Chapter 5

Determinants of antiretroviral prices: An analysis of Global Price Reporting Mechanism data

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Abstract

This paper examines factors determining the price of antiretroviral drugs, using a dataset of procurement transactions from the Global Fund Price Reporting Mechanism. Regression analysis reveals that originator pharmaceutical firms are practicing "differential pricing" whereby they set prices lower in the poorest countries—by around $1.3 per defined daily dose. Generic firms, in contrast, show no evidence of pursuing such policies. The study also finds that the existence of patents is associated with lower originator drug prices in developing countries, which is contrary to the findings in the previous literature. However, this finding does not necessarily imply that patents are the cause of lower prices.

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1. Introduction

The international community still faces a formidable challenge, despite its considerable efforts to cope with the HIV/AIDS crisis in developing countries. An estimated 39.5 million people are now living with HIV, in comparison to 36.9 million in 2004[1]. The geographical areas of concern have expanded to cover Eastern Europe and Central Asia, where infection rates have risen by more than 50 percent since 2004. Furthermore, drug resistance has developed in many countries, necessitating complex and expensive second-line treatments. The high price of medicines particularly for second-line treatment requires additional attention from those involved in promoting accessibility and quality of medicines.

It is in this context that this study analyzes the factors that affect the prices of antiretroviral (ARV) drugs. The study examines the relationships between the price of ARVs and possible factors influencing the price of such medicines. These factors are divided into five categories: (1) recipient country characteristics on the demand side, (2) firm characteristics on the supply side, (3) product characteristics, (4) patent status of the medicines concerned, and (5) transaction characteristics.

In examining these relationships, this study compares the pricing behavior of originator pharmaceutical companies with that of their generic counterparts. Generic drugs are defined here as "copies of patented drugs [that are made after] the patent has expired, [or made] outside patent protection, for example in a country that still does not provide patent protection for pharmaceuticals"[2]. It should be noted that this definition is only from the viewpoint of patents, and not regulatory requirements such as bioequivalence to the originator's product. This study uses a sample of actual transactions obtained from the Global Fund Price Reporting Mechanism. This body of transactions represents a significant proportion of ARV purchases recorded by the World Health Organization (WHO) in its Global Price Reporting Mechanism (GPRM). The GPRM transactions, in turn, represent approximately 40% of the ARVs supplied to developing countries (World Health Organization [2006]).

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[1] 2006 report on the AIDS global epidemic, UNAIDS, December 2006.

[2] This definition was obtained in 2001 from a webpage of the World Trade Organization titled "TRIPS and pharmaceutical patents: fact sheet" (http://www.wto.org/English/tratop_e/trips_e/factsheet_pharm03_e.htm). The definition currently appearing on the webpage is a different one.

The main findings of this study are the following:

(i) Branded drugs supplied by originator pharmaceutical firms tend to have higher prices than their generic counterparts in middle income countries, but this premium disappears in the lowest income countries.

(ii) Originator firms tend to offer lower prices in countries with high prevalence of HIV infection.

(iii) The fulfillment of quality standards does not raise the price; in fact the price of ARVs that have been prequalified by the WHO is lower.

(iv) Firms supplying their home country market tend to charge higher prices.

(v) The existence of patents is associated with lower prices for the originator's product in developing countries.

The above findings call into question certain popular beliefs which may have served as fundamental assumptions in discussions relating to the price of drugs, such as that patents raise prices of medicines. This empirical analysis presented in this study shows the varying effects on prices of different factors, including patents, and differentiates the ways in which patents may raise or lower prices. It is hoped that the suggestions this study offers can be taken into consideration by organizations funding the procurement of medicines for life-threatening diseases such as HIV/AIDS, malaria and tuberculosis.

The remainder of this paper is structured as follows. Section 2 describes the research questions in more detail. Section 3 describes the data used in the empirical analysis. The findings are discussed in section 4, followed by a concluding section.

2. What determines antiretroviral drug prices in developing countries?

Since the development of highly active antiretroviral therapy (HAART) in the mid-1990s, the mortality rate from AIDS has dropped by 60–80% in the US and other developed countries (Bartlett [2004]). HAART consists of taking a combination of three or four antiretroviral (ARV) drugs, chosen based on the stage of the patient's HIV infection. A common HAART regimen is composed of two nucleoside analog reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI). Another common regimen consists of two NRTIs and a protease inhibitor (PI). Yet another involves

the use of three NRTIs. By combining several ARVs that target different points in the lifecycle of the HIV virus, HAART is capable of suppressing the viral load far more effectively than could be done using a single-drug regimen. However, when the virus develops drug resistance, it is necessary to move up to a second line of therapy, involving the use of a class of drugs not used in the first-line regimen. For instance, if the first-line regimen consisted of two NRTIs (such as lamivudine in combination with stavudine or zidovudine) plus a NNRTI (such as nevirapine or efavirenz), then the second-line regimen should include a PI (such as ritonavir-boosted lopinavir).

Many of the antiretroviral drugs were developed by the so-called "Big Pharma" companies of the US and Western Europe, sometimes in collaboration with government and academic institutions, while other drugs were developed by smaller, often biotech, innovator companies (see Table 1 for the main patent holders of each drug). In the remainder of this paper, the term "originator" is used to describe the Big Pharma and other innovator firms that were responsible for the development and/or first marketing of these pharmaceuticals.

With the exception of zidovudine, all of the ARVs are still under patent in the US and other developed countries at the time of writing. Partly as a result of this, the prices of ARVs in developing countries were quite high up to around the year 2000 (Médecins Sans Frontières [2006])[3]. Since then, however, low-cost antiretrovirals have become available to patients in developing countries for various reasons. An oft-cited reason is that manufacturers of generic versions of ARV drugs—a number of them located in India—have entered many developing countries' markets, introducing a certain degree of competitive pressure. Another reason for the availability of these low-cost drugs is that large-scale funding for the purchase of ARVs by developing country governments and international organizations such as UNICEF has become available from schemes such as the Global Fund to Fight AIDS, TB, and Malaria (hereafter referred to as the Global Fund) and the US government's Emergency Plan for AIDS Relief. As a result, many of the ARV drugs used today in developing countries are purchased by governments using outside funding, rather than by individual patients.

