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CLINTON FOUNDATION

INSTITUTO NACIONAL DE SALUD PÚBLICA

MEXICAN NATIONAL INSTITUTE OF PUBLIC HEALTH

November 2007

DEMAND FORECAST FOR ANTIRETROVIRAL DRUGS IN LOW- AND MIDDLE-INCOME COUNTRIES, 2007–2008

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1. ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
API	Active Pharmaceutical Ingredient
ATV	atazanavir
AZT	zidovudine (also known as ZDV)
d4T	stavudine
ddI	didanosine
EFV	efavirenz
FTC	emtricitabine
IDV	indinavir
LPV	lopinavir
NFV	nelfinavir
NVP	nevirapine
RTV	ritonavir
SQV	saquinavir
TDF	tenofovir
/r	low dose ritonavir
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization

2. ACKOWLEDGMENTS

The authors are grateful to the senior staff of the national AIDS programmes and ministries of health of the participating countries who completed the 2006 survey on the use of antiretroviral therapy in resource-limited countries. The authors also wish to thank the representatives of the United Nations Children's Fund (UNICEF), the Partnership for Supply Chain Management, John Snow, Inc., Management Sciences for Health, and the United States Agency for International Development for their technical input.

3. EXECUTIVE SUMMARY

In the past five years low- and middle-income countries have scaled up HIV treatment. Such rapid global scale-up has greatly increased the demand on antiretroviral drug producers, with anecdotal reports that some of them are having occasional difficulties in meeting new orders. One factor that has led to supply shortages has been the absence of accurate forecasts for the quantities of antiretroviral drugs needed in the future. These are essential for production planning and to ensure uninterrupted drug supply.

To respond to this situation, WHO and UNAIDS established a technical working group to develop the forecasts of global demand for antiretroviral drugs presented in this report. The working group comprises WHO, UNAIDS, Mexico's National Institute of Public Health, and the Clinton Foundation HIV/AIDS Initiative.

Based on the scale-up observed during 2006, the forecasts provide 2007–2008 estimates of the number of people receiving antiretroviral therapy. The volume of current and future demand for active pharmaceutical ingredients (API) for first- and second-line antiretroviral drugs is calculated using two methods: a normative approach which models implementation of country-specific guidelines, and an empirical model which projects 2006 trends in drug use determined by a survey of national HIV programmes.

By the end of 2008, the number of people being treated will likely reach 3.38 million, 95% of these people would use first-line therapy and about 5% second-line therapy. Using either approach the largest estimated absolute demand volumes (total amount of API needed) for 2008 are for nevirapine, lamivudine, efavirenz and zidovudine. The largest estimated proportional increase for 2007–2008 is for tenofovir.

Comparison of results from the normative and empirical demand models suggests that if national treatment guidelines were fully implemented more tenofovir, zidovudine, abacavir, and didanosine would be required. Meanwhile, empirical survey data indicate that countries have been using more saquinavir, and nelfinavir than their current existing guidelines would suggest. It is worth noting that the use of these protease inhibitors will be declining in favour of heat stable fixed dose formulations of lopinavir/ritonavir and atazanavir/ritonavir.

The predicted expansion of HIV treatment in these models is well below the goals of the international HIV treatment community. It would be incorrect to interpret these numbers as a statement about what should be or will be accomplished in 2007–2008. Rather, these estimates indicate what is likely to be accomplished in the absence of meaningful changes in the conditions driving treatment scale-up.

This forecast will be updated regularly as new data become available, including new data on the number of people receiving treatment and those who need treatment; estimates of survival among people who receive treatment, as well as among those who do not receive antiretroviral therapy; and distribution of regimens, switching rates, and national guidelines. Product preferences also will change in response to evolving variables such as product availability, pricing and funding patterns. Modelling these factors and expected market shifts will be developed for the next forecast exercise.

4. INTRODUCTION

The number of people in low- and middle-income countries who receive antiretroviral therapy has increased drastically from less than 300 000 at the end of 2002, to about two million by the end of December 2006[1]. The ambitious 2003 WHO/UNAIDS "3 by 5" Initiative aimed to provide 3 million people in low- and middle-income countries with antiretroviral therapy by 2005. The target was not reached, but rapid global scale-up since 2003 has greatly increased the demand for antiretroviral drugs, with anecdotal reports of producers having occasional difficulty in meeting new orders. Supply shortages can interrupt access to the medication of people being treated and bring the risk that they will develop drug resistance. In part, supply shortages are caused by not having accurate forecasts of quantities of antiretroviral drugs that will be needed in the future. These are essential for production planning and to ensure uninterrupted supply.

To respond to this situation, WHO and UNAIDS established a technical working group to develop the global forecasts for demand for Active Pharmaceutical Ingredients (API) for antiretroviral medicines presented in this publication. The technical working group includes WHO, UNAIDS, Mexico's National Institute of Public Health and the Clinton Foundation HIV/AIDS Initiative.

The forecasts presented describe a possible future scenario that involves no dramatic changes in resources, delivery capacity or political commitment. The purpose of these forecasts is to assist in optimizing production planning. Based on available information they represent the best estimates of future demand for antiretroviral medicines. Until now, individual pharmaceutical companies have estimated the demand for their own products individually and have usually kept their estimates confidential for commercial reasons.

