Use of Generic Antiretroviral Agents and Cost Savings in PEPFAR Treatment Programs

Context One of the biggest hurdles to the rapid scale-up of antiretroviral therapy in the developing world was the price of antiretroviral drugs (ARVs). Modification of an existing US Food and Drug Administration (FDA) process to expedite review and approval of generic ARVs quickly resulted in a large number of FDA–tentatively approved ARVs available for use by the US President’s Emergency Plan for AIDS Relief (PEPFAR).

Objective To evaluate the uptake of generic ARVs among PEPFAR-supported programs in Guyana, Haiti, Vietnam, and 13 countries in Africa, and changes over time in ARV use and costs.

Design, Setting, and Participants An annual survey from 2005 to 2008 of ARVs purchased in 16 countries by PEPFAR implementing and procurement partners (organizations using PEPFAR funding to purchase ARVs).

Main Outcome Measures Drug expenditures, ARV types and volumes (assessed per pack, a 1-month supply), proportion of generic procurement across years and countries, and cost savings from generic procurement.

Results ARV expenditures increased from $116.8 million (2005) to $202.2 million (2008); and procurement increased from 6.2 million to 22.1 million monthly packs. The proportion spent on generic ARVs increased from 9.17% (95% confidence interval [CI], 9.17%-9.18%) in 2005 to 76.41% (95% CI, 76.41%-76.42%) in 2008 (P < .001), and the proportion of generic packs procured increased from 14.8% (95% CI, 14.79%-14.84%) in 2005 to 89.33% (95% CI, 89.32%-89.34%) in 2008 (P < .001). In 2008, there were 8 PEPFAR programs that procured at least 90.0% of ARV packs in generic form; South Africa had the lowest generic procurement (24.7% [95% CI, 24.6%-24.8%]). Procurement of generic fixed-dose combinations increased from 33.3% (95% CI, 33.24%-33.43%) in 2005 to 42.73% (95% CI, 42.71%-42.75%) in 2008. Estimated yearly savings generated through generic ARV use were $8,108,444 in 2005, $24,940,014 in 2006, $75,645,816 in 2007, and $214,648,982 in 2008, a total estimated savings of $323,343,256.

Conclusion Among PEPFAR-supported programs in 16 countries, availability of generic ARVs was associated with increased ARV procurement and substantial estimated cost savings.

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issue approval for use in PEPFAR programs if the ARVs met FDA standards of safety, efficacy, and manufacturing quality. Although the World Health Organization (WHO) had also established a drug prequalification process, the US government made a policy decision to use an FDA process given the scope of the planned investment in HIV care and treatment and the desire to explicitly demonstrate that drugs supplied by PEPFAR would be of equal quality to those provided to US patients. To further accelerate the reliable procurement for these ARVs, PEPFAR also developed Supply Chain Management System (SCMS), an organization that currently facilitates approximately 50% of PEPFAR procurement of ARVs.

The nonprofit SCMS partnership includes a total of 13 member organizations including nonprofit organizations, African organizations, private sector corporations, and academic institutions, providing forecasting, procurement, distribution, and other services needed to ensure reliable availability of ARVs and other commodities to PEPFAR-funded programs. Other entities that purchase ARVs with PEPFAR funding include nongovernmental organizations based in the United States and developing countries, universities involved in program implementation, and developing country governments.

By 2008, the number of ARVs approved through the FDA tentative approval process had risen to 80, from 15 in 2005. Our objectives were to examine trends in the volume, costs, and types of ARVs purchased with PEPFAR funds since the introduction of the FDA tentative approval process, and to estimate the cost savings achieved through the use of generic drugs from 2005 through 2008.

METHODS

Survey and Data Collection

The survey was conducted annually for the US government fiscal years (FY) 2005 to 2008 (beginning October 1 of the preceding year and ending September 30 of the calendar year) to fulfill a reporting requirement to the US Congress on the use and cost of ARVs funded by PEPFAR for use in 16 countries (Botswana, Cote d’Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, Zambia, and Zimbabwe). Some 2005 and 2007 data were included in a prior analysis of PEPFAR costs presented in a report to Congress.

For the updated more comprehensive analyses in this study, proprietary drug costs used for assessment of cost savings were selected from annual published reports from Médecins Sans Frontières, an international medical and humanitarian aid organization, and country-specific costs of proprietary ARVs were systematically established and used to create a weighted average proprietary drug price for each ARV, based on the volume of generic drug purchased in that country.