[3] That the provision of antiretrovirals on a national scale was prohibitively expensive for the poorest countries in the late 1990s is mentioned in the background papers for an online conference hosted by UNAIDS and the World Bank in 1998 (http://www.worldbank.org/aidsecon/arv/index.htm).

Table 1: Patent holders of antiretrovirals and developing countries where they are patented

International Nonproprietary Name of active ingredient(s)	Patent holder(s)	Developing countries where the active ingredient(s) and/or combination thereof are patented according to Médecins sans Frontières [2003], and that are included in the dataset
abacavir	GlaxoSmithKline	China, Kenya, Malawi, South Africa, Uganda, Ukraine, Zimbabwe
abacavir / lamivudine / zidovudine	GlaxoSmithKline	China, Kenya, Malawi, South Africa, Thailand Uganda, Ukraine, Zimbabwe (1)
didanosine	US Government and Bristol-Myers Squibb	China, South Africa, Thailand
efavirenz	Merck	China, South Africa, Thailand, Ukraine
indinavir	Merck	China, South Africa, Thailand, Ukraine
lamivudine	IAF Biochem and GlaxoSmithKline	China, Kenya, Malawi, OAPI member states(a), South Africa, Uganda, Ukraine, Zimbabwe
lamivudine / stavudine	(No patent holder reported for the combination)	China, Kenya, Malawi, OAPI member states, South Africa, Uganda, Ukraine, Zimbabwe (2)
lamivudine / zidovudine	GlaxoSmithKline	China, Kenya, Malawi, OAPI member states, Andean Community member states(b), South Africa, Thailand, Uganda, Zimbabe (1)
lamivudine / nevirapine / zidovudine	(No patent holder reported for the combination)	China, Kenya, Malawi, OAPI member states, Andean Community member states, South Africa, Thailand, Uganda, Ukraine, Zimbabwe (2)
lamivudine / nevirapine / stavudine	(No patent holder reported for the combination)	China, Kenya, Malawi, OAPI member states, Andean Community member states, South Africa, Thailand, Uganda, Ukraine, Zimbabwe (2)
lopinavir / ritonavir	Abbott	China, South Africa, Thailand (1)
nelfinavir	Agouron (manufactured by Hoffmann-La Roche)	China, Kenya, Malawi, OAPI member states, South Africa
nevirapine	Boehringer Ingelheim	Kenya, Malawi, OAPI member states, Andean Community member states, South Africa, Thailand, Uganda, Ukraine, Zimbabwe
ritonavir	Abbott	China, South Africa, Thailand
saquinavir	Hoffmann-La Roche	China, Malawi, OAPI member states, South Africa, Zimbabwe
stavudine	Yale University and Bristol-Myers Squibb	South Africa
tenofovir	Gilead Sciences	(No patent information available)
zidovudine	GlaxoSmithKline	Kenya, South Africa, Zimbabwe

Source: Médecins Sans Frontières [2003].

Notes:

(1) These are the countries where the individual active ingredients in the combination and/or the combination itself are patented.

(2) These are the countries where the individual active ingredients in the combination are patented.

(a) Member states of the Organization Africaine de la Propriété Intellectuelle (OAPI) that appear in the dataset are Benin, Burkina Faso, Cameroon, Demcratic Republic of Congo, Equatorial Guinea, Guinea-Bissau, Mali, Niger, and Senegal. OAPI members that do not appear in the dataset are Central African Republic, Chad, Côte d'Ivoire, Gabon, Guinea, Mauritania, and Togo.

(b) The Andean Community membership consists of Bolivia, Colombia, Ecuador, Peru, and Venezuela. Of these, Colombia and Peru appear in the dataset.

We have set up the following explanatory variables to see whether or not these factors influence the prices of different ARVs.

1) Do country characteristics matter?

Pharmaceutical firms might maintain differential pricing policies under which price quotes in certain developing countries are lower. One way to identify such a pricing policy is to look for a relationship between the income level of a country and drug prices in that country. Another parameter which may affect the pricing decision of pharmaceutical firms is the rate of HIV infection in a country. According to Médecins Sans Frontières [2006] (p. 8), some originator firms offer their lowest prices to developing countries that have at least a certain level of HIV prevalence. It would also be of interest to see whether or not generic drug manufacturers also adjust their prices according to country characteristics.

2) Do originator firms charge higher prices?

It is said that originator firms have higher prices for their products than their generic counterparts (Vasan et al. [2006], Chien [2007]). However, the relationship between drug prices and manufacturer identities may not be so clear-cut. In particular, originator prices may be higher relative to generic prices in some countries, but not in others.

3) Are newer drugs more expensive?

Already, many AIDS patients in developing countries have developed resistance to first-line treatment, and require the use of newer second-line drugs. Relatively new medicines such as PIs that are often used in second-line treatment (e.g., ritonavir-boosted lopinavir, indinavir, and saquinavir), as well as some of the second-line NRTIs (such as abacavir and tenofovir[4]) are newer, and have longer remaining patent terms in developed countries. They are also more likely to be under patent protection in India and China, where many generic manufacturers are located[5]. Therefore, it is of interest to examine whether these newer drugs tend to be more expensive than older drugs.

[4] Technically, tenofovir is classified as a nucleotide reverse transcriptase inhibitor (NtRTI), which is similar to a NRTI in its mechanism of action.

[5] India did not begin to grant product patents until 2005, but drugs that were first patented after 1995 are eligible for patent protection. China introduced product patents in 1993.

4) Do drug quality standards increase prices?

Another firm-level characteristic that may affect the price of a drug is its quality. Since April 2005, the quality of ARV drugs sold in developing countries has been controlled either by the WHO's Prequalification Project or a "stringent regulatory authority" such as the US Food and Drug Administration (FDA)[6]. Some manufacturers, such as the Government Pharmaceutical Organization of Thailand, have yet to conform to international quality standards, and have not been able to obtain WHO prequalification. It would be worthwhile, therefore, to examine the relationship between WHO prequalification and prices.

