

Decrease in Prices of Antiretroviral Drugs for Developing Countries: from Political “Philanthropy” to Regulated Markets?

STÉPHANE LUCCHINI, BOUBOU CISSE,
SÉGOLÈNE DURAN, MARIE DE CENIVAL,
CAROLINE COMITI, MARION GAUDRY, JEAN-PAUL MOATTI

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Abstract

This paper gives some economic background about recent debates on the feasibility of introducing a “differential pricing” for HIV/AIDS drugs in favour of developing countries. It presents the methodology and the main results of research carried out for the ANRS ETAPSUD programme on determinants of source prices of antiretroviral (ARV) drugs in Brazil and 13 African countries (see page 207) during the period 1998-2002. Analysis of 1,030 observed transactions reveals a declining price trend for antiretroviral (ARV) drugs which is nearly linear between 1997-2000, with an accelerated decrease for the year 2001, followed by a more limited decrease in 2002. This trend corresponds to a significant reduction in price differences between brand drugs and generic substitutes and between countries. It also shows a relationship between higher volumes per transaction and lower prices that has, however, tended to diminish in the last few years.

Econometric analysis, using multiple linear regression, shows that the following factors were associated with price increases: ARV drugs belonging to the more recent classes, such as protease inhibitors (PIs), existence of patent protection for the drug at country level, higher HIV prevalence, national guidelines recommending PI drugs for first-intention treatment, and intervention of intermediary wholesalers in the transaction. On the other hand, transactions in

countries with organised public programmes for ARV delivery and in countries which participated in the Accelerated Access Initiative (AAI), the partnership that was launched in 2001 between UN organisations and six brand-name major pharmaceutical companies, were associated with lower prices. However, even after adjustment for these factors, the introduction of generic competition remains an essential factor for price decreases. Indeed, while countries like Brazil, Nigeria and Malawi have always carried out competitive negotiations with multiple suppliers including generic manufacturers, most African countries in our sample have evolved toward a “hybrid” mechanism of procurement that combines negotiations in the AAI international framework with national tenders or other procurement mechanisms introducing generic competition.

The main policy recommendation that emerges from the study is that excessive reliance on “corporate philanthropy” and international bargaining between UN organisations and the major brand-name manufacturers will not guarantee the long term sustainability of the lower differential pricing of ARV drugs that has de facto been established in some African countries since the year 2001, and its extension to a greater number of countries and to a greater number of drugs that are needed, in addition to ARVs, for HIV-infected patients. The buyer-size effect, that could be obtained through globalisation of purchases of HIV/AIDS drugs between several countries, will only translate into price decreases to the extent that buyers have the power to substitute between multiple suppliers. To achieve the recommendation recently adopted by the Global Fund to Fight AIDS, Tuberculosis and Malaria that countries should purchase quality-controlled HIV/AIDS drugs at the minimum cost, decentralised negotiations, extended market competition to all potential drug suppliers, and regulatory flexibility (in international agreements, and in national legislation) towards local production and imports of generic drugs are essential.

Résumé

Après avoir synthétisé la littérature économique récente sur la faisabilité d'un mécanisme de « prix différentiel » pour les médicaments du VIH/sida en faveur des pays en développement, ce chapitre présente la méthodologie et les principaux résultats d'une recherche conduite dans le cadre du programme ETAPSUD de l'ANRS sur les prix sources des antirétroviraux (ARVs) au Brésil et dans 13 pays africains dans la période 1998-2002. L'analyse de 1 030 transactions effectuées dans ces pays confirme la tendance à la baisse des prix des ARVs, qui s'est avérée quasi linéaire de 1997 à 2000 et s'est

accélérée fortement en 2001 pour se ralentir en 2002. Cette baisse s'est accompagnée d'une réduction de la variabilité des prix pour une même molécule entre pays, comme entre les médicaments de marque et leurs substituts génériques. Sur l'ensemble de la période, les prix sont d'autant plus bas que les quantités achetées par transaction sont élevées, quoique cette relation prix/quantités s'est estompée dans les deux dernières années.

Dans l'analyse économétrique multivariée, les facteurs suivants apparaissent reliés à une hausse des prix: le fait que le médicament appartienne à une classe thérapeutique plus récente comme les inhibiteurs de protéase (IPs) et que les recommandations cliniques officielles du pays recommandent ces molécules pour le traitement de première intention, le fait que la molécule soit protégée par un brevet dans le pays, une prévalence du VIH plus élevée, et l'intervention de grossistes comme intermédiaires dans la transaction. À l'inverse, l'existence de programmes publics organisés de distribution des ARVs, et la réalisation de la transaction dans le cadre du partenariat international introduit en 2001 entre six firmes pharmaceutiques et les Nations Unies (AAI – Accelerated Access Initiative), sont associées à des baisses de prix. Cependant, même après ajustement pour ces différents facteurs, l'introduction d'une concurrence générique demeure un facteur essentiel de la baisse des prix sur la période. Certains pays (Brésil, Malawi, Nigeria) ont d'emblée utilisé une stratégie de négociations avec les firmes productrices fondée sur des appels d'offres et sur la mise en concurrence avec les producteurs des médicaments génériques. La plupart des pays africains étudiés ont progressivement évolué vers une stratégie «hybride» qui associe une participation à l'initiative AAI pour bénéficier de tarifs préférentiels auprès des firmes de marque avec un recours croissant à la concurrence générique.

La principale recommandation qui ressort de cette recherche est que la pérennité à long terme du mécanisme de prix différentiel qui s'est instauré de fait pour les antirétroviraux dans certains pays africains, comme son extension à un plus grand nombre de pays et de médicaments nécessaires au traitement des patients infectés par le VIH, ne peut être garantie par le seul recours à la «philanthropie» (même politiquement intéressée) des principales firmes et à une négociation «fermée» entre celles-ci et les organisations internationales. De plus, l'obtention de baisses des prix par des achats groupés afin d'augmenter les quantités par transaction ne s'avère possible que dans la mesure où les acheteurs ont le pouvoir de substituer entre elles différentes sources d'approvisionnement. Une recommandation récente du Fonds Global de Lutte contre le Sida, la Tuberculose et la Malaria est d'inciter les pays à s'approvisionner

en médicaments du VIH/sida de qualité attestée et au moindre coût. La réalisation de cet objectif suppose la poursuite de négociations décentralisées, la mise en concurrence systématique entre producteurs et le maintien d'une souplesse réglementaire (au plan des accords internationaux comme des législations nationales) permettant la production et l'importation de médicaments génériques.

Introduction

In June 2001, the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS, the first session of the UN in history that has been totally devoted to the fight against a specific disease, unanimously adopted a Declaration of Commitment recognising the need for implementing “national strategies, supported by regional and international strategies [...], to address factors affecting the provision of HIV-related drugs, including antiretroviral drugs”¹. During 2002, significant progress was made in improving access of people living with HIV/AIDS in developing countries to antiretroviral treatment (ART). Following the recommendations of UNGASS, the Global Fund to Fight AIDS, Tuberculosis and Malaria became operational in January with initial pledges from donors of just over US\$2 billion for 3 – 5 year programs, two thirds of these funds being planned for HIV/AIDS prevention and care activities². In March and November, the Global Fund announced its first and second round of grants respectively committing US\$616 million and an additional US\$866 million over two years to enable 85 recipient countries to scale up national programs to fight these diseases, with about 60% of funds allocated to HIV/AIDS³. In March, eleven antiretroviral drugs (ARVs) were added to the World Health Organisation (WHO) list of essential medicines⁴. In April, WHO announced the first treatment guidelines for HIV/AIDS in

1. United Nations General Assembly Special Session on AIDS: *Declaration of Commitment on HIV/AIDS: global crisis-global action*. New York: June 27, 2001.

2. World Health Organization (WHO), Joint United Nations Programme on HIV/AIDS (UNAIDS) and United Nations Children’s Fund (UNICEF). *Access to Quality HIV/AIDS Drugs and Diagnostics. Joint news release*. March 20, 2002. Available at: www.who.int/inf/en/pr-2002-19.htm

3. Total pledges to the Global Fund to Fight AIDS, Tuberculosis and Malaria amount to over US\$3.2 billion. In 2001-2002, the Global Fund had pledges of US\$944 million. For 2003, the Fund has pledges to date of US\$647 million. Pledges and contributions as of February 6, 2003. Available at: www.globalfundatm.org

4. Global Fund to Fight AIDS Tuberculosis and Malaria. News release. January 31, 2003. Available at: www.globalfundatm.org

resource-poor settings, and added a twelfth ARV to this list⁵. The World Bank's Multi-Country AIDS Program (MAP) is expected to disburse around US\$1 billion for Africa and US\$155 million for the Caribbean over the next 3–5 years, and many supported projects explicitly include the provision of ARVs [1]. An analysis of the national HIV/AIDS plans of 90 developing countries conducted by WHO indicates that about 60% of these countries have now either incorporated ART into their national strategies to fight the epidemic or have defined specific ART coverage targets. Even governments which have been reluctant to involve the public health-care sector in the delivery of ARVs, as has been the case in South Africa, are revising their position and moving forward a more active policy concerning ART [2].

At both international and country levels, ambitious targets for scaling up access to ART in developing countries have been publicly set. In July 2002 at the XIVth International AIDS Conference in Barcelona, WHO and other UN organisations committed themselves to the goal of expanding access to ART to 3 million people in the developing world by 2005⁶. The Economic Community of West African States (ECOWAS) has committed itself to providing treatment access to 400,000 patients, representing at least one-third of the people in need of HIV treatment in the region, by the end of 2005⁷. At least five countries in Latin America and the Caribbean (Brazil, Costa Rica, Cuba, Mexico, Venezuela) are already implementing public policies for universal access to ART. Two others, Chile and Salvador, are actively preparing to do so.

However, practical accomplishments have, so far, remained modest. UN organisations estimate that 6 million people world-wide are in immediate need of ART, including 4 million in sub-Saharan Africa alone⁸. By contrast, ART was initiated for only an additional 70,000 patients during 2002, leading

5. World Health Organization: *Treatment guidelines and AIDS medicines list announced by WHO*. News release. April 22, 2002. Available at: www.who.int/mediacentre/releases/release28/en/print.html

6. World Health Organization: *News release*. Barcelona, July 9, 2002. Available at: www.who.int/mediacentre/releases/who58/en/print.html

7. The Member States of ECOWAS are: Benin, Burkina Faso, Cape Verde, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Mali, Mauritanie, Niger, Nigeria, Senegal, Sierra Leone and Togo. West African Health Organization. ECOWAS Initiative to Scale Up Access to HIV Treatment. Framework for Dialogue with Partners. Ouagadougou, November 2002.

