Draft Working Paper

The Cost of Antiretrovirals

Maximizing Value for Money

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Executive summary

Background

Antiretroviral medicines (ARVs) are the single most costly component of an AIDS treatment program. Many countries are struggling to provide universal access to ARVs for all people living with HIV and AIDS (PLWHA). Although substantial price reductions of ARVs have occurred, especially between 2002 and 2008, achieving sustainable access for the next 25 years remains a major challenge, especially for low and middle income countries. PLWHA are living longer due to increased access to first line therapy, but this also requires increased access to second and third line therapies which are significantly more expensive. Among other elements in the medicine supply chain, prices, procurement procedures and policies are all crucial to increasing sustainable and universal access to ARVs.

Aim of the paper

To assess the long-term needs and consequences of ARV procurement and to identify policies and practices that could assure long-term sustainable access to ARVs.

Objectives

- To analyze ARV prices variations between 2005 and 2008 and associated factors, particularly procurement methods and key donor policies on ARV procurement efficiency;
- To discuss the options of procurement processes and policies which should be considered when implementing or reforming access to ARV programs.

Methods and data sources

An analysis of ARV price variation between 2005 and 2008 was carried out using Global Price Reporting Mechanism (GPRM) from the World Health Organization (WHO). A selection of 12 ARVs was identified and price reductions were evaluated for both innovator and generic products. Linear regression models for each ARV were used to identify factors which were associated with lower procurement prices. Additionally, logistic regression models were used to identify factors which influenced countries' abilities to procure ARVs close to production costs.

Results

There is a large ARV price variation across countries, even for those countries with a similar socioeconomic status. The price reductions between 2005 and 2008 were greatest for those ARVs which had more providers. Three key factors appear to have an influence on a country's ARV prices: (a) whether the product is generic or not; (b) the socioeconomic status of the country; (c) whether the country is a member of the Clinton HIV/AIDS Initiative (CHAI). Factors which did not influence procurement below the highest direct manufacturing cost (HDMC) were HIV prevalence, procurement volume, whether the country belongs to the least developed countries or a focus country of the United States President's Emergency Plan for AIDS Relief (PEPFAR).

Discussion

Three principal mechanisms which can help to lower prices for ARV over the next decades are: 1) increasing procurement efficiency, 2) encouraging competition among manufacturers and 3) emphasizing the need for improved production efficiency. To achieve higher procurement efficiency the use of global data on prices can provide a useful tool. However, this needs to be complemented with more research on optimizing procurement methods, such as third party negotiation used by CHAI. In addition, strategies should be pursued to increase production efficiency and competition

among manufacturers through the use of trade-related aspects of intellectual property rights (TRIPS) flexibilities with the support of international organizations.

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Acronyms

AIDS	Acquired immune deficiency syndrome
API	Active pharmaceutical ingredients
ART	Antiretroviral therapy
ARV	Anti-retroviral medicines
CHAI	Clinton Foundation HIV AIDS Initiative
CL	Compulsory licensing
GPRM	Global price reporting mechanism
HAART	Highly active antiretroviral therapy
HDMC	Highest direct manufacturing cost
HIV	Human immunodeficiency virus
LDC	Least developed countries
LDMC	Lowest direct manufacturing cost
LMIC	Lower-middle income country
MSF	Médecins sans Frontières
PEPFAR	President's Emergency Plan for AIDS Relief
PLWHA	People living with HIV/AIDS
TRIPS	Trade related aspects of intellectual property rights
UMIC	Upper-middle income country
UNAIDS	United Nations Joint Program on HIV/AIDS
UNGASS	UN General Assembly Special Session on HIV and AIDS
UNICEF	The United Nations Children's Fund
VL	Voluntary licensing
WHO	World Health Organization

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Introduction

One world, one price?

The paper seeks to answer the following question "Do antiretroviral (ARV) prices differ significantly across countries and what influences these price variations?" While some pharmaceutical companies, such as Pfizer, have introduced new medications (e.g. maraviroc) at one global price, without tiered pricing or discounts provided to countries that are poorer or have incurred a higher prevalence of disease (MSF, 2008), other companies have implemented tiered pricing. Establishment of one global price has numerous advantages, including eliminating the risk for arbitrage (purchasing medications in a low price country and reselling them in a higher priced country) (Danzon and Towse, 2003) and limiting complaints from countries when they are charged more than neighboring countries. It may also be argued that having one global price is more equitable than tiered pricing; since every country pays the same price (although alternatively it may be argued that such a pricing policy is inequitable because it does not recognize the lower ability to pay of poorer countries).

The majority of pharmaceutical companies do not use one global price for their products. Actual pricing data on ARVs shows the variation for countries with different socio-economic status. For example, the average price per patient per year paid by lower income countries for lopinavir/ritonavir 133/33mg is USD 500, whereas the price for the same product in middle-income countries is USD 1134 (WHO, 2008). Pharmaceutical companies have tried, in some cases, to establish explicit criteria for determining the price by establishing tiered pricing based on socioeconomic status and/or other factors (Merck, 2008). Socio-economic status is not the only criteria that impacts pricing, many countries have been able to negotiate significant discounts on ARVs which are not available to other neighboring countries with the same socio-economic status (MSF, 2008). As a result, many ARVs price variations cannot be explained only by the income level of the country or the burden of disease.

Why do antiretroviral medicine (ARV) prices matter?

Antiretroviral treatment (ART) is the cornerstone of pharmacotherapy for people living with HIV and AIDS (PLWHA) and comprises a substantial part of the total expenditure on HIV in the each country. One reason for the large differences in relative expenditure on ART could be variation in the procurement prices of ARV.

Since the mid 1990s, highly active antiretroviral treatment (HAART) has become the standard recommended treatment for PLWHA. Between 2002 and late 2007, the number of PLWHA receiving ART worldwide has grown from around 300,000 to approximately 3 million people (UNAIDS, 2008).

However, there remains a large gap between those in need of receiving HAART and those who receive it. According to estimates, out of the 33.5 million people living with HIV, 10 million need HAART, which leaves 7 million PLWHA currently untreated. This is particularly problematic in Sub-Saharan Africa, which accounts for two-thirds of all PLWHAs (UNAIDS, 2007). Furthermore, it is estimated that in 2010 and 2015, 13.7 million and 21.9 million people respectively will need ART (UNAIDS, 2007).

Affordability remains a critical issue, despite the fact that between 2000 and 2007, the median price for *first line* combination therapy in developing countries fell from USD 10,000 to about USD 90 per patient per year (MSF, 2008). But even USD 90 remains unaffordable for many low-income countries, even when considering the growing availability of donor funds. In addition, an increasing number of PLWHA require second-line treatment because of resistance to first-line drug treatment or an inability to tolerate first line drugs. As a result, many low- and middle-income countries are struggling to provide sustainable access to HAART which includes both first and second line therapies.

In 2007, the WHO reported that the median price for the most frequently used *second-line* HAART (abacavir + didanosine + lopinavir/ritonavir) for low-income countries was USD 1,214, 13.5 times

higher than for first-line treatment. In middle-income countries, the price for second line therapy was 36.3 times higher than for first line therapy (USD 3,306 for second-line therapy, as compared to USD 91 for first-line therapy) (WHO Report on GPRM, 2008). Similarly, Médecins sans Frontières (MSF) reported that according to *manufacturer* price information, a change from the cheapest first-line regime quoted with USD 87 to the cheapest second line with $US749 (tenofovir + emtricitabine + lopinavir/ritonavir) will increase expenditures at least nine-fold (MSF, 2008)

As PLWHA on HAART live longer, an increasing number will require second- and third-line therapies. The durability of first-line therapy varies greatly between regions; overall it has been estimated that 22% of patients switch to a second-line combination after an average of 20 months (Keiser et al, 2008). An analysis of factors influencing ARV prices is important in order to increase long-term efficiency (best value for money)[1] in the provision of HAART. This would allow designing appropriate policies to fuel the production of low price ARVs or implement the most effective procurement processes.

What factors do influence prices?

Several publications have described factors that may influence drug prices in general:

- It is believed that bulk procurement (large volume) results in price reduction (WHO, 2007).
- Many pharmaceutical manufacturers, particularly innovators of ARV such as Merck, GlaxoSmithKline, Bristol Myers Squibb, state that they are using price tiers depending on the countries socioeconomic status. Some base their classification on the World Bank definition of low, lower-middle, upper-middle and high-income countries (World Bank, 2008). Other companies have used their own classification (MSF, 2008).
- Another factor influencing prices is using particular procurement processes such as third party negotiation. For instance the Clinton HIV/AIDS Initiative (CHAI) negotiates procurement prices on behalf of its member countries with mainly generic manufacturers (CHAI, 2008).

Vasan et al (2008) found that differential prices are inconsistently applied, particularly among lower middle-income countries which are charged prices that are higher than they should be given their socioeconomic status. Similarly to Vasan et al (2006), Chien (2007) used the GPRM database to analyze both volume and ARV prices in Sub-Saharan Africa, concluding that despite differential pricing, generic drugs were still purchased at significantly lower prices than innovator products.

Given the limited analysis on procurement methods and policies on procurement prices, analyzing factors influencing procurement prices could provide important policy recommendations for individual countries and also for donor organizations: Should all countries or HIV/AIDS programs be advised to use a third party negotiation strategy to achieve lower prices? Should countries or HIV/AIDS programs always choose generic ARV over innovator products if patent policies allow doing so? Does bulk procurement result in lower prices? Do countries which did not adopt patent law (such as some of the least developed countries (LDC)) have advantages in obtaining lower prices?

Aim

The aim of the following paper is to support aids2031 to identify processes and policies that can eventually lead to sustainable access to ARVs.