5) How do firms supplying their home countries behave?

Countries having some level of pharmaceutical manufacturing capabilities may be inclined to use domestically manufactured generic drugs. The pricing behavior of home country firms is therefore of some interest. Firms supplying their home countries have lower transportation and distribution costs, which may lead to lower prices. On the other hand, domestic companies may be allowed to charge higher prices if procurement agencies have a bias in their favor.

6) Do patents lead to higher prices?

Many studies and policy discussions have contained an underlying assumption that patents lead to higher drug prices in developing countries (Nogues [1993]). On the other hand, some authors have noted that the protection of pharmaceutical patents and the affordability of drugs in developing countries can be reconciled if originator companies are able to practice "differential pricing", whereby pharmaceuticals manufactured by the same company are supplied at lower prices in certain countries (Danzon and Towse [2003], p.184). However, it has not been shown to what extent, when and in what countries differential pricing has actually been practiced.

[6] http://www.theglobalfund.org/en/about/procurement/quality/

3. Description of data

The main source of data used in this study is the Purchase Price Report of the Global Fund Price Reporting Mechanism (PRM)[7]. The report contains transaction-level prices and quantities of various ARVs and other medicines purchased by developing countries with funding from the Global Fund. These purchases form an important part of the transactions recorded in the WHO's Global Price Reporting Mechanism (GPRM). The mechanism records the details of each transaction, such as recipient country, supplying firm, product specifications, transaction value, transaction quantity, and transaction terms.

The PRM database downloaded in December 2006 contains a total of 4,053 transactions that took place between June 2003 and December 2006. Of these, 2,638 concern ARVs. The products in these transactions include an array of formulations of various active ingredients (including combinations thereof), dosage forms, and strengths. Following the World Health Organization [2006], we focus on a set of the most common oral solid formulations. This leaves 1,851 observations. We also limit our attention to transactions having complete information on International Commerce Terms (Incoterms), which describe the terms of the transaction, such as who pays for the insurance, freight, and customs duties. Previous studies, such as those by the World Health Organization [2006] and Vasan et al. [2006], have ignored the significant price differentials that exist between different transaction types as defined by Incoterms[8]. Because we are interested in the pricing of drugs, we keep in our sample only those transactions that have a non-zero price. Transactions reporting a zero price are likely to have been donations, and thus are dropped. This gives us a dataset containing 1,200 transactions. For each of these transactions, we obtain data on product characteristics (active ingredient(s), strength of each active ingredient), name of recipient country, name of supplying firm, price per smallest unit (tablet or capsule), year of transaction, volume of transaction, and the Incoterm describing the transaction.

Table 2 lists the drug formulations that appear in our dataset. Eighteen of the twenty-six listed drugs are single-ingredient formulations, whereas the remaining eight are

[7] The data can be accessed from the Global Fund Price Reporting Mechanism website (http://web.theglobalfund.org/prm/).

[8] According to United States Government Accountability Office [2005] (p. 24), these price differentials range from 3 to 15%.

fixed-dose combinations (FDCs). Seventeen drugs are categorized by the World Health Organization [2006] as being used in first-line regimens, and the remaining nine drugs are mainly used as part of a second-line regimen. For the purpose of identifying drugs that are novel, and hence relatively expensive, we create an original classification that is similar, but not identical to the WHO's first and second-line classification. Under our classification, any drug formulation containing any one of the following active ingredients was classified into Group 2: abacavir, indinavir, lopinavir, ritonavir, saquinavir, and tenofovir. Group 2 drugs are novel relative to the remaining drugs, which we shall call Group 1.

Information on patenting activity pertaining to these products by the originator firms was obtained from Médecins Sans Frontières (MSF) [2003]. This report contains information on the existence of patents in a subset of the developing countries that appear in our price dataset. In Appendix 1, which lists all the countries contained in the dataset, we indicate the countries for which patent information was available. For each ARV active ingredient and combinations thereof listed in Table 2, Table 1 lists the countries for which MSF reports either (a) existing patents or (b) that a patent is under examination. Estimated expiration dates of these patents are also reported in the MSF report. Most of the patents were valid during the time that the price data were collected, and those that had expired prior to 2003 were treated in our dataset as if they did not exist. For zidovudine, the oldest drug in the dataset, the patent did not expire until 2006 in Kenya, South Africa, and Zimbabwe, but it had already expired in 2002 in Malawi and Uganda. In some cases, MSF could not ascertain whether a patent in question actually existed in a particular country. For instance, it is not clear whether a patent that had been filed internationally under the Patent Cooperation Treaty (PCT) had entered the national phase in a particular country. In these situations, we assume that a valid patent did not exist in the country in question. In our dataset, there are 697 transactions for which patent data are available.

Figure 1 shows the mean price per defined daily dose (DDD) for each product listed in Table 2. The bands represent a range of one standard deviation above and below the mean price. The drugs numbered 17, 18, and 21 (lopinavir/ritonavir, nelfinavir, and saquinavir, respectively; the ―drg numbers" correspond to the row numbers in Table 2) have significantly higher prices. These are all protease inhibitors (PIs), with lopinavir/ritonavir and saquinavir belonging to the second-line segment.

