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GLOBAL HIV/AIDS EPIDEMIC

Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited



G A O

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Highlights of [GAO-05-133](#), a report to congressional requesters

Why GAO Did This Study

In developing countries, only about 7 percent of people with HIV/AIDS receive treatment. In 2003, the Congress authorized the President's Emergency Plan for AIDS Relief, a 5-year, \$15 billion initiative under the Office of the U.S. Global AIDS Coordinator. The Emergency Plan focuses on 15 developing countries, with a goal of supporting treatment for 2 million people. Treatment regimens use multiple antiretroviral medications (ARV), which can be original or generic. Fixed-dose combinations (FDC) combine two or three ARVs into one pill.

Questions have been raised about whether the plan is providing ARVs preferred by the focus countries at reasonable prices. GAO compared the selection of ARVs provided under the plan with that provided under other major treatment initiatives, compared the prices of those selections, and determined what the Coordinator's Office is doing to expand the plan's selection of quality-assured lower-priced ARVs.

www.gao.gov/cgi-bin/getrpt?GAO-05-133.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Janet Heinrich at (202) 512-7119.

GLOBAL HIV/AIDS EPIDEMIC

Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited

What GAO Found

The Emergency Plan provides a smaller selection of recommended first-line ARVs than other major HIV/AIDS treatment initiatives in developing countries. The plan's selection includes six original ARV products—the only ARVs that have met the plan's quality assurance requirement—and does not include some FDCs that are preferred by most of the focus countries because they can simplify treatment. In contrast, the other initiatives provide a selection that in addition to the six original ARVs includes generic ARVs and more of the preferred FDCs.

The original ARVs provided under the plan are generally higher in price than the generic ARVs provided under the other initiatives. The differences in the prices, quoted to GAO during June and July 2004 by 13 manufacturers, ranged from \$11 less to \$328 more per person per year for original ARVs than for the lowest-priced corresponding generic ARVs provided under the other initiatives. At these prices, three of the four first-line regimens recommended by the World Health Organization could be built for less—from \$40 to \$368 less depending on the regimen—with the generic ARVs provided under the other initiatives than with the original ARVs provided under the plan. Such differences in price per person per year could translate into hundreds of millions of dollars of additional expense when considered on the scale of the plan's goal of treating 2 million people by the end of 2008.

The Coordinator's Office has worked to expand the selection of quality-assured ARVs—including FDCs and lower-priced generics—that it provides to the focus countries under the plan. The selection of ARVs available under the plan is primarily limited by its quality assurance requirement. The Coordinator's Office is working with manufacturers to take the steps necessary for more ARVs to meet this requirement. However, if generic ARVs meet the plan's quality assurance requirement, a statutory prohibition on the purchase of any medication manufactured outside the United States if the manufacture of that medication in the United States would be covered by a valid U.S. patent could become a barrier to expansion because all ARVs are currently under U.S. patents. Unless the patent holders for ARVs that have met the plan's quality requirement give permission or the Coordinator's Office exercises its authority to purchase these products notwithstanding the patent requirement, the selection of ARVs provided under the Emergency Plan may not expand rapidly enough to address the AIDS emergency.

In commenting on a draft of this report, the Department of State, the Department of Health and Human Services, and the U.S. Agency for International Development expressed concern about how GAO addressed ARV quality. In the draft report GAO described the quality assurance requirements used by the Emergency Plan and the other initiatives and stated that quality is the primary factor determining the selection of products provided under each. However, evaluating the quality assurance processes used by each initiative was outside the scope of GAO's work.

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Abbreviations

ARV	antiretroviral medication
CDC	Centers for Disease Control and Prevention
d4T	stavudine
EFV	efavirenz
FDA	Food and Drug Administration
FDC	fixed-dose combination
FHI	Family Health International
HHS	Department of Health and Human Services
HIV/AIDS	human immunodeficiency virus / acquired immune deficiency syndrome
JSI	John Snow Incorporated
MSH	Management Sciences for Health
NGO	nongovernmental organization
NVP	nevirapine
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization
ZDV	zidovudine
3TC	lamivudine

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United States Government Accountability Office
Washington, DC 20548

January 11, 2005

The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education, Labor,
and Pensions
United States Senate

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
House of Representatives

The Honorable John McCain
United States Senate

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 3 million people worldwide died from HIV/AIDS in 2003, and an estimated 38 million or more people are currently living with HIV/AIDS. Although there is no cure for the disease, there are treatments that can slow its progression. Yet in developing countries only about 7 percent of people living with HIV/AIDS receive treatment. Since the mid-1980s the United States has supported HIV/AIDS initiatives in developing countries directly and through its contributions to multinational organizations such as agencies within the United Nations (UN) system—including the World Bank and UNAIDS—and, more recently, the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund).¹ In 2004, the President's Emergency Plan for AIDS Relief (Emergency Plan)²—a 5-year initiative

¹The Global Fund was established in January 2002 as a mechanism for attracting and distributing resources to programs targeting AIDS, tuberculosis, and malaria in developing countries. It is an independent private foundation under Swiss law and is governed by an international board that includes recipient and donor countries, including the United States.