Objectives

[1] Best value in terms of ARV means the largest volume of ARV with the highest quality, safety and efficiency for a given price. In this context it is important to mention that the WHO has created a quality testing system of ARV which award the products of those companies which comply with the defined standard a pre-qualification certification (WHO, 2009).

- To analyze ARV price variations between 2005 and 2008 and associated factors, particularly procurement methods and key donor policies on ARV procurement efficiency;
- To discuss the options of procurement processes and policies which should be considered when implementing or reforming access to ARV programs.

Although we will discuss production related costs as important ARV price components such as synthesis costs of active pharmaceutical ingredients, production volumes and processes this study is primarily focused on factors related to procurement processes and countries' characteristics.

Methods and data sources

For this analysis the Global Price Reporting Mechanism (GPRM) (WHO, 2008a) was used. While other sources use price quotes from manufacturers (MSF, 2008), the strength of the GPRM is that it provides ARV price information that countries actually paid. The majority of the information is transactional data for ARV procurements made with donor funds from the Global Fund for AIDS, Tuberculosis and Malaria (GFATM). Other data comes from the country offices that report procurement prices to WHO as well as international organization and procurement agencies such as Mission Pharm, United Nations Children's Fund (UNICEF), and the International Dispensary Association Foundation (IDA).

These prices are all posted by the WHO on their publicly accessible database (http://www.who.int/hiv/amds/price/hdd/)[2]. We used procurement data from January 2005 to December 2008.

For the present study, twelve of the most frequently used adult ARV medicines in first-line and second-line therapy regimens in developing countries were selected to analyze price trends: efavirenz 600mg, lamivudine 150mg, and 200/50mg, nevirapine 200mg, stavudine 30mg, and zidovudine 100mg as first-line therapy and abacavir 300mg, didanosine 100mg and 400mg, lopinavir/ritonavir 133/33mg, ritonavir 100mg, tenofavir 300mg as second-line therapy. (The WHO classification of first and second-line therapy was used (WHO, 2008)).

Between 2005 and 2008 a total of 10,777 transactions (6,216 from low income countries) were available for analysis for the 12 chosen ARVs (the minimum of transactions for ARV was for ritonavir with 312 while the highest was 1,662 for nevirapine). In total, 108 countries reported data to the GPRM, of which 45 classified as low-income countries, while the remaining were lower-middle-, upper-middle- and very few high-income countries. Eighty-two percent of all transactions were made by countries which participated in the CHAI in 2008 and 50% of purchases were made by PEPFAR focus countries. All prices in the present study are reported in US dollars unadjusted for inflation. This is to allow comparison with other international literature on drug prices that also use unadjusted prices for inflation (GPRM, 2008; MSF, 2008). Although the data base had been reviewed by the WHO and checked for consistency we found country reports of procurement prices of over USD 10. Since according to the manufacturers' information for all the 12 selected ARVs the unit prices were lower than USD 10 (MSF, 2008 we excluded unit prices higher than USD 10. Those unit prices reported with USD 0 were eliminated as the focus in this study was a procurement price analysis for those countries' purchasing ARV instead of receiving donations (in total 62 (1%) purchases were reported with a price of USD 0).

The analysis addressed two main questions: How much can prices be reduced in the future? And what can be done to lower prices?

Table 1. Data analysis summary

Research question	Approach	Variables

[2] The data for this analysis was downloaded in March 2009.

How much can prices come down over the next 20 years?	Price variation over time	1. Median price for each ARV in 2008 subtracted from the median price in 2005.
	Price differences between countries	1. Median price for the lowest and highest priced first- and second-line ARV combinations in 2007; 2. Maximum and minimum price paid for these four combinations in 2007; 3. Hypothetical minimum price for the four combinations when procuring innovator in 2007; 4. Lowest and highest direct manufacturing costs for each of the four ARV combinations.
What can be done to lower prices?	Linear regression model for each ARV	Dependent variable: price for the ARV (logarithmic) Independent variables: • HIV prevalence in the country (three categories: <2%, 2-5% and >5%); • Socioeconomic status of the country according to World Bank classification (low income countries, lower middle income countries, upper middle income countries; high income countries were excluded because they were very few observations); • Volume (<33%,33-66%, >66% of the volume distribution); • Least developed country (LDC); • AIDS program Index (developed by UNAIDS, WHO USAID and the POLICY Project (2003) • Innovator; • Purchasing country member of CHAI; • PEPFAR focus country.
	Logistic regression model using the lowest and highest manufactured production cost as benchmark	Dependent variables: • for the first model = price higher than LMPC (=1); • for the second model= price higher than HMPC (=1). Independent variables: • HIV prevalence in the country; • Socioeconomic status of the country according to World Bank classification; • Volume (<33%,33-66%, >66% of the volume distribution); • LDC; • AIDS program Index; • Innovator; • Purchasing country member of CHAI; • PEPFAR focus country.

The price variations of each ARV in the last four years were analyzed in order to foresee how prices may behave in the future. To identify those products which were purchased as innovator (brand) product we reviewed which manufacturer the product was purchased from. Those products which were purchased from the manufacturer holding the patent of the product were classified as innovators MSF (2008). Generic products were classified as those reported to be purchased from manufacturers not registered as patent holders. It is important to note that in the present study, no analysis was carried out regarding the pre-qualification status of the products purchased[3]. The median price for each ARV per patient year and the median price variation between 2005 and 2008 was calculated. Second, a cross-sectional study was performed to identify the ARV price differences

[3] "The Prequalification Programme, set up in 2001, is a service provided by the World Health Organization (WHO) to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. From the outset, the Programme was supported by UNAIDS, UNICEF, UNFPA and the World Bank as a concrete contribution to the United Nations priority goal of addressing widespread diseases in countries with limited access to quality medicines." (WHO, 2008; http://healthtech.who.int/pq/)

between countries. For this analysis, the lowest and highest priced first-line[4] and the lowest and highest priced second-line ARV[5], were chosen to describe the price range for different ARV combinations in 2007. To calculate the median price and the quartile prices (25% and 75%) for these combinations, we only included the procurement prices of those countries which purchased all ARVs necessary for assembling the combinations we chose to study. A 'lowest price innovator product' for each of the four ARV combinations was calculated. This was done by taking the sum of the lowest innovator prices per unit for each of the ARV combinations paid for by a country and converting it into price per patient per year. To benchmark prices for each ARV separately and for the four selected first and second-line ARV combinations, the lowest and highest direct manufacturing cost per patient year (LDMC and HDMC) for 2006 was obtained (Pinheiro et al, 2006). The number of additional patients that could have been treated in 2007[6] if all countries could procure equal or below LDMC price, as well as equal or below HMC price was calculated.

In order to identify the principal factors influencing price trends of each ARV, linear regression models were used choosing the following independent variables based on their theoretical importance on price: HIV country prevalence (<2%, 2-5%, >5%) (UNAIDS, 2008), volume (in terciles) national income per capita using the World Bank classification (low-income, low middle-income, upper-middle income[7]) (World Bank, 2008), AIDS Program Effort Index (API) (UNAIDS, WHO, USAID, POLICY Project, 2003), whether the country belongs to the least developed countries (LDC) that do not need to adopt trade-related aspects of intellectual property rights (TRIPS) agreements until 2016 (MSF, 2008), whether the country is a member of CHAI (CHAI, 2008) and whether the country is one of the 15 focus countries for the United States President's Emergency Plan For AIDS Relief (PEPFAR) (Office of the United States Global AIDS Coordinator, 2008).[8] 'Prevalence' and 'volume' are continuous variables which were grouped together. Prices were transformed in the logarithm as they were not normally distributed and clustered for different years. It is important to note that the model used, only takes into account a certain set of variables, while excluding others such as the market structure in each country and negotiation abilities of each country. Although accounting for these variables would allow a better fit, they are usually difficult to obtain.

To identify the characteristics of those countries which purchased ARVs at the LDMC and HDMC per patient year, two logarithmic regression models were used: one where the dependent variable was a procurement price higher than the LDMC per patient year and one where the dependent variable was a procurement price higher than the HDMC per patient year. Independent variables were the same as used in the linear models above. ARVs were clustered by year and by type (for instance all purchases of lamivudine were clustered by the year in which it was purchased).

[4] Lowest priced first-line ARV: lamivudine 150mg, nevirapine 200mg, stavudine 40mg; highest priced first-line ARV: lamivudine 150mg, zidovudine 300mg; efavirenz 600mg

[5] Lowest priced second-line ARV: lamivudine 150mg, efavirenz 300mg; lopinavir/ritonavir 133/33mg; highest priced second-line ARV: abacavir 300mg; lopinavir/ritonavir 133/33mg; didanosine 400mg

[6] 2007 was taken to account for the time the API price for 2006 would have an impact in the product costs

[7] High income countries were excluded from the regression models since it is likely that the factors influencing prices in those countires are different than in other income groups. In addition, the number of procurements reported was very small.