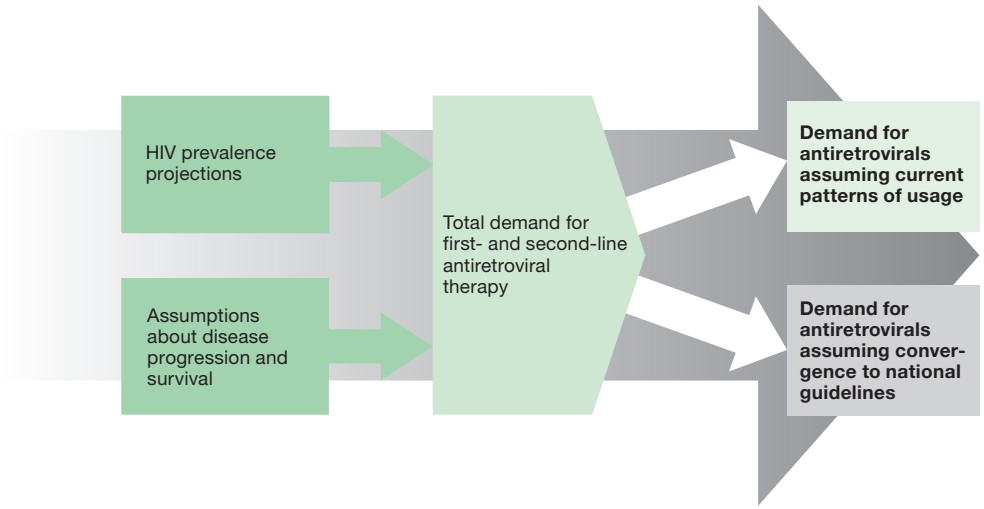
This is the first global estimate of demand for antiretroviral medicines. However, for most countries, the estimates will not meet internationally agreed goals on universal access to prevention, treatment, care and support. The goal of universal access remains a challenge that requires significant increases in future commitment, available resources and implementation.

Based on the scale-up observed during 2006, the forecasts estimate the number of people expected to receive antiretroviral therapy during 2007–2008. Based on this common forecast of the size of the population receiving treatment, two approaches—one empirical and one normative—were adopted to predict the volume of drugs needed to treat people and the quantities of active pharmaceutical ingredients needed to manufacture this volume. This publication describes the methods and assumptions for each of these steps and presents the results. Future annual updates will be produced using the most recent clinical data available, the latest number of people being treated as published by WHO and UNAIDS, and further refinements to the projection models.

5. METHODS

This section presents the methods used to estimate the number of people on antiretroviral therapy. It also spells out two scenarios to translate these estimates into quantities of active pharmaceutical ingredients. The overall objectives were: to produce a clear and transparent forecast that can be easily altered and updated; to reflect the heterogeneity of country-specific circumstances; to be as accurate as possible given the data available; and to be able to present the estimates aggregated across low- and middle-income countries. Hence, the forecasts were developed in two major steps: forecasting the number of people receiving treatment; and forecasting the demand for antiretroviral medicines (Fig. 1).

Fig. 1. Components of the forecasting model



5.1. Forecasting the number of people receiving treatment

5.1.1. Choice of forecasting approach

Various approaches were considered for forecasting the number of people who will be receiving antiretroviral therapy in 2007 and 2008. However, information on future funding and delivery capacity for antiretroviral therapy in countries was not accurate enough for this purpose[2]. The forecasts presented in this publication are therefore based on linear projections of historical trends of the number of people receiving antiretroviral therapy by country, for which there was reliable information, and the possibility of using previous work in this area as reference material[3].

These historical scale-up rates have been constrained by the growth of available funding and delivery capacity, which varies substantially in different regions. This approach implicitly assumes that countries that have been scaling up slowly to date will continue to do so in the future, and that the rate of change of constraining factors will remain the same as in the past.

This exercise defines the number of people receiving treatment as the number of people on antiretroviral therapy at the end of a given year. This includes people who started antiretroviral therapy in that year, as well as those who started in previous years and remain on treatment. The methodology and data used did not permit to make projections disaggregated by age and sex.

5.1.2. Projection methods

The projection is based on the estimated number of people receiving antiretroviral therapy collected by WHO in 127 low- and middle-income countries. The future number of people receiving treatment is forecast using a linear regression prediction based on the last three observations available (December 2005 and June and December 2006).

This forecast was compared with the total treatment need estimated in UNAIDS projections to the end of 2008. These projections used methods described in the literature based on estimates of HIV incidence in the past and AIDS-related deaths[4]. Essentially, the estimate was based on the assumption that in low- and middle-income countries a person becomes eligible for treatment two years before death if they have not previously been on antiretroviral therapy.

Only three high-volume countries have any possibility of reaching 100% of their total treatment need before the end of 2008 and are therefore capped at this level. After 2008, in these countries treatment is projected to grow only to meet the needs of the people newly eligible for antiretroviral therapy.

The treated population includes people on first- and second-line antiretroviral therapy. For these estimates, the few people on third-line therapy and subsequent lines are included in the second-line category. The likelihood that a specific person is receiving second-line therapy depends on the length of time he or she has been receiving treatment. Therefore, it is necessary to estimate the number of people who are newly added to treatment each year, all of whom initially receive first-line therapy. The net increase in the total number of people receiving therapy from one year to the next is the number of people newly added minus the number of people from previous years who stop therapy for any reason (including death, treatment default and loss to follow-up).

5.1.3. Survival assumptions

Country-specific survival data are lacking, so a survival curve was derived based on empirical data from Senegal and Brazil for the initial years on treatment; and from data from the United States of America for later years[5–7]. The resulting composite survival curve was assumed to apply to all the countries in the model. Loss to follow-up was estimated based on data presented by the Antiretroviral Therapy in Lower Income Countries (ART-LINC) Initiative [8].

5.1.4. First- and second-line therapy

The probability that people would migrate to second-line treatment (after a minimum of six months on treatment) was estimated as a cumulative increase in migration rates of 4% each year for Latin American countries and 2% each year for all other countries. So the models assumed that, in a cohort of patients starting first-line treatment at the same time in sub-Saharan Africa, 1% migrated to second-line treatment within 12 months of starting treatment, 3% migrated to second-line treatment within 24 months of starting treatment, 5% of patients migrated to second-line treatment within 36 months of starting treatment, and so on. This choice of migration probability was selected based on evidence from a WHO survey[9], field reports from the Clinton Foundation HIV/AIDS Initiative, and consultation with experts who analyzed switching patterns observed in countries where such data are available.