8. World Health Organization (WHO): *International Action Plan on Scaling-Up Access to HIV Care. A Commitment to Universal Access and Action on HIV/AIDS Treatment*. Geneva: December 2002. Available at: www.who.int

to a maximum of 300,000 HIV-infected persons in developing countries currently receiving ARVs of any kind, nearly one half of them in Brazil alone⁹. According to the Global Fund, funding commitments made in 2002 will allow 490,000 HIV-infected patients to get access to treatment, a two-fold increase in the total number of individuals receiving ART in developing countries, and a six-fold increase in Africa [3].

A large gap obviously persists between the current level of funding for HIV care and treatment and the minimum needed to have an effective global impact against the pandemic. Recent estimates of the funding needs, which have taken into account the goal of increased access to ART, have been consistent in calling for an investment of US\$8 billion – \$10 billion per year to be provided jointly by the international community and national resources [4-6]. To respond to country proposals, the Global Fund alone has called for an additional US\$6.3 billion in 2003 and 2004¹⁰. In January 2003, the US administration made promises to commit US\$15 billion over five years – including nearly US\$10 billion in new money – with the goal of providing ART to 2 million HIV-infected people in 14 of the most affected nations in Africa and the Caribbean¹¹. The extent to which funding will be available for the scaling-up of ART in the next 3 – 5 years however remains a matter of uncertainty and still represents a major challenge for the international community.

When Highly Active Antiretroviral combination Therapies (HAART) were introduced in 1996, conventional wisdom held that it would remain financially beyond the reach of most HIV-infected patients in developing countries, the high price of these innovative drugs being the main obstacle to expanding access. Indeed, at current prices on the international drug market, whereas full coverage of medically eligible patients for HAART represents less than 0.1% of Gross Domestic Product (GDP) in high-income OECD countries, it would exhaust public health expenditures and account for a significant share of GDP in the 16 sub-Saharan countries where HIV prevalence is over 10% of

9. Ministry of Health of Brazil: *National Drug Policy*. Brasilia: February (2001).

10. Executive Director Richard Feachem at the opening of the 4th Board meeting of the Global Fund to Fight AIDS, Tuberculosis and Malaria. Geneva, January 29, 2003. Available at: www.globalfundatm.org

11. These 14 countries are: Botswana, Côte d'Ivoire, Ethiopia, Guyana, Haïti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda and Zambia. Available at: www.whitehouse.gov/news/releases/2003

the adult population [7]. As affordability of drugs is a fundamental starting point for increasing access to ART in low-resource settings, achieving lower prices for ARVs was, and remains, a prerequisite for scaling up HIV care programmes in developing countries. Between 1996 and 2002, there have been spectacular price decreases for ARV drugs in most developing countries, in some cases to 5%-20% of their price in developed countries. Such decreases, that could hardly have been expected five or six years ago, are the result of a complex process combining negotiations between the major pharmaceutical companies and the UN organisations as well as governments, intense controversies and international mobilisation of public opinion and Non-Governmental Organisations (NGOs), emerging competition of generic manufacturers and articulated strategies of some national governments of developing countries to guarantee supply of HIV/AIDS drugs at lower differential pricing.

The UN organisations initially gave the priority to a process of negotiation with the major pharmaceutical companies which own the patents of ARV drugs. This process of negotiations was mainly carried out at international level with limited margins for price bargaining at country level. In 1998, when the UNAIDS secretariat started the so-called Drug Access Initiative (DAI) to explore the feasibility of a “structured introduction of price-reduced ARV therapy in a range of developing countries”, the recommended mechanism for procurement of ARV drugs was based on the introduction, in each country, of a private not-for-profit company (Medical Access) bringing together representatives of the five patent-holding pharmaceutical companies which internationally agreed to support this initiative¹². In this initial phase, it was quite clear that the main rationale pursued by the UN organisations was to convince these multinational companies to adopt a “philanthropic” attitude towards the prices of ARV drugs in the developing countries most in need in exchange for the “political” gains that these companies could obtain from a close partnership with the UN system. In May 2000, five UN organisations¹³ entered in a partnership offered by these same five pharmaceutical companies, joined later by a sixth one¹⁴. The stated goal of this new Accelerated Access Initiative (AAI) was to “make

12. UNAIDS. *Report of the meeting on the evaluation of the UNAIDS HIV Drug Access Initiative*. Geneva, May 30-31, 2000. Available at: www.unaids.org

13. These five organisations are the: United Nations Population Fund (UNFPA), United Nations Children’s Fund (UNICEF), WHO, World Bank and UNAIDS Secretariat.

14. The five initial companies were Boehringer Ingelheim GmbH, Bristol-Myers Squibb, GlaxoSmithKline, F. Hoffmann-La Roche Ltd and Merck & Co. Inc while Abbott Laboratories Inc later joined.

HIV/AIDS drugs more affordable and accessible in developing countries” through a “preferential pricing” mechanism¹⁵. The AAI model was based on a priori international price negotiations that set a standard for procurement in all the countries that adhere to the Initiative. As of June 2002, the AAI has been “used as a framework for dialogue with pharmaceutical companies and has led to successful UN-brokered supply agreements for ARVs in 19 countries”¹⁶. In May 2002, two major regional groups of countries, ECOWAS and the Caribbean Community (CARICOM) coalesced to engage negotiations with these pharmaceutical companies through the AAI and a formal statement of intent was signed with fifteen Caribbean countries in July 2002. In parallel to the AAI, during 2001 and 2002, international manufacturers made selective offers of substantial discounts to governments and non-governmental organisations of the least-developed countries and sub-Saharan African countries [8]¹⁷.

Of course, the trend in price decrease of patented ARV-drugs in the context of the AAI cannot be separated from the numerous external events that have simultaneously occurred during the past three years. Pilot projects of the UNAIDS Drug Access Initiative itself, that were carried out in Côte d’Ivoire, Uganda, Chile and Vietnam, as well as community-based projects of ARV delivery supported by NGOs like *Médecins Sans Frontières* (MSF) [9], quickly highlighted how increased competition, including generic competition, could be a powerful mechanism to achieve the goal of decreasing prices in negotiations for drug procurement directly carried out at country level.

15. Accelerating Access Initiative. *Widening access to care and support for people living with HIV/AIDS*. Progress Report, June 2002. WHO/UNAIDS, 14th International AIDS Conference, Barcelona, July 2002.

16. The 19 countries are the following: Barbados, Benin, Burkina-Faso, Burundi, Cameroon, Chile, Republic of the Congo, Côte d’Ivoire, Gabon, Honduras, Jamaica, Mali, Morocco, Romania, Rwanda, Senegal, Trinidad and Tobago, Uganda and Ukraine. Although not formally mentioned as a member of the AAI, Botswana can be considered as having installed and developed its national ARV program in the AAI framework. Indeed, Botswana’s strategy has even preceded the AAI with the establishment, as early as July 2000, of the Botswana Comprehensive HIV/AIDS Partnership, based on a joint collaboration with the Bill & Melinda Gates Foundation and Merck & Company, Inc. Procurement of ARV drugs for the country goes via this partnership and agreements with other drug companies such as Boehringer Ingelheim GmbH and Bristol-Myers Squibb have followed the AAI procedures.

17. During 2001, the US-based Bristol-Myers Squibb and Abbott Laboratories announced their aims to provide ARV drugs “below cost”, with Merck offering their “at cost”. In addition, UK-based GlaxoSmithKline, German-based Boehringer Ingelheim and Swiss-based F. Hoffmann-La Roche further reduced their prices and increased the provision of free ARVs for prevention of mother-to-child HIV transmission.

Between 1996 and 2000, prices of ARVs were lower in Côte d'Ivoire where the Public Health Pharmacy introduced a tendering mechanism open to all international suppliers, including generic producers, than in Uganda where procurement was restricted to Medical Access Uganda Ltd [10]. In 2001, soon after the Joint Clinical Research Centre in Kampala started using imported generic drugs, a 20% – 45% decrease in the cost of the most frequently prescribed combinations occurred in Uganda. Moreover, the significant impact of generic competition has been obvious in the case of locally produced ARVs in Brazil [11] and Thailand, and the 2001 offer by Indian generic manufacturers to provide some combination antiretroviral therapies at a price of around US\$1 per day in developing countries attracted world-wide media attention. International mobilisation of public opinion in 2001 was also a key element in the price decrease process. It led the US government to retract the complaint it had made against Brazil at the World Trade Organization (WTO) for violation of its obligations under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the 1994 General Agreement on Tariffs and Trade (GATT) [12]¹⁸. It forced the Pharmaceutical Manufacturers Association of South Africa, backed by 39 international drug companies, to drop their lawsuit against the newly introduced South-African legislation allowing the generic substitution of off-patent medicines (a policy already used in many developed countries to control drug expenditures) and the parallel importation of patented medicines [13]. Finally, in November 2001, it facilitated the adoption of the “Doha Declaration” which recognised that HIV/AIDS qualifies as a case of “national emergency” in developing countries and authorised the use of compulsory licensing allowing a third party to use a patent without the owner’s consent under the current rules of WTO¹⁹. As persisting controversies on the practical interpretation of this Declaration have later shown, the extent to which developing countries will be allowed to import generic drugs produced through this mechanism of compulsory licensing in another country, as well as the precise international safeguards against the re-export of these

18. The US complaint was directed against Brazilian legislation, that came into force in 1997, establishing that in order to enjoy exclusive patent rights the holder of a patent on an invention must satisfy a “local working” requirement. In other words, the patent holder must “work” the patent in to enjoy full patent protection. If it fails to do this, the law says it shall be subject to the possibility of the government issuing a compulsory license, allowing someone else to use the invention and pay a royalty fee to the patent holder.

19. World Trade Organization (WTO): *The Doha Declaration on the TRIPS Agreement and Public Health*. Adopted by Ministerial Conference, Fourth Session, Doha, November 14, 2001.

drugs to developed countries²⁰, remain a matter of debate that has not yet been resolved by the TRIPS Council of the WTO.

