Relative market share of different antiretroviral compounds in low and middle income countries in 2004 and 2005: an analysis of 2 public domain data bases

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INTRODUCTION

In recent discussions between WHO and UNAIDS and representatives from innovator and generic pharmaceutical companies, the necessity to forecast the use of antiretroviral drugs in resource limited country markets was identified as a major element in the industry's decision making process about the expansion of their present production capacity. As WHO and UNAIDS forecasted that by the end of 2010 9.8 million people in developing countries will need antiretroviral treatment, and as the G8 pledged in Gleneagles in June 2005 to do all they can to raise funds to cover this need[1], the 2 UN organizations, in conjunction with the Clinton Foundation HIV/AIDS Initiative (CHAI), decided to develop a forecast of ARV use in those countries up to 2010. One of the important elements to inform this forecast is baseline consumption of antiretroviral drugs, about which until recently, and with the exception of Brazil, little data were available in the public domain. This has changed recently, with the publication of developing country transaction data for ARVs by the main procurement agencies supporting the availability of essential drugs and other technical organizations, through the AIDS Medicines and Diagnostics Service (AMDS). CHAI also maintains a database to track all procurement conducted under its agreements. In this paper we review and discuss what can be inferred on the marketshare of different antiretroviral compounds in developing countries from the AMDS Global Price Reporting Mechanism, CHAI data, and data published by the Brazilian Ministry of Health.

METHODS

Sources of information

Data in this paper come from 3 sources: the Global Price Reporting Mechanism established by the AMDS[2], the Clinton Foundation, and the report by the Brazilian Ministry of Health report on the national consumption of ARV drugs in 2004[3].

The Global Price Reporting Mechanism (GPRM) compiles transaction data about ARV drugs procured through or by the organizations that collaborate with the World Health Organization in the AMDS. The main information sources for the GPRM are UNICEF's Supply Division (based in Copenhagen, Denmark), the International Dispensary Association (based in Amsterdam, the Netherlands), and the Global Fund against AIDS Tunerculosis and Malaria (based in Geneva, Switzerland), with additional contributions

from the Central Procurment Service of the WHO (based in Geneva, Switzerland), Management Sciences for Health (based in Boston, USA) and the WHO 3by5 country officers (based in Guyana, Haiti, India, Sri Lanka, Sudan, Thailand, Ukraine). Data available in the GPRM include quantity of defined formulations of ARVs transacted and prices paid for them by treatment programmes in different countries, with INCOTERMS, and a few additional data items. The GPRM contains ARV transaction data from 01 January 2004 and is continuously updated. For the purpose of the analysis presented here, we extracted information on the volume of ARVs ordered between January 1 and July 31, 2005 (7 months), of data available up to 15 August 2005.

The Clinton Foundation collects data on all ARVs procured in CHAI consortium countries under CHAI agreements. These data come primarily from invoices shared by Ministries of Health and other CHAI contacts in countries. This includes both orders placed through procurement agents and orders placed directly with suppliers. UNICEF's supply division also contributes to the tool. Data available is similar to that available from the GPRM. The database includes orders placed in 25 CHAI consortium countries, beginning from November 2002. The information is continuously updated, with the bulk of the volumes coming from orders placed in 2004 and 2005. The most recent data is from September, 2005. The Clinton Foundation data is not currently publicly available.

The Brazilian Ministry of Health 2004 report on ARV covers consumption in the national ARV treatment programme from January 1 to December 31, 2004, and includes data on the quantity of defined formulations of ARVs used and prices paid for them, whether locally produced or imported.

Calculation of the volume of individual ARVs transacted

In all three databases the number of smallest pharmaceutical units (usually tablets or capsules, sometimes bottles or vials) transacted are reported. We converted this number into the number of patient years that can be covered by this quantity by dividing the number of smallest pharmaceutical units reported by the defined daily dose of the drug or formulation (using the recommendations on dosing from the WHO guidelines on antiretroviral treatment in resource limited settings)[4] and 365 days.

