, Hetero, Matrix, Ranbaxy and Strides.
- Heat-stable LPV/r: adult formulations by Aurobindo, Emcure, Cipla and Matrix (reduced price for Aurobindo, Cipla and Matrix versions in the Clinton Foundation's consortium). Pediatric formulations by Aurobindo and Matrix. N.B.: Generic soft gel capsule LPV/r are currently produced by Cipla and Hetero (no pediatric formulations).
- D4T/3TC + EFV: adult formulations by Cipla, Emcure, Strides and Ranbaxy. No pediatric formulations. Not available from originator companies.
- AZT/3TC + EFV: adult formulations by Aurobindo, Cipla, Emcure and Ranbaxy. No pediatric formulations. Not available from originator companies.
- **PMTCT**: NVP + AZT: granule formulations by Strides. Not available from originator companies.
- TDF/FTC: adult formulations by Cipla, Emcure, Hetero and Matrix (reduced price for Matrix version in the Clinton Foundation's consortium). Not for pediatric use.
- TDF/3TC: adult formulation by Matrix and Cipla (reduced price in the Clinton Foundation's consortium). Not for pediatric use. Not available from originator companies.
- TDF/FTC/EFV: adult formulation by Matrix (reduced price in the Clinton Foundation's consortium), Emcure and Cipla. Not for pediatric use.
- TDF/3TC + EFV: adult formulation by Cipla. Not for pediatric use. Not available from originator companies.
- TDF/3TC/EFV: adult formulation by Matrix (reduced price in the Clinton Foundation's consortium). Not for paediatric use. Not available from originator companies.

3TC: Lamivudine; ABC: Abacavir; AZT: Zidovudine; D4T: Stavudine; EFV: Efavirenz; FTC: Emtricitabine; LPV/r: Lopinavir/ritonavir; NVP: Nevirapine; PMTCT: Prevention mother-to-child transmission; TDF: Tenofovir. WHO prequalified ARVs (updated list) at [151].
Information mainly obtained from [102].

be allowed to continue manufacturing adult- and pediatric-strength heat-stable LPV/r tablets. Of note, the same Office just refused, for reasons of 'evergreening', a patent application from Boehringer–Ingelheim (Ingelheim, Germany) for nevirapine syrup; as a result, the Indian companies Aurobindo and Cipla are allowed to carry on with generic production [102].

These insights take into account the recent withdrawal of patent applications in India by GlaxoSmithKline (London, UK) (abacavir-based formulations) and Novartis (Basel, Switzerland) (atazanavir), after the Indian Court, on August 2007, rejected a Novartis challenge to the abovementioned Section of the Country's Patent Law [108–110]. Understandably, Glaxo and Novartis thought it preferable to withdraw their applications rather than be rejected and weaken their chance for success elsewhere.

In the meantime, the US Patent Office rejection in January 2008 of the already enforced Gilead Science's (CA, USA) tenofovir patents in the USA will likely compel the company to withdraw tenofovir patent applications in India based on highly expected rejection by the Indian Patent Office as well [111]. These actions could benefit Indian companies who manufacture a generic version of the drug in India [102].

Intriguingly, all scenarios here also take into account the currently working Indian National AIDS Control Organization's (NACO's) plan to provide approximately 5000 first-line resistant HIV-positive people with free access to second-line ARVs starting from January 2008. For the first 2 years, UNITAID (an international drug purchase facility financed primarily from the proceeds of a tax levied on airline tickets) would endorse the costs; afterwards, the Indian government will partner with Indian drug makers to continue with the program [112].

Why, in such a context (wherein heat-stable LPV/r and tenofovir will largely be supplied by local manufacturers inside the Clinton Foundation–UNITAID alliance), should the Indian

government grant the brand corporations their patent applications, thus disregarding key national interests?

These scenarios alert us to the fact that additional Indian firms will predictably begin manufacturing tenofovir and heat-stable LPV/r, so boosting greater competitiveness on the market and the gradual reduction of generic copy prices, to the detriment of the interests of Gilead and Abbott.

China's pending decision

China currently produces seven types of first-line ARV formulations, as well as the raw materials for first- and second-line ARVs [5,113]. China, however, is under pressure due to its weak pursuance of TRIPS [114], while no Chinese ARVs have been prequalified by the WHO to date. Nonetheless, a WHO Public Inspection Report in June 2006 remarked that Shanghai Desano Ltd (Shanghai, China), as a key manufacturer of ARVs and APIs, exhibited an acceptable compliance level with the principles laid down in the WHO's standards of Good Manufacturing Practices [115].