To collect consistent information on PEPFAR-funded ARV procurement, all US- and field-based procurement partners (organizations using PEPFAR funding to purchase ARVs) were sent a survey from the Office of the US Global AIDS Coordinator, the coordinating office for PEPFAR at the US Department of State. Data for FY 2005 were collected in April 2006, FY 2006 data were collected in October 2006, FY 2007 data were collected in September and October 2007, and FY 2008 data were collected in December 2008 and January 2009. Years refer to US government fiscal years, unless accompanied by a month or otherwise stated. This was a routine, congressionally mandated survey in which data (drug costs and volumes) were collected from procurement systems and not associated with specific individuals, so institutional review board approval was not required.

The annual survey consisted of an Excel spreadsheet form, with populated drop-down lists for each field. Data fields included purchaser, recipient organization, country, product, dosage strength, generic/proprietary, registered in country/waived, dosage packaging unit, quantity (of packaging units), packaging unit price in US dollars, total price in US dollars, international chamber of commerce terms (INCO-TERMS 2000s), vendor (if not manufacturer), manufacturer, country of origin, and date delivered. Data were assembled into a database format and cleaned. Inconsistencies and missing data were resolved through queries to survey respondents as necessary. Because of follow-up communication with respondents, there were no missing data among the core set of variables used in the analyses for this study including country, ARV product, dosage strength, generic status, quantity, unit price, and delivery data. Thus, the denominator data reported in the tables and analyses are consistent throughout, and complete data were available for all variables analyzed in this study.

Data Analysis

Analysis was conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). PEPFAR spending on generic and proprietary FDA tentatively and fully approved ARVs was summed for each year, and the proportion (with 95% binomial confidence intervals [CIs] calculated by the Agresti-Coull method) of spending for generic ARVs was calculated and compared between years using \( \chi^2 \) for trend. The number of monthly packs of generic and proprietary ARVs was summed for each country by year, and the proportion (with 95% CIs) of packs that were generic was calculated for each country and overall, and the overall proportions were compared between years using \( \chi^2 \) for trend. The term pack refers to a 1-month supply of ARVs.

To determine trends within ARV classes, the total number of packs of selected classes and ARVs were calculated for each year including (1) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) stavu-
dine, zidovudine, and tenofovir, the 3 NRTIs most commonly recommended for first-line use in country guidelines (lamivudine was not included in this comparative analysis because it is typically used alongside these 3 anchoring ARVs); (2) nonnucleoside reverse transcriptase inhibitors (NNRTIs) (limited to nevirapine and efavirenz, the 2 NNRTIs most commonly recommended in national guidelines); (3) fixed-dose combinations (FDCs), overall and limited to generic purchases; and (4) pediatric ARVs. For the NRTIs and NNRTIs, the proportion and 95% CIs of each drug compared with the total NRTI or NNRTI purchases was calculated for each year. The proportion of FDCs was calculated as the volume of FDCs divided by the volume of total ARVs for each year, and the proportion of pediatric ARVs was calculated as the volume of pediatric ARVs divided by the volume of total ARVs each year.

Mean and 95% CIs of the price per pack (including purchases of both generic and proprietary brands) were calculated for the 10 ARVs with the highest cumulative pack volumes from 2005 to 2008. Changes in mean price per pack over time were assessed for statistical significance using the analysis of variance test. For each type of ARV purchased in generic form, the estimated cost savings attributable to generic procurement were calculated (generic volume × estimated branded price) – (generic volume × mean generic cost). The mean generic cost for each ARV was calculated by dividing the total expenditure for each generic ARV by the total volume for each generic drug.

Proprietary drug prices were obtained from the Médecins Sans Frontières price list for each year.7 Proprietary drug prices are often specific to the countries in which purchases are made and are based on incomes specific to these respective countries (tiered pricing). This proprietary drug price was multiplied by the volume of the correlating generic drugs that PEPFAR purchased in that country that year, thereby establishing the theoretical expenditure had the same volume of generic drugs been purchased in proprietary drug form. The sum of these expenditures (total expenditure) was divided by the total generic volume of each ARV, yielding the estimated mean proprietary drug price, weighted for differences in proprietary drug price and volume in each country.