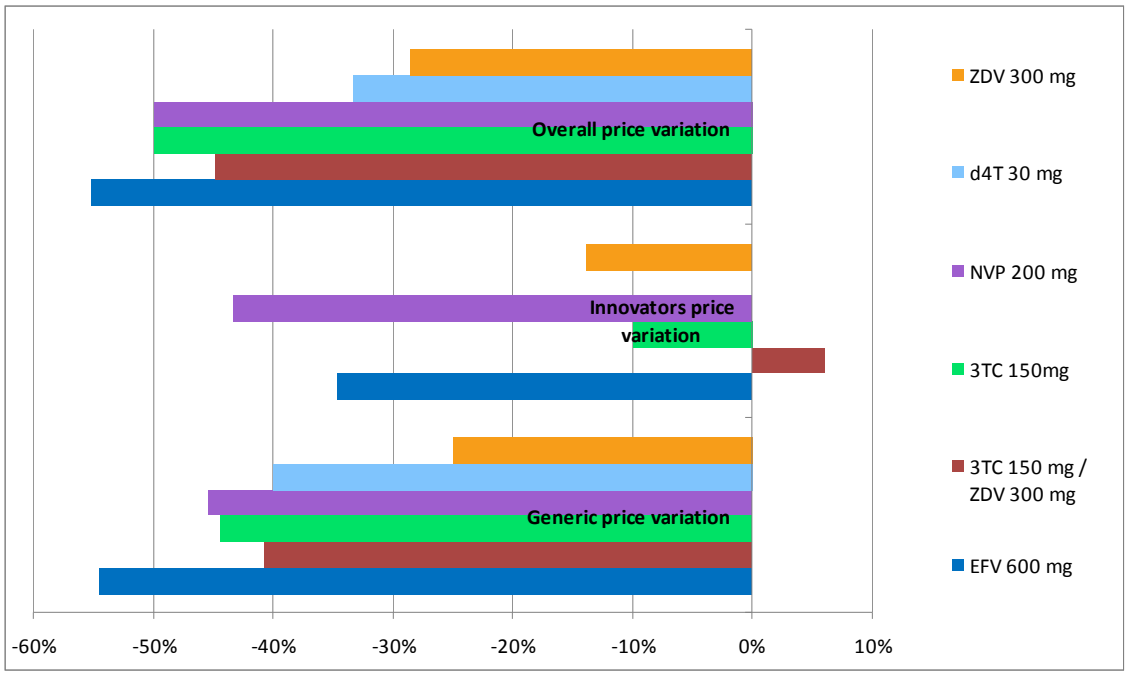
[8] PEPFAR operates in 114 different countries, but only 15 countries are identified as "focus countries".

Results

ARV price trends between 2005 and 2008

Between 2005 and 2008, first-line therapy ARV prices dropped between 29% (zidovudine 300mg) and 55% (efavirenz 600mg). Price variation for second-line ARVs was considerably smaller between no price variation for didanosine 400mg and ritonavir 100mg and a 38% decline for tenofovir (see Figure 1 and 2). An exception was abacavir, with a 62% price reduction. In general, generic prices fell more than those of innovators. The one exception to this was the generic version of lopinavir/ritonavir, which increased in price between 2005 and 2008.

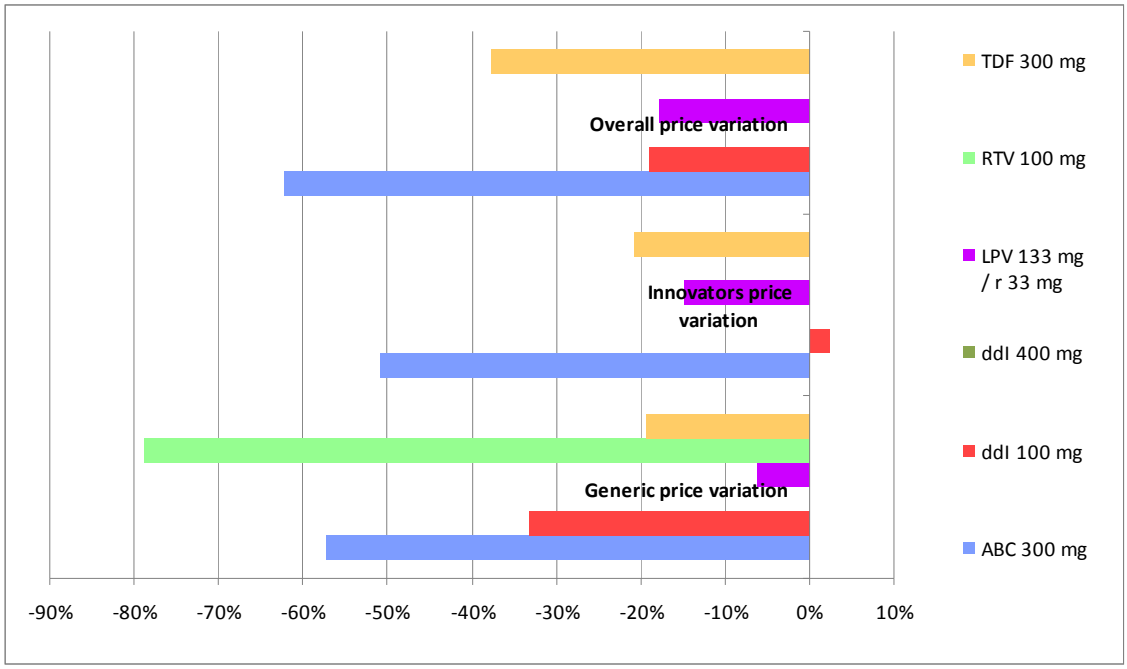
Figure 1. Price variation of first-line ART therapy for generic, innovator and both



Legend: EFV: efavirenz; 3TC: lamivudine; ZDV: zidovudine; NVP; nevirapine; d4T: stavudine; ABC= abacavir; ddl= didanosine; LPV/r= lopinavir/ritonavir; RTV= ritonavir; TDV=tenofovir;

Data source: Authors' own analysis of the Global Price Reporting Mechanism data (Note: The innovator price variation of stavudine 30mg was excluded as it increased more than 100%)

Figure 2. Price variation of second-line ART therapy for generic, innovator and both



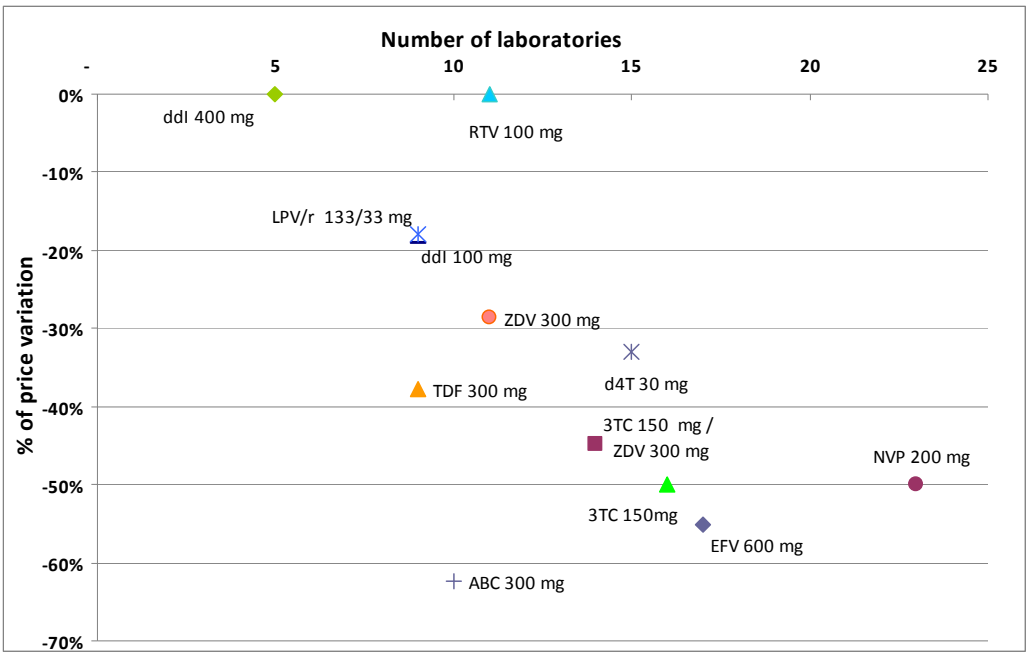
Note: The overall price variation as well as the innovator price variation for ritonavir 100gm and didanosine 400mg was zero. The same applied to the generic price variation of didanosine 400mg.

Legend: EFV: efavirenz; 3TC: lamivudine; ZDV: zidovudine; NVP; nevirapine; d4T: stavudine; ABC= abacavir; ddl= didanosine; LPV/r= lopinavir/ritonavir; RTV= ritonavir; TDV=tenofovir;

Data source: Authors' own analysis of the Global Price Reporting Mechanism data

It is interesting to note that the price of the generic products of abacavir dropped as much as other first-line ARV whereas the price of the innovator product of didanosine 400mg did not change over the four year period. Both abacavir and didanosine 400mg are in a preferred WHO second-line regime, thus one could expect that the volume required and therefore the demand is equal which should result in a similar price reduction. Apart from marketing time, the number of manufacturers that reported providing each ARV between 2005 and 2008 appears to influence price variation: Whereas abacavir was provided by ten different manufacturers, there were only five registered manufacturers for didanosine 400mg (Figure 3).

Figure 3. Number of manufacturers versus price reduction



Legend: EFV: efavirenz; 3TC: lamivudine; ZDV: zidovudine; NVP; nevirapine; d4T: stavudine; ABC= abacavir; ddl= didanosine; LPV/r= lopinavir/ritonavir; RTV= ritonavir; TDV=tenofovir;

Price differences between countries

For four of the ARV regimens (the lowest/highest priced first-line ARV combinations and the lowest/highest priced second-line ARV combinations) large price differences between countries were found, even those which had the same income and prevalence (Textbox 1 and Figures 4 to 7). For instance, Congo in 2007 paid USD 95 for lamivudine 150mg+nevirapine 200mg+stavudine 30mg, whereas Nigeria paid more than three times (USD 334) for the same ARV combination (Figure 5). Both are low-income countries with a prevalence of 1.2% and 3.1% respectively in the same region (Sub-Saharan Africa).