China is a country where a final decision is pending between TRIPS flexibilities and business with multinational giants, including branded drug price cuttings [5,7]. With this situation in mind, the Chinese State Food and Drug Administration (SFDA) recently decided to import Abbott's heat-stable LPV/r (while a decision for Gilead's tenofovir is underway), now that the number of estimated HIV/AIDS cases in China has exceeded 700,000, HIV drug resistance is on the rise and at least 85,000 patients are suffering from late-stage AIDS [113].

This move fully disregarded the corresponding Indian copies also available through the Clinton Foundation (a consortium that China is a member of); how much longer will it be worthwhile to the Chinese government to ignore the cost-saving opportunities that Indian generics provide [102]? The China–India trade and policy agreements signed on November 2006 and January 2008 are expected to act as catalysts for bilateral transactions, grounded on mutually profitable conditions, for the manufacturing and marketing of ARVs [5].

Openings in US drug trading policy

Although the USA is witnessing its will to defend the 'brand name' product ('free-trade agreements' with coercive TRIPS-plus clauses are mushrooming) [5], key openings to generic ARVs were achieved recently, following strategic agreements on the 'international chessboard': a USA–India partnership, boosted by the 2 March, 2006 'civil nuclear power' agreement [116], has resulted in exploitation of Indian ARVs inside the President's Emergency Plan for AIDS Relief (PEPFAR). Today, among the ARVs approved by the US FDA, more than 52 have originated from India [117–121].

Intriguingly, rejection of Gilead's tenofovir patents by the US Patent Office, as mentioned before, came just after the FDA had granted the Indian company Matrix permission to allow its copy (already enlisted by the Clinton Foundation) to be included in PEPFAR [120]. This is an unprecedented case, perhaps meaning that strategy balances in South-East Asia now weigh more than brand drug patent defence inside the India–USA partnership.

In such a new context, it is also expected that the current debate on a Democrat move to make the US free-trade agreement language closer in line with the WTO-endorsed Doha Declaration would be successful [8].

The Canadian way

In October 2007, Canada notified the WTO of a government CL authorizing Toronto-based generic manufacturer Apotex to produce WHO-prequalified FDC copies of three patented medicines (zidovudine, lamivudine and nevirapine) for export to Rwanda [122]. On July 2007, Rwanda had notified the WTO of the decision to issue a corresponding CL for import [122]. This made Rwanda the first country to date notifying the use of the WTO's 30 August 2003 waiver to address public health needs by importing a patented medicine produced without authorization of the patent owner (**Box 1**). This is the first time a generic company in the developed world has entered competition to provide an African country with ARVs.

This is a forefront, hopefully contagious, result that Canada has achieved, although 3 years were spent due to the cumbersome law process. Calls are being reiterated in Canada for transforming the barely used regime into a 'one-license solution' that would authorize a company to produce the same drug for export to any country that submits notifications to the WTO. This would be a working method of helping other countries in need of generic ARVs [122].

Brazil: cautiously ahead

By threatening to issue CLs and producing drugs locally, Brazil has almost always negotiated the lowest prices for branded ARVs. By

contrast, current prices for Brazil's locally produced generics are generally much higher than the corresponding global prices [9].

Total Brazilian drug expenditures doubled from 2001 to 2005, to reach US$414 million, with cost increases mainly attributable to enhanced purchase quantities of some branded ARVs (i.e., LPV/r, efavirenz, tenofovir, atazanavir and enfuvirtide) [10–12].

Brazil has the technical capacity to produce all new ARVs, but CLs have very rarely been issued to date (including the one for Merck's efavirenz in May 2007) because of fear of damaging international, mainly US, trade relations. If the government instead made these drugs at the state-owned Farmanguinhos industry, the country would save money. The costs of currently home-made ARVs would be reduced if Brazil started to produce APIs instead of purchasing from India and China [5].

Based on a 6-year price-discount agreement, Brazil is still bound to purchase adult-strength heat-stable LPV/r from Abbott at US$1000 per person/year, which is too expensive compared with the Indian Matrix copy that is currently available through the Clinton Foundation, thanks to UNITAID revenues, at US$550 per person/year to countries in its consortium (which Brazil belongs to) [102].

Why, with skyrocketed domestic expenditure on imported ARVs, should Brazil not issue a specific CL against Abbott to take advantage of Matrix/Clinton/UNITAID opportunities? Possibly, Brazil is ready to do so, while only waiting for rejection of Abbott's LPV/r patent application in India. In such a hard move, Brazil would still be favored by the presently soft, mutually interested USA–India relations. This adds to a Ministry of Health decree on 9 April 2008 alerting that Brazil might refuse Gilead's patent application for tenofovir (due to expense) and import the corresponding generic. Should these forecasts come true, Abbott and Gilead would lose the Brazilian HIV market.