According to some industry representatives, these developments and current price decreases have been sufficient to ensure that “drug price is off the table as an issue, thus transferring the focus in the battle against AIDS from lack of access to the drugs to poor infrastructure and ineffectual government measures” [14]. UNAIDS and the WHO also optimistically state that “as a result of the AAI and related efforts, with companies independently entering into discussions with countries and other purchasers, the prices of antiretroviral medicines have declined significantly in the past two years”. It is however important for the future to make a clearer distinction between, on the one hand, the respective roles of the international “political bargaining” between the UN and other donor organisations and the “corporate philanthropy” of pharmaceutical companies eager to restore their image, and on the other hand the effective emergence of market mechanisms for HIV/AIDS drugs in developing countries. As suggested by the literature on other “emerging markets” [15-16], in order to secure long-term procurement of low-price ARV drugs in the low and middle-income countries that are the most severely hit by the epidemic, it is essential to establish efficient economic mechanisms of negotiation between buyers and suppliers that should be, at least partly, protected from “political volatility”. A better understanding of the determinants of ARV price decreases in recent years is also essential to help define the most appropriate regulatory mechanisms at international and country levels for promoting “differential pricing” without jeopardising future progress in HIV therapies and its associated welfare gains [17]²¹.

In this chapter, we will first give some economic background about recent debates on drug prices. In the second section, we will focus on the methodology and results of research carried out for the ANRS ETAPSUD programme on determinants of source prices of ARV drugs in Brazil and 13 African countries.

20. Commission des Communautés Européennes. *Proposition de règlement du Conseil visant à éviter le détournement vers l'Union Européenne de certains médicaments essentiels*. 02557 ACCC, Bruxelles, 30 Octobre 2002.

21. WHO and WTO Secretariats: *Workshop on differential pricing and financing of essential medicines*. Norwegian Foreign Affairs Ministry, Global Health Council, April 8-11, 2001, Høsbjør, Norway. Geneva: World Health Organization, 2001. Available at: http://www.who.int/medicines/library/edm_general/who-wto-hosbjor/hosbjorexe-eng.pdf

In the last section, discussion of these preliminary results will serve as a basis for policy recommendations about HIV/AIDS drugs procurement strategies.

I

SOME BACKGROUND ON DRUG PRICES

Prices charged by pharmaceutical companies for patented drugs are commonly several orders of magnitude higher than their marginal cost (the cost of producing an additional unit of the drug). Low marginal costs explain why generic drug producers, provided that they do not have to pay royalties to patent holders, are able to offer substitutes to branded products at comparatively very cheap prices. Taking into account current production costs of generic suppliers and potential economies of scale, marginal costs of delivery of some triple drug HAART combination can be expected to be lower than US\$200 per patient/year. In a perfectly competitive market, in which consumers will automatically buy a substitute good if its price is lower, international drug prices would spontaneously tend to be based on such marginal cost.

Of course, in the case of innovative products like ARVs, private firms legitimately need to recover their high overhead costs for Research & Development (R&D) and for fulfilling the regulatory prerequisites of market approval in high income countries [18]. The pharmaceutical industry claims to have invested US\$30.5 billion in R&D in 2001, which would make it the largest direct backer of medical research world-wide²², and legitimately points to the time, risk, and costs associated with new drug development: on average, drugs take about 12 years to develop, and there is a high failure rate at the stage at which drugs enter clinical development. The most widely quoted estimate of the cost of bringing a new drug to market is that of US\$500 million [19]. This figure was updated in 2000 to US\$800 million [20]. A substantial proportion of the cost was the lost income that might have been earned had companies invested their assets rather than making drugs (the opportunity cost of the capital). Economic theory has long recognised that long term incentives for private risky investments in R&D of innovations are needed, and has extensively debated how guaranteeing the intellectual property rights

22. The Pharmaceutical Research and Manufacturers of America. Pharmaceutical industry profile 2001. Available at: <http://www.phrma.org/publications/publications/profile01/>

of the inventors, which, although it corresponds to the attribution of a “temporary monopoly power” to the patent owner, may correspond to such socially useful incentives [21]. Patents grant exclusive manufacturing rights for a period of 20 years from the date of filing for the patent. In practice, because of the time taken to get a new drug to the market, the monopoly selling power is usually around 12-14 years. Pharmaceutical companies rely heavily on patents and go to great lengths to maintain and extend them. The techniques they use are known as “evergreening” and include: introduction of new formulations (including fixed combinations), which are marketed heavily before the generic version of the drug is released; second-medical-use patents for products nearing the end of their basic patent life; repeated patent infringement suits, which trigger an automatic 24-30 month delay in processing the generic product in Canada and the USA; and collusion with generic manufacturers to keep products off the market [22].

In developed countries, competition from generic manufacturers who provide non-patented drugs has increased in recent years. In 1997, the top ten generic drug companies had world sales of around US\$6 billion. Although the extent to which generic drugs are substituted for original branded drugs and their impact on prices vary widely from country to country and across therapeutic categories, generic suppliers have now a substantial effect on health-care delivery: their volume share (by countable units, *e.g.* tablets) of US prescription sales rose from 18.6% in 1984 to 44.3% in 1998 and is also above 40% in countries like Canada, Denmark, Germany or the UK [23]. Interestingly enough, generic competition in developed countries has not led average drug prices to fall but has rather provoked a “bifurcation of the market”: while generics tend to enter the market at wholesale prices which are 40 to 70% of those prevailing before the original drug’s patent expired and generic prices continue to decline through time, originators drug prices tend to increase following generic entry. This “generic paradox” is due to the dominant strategy of the branded drug suppliers which usually find it more profitable to serve a minority fraction of the market at high prices (the price-insensitive consumers willing to pay high prices for the security of a brand name) than to reduce their prices to the low levels required to match generic competition [24-27].

In any case, the current international market of branded ARV products remains characterised by imperfect competition: a limited number of firms (7) supplies a limited number of products (17); inside each of the three

classes of ARV drugs, nucleoside reverse transcriptase inhibitors (NRTIs), the oldest category, non nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), the number of suppliers is even smaller (≤ 4). In such oligopolistic markets, private firms are in a position to impose prices and rates of return that may capture an “excessive rent”. An indirect indicator of such risk is that pharmaceutical companies tend to feature prominently in “antitrust” court actions in North America as well as the European Union²³. Therefore, it is sometimes in the interest of society to associate patent rights with compulsory licensing obligations in order to guarantee an efficient public disclosure of innovative knowledge [28]. As already mentioned, existing WTO rules such as article 6 of TRIPS permit compulsory licensing²⁴.

In the context of imperfect competition, information asymmetries between suppliers and buyers are likely to be exacerbated [29]: in such markets, private firms have a priori no incentive to disclose information on their real production costs or on the lowest sales prices that they would rationally be ready to accept. Indeed, some of the evidence previously mentioned about the presumably high costs of R & D has to be balanced by taking into account additional factors. During the early 1980s in the US, 43% of “failures” in drug development were for “economic reasons” of limited expected profitability, compared with 31% for efficacy issues and 21% for safety problems [30]. Development time is shorter for some classes of drugs, for example, the first 14 ARVs took an average of only 4.4 years from the date of filing of key patents to approval by the US Food and Drug Administration [31]. Published estimations of high R&D costs often do not reflect the contributions made by public research institutions²⁵ and by tax credits from doing R&D, which can reduce total costs by between 16% and 39%, or savings made by licensing drugs from other organisations. Alternative estimates of drug development costs have therefore sometimes been lower than the US\$500-800million endorsed by the industry, between US\$115 and \$240 million including

23. US Department of Justice. *Four foreign executives of leading European vitamin firms agree to plead guilty to participating in international vitamin cartel*. Available at: <http://www.usdoj.gov/opa/pr/2000/April/179at.htm>

24. Correa C.: *Integrating Public Health Concerns into Patent Legislation in Developing Countries*. Geneva: South Centre, 2000.

25. A study of 21 drugs introduced in the USA between 1965 and 1992, and considered to have had the highest therapeutic effect on society, found that public funding of research was instrumental in the development of 15 of them.

adjustment for failures, according to a 1993 study of the Office of Technology Assessment of the US Congress²⁶.

Economic theory also emphasizes the fact that firms in a monopoly (or oligopoly) position can rationally practice price discrimination, *i.e.* they offer different prices for the same product according to the characteristics of each segment of the demand on markets. It would be rational for the firm to offer the highest prices to customers with the lowest price elasticity of demand (and the highest willingness to pay for the product) and vice versa. Price discrimination between markets in different countries and between various sectors in the same national market (especially for different therapeutic indications of the same drug) is a common practice. It sometimes translates into global price increase as was recently the case for pentamidine, a treatment for trypanosomiasis which used to cost \$10 per course of treatment until it found a “new” market in the treatment of infections prevalent in AIDS patients making the price soar to US\$300 [32]. Price discrimination explains why various “intermediary” agents may interfere with the process of retail price determination and share some fraction of the “rent” with the firm exercising monopoly power: a process that partly explains the sometimes huge differences between source and retail prices of drugs in developing countries. Because price discrimination for HIV/AIDS drugs between developed and developing countries is not per se an economic anomaly, it can be argued that differential pricing based on some measure of national wealth or “ability to pay” can be used as a regulatory tool for promoting access to low-cost ARV drugs in the developing countries most in need. It can even be argued that, to the extent that parallel imports of low-cost drugs to developed countries remain under control, the increased volume of drug sales that would be promoted by unit price decreases in developing countries with high HIV prevalence can contribute to the profitability of the drug industry at an international level.

In general, informed consumers (in the sense of consumers who have the most exhaustive information about available prices) produce a “positive externality” in favour of less informed consumers because they contribute to increased competitive pressure on suppliers which creates an incentive for firms to decrease prices and to improve quality of products. Logically, this

26. Office of Technology Assessment: *Pharmaceutical R&D: costs, risks and rewards*. Washington: US Government Printing Office, 1993.

leads to a positive impact of improved dissemination of price information on the collective efficiency of the market mechanism [33]. Theoretical as well as empirical research has already shown that “uninformed” consumers will tend to pay higher prices and that an increase in the proportion of such uninformed consumers favours an increase of the average price level, which also negatively affects better-informed consumers (the latter will ultimately obtain higher prices than those that would have been reached at equilibrium in the absence of uninformed consumers) [34-35]. Economic evidence clearly suggests that appropriate information would never be spontaneously revealed by market mechanisms characterised by imperfect competition. It strongly supports the usefulness for buyers to benefit from a mechanism of systematic information about drug prices and transactions on the different national markets. This kind of information can be considered as a “global public good” whose availability would increase public welfare in the different countries.