In each analysis, only observations with complete data for the outcome and descriptor were used, and all denominators have been reported. A cutoff P value of less than .05 was used for assessing statistical significance. All statistical tests were 2-sided.

RESULTS

Completed surveys were returned by 22 of 40 (55.0%) PEPFAR procurement partners for ARVs in 2005 (these surveys accounted for about 85% of estimated deliveries in 2005), 25 of 25 in 2006, 23 of 24 partners (95.8%) in 2007, and 32 of 32 partners in 2008. The number of PEPFAR country programs with partners purchasing FDA tentatively approved generic drugs with PEPFAR funding increased from 9 in 2005 to all 16 in the survey by 2008.

Reported annual spending on ARVs increased from $116 830 657 in 2005 to $202 241 822 in 2008, and the number of monthly packs of ARVs delivered increased from 6 186 143 to 22 129 692 over the same period. The mean proportion of funds spent on generic ARVs increased significantly each year from 9.17% (95% CI, 9.17%-9.18%) to 76.41% (95% CI, 76.41%-76.42%) by 2008 (P < .001; TABLE 1). By volume, 89.33% (95% CI, 89.32%-89.34%) of monthly packs procured were generic formulations by 2008, increasing from 14.8% (95% CI, 14.79%-14.84%) in 2005 (P < .001).

Eight PEPFAR programs procured more than 90% of their ARVs in generic form by 2008, with deliveries in Ethiopia, Haiti, Namibia, Rwanda, Tanzania, and Zimbabwe being greater than 99% generic (TABLE 2). PEPFAR programs procuring the lowest proportion of their PEPFAR-funded ARVs as generic drugs in 2008 included South Africa (24.7%; 95% CI, 24.6%-24.7%), and Uganda (81.1%; 95% CI, 81.0%-81.1%).

Procurement of dual and triple FDCs of ARVs increased from 943 117

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packs (15.25%; 95% CI, 15.22%-15.27%) in 2005 to 9 316 601 packs (42.1%; 95% CI, 42.08%-42.13%) in 2008. Generic FDCs accounted for 33.3% (95% CI, 33.24%-33.43%) of all generic ARV purchases in 2005 and increased to 42.73% (95% CI, 42.71%-42.75%) in 2008. The procurement of second-line drugs increased in volume from 188 464 to 5 123 411 packs, although it decreased from 3.05% (95% CI, 3.03%-3.06%) to 2.32% (95% CI, 2.31%-2.32%) as a proportion of overall purchases from 2005 to 2008. Procurement of pediatric drugs increased from 996 488 to 1 157 083 monthly packs, yet decreased as a proportion of overall purchases from 16.1% (95% CI, 16.08%-16.14%) in 2005 to 5.23% (95% CI, 5.22%-5.24%) in 2008.

Stavudine procurement increased as a proportion of the total volume of the 3 NRTIs commonly used to anchor first-line regimens ( stavudine, zidovudine, and tenofovir), whereas the proportions of both zidovudine and tenofovir decreased despite increasing numbers of packs procured (Figure 1). Nevirapine procurement increased as a proportion of total NNRTIs (nevirapine and efavirenz) procurement, from 50.5% (95% CI, 50.40%-50.53%) in 2005 to 67.95% (95% CI, 67.93%-67.98%) in 2008 (Figure 1).

The mean PEPFAR purchase price per pack for each of the 10 highest volume drugs (including both proprietary and generic ARVs) to demonstrate the overall mean PEPFAR price for each drug) decreased significantly from 2005 to 2008.
(P < .001), with a mean overall decline of 41.8% from 2005 to 2008 (FIGURE 2). The greatest percentage declines in per-pack prices among these high-volume drugs were for nevirapine 200 mg (86.4%), efavirenz 600 mg (59.8%), and zidovudine/lamivudine 300/150 mg (45.1%). Estimated yearly savings generated through use of generic ARVs increased over the 4-year period from $8108444 in 2005 to $21468982 in 2008, a total savings of $323343256 over the 4-year period (eTable; available at http://www.jama.com). Those ARVs contributing the most to estimated cost savings were ones with high volumes of lower-cost generic procurement, including stavudine/lamivudine/nevirapine 30/150/200 mg (28.3% of overall savings, based on a volume of 4607561 packs), nevirapine 200 mg (28.3% of overall savings, based on a volume of 5698535 packs), zidovudine/lamivudine 300/150 mg (9.4% of overall savings, based on a volume of 5235777 packs), and efavirenz 600 mg (8.8% of overall savings, based on a volume of 5176861 packs).