We then calculated the amount of each antiretroviral compound used, by adding the number of patient years covered by each sale, per compound. Where fixed dose formulations were used, the amount of each antiretroviral compound included in the product was added to the amount of antiretroviral compound sold as a single dose product. Thus, if 0.45 patient years of the fixed dose combination of zidovudine and lamivudine were transacted, the total amount of zidovudine transacted increased with 0.45 patients years, and the total amount of lamivudine transacted also increased with 0.45 patient years. These calculations were performed for low income countries and middle income countries - the latter including both low and upper middle income countries but excluding Brazil -, and the Brazilian market separately. Countries were characterized in income groups using the 2004 World Bank classification[5]. The decision to present the data according to these groupings was made after, in an exploratory data analysis, we found

that the pattern of ARV transactions with low, low-middle and upper middle income markets from which data were available in the GPRM, was quite similar, but that the pattern of drugs transacted in Brazil differed dramatically from that of the other markets. CHAI data is presented in an aggregate form, as the data comes exclusively from low income (93% of total volume) or low-middle income (7% of total volume) countries. Presenting a breakdown of this data by income groups would reveal little given the small size of the dataset for the low-middle income group.

Calculation of relative market share

The ratio of the volume of individual ARVs transacted in patient years over the total amount of ARVs transacted, expressed in patient years, was taken to represent the relative market share for different ARV compounds.

Characterization of the market in terms of first line and second line treatments used

The sales of the 5 ARVs, recommended by WHO for first-line treatment (stavudine, zidovudine, lamivudine, nevirapine and efavirenz), were taken to represent the total volume of first line treatments used, and all other drugs were taken to represent the volume transacted to satisfy demand for second-line treatment.

Market share of originator and generic pharmaceutical companies

The number of patient years of each compound supplied by the originator companies was subtracted from the total volume of those compounds transacted in both the low income and middle income countries. Originator company data has not been subtracted out of the Clinton Foundation data, as these orders make up a very small percentage of the overall volumes captured in the database.

RESULTS

Global Price Reporting Mechanism (GRPM) Data

Between January 1 and July 31, 2005, the GPRM registered transactions involving a total of 15 ARV products with 42 formulations, from a total of 42 countries. Among those were 27 countries characterized as low income countries by the current World Bank Country Classification (gross national income per capita up to $ 825 in 2004) and 11 countries characterized as middle income or upper middle countries ($826-$3,255).

The low income countries included were Benin, Burundi, Cambodia, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of Timor-Leste, Eritrea, Ethiopia, Guinea, Haiti, India, Kenya, Lesotho, Liberia, Malawi, Mauritania, Mozambique, Myanmar, Nicaragua, Niger, Nigeria, Republic of Moldova, Sudan, and Zambia.

The middle income countries included were the low middle income countries Guatemala, El Salvador, Fiji, Georgia, Honduras, Jordan, Kazakhstan, Swaziland, Thailand, Ukraine, and the upper middle countries Estonia, Gabon, and South Africa.

The most commonly first line ARVs used in low and middle income countries were stavudine (25% and 27%, respectively), lamivudine (31% and 30%, respectively) and nevirapine (28% and 26%, respectively). Most of the stavudine, lamivudine and nevirapine was transacted as a fixed dose combination of those drugs in both LI and MI countries (45% and 52% of 1st line ARV formulations). Zidovudine and efavirenz - the other ARVs recommended by WHO for first line treatment - were less often used in the LI and MI countries, with a market share of triple therapies for zidovudine of 5% and 5%, respectively, and 7% and 8%, respectively, for efavirenz.

In low income countries, the most commonly used 2nd line ARVs were tenofovir (TDF) (1%), indinavir (0.5%), emtracitabine (0.4%), didanosine (ddI) (0.3%), lopinavir (0.3%), nelfinavir (0.2%) and abacavir (ABC) (0.2%). In middle income countries, 2nd line ARVs used were didanosine (0.9%), indinavir (0.8%), nelfinavir (0.3%) and abacavir (0.2%).

Of the total volume of transactions reported in the GPRM for low and middle income countries, 24% and 15% respectively were supplied by the originator pharmaceutical companies [$p=10^{-6}$]. The relative volume supplied by originator companies for individual compounds is shown in table 2.