However, it should be recognised that the impact of increased price information may not always lead to price decreases. For instance, when consumers a priori discriminate between products belonging to a similar class of goods (for example, by exhibiting an a priori preference for brand rather than generic products), diffusion of information may paradoxically translate into price increase. In such a case, informed consumers may reveal their preferences by giving priority for seeking transactions concerning their a priori preferred products, and by stopping their market search as soon as they find a price below their maximum willingness to pay; this behaviour will render firms’ demands more inelastic (informed consumers will not check out another firm’s product if the preferred firm’s price exceeds the anticipated price by less than the search cost) and will contribute to price increase at equilibrium [36]. It explains why perceptions of product characteristics may strongly influence the outcome of competition between brand-named and generic drugs [37], and how misperception of respective qualities may bias the emergence of market mechanisms [38-39]. It shows that, in the case of HIV/AIDS drugs any public effort to improve information on prices should be combined with quality control mechanisms in order to avoid undesirable effects on prices related to a priori consumer preferences which do not adequately reflect effective differences in quality of products. In 2002, WHO has therefore made an important contribution by publishing the first results of its new initiative to promote internationally guaranteed quality control for HIV-related

medicines on a voluntary basis by branded and generic manufacturers²⁷. Compliance with quality standards set by this international initiative will automatically guarantee the eligibility of the product for purchase with Global Fund resources²⁸.

II

DETERMINANTS OF SOURCE PRICES FOR ARV DRUGS IN 13 AFRICAN COUNTRIES AND BRAZIL: AN ECONOMETRIC ANALYSIS

Debates about scaling up access to HIV/AIDS drugs have accelerated international efforts to collect and exchange information about prices of drugs in developing countries. These efforts were elaborated with quite different objectives, and collect data at various levels of the drug procurement and delivery channels in the countries.

The joint UNICEF/UNAIDS/WHO/MSF project on Sources and Prices of selected drugs and diagnostics for people living with HIV/AIDS is considered as a reference database for indicative manufacturers' prices for ARVs, drugs used for the treatment of HIV-related opportunistic infections, and for diagnostic tests²⁹. This database contains a list of manufacturers who have the capacity to supply quality drugs at these indicative prices. The information system implemented by MSF called "Access to Essential Drugs Campaign" with the objective to improve access to equitable drug prices, is a database of lowest source prices obtained, by either public institutions or NGOs, within different countries, from manufacturers of brand or generic drugs³⁰. It includes the patent status of the molecule in the country. The AFRO-Essential Drug Price Indicator project is an initiative focused on African countries, and constitutes an original example of south/south cooperation with an operational

27. World Health Organization: *Initiative to promote access to quality HIV medicines releases first batch of results today*. News release. March 20, 2002, Geneva. Available at: www.who.org The Global Fund will also allow purchases of products that "have been authorized by the national regulatory authority in the Recipient's country".

28. The Global Fund will also allow purchases of products that "have been authorized by the national regulatory authority in the Recipient's country".

29. UNAIDS/UNICEF/WHO-EDM: *Sources and prices of selected drugs and diagnostics for people living with HIV/AIDS*. Geneva: February 2000.30. Pérez-Casas C. (Ed.). *Assessing ARVs: untangling the web of price reductions for developing countries*. October 2001. MSF Access to Essential Medicines Campaign. Available at: www.accessmed-msf.org

institutional framework already approved by the 24 member states³¹. All these data bases offer operational information on indicative prices of HIV/AIDS drugs and are helpful tools for buyers at country level.

However, information available in these data bases is not fully appropriate for econometric analysis aimed at explaining the dynamic of HIV/AIDS drugs source prices on the markets: the recorded prices are indicative (mean price, minimum price), and rarely reflect the actual purchase price of the drug, or the effective conditions of transaction; price information is rarely associated with the quantity procured and is mainly collected from firms rather than at country level. For these methodological reasons, the ANRS ETAPSUD programme has supported a research project based on retrospective observation of effective transactions dealing with HIV/AIDS drugs in African countries between 1996 and 2002. The project was carried out in close collaboration with the Brazilian National AIDS Programme which gave the opportunity to compare African data with the Brazilian experience of universal coverage of HIV-infected patients for ART. The research goal of the project was focused on analysing the major determinants of inter-country and inter-temporal variations of prices of HIV/AIDS drugs (although in this chapter, we will only focus on ARVs). An associated operational goal was to contribute to the definition of the most appropriate format for establishing inter-country prospective observatories of HIV/AIDS drugs with the goal of optimising the process of procurement.

Data collection

In 2002, visits were carried out in 13 Sub-Saharan African countries to collect retrospective data describing the real transactions for procurement of ARVs that occurred in each country between 1996 and 2002. For each transaction, in each country, a standardised questionnaire was filled out with the help of representatives of the institution which was in charge of buying the drugs (either public pharmacies or Ministries of Health, private wholesalers, or private-not-for profit NGOs). All recorded prices were source prices, in US dollars at time of the transaction, when entering the country and were standardised using Cost-Insurance and Freight (CIF) prices that include the added costs of freight, insurance, import duties or taxes. Detailed data about each transaction

31. WHO/AFRO/EDP: *AFRO Essential Drugs Price Indicator*. Geneva: December 2000.

included the price, quantities, dosage pharmaceutical form and packaging of each individual drug as well as the supplying firm (which makes it possible to distinguish between brand and generic drugs). It also included precise characteristics of the buying institution and of the process of negotiation associated with the transaction: whether it was carried out through a tender mechanism (either “restricted” to some manufacturers or “open” to all international potential suppliers) or through bilateral mutual agreement with manufacturers (either supported by the AAI or not), and whether it was associated or not with donations of additional quantities from the manufacturer. Data about patent protection for each drug, in each country, were based on available information from the literature that relied on inquiries to the intellectual property divisions of major pharmaceutical companies [40].

In addition, interviews were carried out with representatives of National AIDS programmes and/or Ministries of Health, as well as representatives of international donor agencies to collect data about the institutional, economic and epidemiological context of procurement, including whether or not national guidelines and recommendations for use of ARVs existed and had been disseminated in the country as well as information about the national drug patent system and the regulatory procedures for drug market approval. Basic socio-economic indicators, such as the size of the population, GDP and health expenditures per capita, percentage of GDP devoted to public expenditures for health and number of physicians per 100,000 inhabitants, as well as estimations of HIV seroprevalence in the adult population were obtained through UNAIDS, UNDP and World Bank data bases.

The 13 countries visited in Africa were quite different in size (varying from a population of less than 3 million in Botswana, Congo and Gabon to more than 100 million in Nigeria) and in prevalence of HIV infection in the adult population (from less than 2% in Mali and Senegal to more than 10% in Botswana, Cameroon and Malawi). Six of them (Benin, Burkina-Faso, Burundi, Malawi, Mali and Togo) are currently designated as one of the 49 least-developed countries while an additional five (Cameroon, Republic of the Congo, Côte d’Ivoire, Kenya and Nigeria) rank among the World Bank’s low-income countries (GNP per capita < US\$745). Only Botswana and Gabon are classified as middle-income countries. The percentage of government budget spent on health care is however low in all 13 countries always ranging under 5%.

For Brazil, we had access to the exhaustive data base on HIV/AIDS drugs procurement of the Brazilian STD/AIDS Program which allowed us to obtain

similar standardised data about transactions carried out in this country between 1998 and 2002. In addition to immediate availability of data, the choice of Brazil was obviously justified by the fact that it is the only developing country to date which has been able to successfully implement a public policy for universal ART coverage for medically eligible HIV-infected patients.

Statistical analysis

Evolution of drug prices per country and per year was described using price per unit. Prices per daily dose were also computed by multiplying the unit price by the number of units required for standard adult dosage³². The logarithm³³ of the price per daily dose was used as the dependent variable to conduct multiple linear regressions with characteristics of products and characteristics of the transaction (including year of transaction introduced as a dummy variable) and variables describing its context being the explanatory variables. This kind of econometric models, as applied to drug prices [41], basically consists of ordinary least squares (OLS) regressions where the observed price is the dependent variable and the different characteristics of the transaction the explanatory variables. Such regressions allow us to determine (statistical) relationships between prices and quantities but also to test the effects of additional characteristics on prices.

III RESULTS

Emerging markets of ARV drugs in Africa

Table 1 shows that we were able to collect data about a total of 1030 transactions for ARV drugs in the 14 countries, with Brazil and Côte d'Ivoire being the two countries with the highest number of observations. Not surprisingly, Brazil accounts for the majority of total quantities purchased (respectively 94.3% of NRTIs, 91.0% of NNRTIs, 98.6% for PIs and 95.6% for multiple combination drugs).

32. Definition of daily doses (number of tablets, volumes for oral solutions or syrups) were based on adult posology defined in Dorosz Ph.: *Guide pratique des médicaments*. Paris: Éditions Maloine, 23^e éd., 2003.

33. Since observed prices are always positive, one must use the logarithm of prices to avoid problems due to the left censoring of the dependent variable.

Although not exhaustive, data in Table 1 remind us of a trivial but major fact. At the end of 2002, not only was access to ART in African countries still totally inadequate in relation to estimated needs, ARV delivery had not even reached a sufficient level to start having a significant impact on public health. According to the countries' official estimations, only one out of the thirteen African countries in our sample (Nigeria) could already claim some large scale clinical experience with more than 10,000 ART-treated patients. To our knowledge, the only two other African countries, that were not included in our sample, with a similar level of experience with ART are South Africa and Uganda. In some other countries (Botswana, Cameroon, Côte d'Ivoire), experimental public programmes dealing with 2 to 3,000 ART-treated patients, already existed in 2002 and a similar figure had been reached in Kenya in the absence of any direct public involvement. All other countries studied had only pilot projects at early stages with less than 1,000 patients treated, although some of them, like Benin and Burundi, had already accumulated systematic experience of HIV/AIDS care including ART.