In 2005, the mean PEPFAR price per pack for the 12 formulations purchased in generic form was 28.0% less expensive than the weighted mean proprietary drug price calculated from the Médecins Sans Frontières price list (eTable). The most substantial difference was for nevirapine 200 mg, which was $30.69 (or 84.7%) less expensive per pack in generic form. By 2008, the mean difference between the generic and proprietary drug prices for the same 12 formulations had increased to 50.0%. Although the proprietary drug price for nevirapine 200 mg decreased by $18.00 per pack, the generic price also decreased substantially, and there remained an 80.2% difference in per-pack price. In contrast, the generic price of stavudine 30 mg ($3.67) in 2005 was only 8.2% less than the proprietary drug price ($4.00). The proprietary drug price remained essentially unchanged by 2008 ($4.10), while the generic price had decreased to $1.69, nearly 60% less than the proprietary drug price.

**COMMENT**

By 2008, generic formulations accounted for almost 90% of the 22 million ARV packs purchased with PEPFAR funds, increasing from 14.8% in 2005, the first year after the FDA tentative approval process was established. PEPFAR programs in 8 countries procured more than 90% of their PEPFAR-funded ARVs in generic form by 2008, with the lowest procurement by the PEPFAR program being in South Africa. By 2008, more than 40% of PEPFAR purchases of ARVs were FDCs, 5.2% percent were pediatric formulations, and 2.3% were second-line drugs. Stavudine- and nevirapine-based regimens represented the majority of NRTI and NNRTIs purchased through 2008.

The mean PEPFAR purchase prices (including both generic and proprietary drug purchases) for the 10 highest-volume ARV formulations have declined an average of 41.8% since 2005, with declines of as much as 86.4% from 2005 prices. The estimated cumulative savings attributable to the use of PEPFAR-funded generic ARVs from 2005 to 2008 was more than $320 million. The savings attributable to generic ARV use has allowed PEPFAR country programs to shift funds from their ARV budget categories and invest further in other priority activities including training for health care workers, and expansion of direct service provision to patients.

From the onset of the program, there was controversy regarding the need for the FDA tentative approval process. Some argued that PEPFAR should accept WHO prequalification. Had prequalification been adopted, it is likely that generic formulations would have been purchased earlier, leading to greater cost savings. However, because far fewer drugs were purchased in the early years than in the later years of PEPFAR, the cost savings would not be proportional to the duration of drugs purchased. As noted previously, a policy decision was made that the same quality standards should be used for drug purchases in low-income and middle-income countries as for US residents with US tax dollars.

During the tentative approval process, US Government officials work closely with the WHO. As a result, 67 products have been automatically
exacerbate funding shortages and are potentially higher ARV prices than those available globally through other mechanisms that use the WHO system for both adult and pediatric patients. Although the current analysis does not include the costs associated with the regulatory process itself, these costs could be estimated and included in such a cost/benefit analysis. It should also be noted that the use of the tentative approval process allowed generic formulations of didanosine and zidovudine to become available in the United States in an expedited way.

Greater generic purchasing represents an important opportunity for several PEPFAR country programs identified as having lower rates of generic ARV drug use. The greatest opportunity costs (consequences of continued low uptake of generic procurement) are evident in South Africa. Generic procurement for both ARVs is being driven by patient and programmatic demands for simpler regimens, and this trend is expected to accelerate with numerous recent FDA tentative approvals of generic FDCs, including once-daily tenofovir/lamivudine/efavirenz.

The declining rates of pediatric and second-line ARVs are a consequence of agreements at the country program level between PEPFAR, national governments, and other funders, including the 3-year UNITAID grant for pediatric and second-line ARVs. This has allowed PEPFAR to focus on implementing service delivery capacity for pediatric care and treatment, while others have purchased many of the ARVs during this period. Increasing close collaboration between funders at the country level and headquarters level is expected to further enhance coordination and economic efficiency moving forward.