Table 1: Volume of ARV transactions reported in the GPRM between January 1 and July 31, 2005, in patient-years

	LOW INCOME COUNTRIES	MIDDLE INCOME COUNTRIES
	% of total volume of patients/years	% of total volume of patients/years
stavudine (d4T)	25%	27%
zidovudine (ZDV)	5%	5%
lamivudine (3TC)	31%	30%
Nevirapine (NVP)	28%	26%
efavirenz (EFV)	7%	8%
abacavir (ABC)	0,2%	0,2%
Didanosine (DDI)	0,3%	0,9%
indinavir (IDV)	0,5%	0,8%
lopinavir + ritonavir (LPV/r)	0,3%	0,1%
tenofovir (TDF)	1%	0,0%
emtracitabine (FTC)	0,4%	0,0%
nelfinavir (NFV)	0,2%	0,3%
ritonavir bust (RTV)	0.7%	0,6%
Saquinavir (SQV)		0.15

Total volume		
Total volume of API patients/year	321770	83450
Number of patients years of triple therapy (approximation)	106500	27800

Table 2: Percent of volume of ARVs transacted with the originator pharmaceutical companies in GPRM

Name	Percentage of patient year treatment supplied by originator companies
Abacavir	100%
Didanosine	74%
Efavirenz	85%
Indinavir	98%
Lamivudine	15%
Lopinavir/ritonavir	100%
Nelfinavir	97%
Nevirapine	10%
Ritonavir	100%
Saquinavir	100%
Stavudine	5%
Tenofovir	100%
Emtricitabine	100%
Zidovudine	60%
Total percentage of volume of ARVs transacted with originator pharmaceutical companies	22%

CHAI Data

The dataset compiled by the Clinton Foundation captures ARV procurement data from 25 countries: Anguilla, Antigua & Barbuda, Bahamas, Benin, Burundi, Dominica, Dominican Republic, Ethiopia, Grenada, Haiti, Jamaica, Lesotho, Malawi, Mali, Mozambique, Namibia, Rwanda, St. Kits, St. Lucia, St. Vincent & Grenadines, Swaziland, Tanzania, Uganda, Ukraine and Zambia. This dataset covers the equivalent of

184,000 patient years of treatment. The pattern of ART use in this dataset was very similar to that reported in the GPRM (table 3).

The most commonly used first line ARVs were stavudine (27%), lamivudine (33%) and nevirapine (28%). This is due to the fact that nearly all countries in the CHAI procurement consortium utilize the fixed dose combination formulation of these three APIs in their first line. The most common second line ARVs were didanosine (0.4%), nelfinavir (0.3%), lopinavir (0.3%) and indinavir (0.2%).

These data consist primarily of generic products, as CHAI agreements are currently with generic manufacturers only. Also, it is likely that there is some overlap between the transactions recorded in the GPRM and the CHAI database, as CHAI has procurement collaborations with 3 of the suppliers (IDA, UNICEF and WHO/CPS) that also contributed data to the GPRM. The extent of this possible overlap is discussed in the Discussion section below.

An initial analysis of the CHAI data by region reveals that the Latin American and Caribbean markets may behave differently from other markets. It is possible that LAC markets may be more comparable to the Brazilian market in terms of market share distribution (see description of Brazil market below). However, this analysis is very preliminary and is based on a small dataset. Further examination of this trend is needed.

Table 3: Sales volume (in patient years) and market share of different ARV molecules in the Clinton Foundations' HIV/AIDS Initiative database

Clinton Foundation 2003-2005		
Molecule	No. of patients/years by API	% of total volume of patients/years
Stavudine	165.161	27,1%
Zidovudine	43.946	7,2%
Lamivudine	200.948	33,0%
Nevirapine	173.002	28,4%
Efavirenz	16.205	2,7%
Abacavir	588	0,1%
Didanosine	2.108	0,4%
Indinavir	1.047	0,2%
Lopinavir	1.570	0,3%
Tenofovir	202	0,03%
Emtricitabine	-	-
Nelfinavir	1.969	0,3%
Ritonavir	2.601	0,4%

Atazanavir	-	-
Saquinavir	-	-
Delavirdine	-	-
Amprenavir	-	-
Total volume of API patients/year	609.348	
Number of patients years of triple therapy		

Brazil

A total of 15 ARV products with 19 formulations were bought by the Brazilian ARV therapy programme in 2004. All ARVs bought were single drug formulations except for the two following fixed dose combinations: lamivudine/zidovudine and lopinavir/ritonavir.

The most commonly used first line ARVs were lamivudine (28%), zidovudine (22%) and efavirenz (12%). Compared to the volumes reported through the GPRM from low and middle countries, there were significant differences: in Brazil, the volume of stavudine was significantly less than that of zidovudine, and that of nevirapine less than that of efavirenz [both $p<10^{-6}$].

The most commonly used 2nd line ARVs were didanosine (ddI) (5%), lopinavir (4%), nelfinavir (4%), indinavir (2%), tenofovir (TDF) (0,8%).