Table 2: Drug formulations appearing in the dataset

Drug number	International Nonproprietary Name (INN) of active ingredient(s)	Strength	First or second line	Group*	Class	Number of transactions in dataset
1	abacavir (ABC)	300mg	2nd	2	NRTI	27
2	abacavir / lamivudine (3TC) / zidovudine (ZDV or AZT)	300mg / 150mg / 300mg	1st	2	NRTI	5
3	didanosine (ddI)	100mg	2nd	1	NRTI	47
4	didanosine	200mg	2nd	1	NRTI	9
5	didanosine	400mg	2nd	1	NRTI	17
6	efavirenz	50mg	1st	1	NNRTI	33
7	efavirenz (EFV or EFZ)	200mg	1st	1	NNRTI	70
8	efavirenz	600mg	1st	1	NNRTI	79
9	indinavir (IDV)	400mg	2nd	2	PI	29
10	lamivudine	150mg	1st	1	NRTI	135
11	lamivudine / stavudine (d4T)	150mg / 30mg	1st	1	NRTI	13
12	lamivudine / stavudine	150mg / 40mg	1st	1	NRTI	10
13	lamivudine / zidovudine	150mg / 300mg	1st	1	NRTI	72
14	lamivudine / nevirapine (NVP) / zidovudine	150mg / 200mg / 300mg	1st	1	NRTI + NNRTI	10
15	lamivudine / nevirapine / stavudine	150mg / 200mg / 30mg	1st	1	NRTI + NNRTI	85
16	lamivudine / nevirapine / stavudine	150mg / 200mg / 40mg	1st	1	NRTI + NNRTI	48
17	lopinavir / ritonavir (LPV/r)	133mg / 33mg	2nd	2	PI	46
18	nelfinavir (NFV)	250mg	1st	1	PI	31
19	nevirapine	200mg	1st	1	NNRTI	98
20	ritonavir (RTV)	100mg	2nd	2	PI	36
21	saquinavir (SQV)	200mg	2nd	2	PI	11
22	stavudine	30mg	1st	1	NRTI	80
23	stavudine	40mg	1st	1	NRTI	104
24	tenofovir (TDF)	300mg	2nd	2	NtRTI	12
25	zidovudine	100mg	1st	1	NRTI	38
26	zidovudine	300mg	1st	1	NRTI	55

* Groups 1 and 2 closely mirror the first and second-line classifications, respectively, with the following exceptions: (1) the triple combination abacavir/lamivudine/zidovudine is classified as Group 2 even though it is recommended as a first line treatment by the WHO; (2) didanosine is classified as Group1 even though it is recommended as a second-line drug.

Figure 1: Price range of ARV formulations

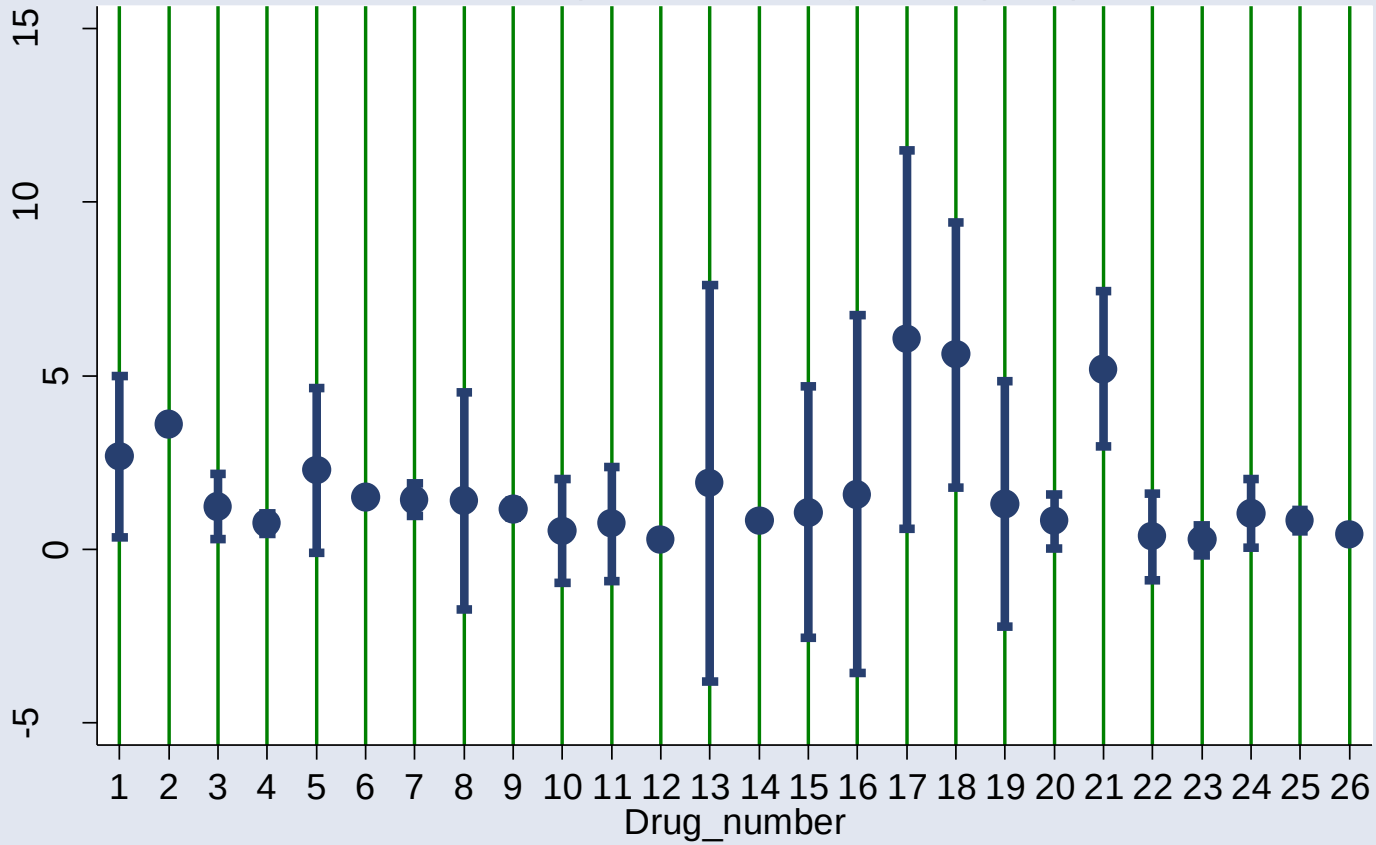

Table 3: Pharmaceutical companies appearing in the dataset

Company name	Classification	Headquarter location	Number of transactions appearing in dataset
Abbott	Originator	USA	69
Aspen	Generic	South Africa	121
Aurobindo	Generic	India	21
Bayer	Originator	Germany	1
Boehringer Ingelheim	Originator	Germany	7
Bristol-Myers Squibb	Originator	USA	135
Zydus Cadila	Generic	India	4
Cipla	Generic	India	430
Emcure	Generic	India	2
Gilead Sciences	Originator	USA	11
Government Pharmaceutical Organization	Generic	Thaliand	21
GlaxoSmithKline	Originator	UK	117
Hetero	Generic	India	42
McLeods	Generic	India	7
Merck	Originator	USA	103
Missionpharma	Generic	Denmark	2
Patheon	Contract manufacturer	Canada	1
Ranbaxy	Generic	India	53
Refasa	Generic	Peru	1
Hoffman-La Roche	Originator	Switzerland	34
Strides Arcolab	Generic	India	18