Table 1: Observed transactions for ARVs in 14 developing countries 1997-2002 (ANRS ETAPSUD-INSERM U379 project)

Country (purchase period)	Number of transactions Total number of purchased daily doses % of generic drugs in total purchase of daily doses				Total Nb of transactions
	NRTI	NNRTI	PI or association of 2 PI	Multiple combination drug*	
<i>Benin</i> (2000-2001)	17 62,250 0%	1 6,000 0%	7 12,314 0%	2 1,050 0%	27
<i>Botswana</i> (2001-2002)	47 216,445 0%	3 42,165 0%	2 30,645 0%	4 198,000 0%	56
<i>Brazil</i> (1998-2002)	137 168,611,573 93.5%	40 40,119,845 35.6%	39 69,728,934 21.9%	18 47,891,340 76.2%	222
<i>Burkina Faso</i> (1999-2000)	42 364,459 0%	5 145,620 0%	11 81,060 0%	8 176,850 0%	66
<i>Burundi</i> (1999-2002)	21 293,540 23.8%	6 59,400 54.5%	1 18,000 0%	5 70,500 72.3%	33
<i>Cameroon</i> (2000-2002)	34 418,265 20.9%	14 235,564 13.1%	12 73,347 0%	19 597,420 100%	79
<i>Congo (Rep)</i> (2001-2002)	13 59,156 0%	7 31,668 0%	3 16,500 0%	3 2,400 0%	26

<i>Côte d'Ivoire</i> (1996-2002)	132 2,391,456 10.2%	9 372,780 0%	41 619,130 0%	13 750,480 0%	195
<i>Gabon</i> (2001-2002)	21 190,202 0%	4 39,720 0%	2 45,120 0%	5 64,800 0%	32
<i>Kenya</i> (1997-2002)	113 86,770 21.2%	25 37,104 0%	31 10,200 0%	23 33,540 0%	192
<i>Malawi</i> (2000-2002)	2 32,933 0%	0 0	0 0	9 127,800 92.0%	11
<i>Mali</i> (2001-2002)	32 98,198 21.1%	6 23,453 24.3%	6 26,190 0%	2 16,500 0%	46
<i>Nigeria</i> (2001-2002)	7 5,927,040 100%	3 2,981,520 100%	0 0	1 115,200 100%	11
<i>Togo</i> (1997-2002)	19 67,778 0%	0 0	10 35,280 0%	5 55,256 21.7%	34
<i>Total</i>	637 178,820,064 91.7%	111 44,094,839 39.3%	165 70,696,720 21.6%	117 50,114,640 74.6%	1,030

* Multiple combination drug corresponds to association of 2 NRTIs (Combivir™ or generic equivalent) or 2 NRTI + 1 NNRTI (Triomune™) or 3 NRTI (Trizivir™).

The term generic here includes real generic drugs and also “copies” which may not have established bioequivalence testing with the original brand medicine.

It must also be noted that the majority of transactions (64.7%) and more than 90% of the purchased quantities in the African countries of our sample were observed in the most recent period (2001-2002). This reflects the major change that has occurred since 2001. Before this date, only Côte d'Ivoire (and Uganda not included in our sample) had started experimental programmes as early as 1998 in the context of the UNAIDS sponsored Drug Access Initiative (DAI), while Senegal (also not included in our analysis) and Cameroon had also started pilot projects for ART in the public health care sector in 1998 and 2000 respectively. There was elsewhere no clear commitment of governments to facilitate delivery of ARV drugs, with the exception of their preventive use (either for prevention of mother to child transmission or post-exposure prophylaxis). Such a situation still prevails in Kenya which remains typical, as is also the case for South Africa, of exclusive diffusion of ARVs in the private and private-not-for profit health care sectors. In spite of the courageous efforts of some NGOs, these two countries remain archetypal of a priority given to pure market mechanisms for ARV procurement and delivery, that was dominant in the whole continent before 2001, and led to what some authors have called

“antiretroviral anarchy” [42-43]. It must however be noted that access through the private sector has led these countries to be in the upper range in Africa for the number of ART-treated patients (respectively 3,000 in Kenya and 20,000 in South Africa). By contrast, in the twelve African countries, other than Kenya, for which we were able to collect data, access to ART is now explicitly included in national strategic plans for the fight against AIDS (or in documents that express a similar level of endorsement by the government such as official country proposals to the Global Fund).

Since 2001, 9 out of the 13 African countries in our sample (Benin, Botswana, Burkina-Faso, Burundi, Cameroon, Republic of the Congo, Côte d’Ivoire, Gabon, Mali) have contracted agreements with brand-name pharmaceutical companies in the context of the AAI, and a majority of the total number of observed transactions in Table 1 is related to AAI in these countries with the exception of Burundi, Cameroon and Côte d’Ivoire. In Kenya, although there was no direct involvement of government, the majority of observed transactions also happened in reference to the AAI. As clearly suggested in Table 1, attitudes of countries toward purchasing generic drugs have however been quite contrasted in the period studied. On the one hand, some countries participating in the AAI (Benin, Botswana, Burkina-Faso, Congo, Gabon) have never introduced generic drugs and have strictly followed the “AAI model” that restricted procurement to bilateral negotiations with six brand pharmaceutical companies in the framework of the international agreement they have signed with the UN-organisations at international level. On the other hand, Nigeria and Malawi have systematically carried out negotiations with multiple suppliers ending up with purchases of drugs supplied by Indian generic manufacturers. Interestingly enough, as shown in table 1, countries with the oldest experience of UN-related ARV procurement, like Côte d’Ivoire, as well as countries which participate in the AAI with the most ambitious plans for scaling up access to ART (Burundi, Cameroon, Mali), have purchased various amounts of generic NRTIs, NNRTIs and multiple combination drugs [44]. Indeed, these countries have evolved toward a more “hybrid” mechanism of procurement that combines negotiations in the AAI international framework with national tenders or other procurement mechanisms introducing generic competition. A similar trend toward such a “hybrid model” of procurement has happened in other countries not included in our sample (Senegal, Uganda) and is in the process of happening in countries like Benin or Burkina-Faso.

In the majority of African countries (Benin, Botswana, Burkina-Faso, Cameroon, Côte d'Ivoire, Gabon, Malawi, Mali, Nigeria) all observed transactions were ARV purchases by public pharmacies or other public authorities in charge of national drug procurement policy. Indeed, in six of these countries (Benin, Botswana, Burkina-Faso, Cameroon, Côte d'Ivoire and Mali), these public agencies have a regulatory monopoly for importing ARV drugs into the country, whereas public purchasers only account for the majority of imports of ARVs in Gabon, Malawi and Nigeria. In Burundi and Togo, the majority of observed transactions were carried out by public pharmacies although some transactions (20-30%) concerned private buyers in accordance with the global situation of ARV delivery in the country. In Congo, the majority of transactions were actually purchased by the Red Cross (private-not-for-profit) but in close connection with the Ministry of Health. Finally, Kenya is the only example of ARV procurement directly carried out through private and public health centres as well as private wholesalers. Of course, the case of Brazil, whose policy is detailed in this book (*cf.* Teixeira *et al.* article, chapter 1), is quite different: national production of ARV drugs has allowed the country not to depend on imports for the majority of transactions dealing with NRTIs and multiple combination drugs, and to supply a significant amount of NNRTIs and even of PIs.

The converging trend toward decrease of ARV prices

Figures 1 to 7 describe the evolution of average unit prices per year and per country of the 7 ARV drug dosages which accounted for the highest number of transactions in each of the three therapeutic categories: Lamivudine 150 mg (n=96), Didanosine 100 mg (n=90), combination Zidovudine 300mg + Lamivudine 150 mg (n=78), Stavudine 40 mg (n=73), for NRTIs; Efavirenz 200 mg (n=58) and Nevirapine 200 mg (n=36) for NNRTIs; Indinavir 400 mg (n=79) for PIs. The selected dosages correspond to usual dosages for adult care and are included in the most used HAART therapies indicated in WHO guidelines. Figures 1 to 7 confirm the declining trend of prices for all therapeutic categories as well as a trend for reduction in variability of prices across countries. This latter trend has to be partly related to the introduction of the AAI in transactions which occurred in 2001-2002, to the extent that the international framework of this initiative has tended to introduce a kind of reference pricing for bilateral negotiations with brand-name pharmaceutical companies at country level.

Figure 3: Evolution of average unit prices per year and per country of combination Zidovudine 300 mg + Lamivudine 150 mg (n = 78)

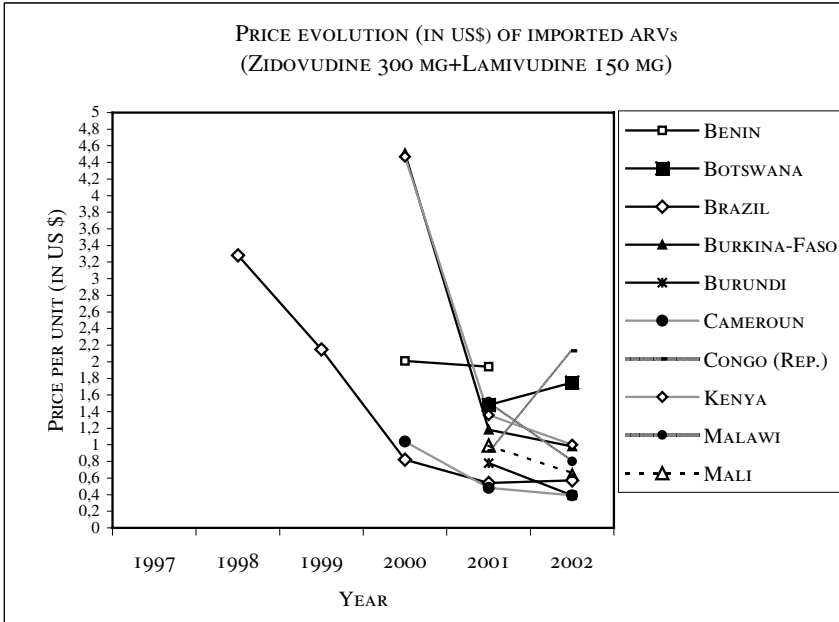


Figure 4: Evolution of average unit prices per year and per country of Stavudine 40 mg (n = 73)

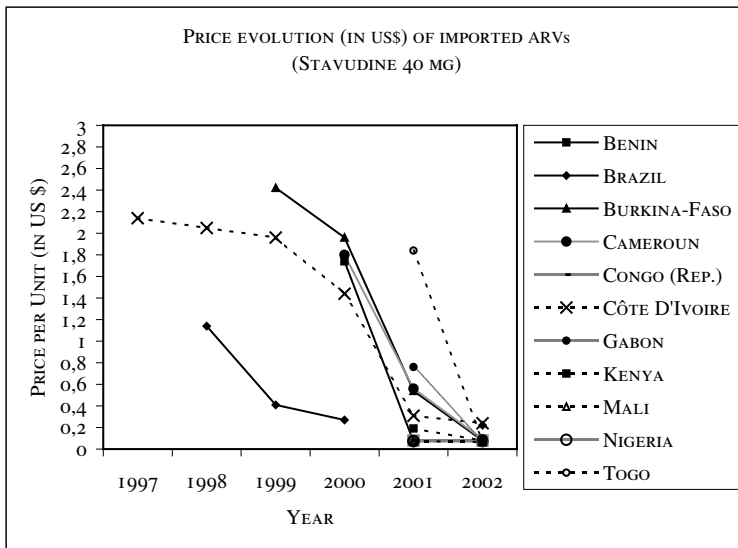


Figure 5: Evolution of average unit prices per year and per country of Efavirenz 200 mg (n = 58)