5.2. Forecasting demand for antiretroviral drugs

This publication presents two approaches to forecasting the demand for antiretroviral drugs: empirical and normative. The empirical approach used the current pattern of antiretroviral drug use as measured by a survey conducted by WHO[9]. The normative approach assumes that a country's use of various drug regimens follows the algorithms in its national treatment guidelines. In the two approaches, the forecast demand for antiretroviral drugs is calculated using the same number of people estimated to be on treatment in 2007 and 2008.

The normative model assumed changes in first- and second-line regimen use for the two-year projection by modelling epidemiological determinants and needs. In the empirical model, the main assumption was that, although overall demand increased and the distribution among patients receiving first- and second-line was changing over the two-year projection period, the relative share of each regimen used in these regimen categories remained constant for 2007 and 2008.

The reality will be more complex since product preferences are changing due to evolving variables such as therapeutic choices, product availability and pricing, levels of funding, as well as epidemiological needs. Available data were not sufficient to develop a robust model of the changes occurring in relative shares for each country. This would require either extrapolation based on repeated observations of regimen mix over time (not available), or a forecasting model that considers determinants of change in drug use. These include variables such as epidemiological need, technological change, funding patterns and pharmaceutical elements including medicine registration and pricing. Modelling such an array of factors was beyond the scope of this exercise, but will be developed for the next forecast undertaking.

5.2.1. An empirical approach to forecasting demand for antiretroviral drugs

Mexico's National Institute of Public Health designed the empirical approach, which used a specific distribution of drugs for first- and second-line regimens for each country. These assumptions were drawn from a WHO survey that collected information about the current distribution and composition of antiretroviral therapy regimens used in low- and middle-income countries, and future plans for revising treatment guidelines that would influence future demand. In March 2006, questionnaires were sent via WHO country offices to national AIDS programmes in 24 low- and middle-income countries to assess the current distribution and uptake of antiretroviral therapy regimens. These countries were chosen based on procurement information in the Global Price Reporting Mechanism established by WHO's AIDS Medicines and Diagnostics Service[10].

To estimate the demand for each specific drug, the empirical approach used WHO daily dose recommendations[11] and assumed that 100% of the drugs needed are dispensed to everyone receiving treatment. To obtain a global estimate, the empirical model extrapolated the drug distribution patterns in the WHO survey to all low- and middle-income countries not represented in the survey, based on region and income level. Different regional averages were derived for both low- and middle-income countries in each WHO region.

Using the derived drug use pattern for each country, the model estimated the demand for specific antiretroviral drugs according to first- and second-line regimens. The final output forecast the total number of individual doses for the given years and the number of metric tonnes that would be needed to treat the estimated number of people. The people starting treatment in a given year are assumed to have an equal probability of entering in each month, thus requiring 6.5 months of treatment dispensed on average in that year.

5.2.2. A normative approach to forecasting demand for antiretroviral drugs

The normative estimates come from a patient-based month-to-month discrete event simulation model developed by the Clinton Foundation HIV/AIDS Initiative.

This approach assumes that countries implement their standard guidelines and protocols to assign first-line and second-line regimens for adults and children. In cases in which countries have either changed or planned a future revision of their guidelines, time-varying dosing algorithms were derived to reflect the version of the guidelines in place at each point in time, and thus account for changes to the prescribing practice in each country.

Data from WHO and UNAIDS, published literature and country treatment programmes were used to create epidemiological profiles for each country, and their national antiretroviral therapy protocols were used to create a protocol profile and dosing algorithm. The normative model was created for 21 high-treatment volume low- and middle-income countries.

For each country, starting in 2001 the epidemiological profile and national protocol data were combined with the scale-up projection and used to simulate the natural history of people receiving treatment. The model created and updated the distribution of a collection of factors that determine how the treatment guidelines are applied in a population. These include body weight, severe anaemia, severe peripheral neuropathy, pregnancy, concomitant tuberculosis treatment, drug toxicity and diagnosed treatment failure. Based on the national guidelines in the country, the model then applied an algorithm to determine the antiretroviral drugs and volumes that correspond to the joint distribution of these factors. Combined product volumes were extrapolated to obtain regional and global estimates.

6. RESULTS

The following section presents the main results: it provides the estimated number of people receiving treatment and the demand forecast for the active pharmaceutical ingredients for antiretroviral drugs. It also describes the sample countries used in both approaches and summarizes WHO's survey results.

6.1. Description of the sample countries

Table 1 shows the countries used as the basis for estimating global demand for antiretroviral drugs. The normative approach used 21 countries that represented 83% of the total number of people receiving antiretroviral therapy in low- and middle-income countries as of December 2006. The countries with the highest volume in this sample were: South Africa (16.1% of the total), Brazil (8.9%) and Kenya (6.2%). The sample for the empirical approach included 23 countries representing 54% of the total volume in low- and middle-income countries. In the empirical sample, the largest contributors were Kenya (6.2%), Thailand (5.5%) and Uganda (4.7%).