Table 3 lists those pharmaceutical manufacturers which appear in the dataset. A balanced mix of originator and generic firms can be observed. Originator firms generally have more transactions appearing in the data, but one Indian generic company—Cipla—overwhelms all other firms with 36% of all transactions. Most, but not all firms listed in Table 3 have had their products prequalified by the WHO. Prequalification is obtained on a product-by-product basis. Therefore, some products of a given firm are prequalified, while others are not. A list of products prequalified by the WHO was obtained from its website, and was matched with the dataset at hand[9]. This enables us to construct a variable indicating whether or not a given transaction in the PRM dataset involved WHO-prequalified drugs.

For each transaction, we are able to identify the country receiving the drugs. In total, there are 56 different recipient countries (see Appendix 1). Of these, 19 belong to the least developed countries group defined by the United Nations[10]. A different group of 19 countries belong to the low human development group defined by the United Nations Development Programme (UNDP) in its Human Development Report[11]. A larger group of 26 countries are defined by the World Bank as low-income economies[12]. We construct a new group called "low development (LD)" as a union of the three groups mentioned above. Additional country characteristics, namely population, GDP per capita, and HIV infection rates among people of ages 15–49 were collected from the World Bank's World Development Indicators Online. Appendix 1 contains the values of these variables. The definitions of all the variables used in the empirical analysis in section 4 are found in Table 4.

[9] A current list of prequalified products was obtained from the following webpage: http://mednet3.who.int/prequal/lists/hiv_suppliers.pdf

[10] See http://www.un.org/special-rep/ohrlls/ldc/list.htm

[11] See http://hdr.undp.org/reports/global/2005/pdf/hdr05_HDI.pdf

[12] See http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20421402~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html

Table 4: Description of variables

Variable name	Unit	Description
Country characteristics		
LD	zero-one indicator	Indicates that the country belongs to at least one of the following categories: least developing countries (LDC) as defined by the United Nations; countries with —low human development", as defined by the UNDP's Human Development Report; low-income economies, as defined by the World Bank
HIV	%	Percentage of the population, ages 15-49, who were HIV-positive in 2005
POPULATION	100 million	Total population in 2004
Firm characteristics		
PREQUALIFIED	zero-one indicator	Indicates that the firm has obtained prequalification for the product in question under the WHO Prequalification Project
ORIGINATOR	zero-one indicator	Indicates that the firm is an originator pharmaceutical company
HOME	zero-one indicator	Indicates that the firm is located in the same country where the drug is being procured/consumed
Product characteristics		
GROUP2	zero-one indicator	Indicates that the product belongs to a group of newer, more expensive ARVs
FDC	zero-one indicator	Indicates that the product is a fixed-dose combination
Patent variable		
PATENT	zero-one indicator	Indicates that a patent existed – or was under examination – for the product in question, in the country in question, according to MSF [2003]
Transaction characteristics		
TIME	year	Annual time trend variable taking the value of zero at year 2003
QUANTITY	DDD	Number of defined daily doses (DDDs) per transaction
FOB	zero-one indicator	Indicates that transaction took place under —Free On Board" terms
EXW	zero-one indicator	Indicates that transaction took place under —Ex Works" terms
FCA	zero-one indicator	Indicates that transaction took place under —Free Carrier" terms
CIF	zero-one indicator	Indicates that transaction took place under —Cost, Insurance, and Freight" terms
CPT	zero-one indicator	Indicates that transaction took place under —Carriage Paid To" terms
CIP	zero-one indicator	Indicates that transaction took place under —Carriage and Insurance Paid To" terms
DDU	zero-one indicator	Indicates that transaction took place under —Delivered Duty Unpaid" terms
DDP	zero-one indicator	Indicates that transaction took place under —Delivered Duty Paid" terms

4. Results of regression analysis

In order to uncover the factors affecting ARV prices, regressions are run with each transaction as the unit of observation. The price applied in each transaction is employed as the dependent variable, with recipient country characteristics (*LD, HIV, POPULATION*), supplying firm characteristics (*PREQUALIFY, ORIGINATOR, QUANTITY*), product characteristics (*GROUP2*, *FDC*), and transaction characteristics (*TIME, QUANTITY,* Incoterms) as the explanatory variables. In some specifications, a variable describing the existence of patents (*PATENT*) is also employed. Furthermore, several interaction terms are used. The *ORIGINATOR×LD* and *ORIGINATOR×HIV* variables are meant to identify the difference in coefficients on the *LD* and *HIV* variables between originator and generic firms. The *PATENT×GROUP2* interaction term will capture any difference between Group 1 drugs and Group 2 drugs in the effect of patenting on prices.

Two different measures of price are employed. The first one, called *PRICE PER DDD*, is the price per tablet/capsule, in US dollars, multiplied by the defined daily dose. Although this is an accurate representation of the price of a drug, it has the disadvantage of not being comparable across products. In particular, the price of a fixed-dose combination that contains three active ingredients cannot be meaningfully compared to the price of a single-ingredient formulation. The second price measure, called *RATIO TO US PRICE*, is meant to be comparable across different products. It is the ratio of the reported price per tablet/capsule to the price of an equivalent product—supplied by the originator firm—in the US market. For FDCs that are not marketed in the US, the US prices are computed by adding up the prices of each component drug.

All transactions in the dataset are pooled when running regressions using *RATIO TO US PRICE* as the dependent variable. This allows us to estimate the relationship between product characteristics and prices. In contrast, when we employ *PRICE PER DDD* as the dependent variable, we estimate a fixed effects model which generates coefficient estimates from within-group variation, where the groups are defined by the individual rows in Table 2. The fixed effects model does not allow us to estimate the relationship between product characteristics and prices, but it allows us to control for unobserved product characteristics.