Table 4: Volume of ARV transacted in Brazil January 1 to December 31, 2004, in patient-years

BRAZIL	
	% of total volume of patients/years
stavudine (d4T)	8%
zidovudine (ZDV)	22%
lamivudine (3TC)	28%
nevirapine (NVP)	4%
efavirenz (EFV)	12%
abacavir (ABC)	0,5%
didanosine (DDI)	5%
indinavir (IDV)	2%
lopinavir + ritonavir (LPV/r)	4%
tenofovir (TDF)	0,8%

emtracitabine (FTC)	0,0%
nelfinavir (NFV)	4%
ritonavir bust (RTV)	8%
atazavavir (ATZ)	1%
saquinavir (SQV)	0,5%
amprenavir (APV)	0,2%
Total volume of API patients/year	487 307
Number of patients years of triple therapy (approximation)	156 300

Relative market share of first line and second line treatments

Drugs recommended by WHO as first line drugs were the most commonly transacted drugs in both low income countries (96,3%) and middle income countries (96,8%). In Brazil, first line drugs were also the most frequently transacted, with 74,5% of the volume, but drugs considered second line drugs comprised 22% of the volume.

DISCUSSION

When we set out analysing the data presented here different authors contributing to this manuscript had different perceptions about what drugs were most frequently used in developing countries, and we were quite pleased that we were able to test whether our perceptions were supported by data.

The data included in this analysis includes the equivalent of 290600 patient years of treatment (106500 for low income countries, 27800 for middle income countries and 156300 for Brazil). The 184.000 patient years from the CHAI dataset included here adds additional data, but there may be some overlap between the GPRM and the latter dataset. This compares to the WHO estimate that 970.000 people in resource limited countries were on ARV treatment at the end of 2004. The sample used in our analysis therefore covers between 30% and 48% of the total ARV market in those countries, depending on whether all or none of the CHAI dataset were duplicated in GPRM. The study is unfortunately restricted to adults patients as we were unable to access a significant amount of data on pediatric ARV use. There will be a need to focus on pediatric ARVs when assessing ARV consumption in the future.

While the amount of consumption data included in this paper is very significant, we also realize that it is not necessarily representative of the rest of developing country ARV market. Reports from the originator companies on the volume of ARVs they shipped to resource limited countries, quoted in the WHO report on 3 by 5 in June 2005[6],

suggests that they supplied 427 000 patient equivalent of triple therapy in 2004, or about 50% of the resource limited country ARV market, whereas in the GPRM, only 22% came from the originator companies. The majority of the data from the CHAI dataset is also from generic manufacturers. The sample of transactions studied here is thus clearly biased in favor of generic suppliers. However, it is not so clear whether this introduces a significant bias in the estimation of the relative importance of the different molecules / compounds used. Another potential bias in the data is that these datasets are limited to transactions made through public sector ARV programs. ARV purchases made in the private sector are not accounted for, due to difficulty in obtaining this information. In low income countries, we do not believe that this poses a major limitation, as the majority of procurement is done in the public sector. In middle and high income countries, however, it is possible that "out of pocket" public sector procurement may follow a different pattern. We will continue to pursue this data and will incorporate it into the baseline when it becomes available.

Other sources reporting on the use of ART in developing countries report breakdowns that are similar to the pattern reported in the GPRN.

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration, a network of HIV/AIDS treatment programmes and cohorts in Africa, South America and Asia was set-up in 2003[7]. The consortium recently published a cohort profile covering 8734 patients followed up in 18 ART centers (6 in North and West Africa, 3 in Central and East Africa, 5 in South Africa, 2 in Brazil, and 2 in Asia), in which it described the treatment regimens most commonly prescribed between 1996 and 2003 for 7938 patients. While the report on a relatively small number of prescriptions (6783) only, the pattern of ARV use was similar to that reported in the GPRM. The marketshare for each molecule is represented as a percentage of the total number of drugs mentioned in all prescriptions. This is due to the fact that many prescriptions mention several drugs, so to determine the marketshare based on total number of prescriptions would not be accurate.