Furthermore, there were also large differences between countries procuring both the same innovator products. For instance, Morocco paid $1,053 for the innovator ARV combination of lamivudine, zidovudine and efavirenz, whereas the lowest price for the same innovator combination was $513. The difference between the maximum price paid for the ARV innovator combinations and the lowest price for the ARV innovator combination was about 1.1 to 8.6 times (Figure 5 to 8). For the lowest priced first-line ARV combination, 30% of countries were paying more than the HDMC (Figure 5) and for the second-line ARV combinations 31% and 36% of the countries were purchasing them at HDMC respectively (Figure 7 and 8).

Text box 1. **Examples of price differences between countries with similar characteristics**

Guatemala and El Salvador are both lower-middle income countries, have a prevalence of 0.8%, are members of the CHAI but not PEPFAR focus countries. In 2007 for the innovator product of Efavirenz 600mg, Guatemala was paying USD 237 per patient year and El Salvador USD 665. Another example is that of **Burundi and Benin** with prevalences of 2.0% and 1.5% respectively, and which are both classified as low-income countries, members of CHAI but not PEPFAR focus countries. In 2007 Burundi was procuring the innovator product of lopinavir/ritonavir 133/33mg for USD 504 per patient whereas Benin paid USD 1,051. This difference was not only found for innovator products: When comparing the prices paid for generic lamivudine/zidovuine 150/300mg from the same manufacturer, **Cameroon** paid USD 210 per patient year and **Congo** USD 99. Both countries are lower-middle income countries with a prevalence of 5.1% and 3.5% respectively and are members of CHAI but not PEPFAR focus countries.

Figure 4. Price per patient per year for Lamivudine 150mg+nevirapine 200mg+stavudine 30mg

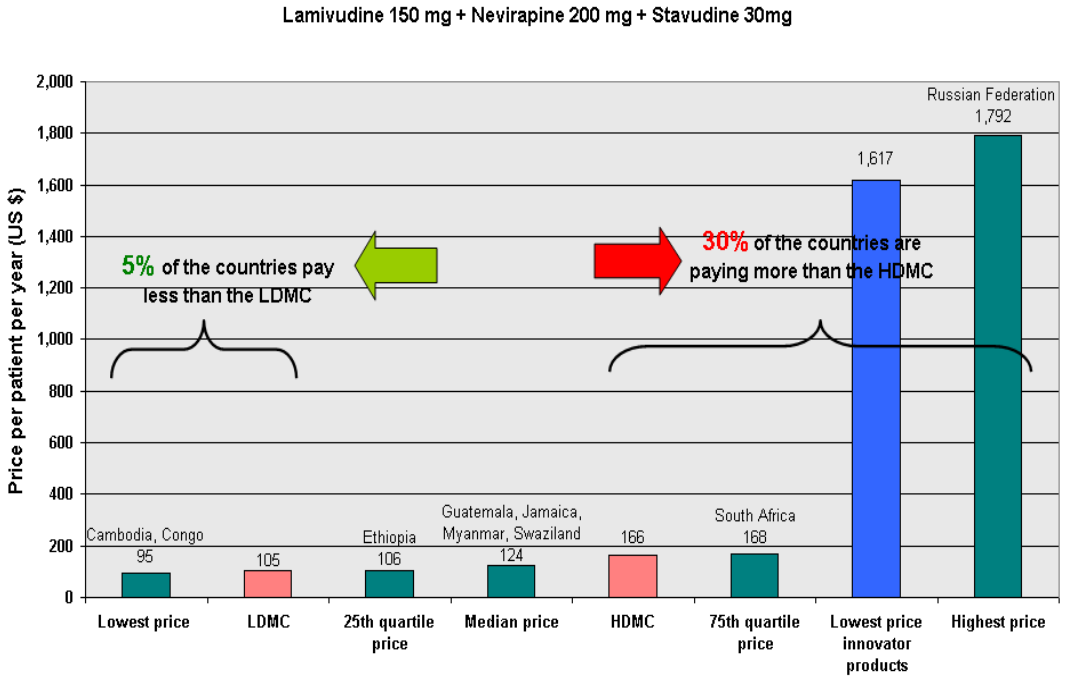


Figure 5. Price per patient per year for Lamivudine 150mg+ zidovudine 300mg+efavirenz 600mg

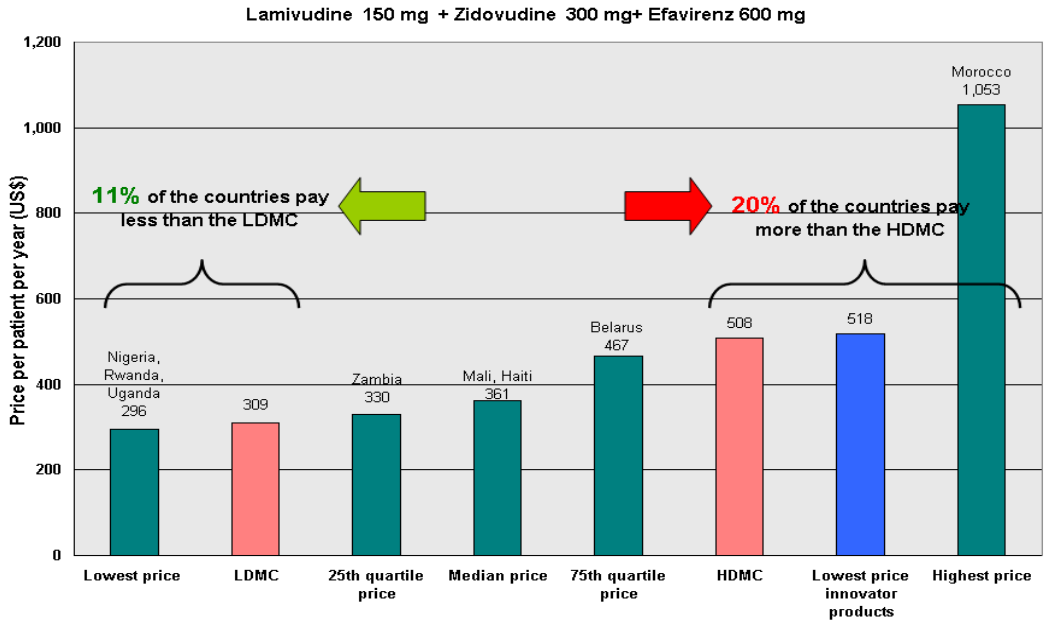


Figure 6. Price per patient per year for Lamivudine 150mg+ efavirenz 600mg+lopinavir/ritonavir 133mg/33mg

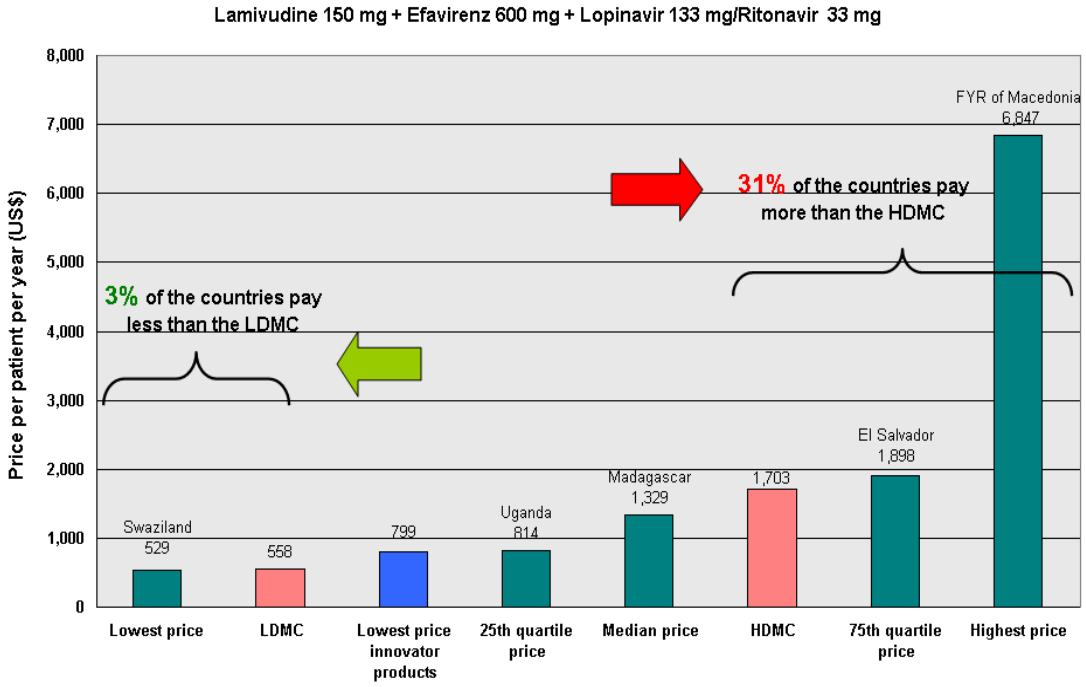
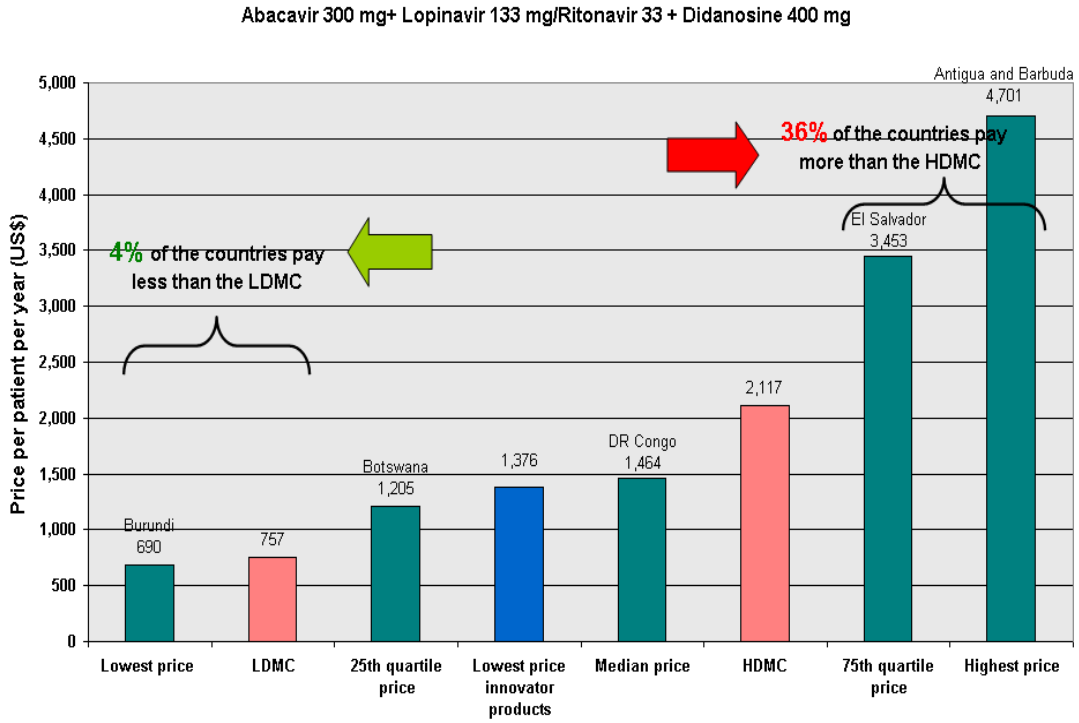