1) Results without the patent variables

Table 5 presents regression results where the patent variables were not employed, but where the full dataset consisting of 1,200 transactions was utilized. The coefficients on the first two country characteristics, *LD* and *HIV*, can be thought of as the effect of these variables on prices when the supplier is a generic firm. This is due to the inclusion of the interaction variables *ORIGINATOR×LD* and *ORIGINATOR×HIV*. The LD variable has a positive coefficient which is statistically significant at the 5% level in the fixed effects specification. This implies that countries belonging to the low development group receive higher generic prices. The negative and highly significant coefficient on *HIV* in both of the specifications implies that higher HIV prevalence rates in the recipient country tend to reduce generic ARV prices.

Of the firm characteristics, the *PREQUALIFY* variable has a negative coefficient, and it is statistically significant at the 10% level in the pooled specification. This suggests that prequalified products tend to have lower prices.

The positive and significant coefficient on *ORIGINATOR* shows that originator prices are more expensive than generic prices by approximately $2 per DDD in non-LD countries. However, the interaction variable *ORIGINATOR×LD* has a negative coefficient that is significant at the 1% level. Its absolute value of 2.017 is similar to that of the coefficient on the *ORIGINATOR* variable, 1.994. This implies the following: while originator products tend to have higher prices than generics in middle-income countries, this price difference more or less disappears in the LD countries. According to the point estimates, originator firms charge a price that is lower by 1.343 dollars per defined daily dose in countries belonging to the LD group, when compared with prices in non-LD countries[13]. In contrast, generic firms charge a price that is 0.674 dollars *higher* in countries that belong to the LD group. As a result, whereas originator prices are higher than generic prices by approximately two dollars in non-LD countries, originator and generic prices are similar in LD countries.

The other firm characteristic, *HOME*, has a significantly positive coefficient, suggesting that countries purchasing ARVs from local companies are paying higher prices (approximately $1.2 per DDD).

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13 This figure is derived from the difference between the coefficient on *ORIGINATOR ×LD* and the coefficient on *LD*: 2.0170 – 0.6742 = 1.3428.

Table 5: Determinants of ARV prices, not including patents

	Dependent variable:					
	PRICE PER DDD			*RATIO TO US PRICE*		
	Coefficient	Std. Err.	t-statistic	Coefficient	Std. Err.	t-statistic
Country characteristics						
LD	0.6742	0.2830 **	2.38	0.0213	0.0172	1.24
HIV	-0.0477	0.0108 ***	-4.44	-0.0024	0.0007 ***	-3.66
POPULATION	-0.0379	0.1438	-0.26	-0.0078	0.0090	-0.87
Firm characteristics						
PREQUALIFY	-0.1202	0.2536	-0.47	-0.0293	0.0133 *	-2.20
ORIGINATOR	1.9937	0.3341 ***	5.97	0.1943	0.0192 ***	10.13
HOME	1.2207	0.3721 ***	3.28	0.1210	0.0228 ***	5.31
Country-firm Interaction terms						
ORIGINATOR×LD	-2.0170	0.3936 ***	-5.12	-0.1507	0.0236 ***	-6.38
ORIGINATOR×HIV	-0.0100	0.0151	-0.66	-0.0009	0.0009	-0.95
Product characteristics						
GROUP2				0.0312	0.0155 *	2.01
FDC				0.0034	0.0130	0.26
Transaction characteristics						
TIME	0.0405	0.1268	0.32	0.0067	0.0078	0.86
QUANTITY	-0.2329	0.2080	-1.12	-0.0196	0.0129	-1.51
EXW	0.0733	1.1455	0.06	0.0691	0.0711	0.97
FCA	0.4354	1.0347	0.42	0.0606	0.0625	0.97
CIF	1.6121	0.3076 ***	5.24	0.1332	0.0186 ***	7.17
CPT	-0.0137	0.9503	-0.01	0.0741	0.0595	1.25
CIP	0.2640	0.3572	0.74	0.0710	0.0220 ***	3.23
DDU	0.9154	0.5421 *	1.69	0.1131	0.0332 ***	3.41
DDP	3.4537	0.6029 ***	5.73	0.2812	0.0375 ***	7.50
CONSTANT	0.3297	0.4060	0.81	-0.0214	0.0245	-0.87
Specification:	Fixed effects regression			Pooled regression		
Number of observations:	1,200			1,200		

Note: ***, **, and * represent statisitical significance at the 1%, 5%, and 10% level respectively.

Coefficients on the product characteristics can only be estimated from the pooled specification. Of the two variables, only *GROUP2* is statistically significant, with a positive coefficient. This confirms the common perception that novel drugs are expensive.

Looking at the transaction characteristics, some of the Incoterm dummy variables have significant coefficients, namely those representing "Cost, Insurance, and Freight (*CIF*)", "Carriage and Insurance Paid To (*CIP*)", "Delivered Duty Unpaid (*DDU*)" and "Delivered

Duty Paid (*DDP*)". Transactions under these terms have significantly higher prices than those under "Free On Board (*FOB*)", which is the standard of comparison and hence not included in the estimation. The statistical significance of Incoterm variables suggests the possibility that previous studies ignoring transaction terms have suffered from omitted variable bias, particularly if certain countries or regions are more likely to trade under specific Incoterms.

2) Results using the patent variables

Table 6 presents estimation results when the patent variables were utilized. Because patent information was available from the MSF report for only 21 countries, as indicated in Appendix 1, the number of observations used in regression analysis is smaller at 697. It must therefore be noted that the sample of transactions analyzed here differs from that above.

The coefficient estimates on the country characteristics in Table 6 are different from those in Table 5. The *LD* variable has a negative coefficient that is significant at the 5% level in the pooled regression. This implies that generic firms charge lower prices in the poorer countries. The coefficient on *HIV* is significant and positive, unlike that in Table 5. This suggests that countries with higher HIV prevalence have higher generic prices. The coefficient on *POPULATION*—which was statistically insignificant in Table 5—has turned significantly negative, suggesting that countries with bigger markets are able to attract lower prices.