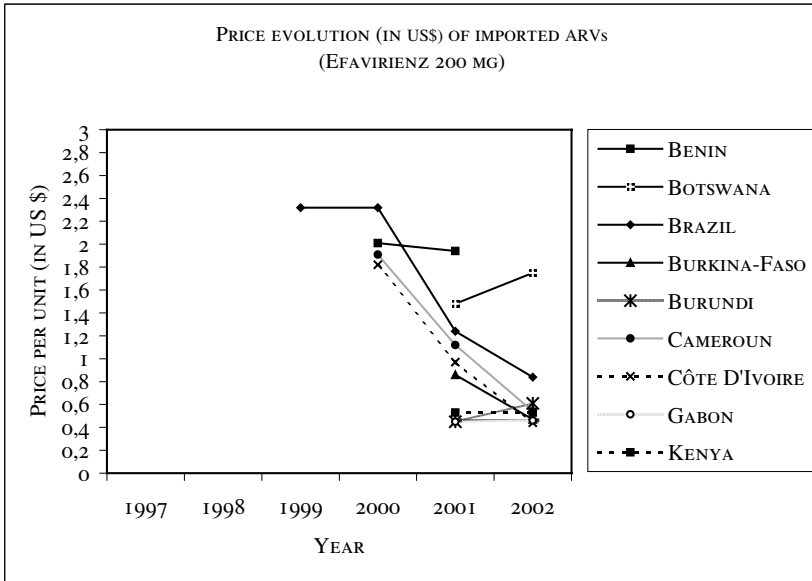


Figure 6: Evolution of average unit prices per year and per country of Nevirapine 200 mg (n = 36)

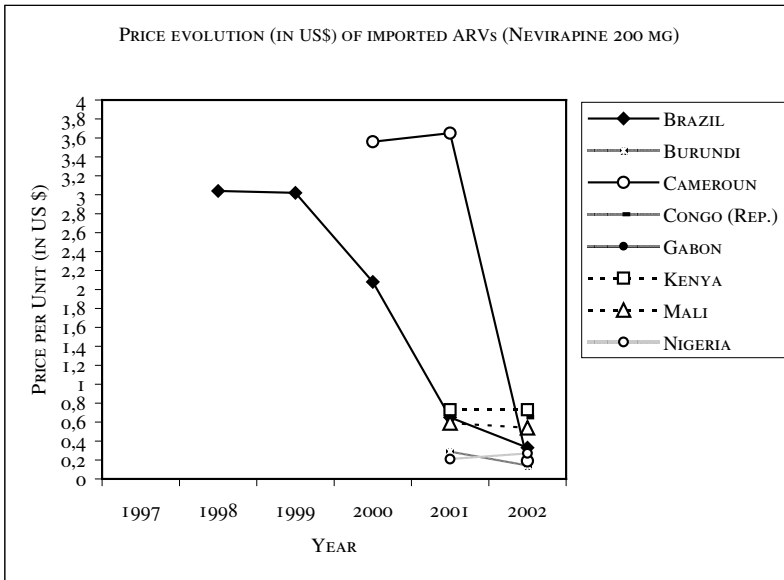


Figure 7: Evolution of average unit prices per year and per country of Indinavir 400 mg (n = 79)

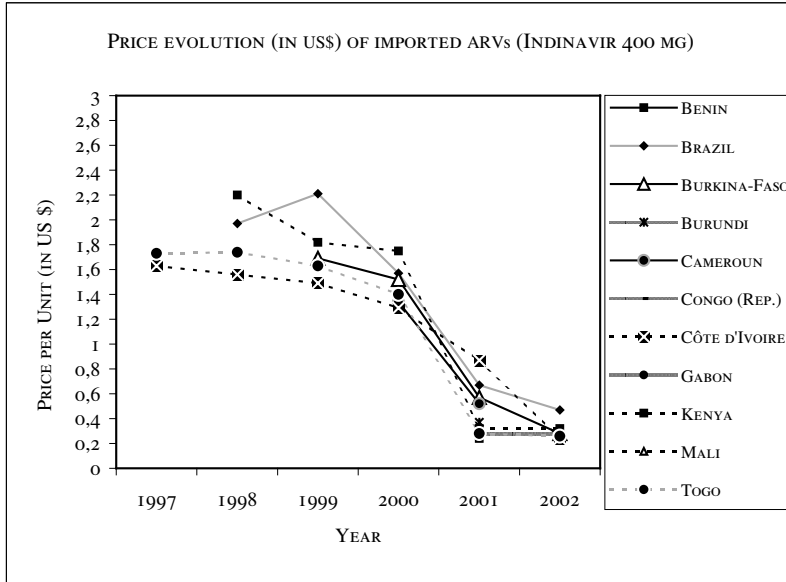
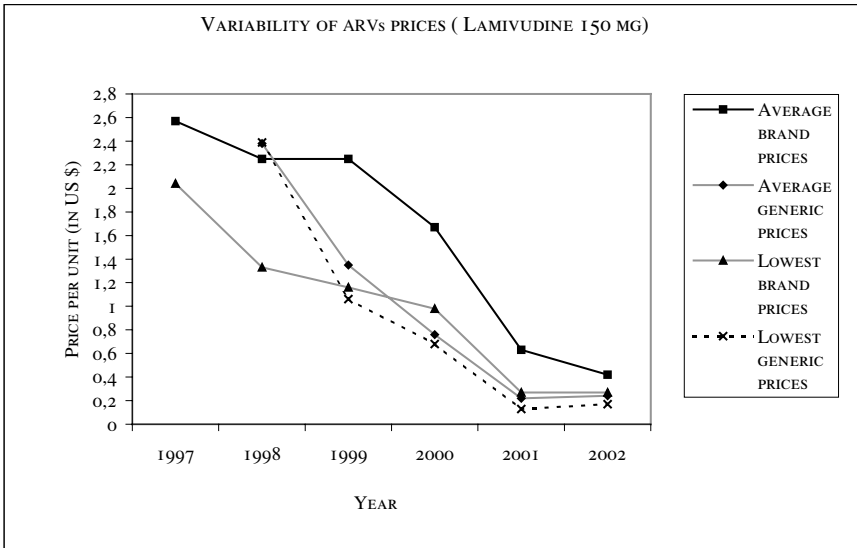


Figure 8: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes - Lamivudine 150 mg (n = 96)



For 5 out of these 7 drug dosages which have generic substitutes in observed transactions, Figures 8 to 12 compare the evolution of the average and lowest unit prices observed in each year for both the brand-named drug in the 14 countries and its generic substitutes. These figures show that generic prices have been systematically lower on average although the difference between average prices of brand drugs and their generic substitutes has decreased since 2001 (up to the point that it even disappears in the case of didanosine and lamivudine, two NRTI drugs for which generic substitutes have been available since 1998 on some markets). It must also be noted that the lowest prices offered by the patent-owner's companies in some countries tend to converge with the lowest deals proposed by generic manufacturers in the last two years (2001-2002). Overall, figures suggest that ARV prices have tended to stabilise in the last two years in parallel to the introduction of the AAI and to this convergence between brand and generic prices.

The determinants of ARV price decreases

Table 2 presents the Spearman's rho correlation coefficients between transaction prices and quantities respectively for the 13 African countries, and for Brazil in each year of observation, and suggests that a higher volume of drug purchase per transaction is effectively associated with lower unit price. Although these negative correlations are always significant at the 0.01 level, it must be noted that the value of the correlation coefficients have tended to decrease through time in African countries suggesting that the influence on unit prices of quantities purchased per transaction had a diminishing role in the latest years.

Table 2: Matrix of Spearman's rho correlation coefficients between ARV prices and quantities purchased per observed transaction (n=1030 transactions- 13 African countries and Brazil)

	1997	1998	1999	2000	2001	2002
<i>Brazil</i>		- 0.522	- 0.381	- 0.240 ^{ns}	- 0.302	- 0.405
<i>African countries</i>	- 0.795	- 0.788	- 0.695	- 0.601	- 0.542	- 0.432

All correlations are significant at the level of $p < 0.01$, unless specified (ns).

Figure 9: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes – Didanosine 100 mg (n = 90)

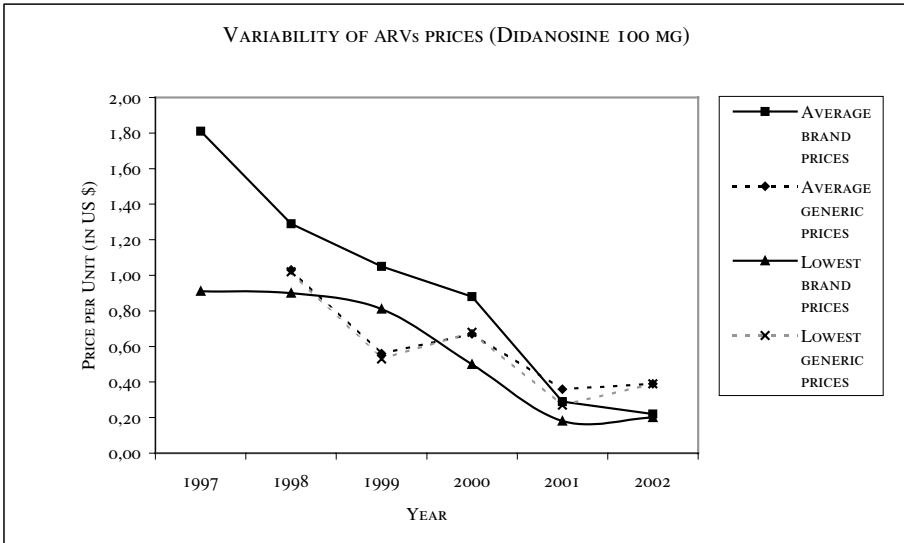


Figure 10: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes – Stavudine 40 mg (n=73)