Figure 7. Price per patient per year for Abacavir 300mg+lopinavir/ritonavir 133/33mg+didanosine 400mg



This means that in theory countries could treat more than triple (in case of didanosine 400mg) or nearly double (in case of stavudine 300mg and didanosine 100mg) the number of patients currently treated if they were able to procure ARV medicines at the HDMC (Table 2 and 3).

Table 2. Additional number of patients which could have been treated in 2007 if first-line ARV would have been procured at the lowest or highest direct manufactured costs per patient year

	EFV 600 mg	3TC150mg/ ZDV 300mg	3TC 150 mg	NVP 200 mg	d4T 30 mg	ZDV 300 mg
Lowest Direct Manufactured Cost Patient Year (LDMC) USD 2006	181	119	39	48	18	89
Highest Direct Manufactured Cost Patient Year (HDMC) USD 2006	312	188	65	77	24	131
Number total of patients who could be treated with the volume procured in 2007	666,896	301,345	214,102	340,966	67,826	35,426
Additional number of patients who could be treated if all countries would procure at equal or lower LMPC (%) in 2007	82,829 **(12.4%)**	114,074 **(37.9%)**	120,399 **(56.2%)**	65,697 **(19.3%)**	91,056, **(134.2%)**	10,736 **(30.3%)**
Additional number of patients who could be treated if all countries would procure at equal or lower HMPC (%) in 2007	17,033 **(2.6 %)**	51,513 **(17.1%)**	48,552 **(22.7%)**	27,738 **(8.1%)**	54,679 **(80.6%)**	1,464 **(4.1%)**

Legend: EFV: efavirenz; 3TC: lamivudine; ZDV: zidovudine; NVP; nevirapine; d4T: stavudine

Table 3. Additional number of patients who could have been treated in 2007 if second-line ARV would have been procured at the lowest or highest direct manufactured costs per patient year

	ABC 300 mg	ddI 100 mg	ddI 400 mg	LPV/r 133/ 33 mg	RTV 100 mg	TDV 300 mg
Lowest Direct Manufactured Cost Patient Year (LDMC)	346	89	73	338	93	--
Highest Direct Manufactured Cost Patient Year (HDMC)	659	149	132	1,326	341	--
Number total of patients who can be treated with the volume procured	31,343	3,237	11,400	8,652	6,557	36,208
Additional number of patients who could be treated if all countries would procure at equal or lower LMPC (%)	5,587 **(17.8%)**	9,829 **(303.6%)**	51,530 **(452%)**	26,753 **(309.2%)**	7,924 **(120.8%)**	--*
Additional number of patients who could be treated if all countries would procure at equal or lower HMPC	150 **(0.5%)**	4,572 **(141.2%)**	23,435 **(205.6%)**	2,332 **(27%)**	1,190 **(18.1%)**	--*

Legend: ABC: abacavir; ddI: didanosine; LPV/r: lopinavir/ritonavir; RTV: ritonavir; TDV: tenofovir

Variables associated with price

The results of the regression model shows that generally speaking, the strongest predictor of price is whether the ARV is purchased as innovator or generic (Table 4 and 5).

Table 4. Factors associated with first-line ARV prices

Antiretroviral drugs+	EFV 600 mg	3TC150mg/ZDV 300mg	3TC 150 mg	NVP 200 mg	d4T 30 mg	ZDV 300 mg
HIV prevalence 2-5%	-0.080 (-0.251, 0.092)	0.055 (-0.126 , 0.237)	0.083 (-0.146 , 0.312)	0.124 (-0.005 , 0.254)	**0.160* (-0.316 , -0.005)**	-0.011 (-0.179 , 0.156)
HIV prevalence >5%	-0.119 (-0.299, 0.060)	0.144 (-0.009 , 0.297)	0.138 (-0.220, 0.496)	**0.102* (0.003 , 0.202)**	0.260 (-0.656, 0.136)	-0.005 (-0.055 , 0.045)
Lower-middle income	0.028 (-0.062 , 0.118)	0.099 (-0.167 , 0.364)	0.091 (-0.139 , 0.321)	0.176 (-0.226 , 0.578)	0.455 (-0.213 , 1.123)	0.037 (-0.187 , 0.261)
Upper-middle income	0.019 (-0.131 , 0.168)	**0.339** (0.254 , 0.424)**	**0.344* (0.217, 0.472)**	**0.365** (-0.268, 0.461)**	**0.580* (0.215 , 0.946)**	**0.202* (0.049 , 0.355)**
LDC[¥]	-0.011 (-0.101 , 0.078)	-0.022 (-0.111 , 0.068)	0.054 (-0.031 , 0.139)	0.036 (-0.099 , 0.027)	**0.150* (0.066 , 0.233)**	0.019 (-0.015, 0.054)
Volume 2nd tercile	-0.041 (-0.237 , 0.191)	-0.040 (-0.144 , 0.063)	-0.038 (0.211 , 0.135)	**-0.149* (-0.296, -0.002)**	-1.01 (-0.253, 0.52)	-0.033 (-0.151 -0.086)
Volume 3th tercile	-0.137 (-0.412 , 0.138)	-0.033 (-0.194 , 0.128)	-0.040 (-0.259 , 0.179)	**-0.273* (-0.527, -0.020)**	-0.121 (-0.378, 0.137)	-0.072 (-0.221, 0.077)
API[±]	-0.002 (-0.015 , 0.012)	**-0.007* (-0.015 , 0.000)**	**-0.013** (-0.019 , -0.006)**	-0.003 (-0.007, 0.001)	0.000 (-0.012, 0.012)	0.001 (-0.011, 0.013)
Innovator	**0.567** (0.299 , 0.836)**	**0.737** (0.408 , 1.065)**	**0.457* (-0.097 , 0.817)**	**1.725** (1.371, 2.079)**	**1.013* (0.405 , 1.620)**	**0.460** (0.219 , 0.701)**
CHAI[Ж]	-0.103 (-0.553, 0.328)	-0.154 (-0.356 , 0.048)	**-0.268* (-0.515 , -0.020)**	-0.100 (-0.360 , 0.160)	-0.197 (-0.769, 0.376)	0.012 (-0.337 , 0.362)
PEPFAR[‡]	0.006 (-0.226 , 0.239)	**-0.095* (-0.188 , -0.001)**	-0.125 (-0.479, 0.228)	-0.054 (-0.383, 0.275)	-0.048 (-0.249 , 0.345)	-0.068 (-0.225, 0.088)
R-square	0.338	0.390	0.306	0.560	0.421	0.183
Observations	**1514**	**1519**	**1244**	**1638**	**929**	**771**

Linear regression models whether the dependent variable is the logarithm of price. The reference categories are: HIV Prevalence <2%; Low income countries; Volume 1st tercile

Table legend: * significant at 5%; ** significant at 1%; Robust 95% confidence intervals in parentheses Index; +Abbreviation of the ARV drugs: EFV= efevirenz; ZDV= zidovudine; 3TC= Lamivudine; NVP= nevirapine; d4T=stavudine;

[¥]LDC=Least Developed Country; [±]API= AIDS Program; [Ж]CHAI=Clinton Foundation HIV/AIDS initiative; [‡]PEPFAR=President's Emergency Plan for AIDS Relief