Turning to the firm characteristics, the coefficient on *PREQUALIFY* is negative and significant, a finding that is shared in Tables 5 and 6. This has important implications for the implementation of quality regulations in developing countries, because it demonstrates that strict regulations will not necessarily lead to higher prices.

Table 6: Determinants of ARV prices, including patents

	Dependent variable:					
	PRICE PER DDD			*RATIO TO US PRICE*		
	Coefficient	Std. Err.	t-statistic	Coefficient	Std. Err.	t-statistic
Country characteristics						
LD	-0.2355	0.1676	-1.41	-0.0298	0.0116 **	-2.57
HIV	0.0335	0.0157 **	2.14	0.0022	0.0011 **	2.06
POPULATION	-0.1696	0.0645 ***	-2.63	-0.0091	0.0046 *	-1.95
Firm characteristics						
PREQUALIFY	-0.5990	0.1478 ***	-4.05	-0.0498	0.0083 ***	-6.04
ORIGINATOR	3.4191	0.2424 ***	14.11	0.2438	0.0161 ***	15.11
HOME	0.3576	0.2061 *	1.73	0.0744	0.0143 ***	5.22
Country-firm interaction terms						
ORIGINATOR×LD	-2.5813	0.2430 ***	-10.62	-0.1666	0.0171 ***	-9.74
ORIGINATOR×HIV	-0.1754	0.0162 ***	-10.85	-0.0074	0.0011 ***	-6.69
Product characteristics						
GROUP2				0.0601	0.0134 ***	4.49
FDC				0.0311	0.0096 ***	3.24
Patent variables						
PATENT	-0.4539	0.1665 ***	-2.73	-0.0375	0.0108 ***	-3.46
PATENT×GROUP2				-0.0891	0.0217 ***	-4.11
Transaction characteristics						
TIME	0.0752	0.0779	0.97	0.0044	0.0055	0.80
QUANTITY	-0.0128	0.1127	-0.11	-0.0067	0.0080	-0.83
FCA	0.0772	0.5185	0.15	0.0491	0.0364	1.35
CIF	0.7658	0.3116 **	2.46	0.0756	0.0214 ***	3.53
CPT	-0.1199	1.1397	-0.11	0.0687	0.0835	0.82
CIP	0.4895	0.3184	1.54	0.0722	0.0218 ***	3.31
DDU	0.5234	0.3789	1.38	0.0849	0.0258 ***	3.29
DDP	0.6188	1.1466	0.54	0.0942	0.0829	1.14
CONSTANT	0.6937	0.3204 **	2.16	0.0064	0.0220	0.29
Specification:	Fixed effects regression			Pooled regression		
Number of observations:	697			697		

Notes: The *EXW* variable was dropped due to the lack of observations in that category.
***, **, and * represent statisitical significance at the 1%, 5%, and 10% level respectively.

The coefficient on the *ORIGINATOR* variable is positive and significant, as in Table 5, implying higher prices for originator products in non-LD countries: $3.419 higher per defined daily dose (DDD). However, the significantly negative coefficient on the *ORIGINATOR×LD* interaction term shows that this price difference is drastically reduced to $0.838 per DDD in LD countries. This is due to the fact that originator firms cut their prices in LD countries by a larger proportion than the generic firms. Moreover, the negative and significant coefficient on *ORIGINATOR×HIV* implies that originator firms offer a larger discount than generic firms in countries with high HIV infection rates.

The remaining firm characteristic *HOME* has a positive and significant coefficient, which replicates the result in Table 5 that countries pay higher prices for ARVs when purchasing from local companies.

Turning to the product characteristics, the positive and significant coefficient on *GROUP2* in the pooled regression shows that newer drugs have higher prices than older drugs when measured in terms of the ratio to US prices for the same drug. Also, the significantly positive coefficient on *FDC* implies that fixed-dose combinations tend to be more expensive. However, it must be noted that the *FDC* prices are measured in terms of the ratio to US prices for the same combination of APIs, rather than the same fixed-dose combination.

The *PATENT* variable, which indicates whether or not the basic patent(s) covering the drug exists in the recipient country, has a negative coefficient that is statistically significant at the 1% level in both specifications. This implies, somewhat counterintuitively, that drug prices are *lower* in countries where the drug is patented. The fixed effects estimates tell us that the existence of patents is associated with a $0.454 reduction in ARV prices. The negative effect is more pronounced in the case of newer drugs, as seen from the negative and significant coefficient on the *PATENT×GROUP2* interaction term in the pooled regression. This finding is also contrary to prevalent expectations.

Taken at face value, these results suggest that the market power afforded by patents is not being used to charge higher prices by the originator firms. While these are novel and significant findings, caution is required when deriving their implications. It is possible that the estimates are biased, due to the endogeneity of the *PATENT* variable. In other words, originator firms may be filing patents in countries where they expect higher demand. In those same countries, the originator firms may be offering discounts. Thus, while we may observe a

negative relationship between patents and price levels, we cannot conclude that patents are a cause of lower prices. From our estimates, we cannot say how patents affect ARV prices, *ceteris paribus*.

In order to uncover the *ceteris paribus* effect of patents on ARV prices, it is necessary to employ more sophisticated techniques such as instrument variable estimation. This is a topic of continuing research by the authors.

5. Conclusion

Using a sample of transactions recorded under the Global Fund Price Reporting Mechanism, this study explored the factors determining the price of antiretroviral (ARV) drugs and compared how and to what extent these factors influence ARV prices in developing countries.

Regression analysis revealed that originator firms tend to have prices that are higher by approximately two to three dollars per defined daily dose in regions other than the poorest countries. However, in the poorest countries, originator firms charge prices as low as those of their generic counterparts. Moreover, originators tend to charge lower prices in those countries with higher HIV prevalence. These results provide the first formal indications that the differential pricing policies widely announced by originator firms have a real impact on pricing patterns.

The analysis using patent data produced the interesting finding that the existence of patents is associated with lower ARV prices. This is contrary to the accepted wisdom that patents lead to higher prices. However, it should be stressed that this finding does not immediately imply a causal impact of patents on prices.