Thailand's bet

The Thai government issued a CL against Abbott's LPV/r in January 2007, 2 months after the government issued a CL for Merck's efavirenz [12,123]. Currently, the country imports efavirenz and heat-stable LPV/r (whose registration has already been made by Thailand's Food and Drug Administration) as generics directly from Indian producers [124]. Thailand has also planned for domestic drug manufacturing as soon as the production by the state-owned Government Pharmaceutical Organization (GPO) comes on line: in the meantime, the Indian firms Matrix and Cipla are providing Thailand with corresponding APIs [125]. Negotiations between the Thai government and brand companies are still continuing, while the US Trade Representative's Office placed Thailand on its Priority Watch List on 30 April 2007 [126]. Follow-up is needed to verify the Thai policy sustainability. In theory, Thailand could be up to the task because:

- The country could indefinitely go on with importing drugs from Indian manufacturers directly or through the Clinton Foundation, as Thailand is a member of its consortium;
- The country is equipped for domestic manufacturing to at least cover home needs;
- Despite the risks bound-up with CL policy (trade retaliations by USA with loss of support in Thailand's tricky relations with China, India and Myanmar), the country is up to resisting either by relying on the persistence of current balances in South-East Asia, or by enjoying the advantages from new South–South partnerships (in May 2007, the Thai Minister of Public Health announced that Brazil and Thailand would sign a cooperation agreement on health development; in the meantime, the GPO was collaborating with the Indian drug manufacturer Hetero Drugs (Hyderabad, India) to build a new WHO standard meeting plant in Thailand) [5,127].

If these prospects were fulfilled, the brand companies should give up their profits in Thailand. Really, it looks like this still would be possible despite Thailand's return to democracy with a right-wing probusiness new coalition government in February 2008 [128,129].

South–South partnerships

South–South partnerships are emerging as a mushrooming phenomenon in the ARV drug production and marketing sector. Partnerships addressing the building and output of malarial, TB and ARV drug plants (also as wide Southern Africa regional companies become cost effective and stronger in resisting pressures by drug multinationals and wealthy countries' governments) are currently operative in Africa between country governments (i.e., Mozambique–Zimbabwe and Mozambique–Brazil) or generic drug companies (i.e., Ugandan Quality Chemicals–Indian Cipla Pharmaceuticals Ltd; South African Aspen Pharmacare–Indian Matrix Laboratories

Ltd) [130–133]. They fall into the African Union and the Economic Community of West African States (ECOWAS) self-sufficiency plans, and add to expanding examples of country-owned drug plants in other African countries (i.e., Pharmakina: Democratic Republic of Congo; Tanzanian Pharmaceutical Industries: Tanzania) [13,134,135]. These partnerships help to strengthen the competitiveness of the generic pharmaceutical companies against the multinationals.

Some of the world's 'emerging economies', such as Brazil, India and China, have increased their trade with and development assistance to other developing nations, including HIV/AIDS treatment assistance and aid to Africa [136].

Brazil has provided locally manufactured ARVs to approximately 11 developing countries. In addition, Brazil coordinates an international HIV/AIDS technical cooperation network, including Argentina, China, Cuba, Nigeria, Russia, Thailand and Ukraine, that aims at facilitating the transfer of technologies for the production of ARVs [136].

India has allocated approximately US$200 million for the New Partnership for Africa's Development (NEPAD) and provided West African countries with approximately US$500 million in aid [136].

China has pledged to double aid to Africa by 2009 to approximately US$1 billion, as well as to establish a China–Africa development fund of approximately US$5 billion aimed at encouraging Chinese companies to invest in the continent [136]. This sounds consistent with China's exceeding interests in Africa, as shown by bilateral agreements already signed, or currently underway, with many African countries and encompassing trade, energy supply, and infrastructure and health cooperation. China has also cancelled all debt stemming from Chinese interest-free government loans that matured by the end of 2005 for the heavily indebted and least developed countries in Africa that have diplomatic relations with China [14,136,137].