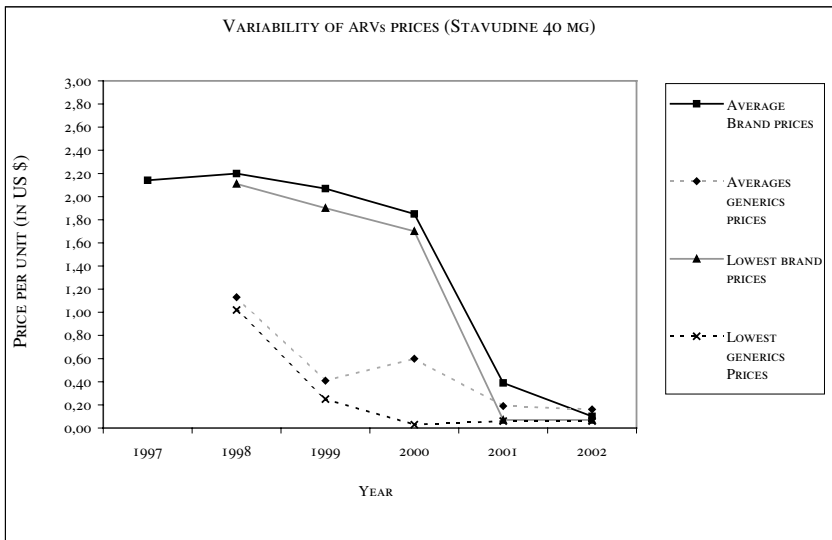


Figure 11: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes – Combination of Zidovudine 300 mg + Lamivudine 150 mg (n = 78)

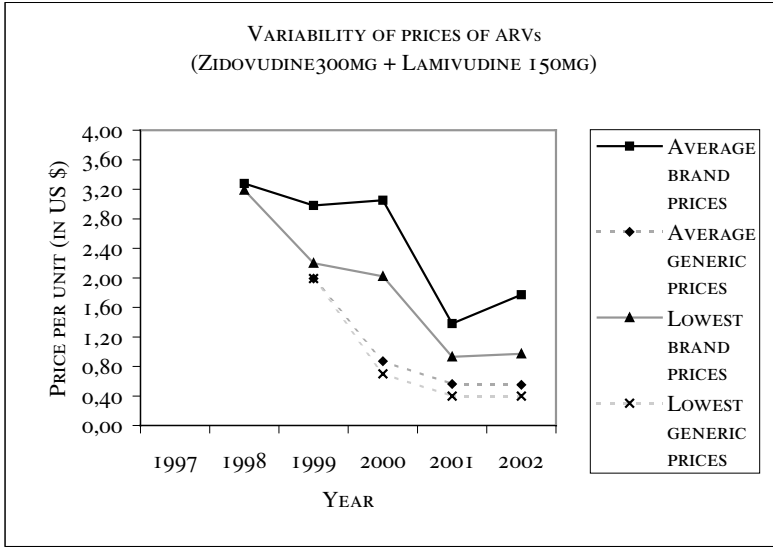


Figure 12: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes – Nevirapine 200 mg (n = 36)

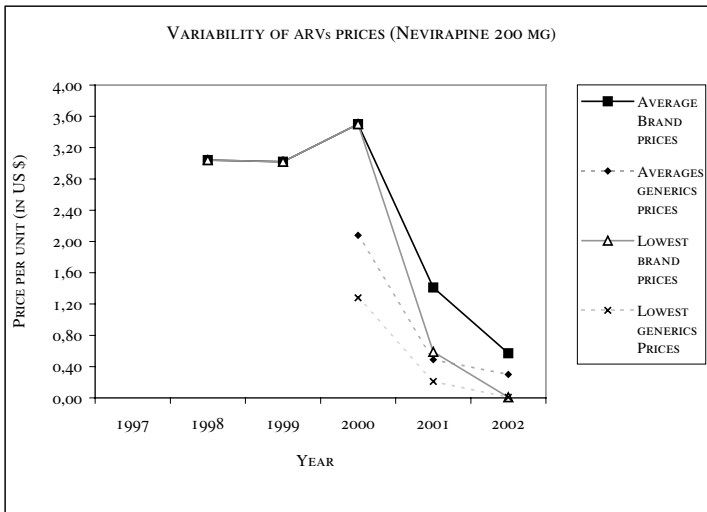


Table 3: Multiple linear regression of prices per daily dose of ARV drugs in 13 African countries and Brazil (n = 952 transactions)

<i>Variable</i>	<i>Parameter Estimate</i>	<i>Standard Error</i>	<i>t-Value</i>	<i>P-Value</i>
<i>Intercept</i>	- 8.89017	31.67015	- 0.28	0.7790
<i>Dates of purchase:</i>				
<i>Year 2001</i>	0.23108	0.06766	3.42	0.0007
<i>Year 2000</i>	0.83678	0.08823	9.48	<.0001
<i>Year 1999</i>	0.95220	0.09751	9.77	<.0001
<i>Year 1998</i>	1.11761	0.11298	9.89	<.0001
<i>Year 1997</i>	1.29211	0.18149	7.12	<.0001
<i>Number of units sold per transaction/per drug</i>	-1.91503E-06	6.603E-9	-2.90	0.0038
<i>PI drugs</i>	1.19256	0.10591	11.26	<.0001
<i>NNRTI drugs</i>	0.55571	0.10561	5.27	<.0001
<i>Date of patent in country of origin</i>	0.00462	0.1595	0.29	0.7720
<i>Patent protection in purchasing country</i>	0.30357	0.07112	4.27	<.0001
<i>AAI-related transactions</i>				
<i>Generic drugs</i>	- 0.84488	0.07857	-10.75	<.0001
	-1.00081	0.08638	-11.59	<.0001
<i>GDP per capita</i>	0.000232	0.000232	1.00	0.3178
<i>HIV/Aids Prevalence</i>	0.01411	0.00422	3.35	0.0009
<i>PI in first-line HAART recommended by national guidelines</i>	0.52665	0.11995	4.39	<.0001
<i>National programme for ARV delivery</i>	- 0.31506	0.06786	- 4.64	<.0001
<i>Transaction through an intermediary wholesaler</i>	0.28929	0.11414	2.53	0.0114
<i>R-Square</i>	0.59			
<i>Adj R-Sq</i>	0.58			
<i>Error variance</i>	104.29			

Due to some missing values for explanatory variables, regression analysis was carried out on 952 transactions for which complete data were available. All variables were initially introduced in the multivariate model and tested for statistical relevance with Student t-test. Table 3 presents the variables which remained significant in the final multiple regression model. The transaction of reference (represented by the intercept) is a transaction made in year 2002 for a brand NRTI drug. We describe in detail below each marginal effect on logarithm price per daily dose in current US dollars.

Table 3 confirms the already mentioned relationship between higher volumes per transaction and lower prices for the whole period. It also confirms the declining price trend for ARV drugs since 1997, the year Brazil introduced

its national programme for supply of generic ARVs. Indeed, the year in which the transaction was made (included as a dummy variable) is significant whatever the date considered. The parameter estimates present a decreasing trend which is nearly linear during the period 1997-2000, with an accelerated decrease for the year 2001, followed by a more limited decrease in 2002. In addition, results of econometric analysis presented in table 3 show that both generic competition and the introduction of the AAI since 2001 had significant impact on price decreases. In our model, the impact of these two parameters is of the same order of magnitude (when a Fisher test was applied to test the statistical difference between the two parameter estimates, it ended up not rejecting the null hypothesis of equivalence). However, as we will discuss below, interpretation of this result must take into account the temporal sequence of events that “determined” the price decrease of ARVs: it does not necessarily mean that the two mechanisms (international AAI agreements on the one hand, generic competition on the other hand) had independent effects of similar size on prices; it may alternatively be argued that this result rather suggests that the “philanthropic” attitude of the major brand ARV producers to lower their prices in the context of the AAI has indeed been a strategic “political” behaviour reacting to the competitive pressures of generic suppliers as well as international mobilisation of public opinion.

Not surprisingly, prices of PI and NNRTI drugs are statistically higher than those of NRTI drugs, with a larger impact on price for drugs belonging to the PI class than for NNRTI. Older drugs whose original patent was registered earlier in developed countries are associated with lower prices in univariate analysis. However, this relationship is not anymore statistically significant in multivariate analysis, when the existence (or absence) of patent protection for the drug in the country where the transaction occurred, is introduced in the model. Our results contradict the preceding allegations according to which intellectual property rights have no influence on access to antiretroviral treatment in developing countries [40]. Table 3 clearly shows that the existence of patent protection at country level is significantly related with an increase in the price of the drug.

While socio-economic characteristics which differentiate countries, such as GDP per capita, do not seem to influence the variability of prices in this sample, Table 3 reveals that a higher HIV/AIDS prevalence is associated with price increases. On the other hand, transactions which have occurred in countries

which have organised public strategies for ARV delivery are associated with lower prices. Clinical practices, at least as measured through the existence of national guidelines, also seem to influence prices: when guidelines include PI drugs for first-intention HAART therapies, which may suggest that cost-minimisation is not a priority concern for health care professionals, prices tend to be higher. As expected, transactions in which intermediary wholesalers have intervened between manufacturers and buyers to organise supply end up with higher prices.

IV

LESSONS LEARNT FOR PROCUREMENT OF HIV/AIDS DRUGS IN DEVELOPING COUNTRIES

To our knowledge, this study supported by the ANRS ETAPSUD programme is the first to be based on the observation of real transactions of HIV/AIDS drugs in a sample of developing countries severely hit by the epidemic. Of course, many limitations of these data must be acknowledged. First, our sample of African countries does not yet include all countries that have developed pilot projects for ARV delivery, like Senegal [45] or Uganda [46], as well as countries like South-Africa with significant dissemination of these drugs in the private sector [47]. Analysis should also be extended to other countries in Latin America and the Caribbean than Brazil, and in Asia, where both institutional and epidemiological contexts, as well as market structures may be quite different. Second, comparison between the dynamics of prices of ARV drugs and that of other drugs in the same countries, especially drugs that are used for treatment of HIV-related opportunistic infections, would certainly contribute to a better understanding of the degree of specificity of ARV procurement which has attracted the greatest attention at international level.

Third, some explanatory factors, that were introduced in this preliminary analysis, need further investigation. Current evidence about the impact of ARV patents at country level on the availability and prices of these drugs remains very heterogeneous across countries and over time [40, 48]. Our results clearly show that introduction of generic substitutes is influential for price decrease and that patent protection in a country is associated with price increase. However, the decision by a major pharmaceutical company to claim a patent for a drug in some developing countries rather than others may be a

proxy for various types of “strategic behaviour” from the management of the firm that should be better understood. Finally, our study was focused on source prices at entry inside the country in order to respect standardisation criteria which is often lacking in such international comparisons of drug prices [49]. Of course, we consequently do not capture other sources of variability in prices which may strongly affect HIV-infected patients’ access to ART: high taxes, mark-ups, and dispensing fees, poor purchasing and distribution programmes all affect the difference between source and retail prices in many developing countries, including those in our sample, and may continue to undermine the availability of drugs at the consumer level³⁴.