The countries represented in both approaches were: Cameroon, Côte d'Ivoire, Ethiopia, India, Kenya, Malawi, Mozambique, Namibia, Nigeria, Rwanda, Thailand, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

Table 1. Sample countries for the normative and empirical models for global demand for antiretroviral drugs in low- and middle-income countries

Country	% of the estimated total volume of antiretroviral drugs in low- and middle-income countries (December 2006)	Ranking by % of volume	Normative sample	Empirical sample
Argentina	1.6	17	√	
Botswana	4.2	7	√	
Brazil	8.9	2	√	
Burkina Faso	0.6	26		√
Burundi	0.4	28		√
Cambodia	1.0	22		√
Cameroon	1.3	21	√	√
China	1.5	20	√	
Côte d'Ivoire	1.5	19	√	√
Ethiopia	2.6	11	√	√
Guatemala	0.3	29		√
Haiti	0.4	27		√
India	4.7	6	√	√
Kenya	6.2	3	√	√
Lesotho	0.9	23		√
Malawi	4.0	8	√	√
Mexico	1.7	15	√	
Mozambique	2.0	14	√	√
Namibia	1.6	18	√	√
Nigeria	4.0	9	√	√
Russian Federation	0.8	25		√
Rwanda	1.7	16	√	√
South Africa	16.1	1	√	
Swaziland	0.9	24		√
Thailand	5.6	13	√	√
Uganda	4.8	4	√	√
United Republic of Tanzania	2.5	5	√	√
Zambia	4.0	10	√	√
Zimbabwe	2.6	12	√	√
Total (% of the global total)	**88.5**		**83.2**	**54.4**
Total (number of countries)	**29**		**21**	**23**

6.2. Number of people receiving treatment

Table 2 shows the number of people forecast to receive treatment in 2007 and 2008. The number of people receiving treatment in low- and middle-income countries was 2.01 million in December 2006 and is forecast to increase to 2.69 million by the end of 2007, and 3.38 million by the end of 2008. Figure 2 shows the historical trend in the number of people treated and the linear extension corresponding to the current two-year forecast.

Table 2. Number of people (in millions) in low- and middle-income countries receiving antiretroviral therapy by WHO region, reported for December 2006 and projected for December 2007 and December 2008

WHO region	Reported in December 2006	Estimated for December 2007	Estimated for December 2008
African Region	1.34	1.85	2.39
Region of the Americas	0.36	0.37	0.39
European Region and Eastern Mediterranean Region	0.03	0.08	0.12
South-East Asia Region	0.22	0.30	0.37
Western Pacific Region	0.06	0.09	0.11
Total	**2.01**	**2.69**	**3.38**

Fig. 2. Actual and predicted number of people in low- and middle-income countries receiving antiretroviral therapy based on the scale-up observed during 2006

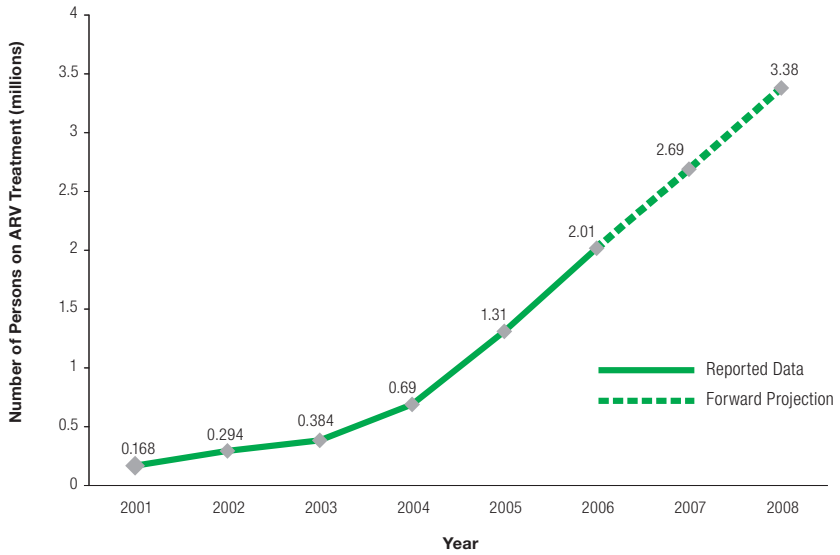


Table 3 shows that between December 2007 and December 2008 the number of people on second-line therapy at the global level is estimated to increase from about 120 000 in December 2007 to more than 180 000 in December 2008. This is respectively 4.6% and 5.4% of the total number of people on antiretroviral therapy.

Table 3. Estimated total number of people in low- and middle-income countries receiving antiretroviral therapy by type (in millions and percentage of total), December 2007 and December 2008

	December 2007	December 2008
Number of patients on first-line therapy	2.57	3.20
(% of total)	95.4	94.6
Number of patients on second-line therapy	0.12	0.18
(% of total)	4.6	5.4
Total	**2.69**	**3.38**

6.3. Results of a WHO survey on the use of antiretroviral therapy in 2006

The WHO survey is a key input to the empirical approach in estimating demand for antiretroviral drug products. The following subsection summarizes the results of that survey.

Of the 24 questionnaires sent, 23 (96%) were returned. The 23 countries that responded included Burkina Faso, Burundi, Cambodia, Cameroon, Côte d'Ivoire, Ethiopia, Guatemala, Haiti, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, Russian Federation, Rwanda, Swaziland, Thailand, Uganda, United Republic of Tanzania, Zambia and Zimbabwe. According to the June 2006 report[12], an estimated 851 000 people were receiving antiretroviral therapy in these 23 countries, representing 54% of the total number in low- and middle-income countries at that point in time. In the 23 countries, 92% of the people on antiretroviral therapy were adults and 8% were children.

The vast majority of adults, 96%, were reported to be on first-line regimens. Compliance was very high for this group, with information on the specific regimens used available for 97%. The countries reported that 95% of all adults on first-line regimens were using regimens consistent with the preferred first-line approach, including: stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP) (61%); zidovudine (ZDV) + lamivudine + nevirapine (16%); zidovudine + lamivudine + efavirenz (EFV) (9%); and stavudine + lamivudine + efavirenz (8%) (Fig. 3).