Forecasts from the South–South partnerships would possibly imply erosion of profits and overseas markets for the brand enterprises. These threats (adding to the fear of CL issuing) will expectedly push the brand corporations into more flexible transactions with the generic competitors. The following agreements have already been signed:

- The Bristol–Myers Squibb (BMS, NY, USA) VL agreement with Aspen Pharmacare and Emcure Ltd to manufacture and sell the protease inhibitor atazanavir in sub-Saharan Africa and India, respectively (February 2006): a royalty-free license to operate under relevant patents was encompassed, along with transfer to Aspen and Emcure of BMS technical know-how related to the manufacturing, testing, packaging, storage and handling of the API and the finished dosage form of atazanavir. BMS provision of technical training both at its manufacturing facilities and at Aspen's and Emcure's facilities in South Africa and India was included too, along with support to the two companies for regulatory filings [138];
- The Johnson & Johnson subsidiary, Tibotec Pharmaceuticals, VL agreement with Aspen Pharmacare to package and cheaply distribute the protease inhibitor darunavir in sub-Saharan Africa (April 2007) [139];
- The Roche (Basel, Switzerland) VL agreements with Addis Pharmaceutical Factory (Addis Ababa, Ethiopia) and Varichem Pharmaceuticals (Harare, Zimbabwe) for ARV production training (May 2007): the two African companies are provided with no-cost technical training and guidance to manufacture generic ARVs based on the processes used to develop Roche's second-line ARV saquinavir. Roche staff will work onsite at the manufacturing facilities in Ethiopia and Zimbabwe and from the company's headquarters in Switzerland. Generic saquinavir marketing is not allowed outside sub-Saharan Africa and least developed countries. A total of 32 manufacturers in 15 eligible countries – including Ghana, Kenya, Nigeria and Zimbabwe – have expressed interest in participating in the initiative [140].

Awareness of all scenarios above, coupled with TRIPS and TRIPS-plus hindering obligations (**Boxes 1 & 2**), should spur the generic manufacturers into boosting innovation, aiming at new drugs development. This would let them more easily gain the western markets, while enhancing competition with the brand counterparts [5]. Actually, Taiwan's National Development Fund has already disclosed plans to finance the biotechnology company TaiMed Biologics to develop new ARVs within 3 years [141]. The South African company ARVIR is exploring novel process technologies to build local API manufacture and develop new ARV drug leads [142].

With these perspectives in mind, why should the generic manufacturers not fuel multipronged VL deals with the brand industry to exploit the

entwined know-how, training and technology transfer opportunities for new ARVs production? This would imply gain in economic value added, job creation, foreign exchange savings and security of supply.

Thoughts so far underscore the reasons for setting up country-owned plants for generic ARVs in sub-Saharan Africa also [2,5,13]. Home plants would add strength to negotiating profitable VLs encompassing expanded ARV drug access. An industrial potential will likely be the opportunity of drawing the branded drug producers into more flexible agreements, securing mutual advantages. Under such a perspective, China's cheapest APIs could serve as a key source for the take-off of sub-Saharan plants.

Clinton Foundation–UNITAID alliance

The Clinton Foundation HIV/AIDS Initiative (CHAI) is increasingly lowering the prices of ARVs by partnering with UNITAID and working with generic and brand pharmaceutical manufacturers [143,144].

In the meantime, lists of countries eligible for differential pricing have been made available by Abbott, BMS, Boehringer–Ingelheim, Gilead, GlaxoSmithKline, Merck & Co. Inc. and Roche brand enterprises; unfortunately, the prices they offer are almost always substantially higher than the reduced ones offered by CHAI for the corresponding generics to countries in its consortium [102,145].

It is risky for the brand corporations to keep prices higher than those of the Clinton Foundation, especially if the counterpart is a CHAI consortium member country. The magnitude of risk is perceivable by considering that:

- Some FDC ARVs, still solely produced by generic firms (**Box 3**), have been made available to resource-constrained countries only thanks to CHAI discounts [102];
- The Clinton consortium is expected to add further countries to its 69 present members, leading to an even greater number of cheaper ARVs as a result of enhanced bulk procurement [145].

UNITAID is an international facility established to provide long-term funding to increase access to drugs and diagnostics for HIV/AIDS, malaria and TB in the developing countries [146]. It entwines with a number of partners including the Global Fund, the World Bank, the WHO, UNAIDS and the Clinton Foundation.

CHAI was selected as UNITAID's implementing partner for two programs for HIV/AIDS care and treatment: the scale-up of pediatric care and the expansion of availability of second-line ARVs for adults [147]. In May 2007, UNITAID committed US$36 million in partnership with CHAI towards the purchase and delivery of second-line ARVs in 27 countries [143]. At the end of October 2007, the partnership had:

- Reduced the average price for second-line ARVs by 25% compared with the lowest available market rates in low-income countries, and 50% compared with the lowest available rates in middle-income countries outside of Africa;
- Initiated procurement for 20 countries and delivered products to 17 countries; volumes associated with second-line treatments for 29,000 patients.