According to conventional economic theory, price discrimination across different national markets must naturally emerge since firms will maximise their profits if they are able to segment their markets according to consumers’ willingness-to-pay for their products. Firms will be in the best position to do so if they have some monopoly power on their markets. Evidence about drug price discrimination across developing countries remains unclear. A study about ARV drugs carried out on behalf of the WHO Commission on “Macroeconomics and Health” found that although brand drug companies seemed to follow such a price discrimination strategy in the first years, the relationship between prices and per capita income eroded over time, with virtually no evidence of lower prices with lower incomes in 1999³⁵. Indeed, in our own sample of countries, although they vary considerably in terms of economic development, no clear relationship emerged between basic indicators like GDP per capita and prices of ARV drugs. It must however be noted that countries with the highest HIV prevalence tended to have higher prices, suggesting that firms tend to adapt to situations in which the urgency of the epidemic may induce a lower elasticity of demand for ARVs to price in the segments of population with some ability to pay for these drugs.

Making an explicit reference to the case of HIV/AIDS drugs, the 2001 report of the WHO Commission on “Macroeconomics and Health” strongly advocated that “the best solution will be for the global community to establish diffe-

34. WHO: *Essential drugs and medicines policy: the rationale for essential drugs*. Geneva: 2002. Available at: <http://www.who.int/medicines/rationale.shtml>.

35. Barton, J.H.: *Differentiated pricing of patented products. Working Paper for the Group 4 (Health and the International Economy) of the Commission on Macroeconomics and Health*. Geneva: WHO, 2001.

rential pricing in low-income markets as the operational norm, not the exception”³⁶. Our results clearly confirm that since 2001, differential lower prices have been introduced for ARVs in African countries in comparison to the developed world. ARV prices have tended to come closer to marginal costs of production as suggested by the significant reduction in price differences between brand drugs and generic substitutes in these African countries and by the convergence of these prices with those of nationally produced ARV drugs in Brazil. Conclusions however remain ambiguous about the extent to which this observed North/South differential pricing for ARVs is rather the product of a temporary institutionalisation of “corporate philanthropy” from major pharmaceutical firms, in fact largely forced by international political pressures that have been handed over by UN organisations and that have been nourished by the political threat from some governments of developing countries, like Brazil, to use compulsory licensing to develop national capacities for production of generic drugs, or to the establishment of effective competitive mechanisms of procurement at country level which may even spread to other drugs than ARVs.

Remaining ambiguities are partly related to technical limitations of our analysis. There are important methodological considerations in the econometric literature that emphasise that price estimates require two stages and enough information to disentangle supply and demand aspects [49, 50]. In our preliminary OLS estimation, supply and demand factors are not clearly distinguished. In addition, some endogeneity bias, related to the implicit aggregation of error terms, may have occurred in the absence of differentiated structural equations for both supply and demand.

However, remaining ambiguities are also related to the actual situation of HIV/AIDS drugs procurement at international level. In particular, the actual status of the Accelerated Access Initiative (AAI) sponsored by the UN-organisations in partnership with six of the major brand companies involved in ARV supply remains unclear. The only explicit rationale for giving priority to this partnership, centrally negotiated by the UN at international level, dates back to its predecessor (the Drug Access Initiative), and refers to the idea that such international framework of negotiations for procurement would be consistent

36. Sachs, J. (Ed.): *Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health to the Director General of the World Health Organization*. Geneva: December 2001.

with the establishment of national channels of ARV delivery that would allow strong public control and guarantee a rational diffusion of these drugs. Experience in countries like Brazil has indeed shown that procurement mechanisms open to generic competition do not necessarily translate into a lack of public control on the delivery channels of ARV drugs to health care centres and ultimately to HIV-infected patients. The risk of dissemination of HIV strains that have become resistant to existing ARV drugs may flow from the unregulated availability of ARVs that will inevitably occur in developing countries in the absence of organised efforts by public health authorities to improve access to treatment, but restrictions on competition for ARV procurement at national level have nothing to do with mitigating this risk.

It is far from granted that the international reference pricing mechanism which has been established since 2001 for procurement of ARV drugs for limited experimental programmes in Africa will become perennial (and will be adapted to developing countries in other continents) as soon as the on-going process of scaling up access to ART will concern greater numbers of HIV-infected patients. The trend we have identified in the last two years of a relative disconnection between prices and quantities purchased may be an indicator of an increased pre-eminence of political and institutional factors in ARV procurement. Excessive reliance on “philanthropy” and international bargaining between UN organisations and representatives of the major brand named manufacturers will remain sensitive to the fickleness of public opinion and of media attention and to anecdotal reports of fraudulent parallel importing of drugs from the South to the North. It has already been shown that “philanthropic” drug donations by private companies or international agencies, although they have short-term benefits for limited groups of patients, may jeopardise the process of establishing safe and rational channels of drug procurement in the public health sector of developing countries [51].

As suggested by the spectacular reduction in inter-country price variations in our sample of 13 African countries during the last two years, it is quite clear that the major pharmaceutical companies have accepted (or more realistically have been forced to accept) an implicit international mechanism of reference pricing for ARVs in Africa. Our data also suggest that the cheapest generic product tends to set the reference in these countries. Reference pricing, which consists in assigning a drug to a group of products which receive the same level of reimbursement, has already been used to control drug prices in

some OECD countries (especially in New Zealand and Canada) and has produced substantial savings in drug expenditure [52, 53]. However, in these countries, the overall effects of this policy on patients' health and associated health care and administrative costs remain unclear [54].

Although the AAI never went as far as trying to institute a unique international mechanism for purchasing ARV drugs in the developing world and has only attempted to create a common framework for national procurement negotiations, an alternative rationale for this UN strategy could be found in previous international attempts to promote low-cost supply of medical goods for countries with limited ability to pay, such as the UNICEF/WHO Expanded Program for Immunization [55-56]. These attempts were based on the conventional wisdom that large buyers have an advantage in extracting price concessions from suppliers: globalisation of purchases would give the buyer some "monopsony" power which would be able to compensate for the power of a restricted number of firms operating in oligopolistic markets, while encouraging further private R&D efforts by guaranteeing the solvency of markets in developing countries. They have experienced some limited success in the field of vaccines and drugs for "neglected tropical diseases" [57], but they may be quite inappropriate in the case of drugs that already correspond to highly profitable markets in developed countries.

In fact, the economics literature on the sources of buyer-size effects offers two competing classes of theories. For the first category of models, often qualified as "bargaining models", there are conditions under which buyer-size discounts can emerge at equilibrium with a monopoly supplier under symmetric information [58] or even asymmetric information [59]. On the other hand, the second category of models, the so-called "countervailing power" models, concludes that the buyer-size effect cannot emerge with a monopoly supplier [60]: tacitly-colluding suppliers will compete more aggressively for the business of large buyers and are forced to charge lower prices to large buyers to sustain collusion only to the extent that buyers have the power to substitute between multiple suppliers. Empirical evidence about the source prices of drugs according to the channels of distribution in developed countries is generally in favour of this second hypothesis³⁷. A similar lesson emerges

37. Ellison SF, Snyder CM.: *Countervailing power in wholesale pharmaceuticals*. Massachusetts Institute of Technology. Department of Economics, Working Paper 01/27, July 2001.

from our data, and more globally from the experience of procurement of ARV drugs in developing countries, including the most advanced one that of the Brazilian programme. International “political bargaining” with the pharmaceutical industry centrally carried out by UN representatives would not have succeeded in lowering prices in the absence of the “countervailing power” that has been generated by the economic mechanism of decentralised negotiations at country level that have extended market competition to all potential drug suppliers, including manufacturers of generic substitutes. The long term sustainability of a differential pricing mechanism for HIV/AIDS drugs in favour of developing countries clearly implies an iterative process of competitive purchasing from all qualified suppliers at each country level. Of course, promotion of national effective market competition does not preclude inter-country cooperation at regional level for bulk purchasing of drugs (especially for countries with limited market size). As mentioned above, a growing number of African countries are evolving toward a “hybrid” model of ARV procurement in which they introduce generic competition in parallel to negotiations with brand companies through the AAI. UN-sponsors of the AAI have also come to recognise that a major limitation of this initiative has been its focus on the six major pharmaceutical companies and “a lack of promotion of generic pharmaceutical partners”³⁸.

Regulatory flexibility in local production and imports of generic drugs, which was supposed to be guaranteed by the November 2001 Doha Declaration on TRIPS, is an additional component of the establishment of competitive market mechanisms. The recent decision of the Global Fund to Fight Aids, Tuberculosis and Malaria to respect a country’s freedom of choice for purchasing ARV drugs from any quality-controlled manufacturers (including generic manufacturers) in programmes supported by the Global Fund, coupled with incentives to buy drugs at the lowest price, goes in a similar direction to the main policy recommendation of our study³⁹. Regulation of emerging market mechanisms for procurement also implies, as a prerequisite, public international support for systematic exchange of information about prices and characteristics between buyers. An indirect positive effect of our research is

38. On February 26, 2003, WHO and UNICEF have issued a joint statement in which they call for an increased collaboration between UN agencies and generic pharmaceutical companies to expand access to essential medicines.

39. Global Fund to Fight Aids, Tuberculosis and Malaria (Third Board Meeting). “Procurement and supply management”. Decision text. Geneva, 10-11 October 2002.

its modest practical contribution to the establishment of an operational observatory for prices of HIV/AIDS drugs in some regions. Ministries of Health of the Economic Community of West African States (ECOWAS) have recently committed themselves to establish such a regional observatory to track the prices of HIV-related medicines and diagnostics with technical support from UNAIDS and ANRS⁴⁰. The Horizontal Technical Cooperation Group (GCTH), which associates 21 countries from Latin America, Central America and the Caribbean, has a previous experience of exchange of information about drug prices and is also considering further improvements of this collaborative effort.

The 13 African countries visited by the authors are:
Benin, Botswana, Burkina Faso, Burundi, Cameroon, Congo (Republic), Côte d'Ivoire, Gabon, Kenya, Malawi, Mali, Nigeria and Togo.

40. ECOWAS/CEDEAO: *For a subregional observatory of HIV-related medicines and diagnostics*. Meeting of the Ministries of Health, Accra, July 26, 2002.

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