Data source: Global Price Reporting Mechanism

Table 5. Factors associated with second-line ARV prices

Antiretroviral drugs+	ABC 300 mg	ddI 100 mg	ddI 400 mg	LPV/r 133/ 33 mg	RTV 100 mg	TDV 300 mg
HIV Prevalence 2-5%	-0.055 (-0.176 , 0.063)	-0.104 (-0.214 , 0.006)	**-0.507** (-0.705 , -0.308)**	**-0.544** (-0.933 , -0.154)**	-0.056 (-0.550 , -0.439)	**-0.119** (-0.224 , -0.013)**
HIV Prevalence >5%	-0.096 (-0.253 , 0.061)	-0.158 (-0.334 , -0.017)	**-0.389** (-0.597 , -0.182)**	**-0.747** (-1.290 , -0.205)**	-0.234 (-1.352 , 0.884)	-0.117 (-0.285 , 0.050)
Lower-middle income	0.006 (-0.136 , 0.148)	0.108 (-0.535 , 0.750)	0.338 (-0.076 , 0.753)	0.240 (-0.741, 1.220)	-0.183 (-0.494 , 0.128)	0.128 (-0.018 , 0.274)
Upper-middle income	-0.013 (-0.237 , 0.211)	0.294 (-0.142 , 0.731)	0.084 (-0.244 , 0.413)	-0.147 (-0.951 , 0.656)	-0.200 (-0.891 , 0.491)	0.234 (-0.128, 0.597)
LDC[¥]	0.020 (-0.075, 0.147)	0.036 (-0.341 , 0.009)	**-0.166** (-0.465 , -0.295)**	-0.380 (-1.152 ,0.031)	-0.561 (-0.959 , 0.155)	-0.402 (-0.309 , 0.203)
Volume 2nd tercile	-0.009 (-0.125 , 0.106)	0.016 (-0.155 , 0.187)	0.131 (-0.060 , 0.322)	-0.030 (-0.279 , 0.218)	**0.009** (0.494 , 0.513)**	-0.120 (-0.282 , 0.041)
Volume 3th tercile	-0.005 (-0.106 , 0.096)	0.040 (-0.174 , 0.254)	0.110 (-0.179 , 0.399)	**-0.409** (-0.632, -0.186)**	-0.359 (-0.798 , 0.081)	-0.158 (-0.331 , 0.015)
API[±]	-0.005 (-0.008 , 0.001)	0.007 (-0.011 , 0.026)	-0.014 (-0.027 , -0.001)	-0.007 (-0.018 , 0.005)	0.004 (-0.017 , 0.025)	0.001 (0.002 , 0.004)
Innovator	**0.661** (0.449 , 0.873)**	**0.576** (0.409 , 0.743)**	**0.220** (0.139 , 0.302)**	**-0.736** (-1.043 , -0.428)**	-0.780 (-0.906 , 0.749)	**0.277** (-0.146, 0.409)**
CHAI[ж]	**-0.144** (-0.275, -0.014)**	-0.445 (-1.064 , 0.173)	**-0.467** (-0.908 , -0.026)**	-0.218 (-0.521 , 0.084)	**-0.564** (-1.022 , -0.106)**	-0.195 (-0.597, 0.206)
PEPFAR[‡]	0.062 (-0.030 , 0.153)	0.005 (-0.330, 0.340)	**0.359** (0.086 , 0.632)**	**0.565** (0.293 , 0.836)**	-0.297 (-0.927 , 0.333)	0.062 (0.007 , 0.117)
R-square	0.579	0.464	0.531	0.292	0.235	0.411
Observations	**793**	**492**	**397**	**484**	**309**	**489**

Linear regression models whether the dependent variable is the logarithm of price. The reference categories are: HIV Prevalence <2%; Low income countries; Volume 1st tercile

Table legend: * significant at 5%; ** significant at 1%; Robust 95% confidence intervals in parentheses

+Abbreviation of the ARV drugs: ABC= abacavir; ddI= didanosine; LPV/r= lopinavir/ritonavir; RTV= ritonavir; TDV=tenofovir;

[¥]LDC=Least Developed Country; [±]API= AIDS Program; [ж]CHAI=Clinton Foundation HIV/AIDS initiative; [‡]PEPFAR=President's Emergency Plan for AIDS Relief

Data source: Global Price Reporting Mechanism

Except lopinavir/ritonavir, the innovator is more expensive than the generic product, despite price reductions for many originator ARVs. Another relevant predictor of price of first-line ARV is a country's socioeconomic status; for lamivudine, lamivudine/zidovudine, nevirapine, stavudine, zidovudine upper-middle-income countries are paying statistically more than other developing countries. Regarding HIV prevalence, for three second-line ARVs, the higher the country's HIV prevalence, the lower the price. For other second-line and first-line ARVs, prevalence was not significantly associated with price, expect for nevirapine, for which countries with higher prevalence paid more.

Although the commonly held assumption is that countries procuring large volumes have lower prices, the GPRM data do not support this conclusion. Only in two out of 12 regression models, was larger volume associated with lower price (nevirapine and lopinavir/ritonavir).

Whether the country is a member of CHAI was statistically significantly associated with lower prices for three second-line drugs (abacavir, didanosine 400mg, ritonavir) and one first line ARVs (lamivudine). In regards to the importance of being a PEPFAR priority country, the data indicate that PEPFAR priority countries were, in the majority of cases, not associated with either higher or lower ARV prices; only in the cases of didanosine 400mg and lopinavir/ritonavir did PEPFAR focus countries pay more and in the case of lamivudine/zidovudine they were paying less. Although statistically significant for two first-line ARVs, the API was not strongly influencing prices.

Characteristics of countries paying more than minimal and maximum marginal costs for ARV

Paying more than the HDMC per patient per year was very strongly associated with innovator products (Table 6). Countries defined as "lower-middle-income" and "upper-middle-income" were identified as paying significantly more for ARVs than "low-income countries." Paying less than the HDMC per patient per year was associated with being a member of the CHAI. No association was found between being a LDC or a PEPFAR focus country.

Table 6. Factors influencing purchases higher than the lowest (LDMC) and highest direct manufactured costs (HDMC)

	More than lowest direct manufactured costs (LDMC)				More than the highest direct manufactured costs (HDMC)			
	Odds ratio	p-value	Lower 95%CI	Upper 95%CI	Odds ratio	p-value	Lower 95% CI	Upper 95% CI
Prevalence HIV 2-5%	0.77	0.195	0.51	1.15	1.17	0.395	0.81	1.70
Prevalence HIV >5%	0.85	0.272	0.64	1.13	1.36	0.103	0.94	1.98
Lower-middle Income	1.60	0.008**	1.13	2.25	1.57	0.011*	1.11	2.23
Upper-middle Income	4.53	0.000**	2.45	8.35	1.94	0.005**	1.22	3.10
LDC[¥]	1.17	0.158	0.94	1.47	0.94	0.602	0.76	1.17
API[±]	0.99	0.356	0.98	1.01	1.00	0.437	0.99	1.01
Volume 2nd tertil	0.77	0.220	0.50	1.17	1.28	0.060	0.99	1.65
Volume 3th tertil	0.56	0.016*	0.35	0.90	0.69	0.055	0.48	1.01
Innovator	411	0.003**	1.61	10.48	6.09	0.000**	3.08	12.05
CHAI[Ж]	0.76	0.223	0.48	1.18	0.53	0.001**	0.37	0.77
PEPFAR	0.90	0.553	0.64	1.27	1.26	0.148	0.92	1.72

Table legend: [¥]LDC=Least Developed Country; [±]API= AIDS Program; [Ж]CHAI=Clinton Foundation HIV/AIDS initiative; [‡]PEPFAR=US President Emergency Plan for AIDS Relief. *statistically significant

Data source: Global Price Reporting Mechanism

Discussion

To forecast ARV price trends for the next twenty years based on the information of the last four years is problematic, particularly given the rapid change in prices which have recently occurred as well as the limitations of the data source. However, the results of the present study, together with findings from the literature, help to identify factors that influence prices and allow the authors to make some recommendations of how procurement processes and policies could contribute to achieve better value for money.

Large inefficiencies

The large innovator or generic price variation for countries with very similar prevalence and income level could be a sign of large opportunities for further price reductions through better procurement and negotiation policies and practices. The LDMC/HDMC range allows countries to benchmark their prices and to hypothetically estimate the number of patients who could be treated if the country would be able to obtain the LDMC or HDMC. It was calculated that with the total expenditure above the HDMC, many more patients could be treated, particularly with second-line ARV. However, the ability of countries to obtain lower prices (particularly for generic ARVs) depends on two factors: The intellectual property rights (IPR) policies which would allow them to obtain generic products and their ability to negotiate lower prices. Both will be discussed below.

Less price reduction in future years

The prices for second-line therapy remain significantly higher than for first-line therapy, according to the data from 2007: the lowest priced second-line ARV combination was found 5.6 times higher than the lowest priced first-line ARV. Furthermore, the recent price reductions of second-line ARV have been smaller than for first-line therapy. Although for most first-line ARV there are fewer opportunities to lower prices there are some exceptions such as the newer first-line tenofovir and emtricitabine (the latter was not studied, as the procurement volume in the GPRM is still very limited compared to other first-line ARVs). As *production* volumes are increasing, prices are expected to fall more rapidly than other first-line ARVs.

More manufacturers needed to lower prices for second-line ARV

Comparing the number of companies providing first and second-line ARV and their price reductions suggests that the higher the number of manufacturers, the higher the price reduction over time.

Increasing the number of manufacturers depends on granting compulsory licenses (CL) or voluntary licenses (VL), since most of the second-line drugs are patented in a majority of countries (the manufacturer of the innovator owns the monopoly to produce the drugs for a maximum period of 20 years). If another manufacturer would like to produce these ARVs, it must apply for a voluntary license (VL) to the innovator manufacturer. Compulsory licenses could also be issued by the countries in a health emergency; however, most countries have avoided its use due to international pressure and the threat of economic sanctions (Steinbrook, 2007). Some authors recommended that increasing the number of VL issued by patent holding manufacturers is crucial to increasing the number of people receiving ART (Dionisio et al, 2008a). However, there are several barriers for generic companies to apply for VL to produce second-line ARV, among them are the high start up costs of production and the fact that the total volume sold is relatively low compared to first-line ARV (WHO, 2008b). Some authors have argued that international donor support could make a difference to lowering second-line ARV costs by optimizing the technical development to minimize the start-up costs (Dionisio et al, 2008b). More analysis needs to be carried out on whether international donor funds would make a difference and which mechanisms would incentivize the production of particular second-line ARVs. In addition, the negotiation of voluntary licensing is not always a remedy to lower prices. About 50 to 95% of the direct manufactured cost is due to the active pharmaceutical ingredient (API). Even countries with a heavy reliance on generics still rely on foreign API imports, which largely determine the end price of the ARV (Greco and Simão, 2007).