Less than 1% of this group was reported to be taking either alternative first-line regimens, including the triple nucleoside combinations of zidovudine + lamivudine + abacavir (ABC) and stavudine + lamivudine + abacavir, or regimens not considered or not recommended by WHO. Reassuringly, only one country reported use of first-line therapy containing stavudine + didanosine (ddI), a regimen that WHO explicitly does not recommend because of overlapping toxicity between these two nucleoside reverse-transcriptase inhibitors.

Countries reported second-line regimens less consistently than first-line regimens, with greater diversity among regimens, lower rates of adherence to WHO recommendations and lower reporting rates.

In the study cohort, 4% of adults were reported to be on second-line regimens, with information on specific regimens used only reported for 76%. Despite the underreporting, 61% of the entire group was reported to be on regimens consistent with the preferred and alternative second-line approaches recommended by WHO in the 2006 guidelines. However, only 25% were following the preferred approach, including: abacavir + didanosine + lopinavir with a ritonavir boost (LPV/r) (24%) and tenofovir (TDF) + didanosine + lopinavir with a ritonavir boost (1%) (Fig. 3).

A total of 36% were following regimens consistent with the alternative second-line approach: including didanosine + lamivudine + lopinavir with a ritonavir boost (19%); didanosine + lamivudine + indinavir with a ritonavir boost (IDV/r) (9%); zidovudine + didanosine + lopinavir with a ritonavir boost (4%); tenofovir + didanosine + nelfinavir (NFV) (1%); zidovudine + didanosine + nelfinavir (1%); and abacavir + didanosine + nelfinavir (1%). Other second-line regimens consistent with the WHO alternative second-line approach were listed by less than 1% in this cohort; these included tenofovir + lamivudine + lopinavir with a ritonavir boost, abacavir + didanosine + indinavir with a ritonavir boost, didanosine + lamivudine + saquinavir with a ritonavir boost (SQV/r), tenofovir + didanosine + indinavir with a ritonavir boost and abacavir + zidovudine + nelfinavir.

In contrast, 4% were reported to be on regimens considered to be within the WHO first-line approaches, and 12% were on regimens not considered or not recommended in the 2006 guidelines (Fig. 4).

Fig. 3. **Use of first- and second-line antiretroviral therapy regimens among adults in 23 low- and middle-income countries**

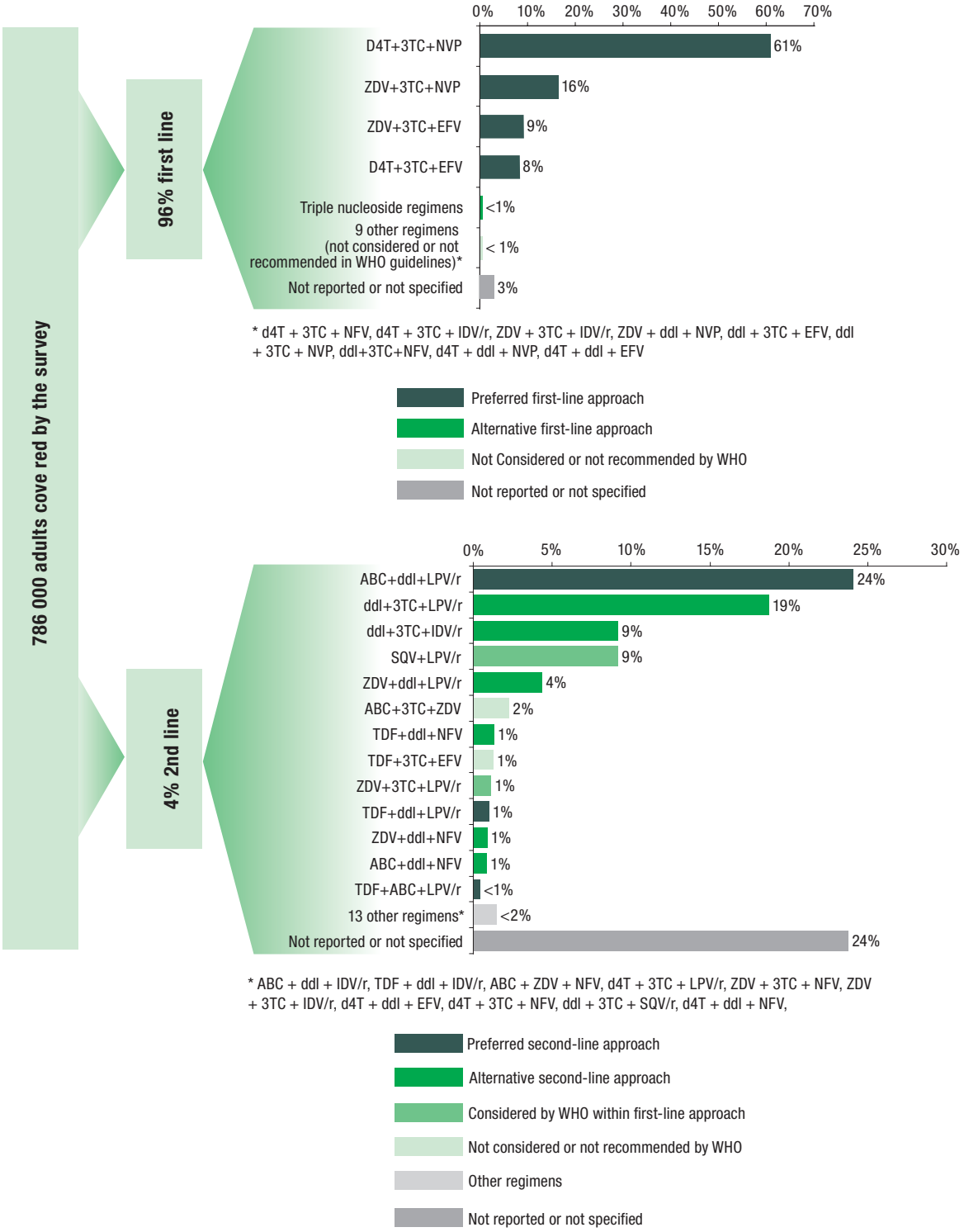
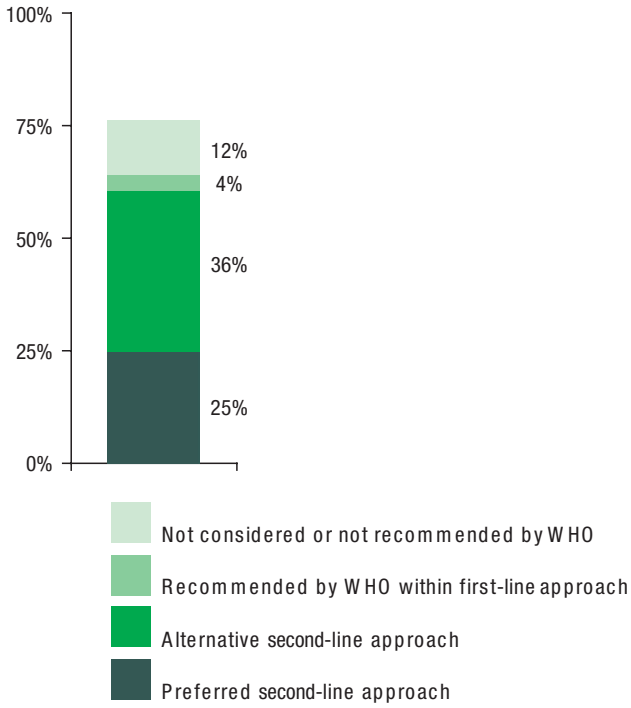