Recently, the UNITAID Board approved plans detailing the continuation of their collaboration with CHAI through 2010 [147].

UNITAID may be assigned a special role to help a for-access incentive strategy succeed. Country governments could be allocated UNITAID revenues to finance fiscal relief to their generic firms. These revenues can allow (as in a CHAI–UNITAID–Cipla and Matrix recently signed agreement) multiyear large-volume purchasing programs with generic drug companies to be negotiated by international players [5].

The information above alerts us to the fact that the Clinton–UNITAID alliance has created a minefield for ARVs policies currently driven by the brand pharmaceutical sector.

Looking for an attuned model

Could there conceivably be a model that will allow brand and generic manufacturers to safeguard their interests, while securing the poorest expanded access to fairly priced ARVs (including second and third lines) either for the present or the future?

The dynamics explored in this perspective article have highlighted the generic industry's interest in VL agreements with the originator companies, wherein incentives should be included to ensure the lowest possible prices and most expanded access to ARVs. These incentives are awaited by the governments and the international players, and must encompass funding to give the generic manufacturers prompt reasons for keeping prices low. Funding could even arise through full debt cancellation to poor countries, wherein the 'Debt2Health' Global Fund initiative (whereby a portion of a country's debt is cancelled if an agreed-upon amount is invested in a Global Fund programme) could be instrumental [148].

Basically, an incentive strategy should comprise:

- Exclusive bulk purchasing of generic ARVs by international donors, provided the prequalification by WHO is accepted. This would result in price reductions, while the transparency enjoyed through WHO checks would make the model trustworthy;
- Fiscal relief to generic firms by country governments. Sources of tax allowance may include: enhanced disbursement by donors, domestic expenditure priority reallocations, and debt relief savings from debt cancellation;
- WHO brokerage inside the negotiations between brand and generic companies to maximize the equitable access to drugs. This would be attuned with the resolutions adopted at the 61st WHO World Health Assembly in May 2008 [149].

Cross-information here would advise the brand corporations:

- To look for quick registration of their ARV formulations by regulatory authorities in all countries on differential pricing lists;
- To apply differentiated prices to all their pediatric and for-adult formulations;
- To align their prices with those fixed by the Clinton Foundation for the corresponding generics in its list (so ensuring competition, based on the CHAI, is oriented towards high-quality drugs already approved by the WHO and/or FDA);
- To consider flexible VL transactions with generic competitors to secure both counterparts sustained advantages. As far as this model is concerned, China looks like it would be an eligible counterpart as it does not yet import generic ARVs and exhibits a reliable industrial potential, self-sufficient API sources, a huge national market, and deeply entwined interests with the brand multinationals. The Chinese government should be attracted by VL-based agreements for the following needs:
  - Technological catch-up while aiming to compete with the brand corporations;
  - Enhanced and diversified ARVs production, including second and third lines, as well as FDCs and pediatric formulations, all of which are not yet produced in China;
  - Sustainable self-sufficiency in pharmaceutical manufacturing to break away from price fluctuations by foreign enterprises.

Again, cross-information here would advise the generic companies and governments in the underserved markets:

- To be tireless in negotiating VLs or differential prices with the brand competitors, wherein the CL threat looks fruitful to bring the patent holders to more reasonable positions, while giving the generic firms stronger negotiation power;
- To direct all efforts towards the attainment of CHAI consortium membership.

Conclusion

The model explored here would allow the brand corporations to appropriately tackle the evolutionary directions from emerging South markets. Again, this model looks like it would be reliable to bring, through the WHO's brokerage, several opportunities to the generic enterprises, while cutting prices and promoting equitable access to ARVs. Additionally, it looks suitable for coupling with patent pool mechanisms (as endorsed by UNITAID), to further enhance competition and make second-/third-line ARVs and new FDCs even more affordable and available [150]. The highlighted model would take advantage of concurrent interventions in the overall ARV drug access sector in resource-limited countries; these include investing in infrastructures, dealing with the loss of healthcare workers, improving accountability and policies of local governments over counterfeit and substandard ARVs, over drug leakage and diversion and over tariffs on imported medicines.

Author note

While this paper was in the final press stage, the Brazilian Patent Office rejected (September 2nd, 2008) the patent application by Gilead for the drug tenofovir (TDF).

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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