It is expected that in the future, fewer generic companies will be able to produce newer ARV. Many of the companies currently producing generic ARV are based in India and did not require a VL from the patent holder because the ARVs were not under patent in India (including lopinavir/ritonavir, abacavir and ritonavir) (Appendix 3). Various authors have argued that due to changes in the IPR regulations in India after 2005 newer ARVs (not included in the present analysis) **will not be available as generics**

and therefore, price reductions will be slowing down (MSF, 2008). For example, newer ARVs such as maraviroc, etravirine and raltegravir have been granted a patent in India (Dionisio et al, 2008).

It is important to consider not only the patent laws of the supplier country, but also of the recipient country. Chien (2006) in his analysis of GPRM data found that in many Sub-Saharan African countries, second-line ARVs are patented, yet they also import generic version of these medications. He concluded that patent laws are not enforced in these countries. Under the TRIPS Agreement, LDC have to enforce patent laws until 2016. However, the present study indicates that being a LDC was not associated with paying less than the lowest direct manufacturing cost. This might be attributed to the fact that patent laws have been inconsistently applied within countries which blurred the distinction between LDC and other low- or lower-middle-income countries.

Generic products are an important factor in lowering prices

Generic prices were generally found to be lower than innovator prices which means that despite tiered pricing for patented medications, prices have not yet caught up with the lower price offered by generic manufacturers. However as there are exceptions, a recommendation to *always* rely on generic products would not be beneficial. For example, the innovator product of lopinavir/ritonavir was associated with lower prices than the generic products. However, it was found that innovator products were strongly associated with paying more than the HDMC. Countries that, due to patent law, are obligated to procure innovator products are in a very difficult position because they have no option other than negotiation with a monopoly provider for lower prices. Finding mechanisms to increase the negotiating power of the purchasing country may help. However, it is important to note that not all approaches to strengthen the bargaining position of purchasers have been successful. For example, data from the Andean region suggests that negotiating as a block of countries does not necessarily result in lower prices (Seoane-Vazquez and Rodriguez-Monguio, 2007).

Country income-level

Country income-level had an important impact on the ability of a country to obtain prices lower than the LDMC or HDMC. Only in exceptional cases, countries with a higher income paid lower prices. This result is consistent with the expected result in a non-competitive market, where the manufacturers are able to sell at a price level that corresponds with the country's willingness and ability to pay. In this context, it seems important to mention that many lower- and upper-middle-income countries pay a significant proportion or all costs for ARVs compared to low-income countries often relying on donor funds.

Procurement methods

One procurement method to influence prices is bulk procurement. Contrary to the common assumption that large volume procurement by countries results in lower prices, the results of the present study indicate that volume is in only associated with lower prices in very few cases. It was not associated with obtaining less than the lowest direct manufactured cost per patient per year, which is in line with recent findings from other authors (Waning et al, 2009). Some authors have found that small volumes are sometimes used to introduce a product to the country at a special low price (Vasan et al, 2006). Interestingly, on one hand volume gives countries more power to negotiate; on the other hand, the higher volume means that there are more people who will demand treatment and the countries are facing political pressure to respond to this need which could reduce their negotiating power. It is important to note that procurement volume is distinct from production volume which we will discuss further below.

Another procurement method to lower prices in theory is third party negotiation, which is used by the CHAI. In our analysis, the CHAI was associated with paying less than the HDMC. However, when analyzing each ARV separately, being a member of the CHAI was only associated with a lower price for

some ARVs. As CHAI third party negotiations will affect other suppliers' prices and there is some lag time between CHAI negotiation and the procurement of CHAI member countries, it is difficult to demonstrate their impact in the present analysis. More nuanced time-series analysis is needed to determine the benefits of CHAI negotiations, which countries would benefit most from being CHAI members and how the strategies used by the CHAI could be optimized to achieve further price reductions.

Donor-policies

In terms of the effect of large donors on ARV prices, being a PEPFAR focus country did not result in a lower price for all except one of the ARVs studied. It has been argued that higher prices for PEPAR countries do not necessarily mean less value for money (United States Government Accountability Office, 2005). In this study, quality was not taken into account. The ARVs that are procured by PEPFAR need to be registered with the FDA, which means that the program may choose a higher priced product over a lower priced one, in a case in which the latter does not have a tentative approval process with the FDA (Office of the United States Global AIDS Coordinator, 2008; United States Government Accountability Office, 2005). However, in its 2008 program report, it is stated that 70% of the products from the supply chain management support of PEPFAR have the lowest international listed price (Office of the United States Global AIDS Coordinator, 2008). Interestingly, the report mentions two obstacles that make it difficult to increase the use of generics despite the objective of PEPFAR to do so: (a) the slow approval process of generics in some countries and (b) the quality concern of some buyers. It is worthwhile to investigate how many countries these barriers apply to and potential strategies to overcome them.

Another donor policy worthwhile discussing here is the Global Fund and CHAI requirements for countries to report their pricing data. In the past decade, medicine procurement prices have been an area "that has been plagued by a troubling lack of transparency" (Vasan and Kim, 2009). However, this requirement of price reporting has resulted in an unprecedented accumulation of procurement price information at the global level. There has been some controversy whether increasing the transparency of prices would result in lower prices for countries. The key argument against it is that it would undermine the prices charged in higher income countries since the higher income countries would demand to pay comparable prices of low-income countries (Danzon and Towse, 2003; Ridley, 2005). Even though it is not possible to determine how ARVs would have developed without the GPRM, without a doubt the creation of the global database and the unprecedented global effort to increase price transparency provides an important tool for more efficient procurement through benchmarking. However, there is room for improvement: first, the GPRM data base is more comprehensive for low- and lower-middle-income than upper-middle-income and high-income countries, resulting in a lack of publicly available, systematically gathered information about prices for these latter countries. Particularly upper-middle-income countries are at a double disadvantage: 1) limited price information on a global level and 2) many manufacturers do not include upper-middle-income countries in their tiered pricing system. As a result, upper-middle-income countries must negotiate individually, thus in some cases limiting the country's ability to achieve lower prices.

Second, more analysis is required on how the data is currently used by staff involved in procurement decisions and how it can be optimized to support procurement efficiency.

Limitations

The GPRM data mainly include donor funded procurement transactions from low-income and lower-middle-income countries, so it may not be representative of the total procurement of ARVs worldwide and results may not be generalized to all countries. Although staff of donor organizations sending the transaction data and those receiving them at WHO routinely review the reported information for entry mistakes, we checked all entries before analysis according to the procedure described above.

However, we did not interview country procurement offices to verify the information reported to the donor organizations, which means that it was not possible to correct all potential errors. Taxes, tariffs and international commercial terms (INCOTERMS) are not consistently reported so we did not include them in the analysis. Based on the US Government Accounting Office (GAO) and Management Sciences for Health (MSH), the WHO has reported that taxes, tariffs and INCOTERMS are between 3% and 15% (WHO, 2008). Our results need to be interpreted while keeping in mind the limitations of the data base. As improved procurement data will be available in the near future, more analysis will need to be done to confirm our results.

Although one of the most relevant considerations in saving ARV costs is their appropriate selection, this study did not evaluate the clinical appropriateness of the ARV selection procured by a country as it falls outside the scope of this analysis. This analysis did not consider pediatric formulations, only adult formulations. Other authors have analyzed the need to scale up production and increase distribution of ARV formulations that are suitable for children (Dionisio et al, 2008). It is important to mention that some of the factors in our regression models are confounding, for instance PEPFAR focus countries are mainly low-income, high prevalence countries. Our models do not explain most of the observed variance in the data. This suggests that a substantial part of the variation is due to factors which are not included, indicating that price determinants may be much more complex than our model suggests. Other factors much more difficult to measure are corruption, the countries' willingness, the capacity to negotiate with monopoly providers could explain some differences or the political pressure within the country to provide access to ARV. We used the API to account for some of these country specific characteristics.

Recommendations

In the present study, 39% of countries in our sample procured the lowest priced first-line ARV combinations at higher than the HDMC, which indicates that there is ample room for further price reductions. This can be achieved through multiple strategies:

- Using existing pricing data for benchmarking to improve procurement efficiency.
- Moving away from only relying on larger procurement volume to lower prices. It has been shown that bulk procurement alone is insufficient to lower prices.
- More empirical research is needed to identify strategies which optimize third party negotiation particular for CHAI.
- PEPFAR focus countries do not have an advantage or a disadvantage over other countries to obtain lower prices. More research should focus on how to overcome quality concerns of buyers and slow registration processes of generic ARVs in affected countries as identified by PEPFAR as one of the main obstacles for the use of generics.
- More empirical research is needed to identify which other procurement methods result in more value for money in the future, for instance, whether strengthening negotiation skills for countries would result in lower prices.

Apart from procurement methods, two other strategies which would provide better value for money are:

1) Increasing competition among manufacturers: This depends partly on how countries can take advantage of the flexibilities allowed under TRIPS (principally parallel import, compulsory licensing) (Scherer and Watal, 2002). However, many countries face multiple barriers in using these flexibilities. The WHO initiative to strengthen the countries' ability to use TRIPS flexibilities is therefore very important (WHO, 2008c). Many have advocated for the importance of the WHO and other international organizations as brokers to negotiate VL with originator companies and to provide technical assistance in the production of generic ARV.