Fig. 4. Consistency of reported second-line antiretroviral therapy regimens among adults with 2006 WHO guidelines in 23 low- and middle-income countries



6.4. Demand for antiretroviral drugs

Table 4 shows the forecast quantities of API for antiretroviral products required in low- and middle-income countries, using both empirical and normative estimations. Table 5 shows similar data, with API volumes converted to adult person-years.

Using either approach, the largest volumes of active pharmaceutical ingredients required for 2007 and 2008 were predicted to be for lamivudine, zidovudine, efavirenz and nevirapine. The tables show that the demand will grow for most antiretroviral drugs between 2007 and 2008. The largest relative increases are for nelfinavir and tenofovir in the empirical estimates and for tenofovir, and emtracitabine in the normative estimates. These observations reflect the fact that an increasing number of countries are adopting tenofovir-based regimens in their national treatment guidelines for first-line and/or second-line therapy. As most recent adaptations in national guidelines achieved during the year 2007 in some countries could not be incorporated in the normative model, the estimates of volumes for tenofovir may even be lower that what can be expected for 2008.

There were important differences between the two approaches. As expected, the greatest relative differences were among drugs that reflect the changes in country guidelines. Estimates in the normative model suggest higher volumes of tenofovir, zidovudine and abacavir and lower volumes of saquinavir, nelfinavir and ritonavir, relative to the empirical model. The relatively lower projected volumes of tenofovir and emtricitabine in the empirical model are related to the fact that tenofovir and emtricitabine were rarely used in countries in 2006.

In the empirical model, the total estimated volumes of protease inhibitors for 2007 and 2008 are higher than the total number patients projected to be on a second-line regimen because of the reported data of current use of a combination of saquinavir and lopinavir/ritonavir. Countries are moving away from saquinavir, indinavir and nelfinavir in favor of more attractive protease inhibitor options—mostly lopinavir/ritonavir to date, but likely also towards atazanavir/ritonavir in the near future—thus making the empirical model's estimates of volumes for indinavir, nelfinavir and saquinavir too high.

The lack of reported data related to the current use of atazanavir and emtricitabine in the 2006 survey did not allow for accurate estimates to be made for these products in the empirical model.

In 2008, the smallest relative differences between the two approaches were among nevirapine, lamivudine, stavudine and efavirenz.

Table 4. Volume of demand for APIs for antiretrovirals and differences by model (metric tonnes, raw and percentage difference between models)

	2007				2008			
	Normative	Empirical	raw diff.	% diff.	Normative	Empirical	raw diff.	% diff.
D4T	39.3	35.0	4.3	12.3	49.7	46.0	3.7	8.0
3TC	249.6	240.1	9.4	3.9	316.4	315.6	0.7	0.2
NVP	255.3	246.4	8.9	3.6	326.0	324.8	1.1	0.3
AZT	173.0	125.6	47.4	37.7	221.1	165.2	55.9	33.8
EFV	108.4	103.7	4.6	4.5	140.3	134.7	5.6	4.1
ddI	10.3	8.3	1.9	23.0	13.9	11.6	2.2	19.1
TDF	4.7	1.3	3.4	254.7	10.2	2.0	8.2	403.9
ABC	14.4	10.8	3.6	33.0	21.0	15.1	5.9	39.0
IDV	n/a	9.8	n/a	n/a	n/a	13.6	n/a	n/a
RTV	6.7	8.7	-2.0	-22.9	10.3	12.0	-1.7	-14.3
SQV	0.01	10.5	-10.5	-99.9	0.01	14.1	-14.1	-99.9
LPV	25.4	30.1	-4.7	-15.5	39.4	41.4	-2.0	-4.8
NFV	0.1	6.2	-6.1	-99.0	0.1	9.0	-8.9	-99.3
ATV	1.2	n/a	n/a	n/a	1.4	n/a	n/a	n/a
FTC	0.8	n/a	n/a	n/a	3.8	n/a	n/a	n/a

Table 5. **Volume of demand for APIs for antiretrovirals and differences by model (adult person-years, raw and percentage difference between models)**