The results indicate factors that should be taken into consideration by both developing countries and donor countries when formulating AIDS drug procurement policy. The most notable observations and recommendations are the following:

First, the least developed countries have better chances of being offered reduced prices by originator companies.

Second, donor countries are advised to enlarge the size of recipient groups in such a way that a large number of patients can be covered by one procurement program. For instance,

grouping together several recipient countries may make it easier to obtain quantity discounts from manufacturers. Regional procurement programs for HIV/AIDS treatment may provide one such venue.

Third, no country should be allowed to sacrifice quality control for the sake of keeping down drug costs. Our data analysis finds that prequalification does not raise drug prices. This means that high quality medicines should be available without extra cost to the patients. Given that poor quality medicines contribute to adverse effects as well as the growth of drug resistance, quality control should be one of the foremost requirements for a supplier.

This study also highlights some avenues of future research. One avenue is to take into account the endogeneity of the patent variable. Doing so would make it possible to measure the true impact of patents on drug prices. Another possible field of exploration includes the incorporation of more detailed patent data in the sample countries. However, detailed information on patents in developing countries is notoriously difficult to come by, as described by the International Intellectual Property Institute [2000].

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Appendix 1: Countries appearing in the dataset

Country name	Least developed countries group	Low human development group	Low-income economies group	LD	GDP per capita (US $)	Total population (million)	HIV Prevalence (%)	Patent information available from MSF	No. of trans-actions in dataset
Sub-saharan Africa									
Benin	yes	yes	yes	yes	495	8.2	1.79	yes	1
Burkina Faso	yes	yes	yes	yes	377	12.8	2.01	yes	19
Cameroon	no	yes	no	yes	988	16.0	5.43	yes	8
Dem. Rep. of Congo	yes	yes	yes	yes	116	55.9	3.23	yes	1
Djibouti	yes	yes	no	yes	847	0.8	3.11	no	42
Equatorial Guinea	yes	no	no	yes	6,562	0.5	3.20	yes	17
The Gambia	yes	yes	yes	yes	271	1.5	2.44	no	10
Ghana	no	no	yes	yes	409	21.7	2.27	no	3
Guinea-Bissau	yes	yes	yes	yes	175	1.5	3.79	yes	18
Kenya	no	yes	yes	yes	481	33.5	6.09	yes	7
Madagascar	yes	yes	yes	yes	241	18.1	0.51	no	4
Malawi	yes	yes	yes	yes	151	12.6	14.09	yes	2
Mali	yes	yes	yes	yes	373	13.1	1.73	yes	10
Namibia	no	no	no	no	2,842	2.0	19.56	no	1
Niger	yes	yes	yes	yes	226	13.5	1.10	yes	12
Nigeria	no	yes	yes	yes	559	129.0	3.86	no	2
Rwanda	yes	yes	yes	yes	206	8.9	3.07	no	12
Senegal	yes	yes	yes	yes	669	11.4	0.91	yes	1
Sierra Leone	yes	yes	yes	yes	201	5.3	1.56	no	1
South Africa	no	no	no	no	4,725	45.5	18.78	yes	264
Swaziland	no	yes	no	yes	2,250	1.1	33.38	no	177
Tanzania	yes	yes	yes	yes	301	37.6	6.46	no	8
Uganda	yes	no	yes	yes	245	27.8	6.66	yes	4
Zimbabwe	no	no	yes	yes	364	12.9	20.12	yes	12
Eastern Europe									
Belarus	no	no	no	no	2,351	9.8	0.34	no	1
Bulgaria	no	no	no	no	3,131	7.8	0.10	no	3
Rep. of Macedonia	no	no	no	no	2,645	2.0	0.10	no	2
Moldova	no	no	no	no	614	4.2	1.05	no	11
Russian Federation	no	no	no	no	4,097	144.0	1.09	no	33
Ukraine	no	no	no	no	1,366	47.5	1.40	yes	50
Caucasus, Central Asia, Middle East, and South Asia									
Armenia	no	no	no	no	1,183	3.0	0.15	no	3
Azerbaijan	no	no	no	no	1,045	8.3	0.11	no	2
Georgia	no	no	no	no	1,135	4.5	0.22	no	8
Islamic Rep. of Iran	no	no	no	no	2,433	67.0	0.15	no	6
Kazakhstan	no	no	no	no	2,880	15.0	0.10	no	1
Kyrgyz Republic	no	no	yes	yes	434	5.1	0.14	no	7
Nepal	yes	no	yes	yes	253	26.6	0.53	no	4
Uzbekistan	no	no	yes	yes	458	26.2	0.21	no	8
East Asia, Southeast Asia, and Oceania									
Cambodia	yes	no	yes	yes	354	13.8	1.64	yes	169
China	no	no	no	no	1,485	1,300.0	0.08	yes	2
Mongolia	no	no	yes	yes	640	2.5	0.10	no	3
Papua New Guinea	no	no	yes	yes	736	5.8	1.76	no	1
Philippines	no	no	no	no	1,104	81.6	0.10	no	2
Thailand	no	no	no	no	2,543	63.7	1.40	yes	22
Vietnam	no	no	yes	yes	550	82.2	0.51	no	6
Carribean, Central America, and South America									
Belize	no	no	no	no	3,680	0.3	2.49	no	5
Colombia	no	no	no	no	2,156	44.9	0.61	yes	5
Cuba	no	no	no	no	-	11.2	0.09	no	4
Dominican Republic	no	no	no	no	2,110	8.8	1.11	no	6
El Salvador	no	no	no	no	2,336	6.8	0.92	no	22
Guatemala	no	no	no	no	2,228	12.3	0.90	yes	4
Haiti	yes	yes	yes	yes	456	8.4	3.81	no	1
Honduras	no	no	no	no	1,046	7.0	1.54	no	42
Nicaragua	no	no	no	no	837	5.4	0.24	no	7
Peru	no	no	no	no	2,489	27.6	0.57	yes	82
Suriname	no	no	no	no	2,576	0.4	1.94	no	42

Sources: References listed in footnotes 10, 11, and 12, and Médecins Sans Frontières [2003]