2) Increasing production efficiency depends on the abilities of generic companies to invest in scale up and research to improve production efficiency. If the volume of second-line ARV is small, there is less incentive for generic companies to do so. Some authors have analyzed various ways of synthesis of API of ARV and found that there is large scope for increasing efficiency in production which would result in reduction of production costs (Pinheiro et al, 2008).

Conclusion

In conclusion, the global community has observed significant price declines for ARVs, especially for first-line therapy. While this has meant that first-line therapy has become more affordable for many countries, the prices still remain out of reach for many others. As a result, it remains unclear if universal access for ART will be achieved. Furthermore, the fact that some countries rely significantly on donors such as the Global Fund and PEPFAR raises concerns about sustainability. Even with ongoing declines in prices, it remains unclear how less-developed countries would be able to sustain ART provision if donors were to scale-back their provision of resources for ART.

Second-line therapy also represents a significant concern. Price declines for second-line therapy have been minimal, with the overall prices continuing to be out of reach for many developing countries. Those PLWHA on first-line therapy may eventually develop resistance to the therapy causing an increasing need for second-line therapy. The authors of this paper project that the price of first-line therapy is unlikely to continue its rapid decline (with some exceptions such as tenofovir and emtricitabine), especially given the fact that prices are already near the cost of manufacturing. This is not the case, however, with second-line therapy. As demonstrated in this study many more patients could be treated if second-line therapy would be closer to manufacturing costs. Reducing the price of second-line therapy should remain a priority. This may be achieved, in part, through the provision of generic versions of existing products via voluntary licensing. The number of manufacturers seems to be related to the reduction of price over time.

Price reductions may be achievable by reducing the manufacturing cost of ARVs. If the cost of the active ingredients could be further reduced, there may be opportunities to further reduce the price of first and second-line therapy.

Finally, global data on procurement prices can be an important tool to help countries benchmark prices and identify opportunities to increase procurement efficiency.

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Appendix 1. Median first-line ARV prices by year between 2005 and 2008 and frequency of purchases by country characteristics

	Efavirenz 600 mg	Lamivudine 150mg Zidovudine 300 mg	Lamivudine 150 mg	Nevirapine 200 mg	Stavudine 40 mg	Zidovudine 300 mg
Number of observations	1642	1732	1413	1685	739	874
Price per patient per year Median (price at 25% and 75% of the sample) [price divergence+]						
2005	350.4 (346.8 - 397.9) [0.15]	211.7 (175.2 - 240.9) [0.38]	73.0 (65.7 - 80.3) [0.22]	87.6 (73.0 – 233.6) [2.20]	51.1 (43.8 - 58.4) [0.33]	153.3 (131.4 – 182.5) [0.39]
2006	244.6 (244.6 – 284.7) [0.08]	145 (138.7 – 175.2) [0.26]	58.4 (51.1 - 65.7) [0.29]	65.7 (58.4 - 65.7) [0.13]	36.5 (36.5 - 51.1) [0.40]	146 (131.4 - 146) [0.11]
2007	193.5 (149.7 – 237.3) [0.59]	124.1 (109.5 -146.0) [0.53]	43.8 (36.5 – 58.4) [0.60]	43.8 (43.8 - 51.1) [0.17]	29.2 (21.9 – 36.5) [0.67]	109.5 (102.2 - 138.7) [0.36]
2008	157.0 (142.4 - 180.7) [0.27]	116.8 (116.8 – 135.1) [0.16]	36.5 (36.5 – 58.4) [0.60]	43.8 (36.5 - 51.1) [0.40]	51.1 (21.9 – 65.7) [2.00]	109.5 (102.2 - 116.8) [0.14]
Price variation between 2005 and 2008	-123.2%	-81.3%	-100%	-100%	0%	-40.0%
HIV prevalence <2%	49.8	50.6	42.1	50.8	45.9	41.9
HIV prevalence 2-5%	13.7	16.1	15.6	13.2	13.5	17.4
HIV prevalence >5%	36.5	33.4	42.3	35.9	40.6	40.7
% Low- income	64.2	62.5	48.4	63.7	46.8	57.0
% Lower- middle-income	19.3	24.8	25.6	20.9	24.8	22.8
% Upper- middle-income	14.9	11.0	23.8	14.1	26.8	17.3
% High- income*	1.6	1.6	2.1	1.3	1.6	3.0
% Least Developed Countries	55.6	56.2	41.3	55.9	42,0	47.8
Number of units per purchase Median (at 25 % and 75% of the sample)	50,715 (6,600 - 227,700)	104,910 (15,180 - 390,000)	88,020 (16,860 - 345,300)	49,920 (8,040 - 281,280)	36,000 (5,760 - 113,580)	25,110 (7,200 - 96,000)
% Generic	85.6	84.8	85.1	86.4	85.1	85.6
API* mean±sd	61.6±9.6	61.1±10.1	62.7±10.2	61.0.±9.9	61.0±11.1	62.6±10.1
% Clinton Foundation HIV/AIDS Initiative	88.9	89.1	89.1	90.0	90.4	88.1
% PEPFAR**	37.0	34.4	43.7	35.3	41.4	41.2

Appendix 2. Median second-line ARV prices by year between 2005 and 2008 and frequency of purchase by country characteristics

	Abacavir 300 mg	Didanosine 100 mg	Didanosine 400 mg	Lopinavir 133 mg Ritonavir 33 mg	Ritonavir 100 mg	Tenofovir 300 mg
Number of observations	844	537	423	551	332	504
Price per patient per year Median price (price at 25% and 75% of the sample) [price divergence+]						
2005	890.6 (890.6 - 956.3) [0.07]	306.6 (306.6 – 401.5) 0.31]	288.4 (288.4 -1120.6) [2.89]	613.2 (503.7-3285.0) [5.52]	87.6 (73.0 – 102.2) [0.40]	299.3 (211.7 -324.9) [0.53]
2006	635.1 (540.2 - 894.3) [0.66]	277.4 (233.6 – 335.8) [0.44]	288.4 (277.4 – 507.4) [0.83]	591.2 (525.6 – 2124.3) [3.04]]	87.6 (80.3 – 485.5) [5.04]	208.1 (208.05 - 266.5) [0.28]
2007	401.5 (372.3 – 467.2) [0.25]	306.6 (248.2 - 350.4) [0.41]	288.4 (284.7 – 361.4) [0.27]	1007.4 (591.3 – 1554.9) [1.63]	87.6 (80.3 – 532.9) [5.63]	208.1 (167.9 – 222.7) [0.14]
2008	335.8 (313.9 – 401.5) [0.28]	248.2 (189.8 – 292.0) [0.54]	288.4 (284.7 – 288.4) [0.01]	503.7 (438.0 – 580.4) [1.33]	87.6 (80.3 – 138.7) [0.73]	186.2 (153.3 - 208.0) [0.36]
Price reduction	-165.2%	-23.5%	0%	-21.7%	0%	-60.7%
HIV prevalence <2%	40.3	34.3	52.7	46.5	40.9	40.9
HIV prevalence 2-5%	19.1	10.2	13.7	8.4	16.9	16.9
HIV prevalence >5%	40.6	55.5	29.1	45.2	42,4	42.2
% Low-income	62.1	40.2	65.5	32.3	35.8	63.7
% Lower- middle-income	22.0	21.2	21.3	27.2	28.0	26.0
% Upper- middle-income	14.2	37.1	9.2	38.1	35.0	8.7
% High-income	1.7	1.5	4.02	2.4	1.2	1.6
% Least Developed Countries	48.3	34.1	57.0	25.4	30.7	47.0
Number of units per purchase Median (at 25% and 75% of the sample)	18,000 (3,180 - 60,000)	13,200 (3,360 - 47,280)	12,780 (2,400 - 30,000)	33,600 (13,200 - 100,800)	16,800 (7,248 - 46,200)	21,540 (4,785 - 76,050)
% Generic	65.9	49.7	8.0	8.0	9.0	55.2
API mean±sd	63.0±9.9	65.5±10.1	61.5±10.0	62.8±11.3	63.9±10.4	64.2±9.8
% Clinton foundation HIV/AIDS initiative	84.1	91.4	77.0	81.0	77.2	79.3
% PEPFAR	45.6	54.2	32.9	40.5	46.1	48.8

Table legend: *API= AIDS Program Effort Index; CHAI=Clinton Foundation HIV/AIDS initiative; PEPFAR=President's Emergency Plan for AIDS Relief; Robust 95% confidence intervals in parentheses; * significant at 5%; ** significant at 1%; +price divergence= (price at 75 percentile of the sample/ price at 25 percentile of the sample)-1

Data source: Global Price Reporting Mechanism

Appendix 3. Expiry date of basic patents of antiretroviral medicines and their derivates

INN Name	Company	Expiry date of basic patent	Expiry date of derivate	Description of derivate	Expiry date of other derivate	Description of derivate
Didanosine	BMS	expired	2012	improved formulation	2018	improved formulation
Zidovudine	GSK	expired				
Stavudine	BMS	expired	2008	US	2011	Europe
Abacavir	GSK	2009	2013	hemisulfphate		
Nevirapine	Boehringer Ingelheim	2010	2018	hemihydrate		
Emtricitabine	Gilead	2010				
Saquinavir	Roche	2010				
Lamivudine	GSK	2012				
Efavirenz	Merck & BMS	2013				
Ritonavir	Abbott	2013	2018	crystaline polymorph		
Efuvirtide	Roche	2014				
Nelfinavir	Roche	2014				
Tipranavir	Boehringer Ingelheim	2015				
Lopinavir/ritonavir	Abbott	2017	2024	heatstable		
Tenofovir	Gilead	2017				
Etravirine	Johnson&Johnson	2019				
Maraviroc	Pfizer	2019				
Raltegravir	Merck	2022				

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