	2007				2008			
	Normative	Empirical	raw diff.	% diff.	Normative	Empirical	raw diff.	% diff.
D4T	1,796,118	1,598,174	197,945	12.4%	2,270,069	2,100,457	169,612	8.1%
3TC	2,279,106	2,192,694	86,411	3.9%	2,889,079	2,882,192	6,888	0.2%
NVP	1,748,674	1,687,671	61,002	3.6%	2,232,663	2,224,658	8,005	0.4%
AZT	789,882	573,516	216,366	37.7%	1,009,694	754,338	255,356	33.9%
EFV	494,796	473,516	21,280	4.5%	640,461	615,068	25,393	4.1%
DDI	93,733	75,799	17,934	23.7%	126,652	105,936	20,715	19.6%
TDF	43,212	11,872	31,340	264.0%	93,154	18,265	74,889	410.0%
ABC	65,687	49,315	16,372	33.2%	96,045	68,950	27,095	39.3%
IDV	0	16,781	-16,781	-100.0%	0	23,288	-23,288	-100.0%
RTV	92,359	119,178	-26,819	-22.5%	141,401	164,384	-22,982	-14.0%
SQV	17	14,384	-14,367	-99.9%	10	19,315	-19,305	-99.9%
LPV	86,998	103,082	-16,084	-15.6%	134,971	141,781	-6,810	-4.8%
NFV	65	6,795	-6,729	-99.0%	68	9,863	-9,795	-99.3%
ATV	10,688	n/a	n/a	n/a	12,840	n/a	n/a	n/a
FTC	10,510	n/a	n/a	n/a	52,299	n/a	n/a	n/a

7. DISCUSSION

The two approaches used for forecasting demand for antiretroviral drugs present alternative scenarios of development over two years of consumption of antiretroviral drugs (ARVs) . A fundamental difference between the models is that the empirical model uses country data collected by WHO on the distribution and up-take of first- and second-line regimens in 2006, whereas the normative approach uses simulated natural histories of people receiving treatment based on national protocols.

The empirical model extends 2006 consumption patterns into the future, assuming the relative share of each regimen remains constant within first and second line regimen groups. This assumption assumes the overall demand increases and the distribution among first and second-line regimen changes. The advantage of this approach is that it is closely aligned with recent treatment patterns. The disadvantage is that it fits a static framework to a dynamic reality.

The normative model differs somewhat because it relies on simulation. Its advantage is that it reflects the accumulating effects of such events as single-drug toxicity and migration to second-line regimens, and takes into account past and planned revisions in national protocols. The disadvantage is that it assumes that countries would strictly apply national guidelines while barriers to ARV access and delivery may influence current and future practice.

The differences in the empirical and normative forecasts can be interpreted to represent the basic dichotomy between “what is happening” and “what should be happening” according to the countries’ protocols. The empirical model forecasts a continuation of current practice as reported in the WHO survey. The normative model projects what demand would be if guidelines were being (or could potentially be) followed. It is reasonable to expect that countries will be bringing practice more in line with their own guidelines as barriers to implementing guidelines are addressed.

The main barriers include insufficient product availability, high cost, lack of WHO prequalified generic options, and internal limitations regarding national quantification, importing, registration, tracking and distributing drug stocks. Depending on the rate at which countries bring prescribing ARVs in line with their national guidelines over the next two years, the actual consumption of individual ARVs may be closer to either model.

The raw differences expressed as the normative demand minus the empirical demand, as shown in Table 4, also allow the results to be interpreted as a measure of desired change to the extent that the national guidelines represent countries’ preferred usage patterns. If they are interpreted in such a manner, a positive difference indicates a need or desire for more of a specific type of antiretroviral drug, whereas a negative difference would mean that countries may be expecting to use less of a particular product.

The normative results suggest that between 2007 and 2008, about 3–4 times more tenofovir, and about 30% more zidovudine and abacavir would be required than according to the empirical model. This is consistent with the current trend to phase out thymidine analogs such as stavudine due to its high cumulative rates of toxicity, and the recognition that reasonably-priced non-thymidine drugs such as tenofovir can potentially provide an alternative with an improved efficacy and safety profile. On the other hand, the negative differences suggest that saquinavir and nelfinavir are currently being used about twice as much as desired. This finding is also consistent with a growing preference for new boosted protease inhibitors, including lopinavir and atazanavir.

As previously discussed, it is important to note that the empirical model projects a continuation of current practices, and the normative model may not reflect changes in national guidelines that are either close to being finalized, or that were finalized too recently to be incorporated into this forecast. This means that projected demand for 2008 in the two approaches is less reliable for drugs that are starting to encounter rapid upward (eg, tenofovir, atazanavir) or downward (eg, indinavir, nelfinavir) trends in demand due to changes in clinical preferences, product pricing and availability, than for drugs with relatively stable demand increases, such as lamivudine.

For instance, several key countries have adopted or are currently considering adopting tenofovir in their first-line protocols. These countries include Botswana, Ethiopia, Lesotho, Namibia; Nigeria, and Zambia, with patients expected to be put on tenofovir-based regimens during 2008. Given the large number of patients starting first-line treatment in these countries, demand for tenofovir will increase quite rapidly in next few years. Monitoring of up-take of such products like tenofovir with industry reporting and/or the Global Price Reporting Mechanism[10] would contribute to tracking increases in use over time.

Both approaches implicitly assumed a representative sample of all low- and middle-income countries and that the countries not included in the sample are similar to those in the sample. The assumptions simplified a complex set of unknown parameters for the purpose of making predictions and creating models that can help interpret reality. Some of the differences between the two models may reflect the fact that the models included different countries as a base. The normative model included 21 countries that represent 83% of the treatment volume among low- and medium-income countries, and the empirical model included 23 countries that represent 54% of the treatment volume among low- and middle-income countries.