Table 5: Breakdown of prescriptions reported by ART-LINC (1996-2003)

	ART-LINC (1996-2003)	
Molecule	No. of prescriptions	Percentage prescriptions containing the drug (as a % of total number of drugs mentioned)
Stavudine (D4T)	4440	22%
Zidovudine (AZT)	2236	11%
Lamivudine (3TC)	6087	31%
Nevirapine (NVP)	4021	20%
Efavirenz (EFV)	1657	8%
Abacavir (ABC)	-	-
Didanosine (DDI)	630	3%
Indinavir (IDV)	344	2%

Lopinavir (LPV)	-	-
Tenofovir (TDF)	-	-
Emtricitabine (FTC)	-	-
Nelfinavir (NFV)	326	2%
Ritonavir (RTV)	77	0%
Atazanavir (ATZ)	40	0%
Saquinavir (SQV)	-	-
Delavirdine (DLV)	38	0%
Amprenavir (APV)	-	-
Total # Prescriptions	6783	
Total # drugs mentioned	19896	

The pattern of ART use in countries from which data were included in the GPRM and in the CHAI database was quite different from that in Brazil. The likely explanations are that ARV therapy has a much longer history in Brazil than in any of the other countries included in the GPRM. In Brazil ARV treatment was introduced in 1988, as monotherapy with zidovudine, and triple antiretroviral therapy was introduced in 1996 on a large scale, reaching universal coverage soon after[8]. This long history likely explains why zidovudine is still used as the mainstay of first line treatment, whereas the ability to treat patients without regard to the cost of drugs and the fact that many Brazilian patients are male likely explains why efavirenz is the preferred non-nucleoside in the country. Compared to the middle income countries included in the GPRM (Guatemala, El Salvador, Fiji, Georgia, Honduras, Jordan, Kazakhstan, Swaziland, Thailand, Ukraine, Estonia, Gabon, and South Africa), of which only Thailand recently scaled up ARV treatment to universal coverage[9], the Brazilian market therefore qualifies as a mature middle income market. Other middle income countries with a mature ARV markets likely include Mexico, Argentina, and Chile, which reportedly are close to universal coverage[10]. For the purposes of forecasting future ARV use, the marked difference between these mature and new ARV markets will likely require specific consideration. Forecasts will attempt to model the shift in market dynamics as global treatment programs transition from naïve to mature. The Delphi study, being conducted in conjunction with the forecasting exercise, will be used to aid in understanding of these changing market dynamics.

We were surprised to find that the pattern of ARV use in low and middle income countries that recently introduced sizable ARV programmes was so similar. The potential that sampling bias could have explained this finding was discussed above, but we also think that the availability of specific guidance from the WHO on how to go about scaling up antiretroviral treatment in resource limited settings, the relatively low cost, the strong advocacy of organizations such as Medecins Sans Frontieres, and the availability of attractive procurement options brokered by CHAI may have led to a predominance of stavudine and nevirapine in first line treatment in recent treatment programmes. As

recent programmes appear to respond in significant ways to external guidance and to externally generated opportunities, we think that the recency of treatment programmes and the behavior of supporting partners will likely need to be taken into account in forecasting the future of the developing country ARV market. One of the points of uncertainty we have in this respect is how the US government will influence the decisions on treatment use of the programmes it is supporting or will support in the future.

We were also surprised to see so few transactions involving second line drugs in the GPRM and the CHAI datasets. Based on the attrition rates in first line treatment in developing countries - 5% to 10% annually[11] - we had expected to see slightly more second line drugs in transaction. The recency of most treatment programmes reporting on drug use in the GPRM and the CHAI database, which experience the bulk of their growth in first line treatments, is the likely explanation of this finding. On the other hand, we were also surprised to see so many second line drugs being procured in Brazil. Here the explanation could be that some of the drugs (such as tenofovir or lopinavir/ritonavir) that we deemed to be used in second line treatment were in fact used in first line treatment. As it is impossible to ascertain whether this is the case, and as this is possibly even irrelevant to forecast the future of mature ARV markets, we did not pursue this as an issue for exploratory analysis.

In conclusion, we think that we now have a reasonable amount of data on adult ARV consumption in developing countries, which could be used to forecast the future of the adult developing country ART market. However, as this market will expand very rapidly, it is likely that the relative importance of different products will shift. To inform production planning and advocacy efforts, we therefore think that a yearly up-date of this data set will be needed. Further, we would have increased confidence in the representativeness of our data if we had more information on the use of ARVs from more countries and from more producers. To generate a more comprehensive data set , we will continue to expand our collaboration with ARV treatment programs in developing countries and try to do the same with ARV producing companies.

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