Several developments threaten additional reductions in the cost of ARVs in the short-to-medium term. As shown in Figure 1, PEPFAR’s mean costs of some high-volume drugs have begun to level off. Although some of the drugs may be nearing the limits of potential price reductions due to production and other limitations, others, like efavirenz, are expected to decline further given recent changes in process chemistry related to its synthesis. A more substantial threat to additional reductions in the overall mean ARV prices is the accelerating migration away from stavudine-based regimens, for which many inexpensive generic FDCs exist and for which prices have decreased substantially. The cost of tenofovir and lamivudine, 2 of the drugs increasingly recommended in international and country guidelines, remain at least 2 times that of stavu-
dine.\textsuperscript{11,12} Although tenofovir is considered cost effective in recent analysis, prices would need to decrease further in most settings to be cost neutral, even considering cost savings due to decreased toxicity management.\textsuperscript{13,14} The FDA has tentatively approved several generic forms of tenofovir paired with lamivudine or emtricitabine, and market competition between manufacturers is expected to exert further downward price pressure, particularly with increasing volumes as some countries move to higher CD4 cell count thresholds for treatment initiation. Changes in the ARV patent environment could affect access to ARVs in low-income settings, and it will be important for stakeholders to assess the potential value of mechanisms such as voluntary patent pools (in which originators voluntarily allow the use of their patents by any generic manufacturers making medicines for the developing world) to ensure continued availability of drugs for global HIV programs.\textsuperscript{15}

As treatment programs mature and treatment failure is increasingly recognized because of expanded access to diagnostics such as CD4 cell count and viral load, it is anticipated that demand for second-line regimens will also increase steadily (with possible spikes in demand with the introduction of transformative technology such as point-of-care CD4 cell count and viral load tests). Despite the FDA tentative approval of 2 generic lopinavir/ritonavir combinations, the cost of this combination has remained 4-fold to 5-fold higher than first-line drugs. Other options include generic atazanavir coformulated with heat-stable ritonavir, or newer agents that may ultimately have favorable clinical characteristics and production costs.

One limitation of this analysis is that the primary data were collected via survey and not a real-time data/capture system and are therefore subject to underreporting if surveys were not returned or not fully completed. However, with high survey return rates in 2006, 2007, and 2008, and surveys returned in 2005 that accounted for about 85% of planned procurement for the year, concerns about acquisition bias are lessened and we are confident that the results are representative of all PEPFAR spending. We have also not taken into account differences in INCO TERMS or tariffs (drug import taxes) that may apply to some of the drug costs, although it is unlikely that possible heterogeneity in these costs resulted in any systematic biases in interpretation of the data. Because of the high penalty for tariffs in US government development programs, including PEPFAR, they are unlikely to have been a factor in reported costs. This study focused its evaluation on high-volume adult formulations, and did not formally assess the impact of other funders such as the Global Fund or UNITAID on the variable cost by country, and also did not assess the cost of shipping. Additionally, this study focuses solely on ARV costs and does not incorporate the overall costs of providing ARV therapy, including infrastructure, laboratory support, human resources, and other service/delivery costs. When all of the costs of antiretroviral therapy are considered, the cost of ARVs generally contribute less than 50% of overall program costs and should be considered in that context.\textsuperscript{16}

PEPFAR is also working rapidly to identify and disseminate other programmatic, institutional, and clinical sources of efficiency gains including improved coordination with governments and other donors, improved national forecasting for ARVs and other commodities, strategic use of laboratories and new technologies, and increasing use of lower-cost commodities transport. These and other changes may also yield substantial savings and programmatic value over years to come and are the subject of ongoing monitoring, evaluation, and research within PEPFAR programs.

PEPFAR programs have been able to leverage the FDA tentative approval pathway to achieve greater access to generic ARVs in meeting the need for ARV therapy in high-burden countries, resulting in more than $300 million in savings over a 4-year period. Increased use of FDCs is further allowing PEPFAR programs to provide convenient and safe dosing to individuals served by PEPFAR-supported treatment programs. Additional low-cost equivalents of WHO-recommended first-line and second-line agents are needed in order to further expand and sustain treatment programs and maximize benefits for individuals with HIV.

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Philanthropy is commendable, but it must not cause the philanthropist to overlook the circumstances of economic injustice which make philanthropy necessary.

—Martin Luther King Jr (1929-1968)