In both cases, aggregate data were extrapolated to reflect the volume in countries not explicitly included in the model. To the extent that countries not explicitly included in the model differ from those included, this extrapolation may lead to less accurate estimates. Countries that are explicitly modelled in one model, but assigned the average distribution of products in the other may contribute to differences between the two models as well. In the empirical approach, it is worth noting that underreporting of the use of second-line drug regimen in the survey may also contribute to less accurate estimates for these drugs.

The validity of these results rests heavily on the assumptions of no major changes in the increase in funding and scale-up of HIV treatment programmes and a steady growth of antiretroviral demand. This seems to be a reasonable assumption because demand has grown linearly since 2003, as a result of the WHO/UNAIDS “3 by 5” Initiative, the efforts of the United States President’s Emergency Plan for AIDS Relief, the Global Fund to Fight AIDS, Tuberculosis and Malaria and other factors. Dramatic changes in treatment scale-up or product preference due to changes in funding, new product availability, guidelines changes in high-volume countries or technological breakthroughs are certainly possible, but they are more likely to occur gradually and not instantaneously.

The lack of data is a limitation of both approaches presented in this publication. They rely on data that come from published studies about mortality on and off treatment, migration from first-line to second-line therapy, and other relevant epidemiological parameters that may not reflect the situation in other countries or settings. Both approaches are an attempt to estimate volumes in the absence of better country-level data, and both can be improved if suppliers and countries themselves provide more data.

Finally, a variety of factors that have not been explicitly modelled due to lack of data influence the antiretroviral drug market. Certain countries with large treatment volumes, such as Nigeria and South Africa, will be instrumental in driving demand. Other factors to consider include changes in funding, prices, generic availability, new formulations including fixed-dose combinations and formulations for children, as well as the registration status of products and the capacity of health systems to deliver. Changes occurring among these factors may lead to «market shifts» among ARVs during the two-year forecasting period, while the forecasting methods used here simply assume that past trends in all of these factors will continue in the short term. These and other possible changes may be modelled more explicitly in the future as more data become available.

In March 2007, WHO's AIDS Medicines and Diagnostics Service carried out a survey on the production capacity of the companies that produce API for antiretroviral medicines. Eleven companies responded. Estimates of production were provided for 12 of the 15 different API used in antiretroviral therapy that are included in the demand forecasts, data missing for tenofovir, emtricitabine and atazanavir.

The comparison of demand forecast and reported capacity shows that the reported capacity is adequate to address the volumes estimated for 2007 and 2008 demand except for lopinavir. (Annex 2).

8. CONCLUSION

The forecast presented in this publication is based on an assumed scale-up of antiretroviral therapy in low- and middle-income countries that will reach 3.38 million people by the end of 2008. This number is based on a method that essentially extends a straight line forward from the numbers reported since December 2005 in each country. Some countries may increase their rate of scale-up relative to 2006; some may decrease their scale-up rate; and still others may continue to scale up at the same rate. Without data that delineates these three groups, the researchers assumed that all countries will continue to scale up at the same rate until coverage reaches 100%. As a result, regional and global aggregates are likely to be more accurate than the projections for any one country.

The predicted expansion of HIV treatment in these models is well below the goals of the international HIV treatment community. Interpreting these numbers as a statement about what should be accomplished or even what will be accomplished in 2007–2008 is not in the context of this analysis. Rather, these estimates indicate what is likely to be accomplished in the absence of meaningful changes in the conditions driving the scale-up of treatment. Future changes in funding availability will not affect the forecast over the next 12–24 months as a result of delays in implementation and mobilization of funds. The effect of current fundraising efforts cannot be expected to influence the forecast until after that time.

This attempt is among the first to explicitly quantify current demand for active pharmaceutical ingredients for antiretroviral drugs in low- and middle-income countries, and to predict demand for the future. Earlier results from this work were presented elsewhere[13]. This forecast will be updated regularly as new data become available including new data on the numbers of people on treatment and those who need treatment; disaggregation by age and sex; estimates of survival among people on antiretroviral therapy and those who are not; changes in distribution of regimens, switching rates and product availability and pricing; and updates in national guidelines.

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Annex 1. Daily doses for antiretroviral drugs based on WHO recommendations

First-line treatment	
	Dose (mg per day per person)
stavudine	60
zidovudine	600
lamivudine	300
nevirapine	400
efavirenz	600

Second-line treatment	
abacavir	600
didanosine	300
indinavir	1600
lopinavir	800
tenofovir	300
emtricitabine	200
nelfinavir	2500
ritonavir	200
saquinavir	2000
atazanavir	300

Annex 2. Reported manufacturing capacity for active pharmaceutical ingredients (metric tonnes)

Class	Active pharmaceutical ingredient	Available production capacity
Nucleoside reverse transcriptase inhibitor	**zidovudine**	498
Nucleoside reverse transcriptase inhibitor	**lamivudine**	550
Nucleoside reverse transcriptase inhibitor	**didanosine**	80
Nucleoside reverse transcriptase inhibitor	**abacavir**	46
Nucleoside reverse transcriptase inhibitor	**tenofovir**	not available
Nucleoside reverse transcriptase inhibitor	**stavudine**	252
Non-nucleoside reverse transcriptase inhibitor	**nevirapine**	475
Non-nucleoside reverse transcriptase inhibitor	**efavirenz**	193
Protease inhibitor	**nelfinavir**	231
Protease inhibitor	**indinavir**	104
Protease inhibitor	**ritonavir**	29
Protease inhibitor	**lopinavir**	23
Protease inhibitor	**saquinavir**	19

Source: *Sources and prices of active pharmaceutical ingredients.* Geneva, World Health Organization, 2007 (http://ftp.who.int/htm/AMDS/sourcespricesAPI.pdf, accessed 30 May 2007).

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