²As authorized by the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003 (U.S. Leadership Act). Pub. L. No. 108-25, § 301, 117 Stat. 711, 728 (adding section 104A to the Foreign Assistance Act of 1961, as amended, classified to 22 U.S.C. § 2151b-2) (for fiscal years 2004 through 2008, authorizes a total of \$15 billion to carry out the purpose of the U.S. Leadership Act to combat HIV/AIDS, tuberculosis, and malaria and authorizes such sums as may be necessary to prevent, treat, and monitor HIV/AIDS and carry out related activities).

under the Office of the U.S. Global AIDS Coordinator (the Coordinator's Office) within the Department of State³—added over \$9 billion of funding for HIV/AIDS treatment, care, and prevention in certain developing countries to its ongoing commitments, bringing the total U.S. commitment to addressing the worldwide HIV/AIDS emergency to \$15 billion through 2008.

The goals of the Emergency Plan, which focuses on 15 developing countries with high rates of HIV/AIDS,⁴ are to support treatment to 2 million people living with HIV/AIDS, prevent 7 million new HIV infections, and support care to 10 million people infected or affected by HIV/AIDS, including orphans, by the end of fiscal year 2008. The plan allocates more than half its budget to treatment, approximately \$4 billion of which is specifically for the purchase and distribution of antiretroviral medications (ARV)—the standard treatment for HIV/AIDS—in the focus countries. An HIV/AIDS treatment regimen includes multiple ARVs. ARVs are marketed as either original versions—all of which are currently under U.S. patents—or as copies of the originals, that is, generic versions.⁵ In addition, some manufacturers are marketing products that combine two or three ARVs into one pill—known as a fixed-dose combination (FDC).

The World Health Organization (WHO) recommends five specific ARVs that are used to build four regimens as the first line for treatment programs in countries in which health care resources are limited, such as the focus countries. WHO recommends one of the four regimens as the first choice for rapid implementation of large-scale treatment programs in these countries. Most focus countries have indicated a preference for FDCs, which can simplify treatment and facilitate adherence to the recommended treatment regimens, and for lower-priced generics in their national treatment strategies.

³The U.S. Leadership Act established the position of the Coordinator within the Office of the Secretary of the Department of State. § 102, 117 Stat. 721.

⁴The focus countries are Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia.

⁵The original version of an ARV is the first version brought to market. In this report, any copy of the original is considered a generic regardless of whether it fits any particular national regulatory authority's definition of generic.

While the Coordinator's Office has specified multiple objectives to achieve the Emergency Plan's goals, two are most relevant to the purchase of ARV products under the plan: first, coordination with the national treatment strategies of the focus countries, and, second, provision of ARV products of assured quality at the lowest possible price. Officials from organizations involved in treating HIV/AIDS in developing countries, such as Doctors Without Borders⁶ and Catholic Relief Services Consortium, have criticized the plan for not including the FDCs preferred by the focus countries in the selection of ARV products it provides. In addition, concerns have been raised about the plan's ability to provide ARV products at reasonable prices. You asked us to examine the provision of ARVs under the Emergency Plan, as compared with the provision of ARVs under the initiatives of major multinational organizations.

In this report, we determine (1) how the selection of ARV products provided under the Emergency Plan compares with the selection provided under the initiatives of the World Bank, the United Nations Children's Fund (UNICEF), and the Global Fund; (2) how the prices of the ARV products provided under the Emergency Plan compare with the prices of the ARV products provided under the other initiatives; and (3) what the Coordinator's Office is doing to expand the selection of quality-assured ARV products at the lowest possible price under the Emergency Plan.

To compare the selection of ARV products provided under the Emergency Plan to that provided under the other initiatives, we reviewed the requirements that apply to the purchase of ARV products under the Emergency Plan, as well as the requirements that apply to the purchase of ARV products under the HIV/AIDS treatment initiatives funded by three multinational organizations—the World Bank, UNICEF, and the Global Fund. We interviewed officials from the Coordinator's Office and the U.S. agencies primarily responsible for implementing the Emergency Plan, such as the U.S. Agency for International Development (USAID), regarding how they oversee the purchase of ARV products consistent with applicable requirements. We also interviewed officials from the multinational organizations regarding their requirements and the ARV products they provide through their initiatives. In addition, we reviewed documentation from U.S. agencies, nongovernmental organizations (NGO) that are participating in the Emergency Plan, and the multinational organizations showing the ARV products that have been purchased under their

⁶Doctors Without Borders is the English translation for Médecins Sans Frontières.

initiatives. We focused specifically on the ARVs that are recommended by WHO for first-line treatment of HIV/AIDS in countries where health care resources are limited. We identified the quality assurance process applied to each product, but we did not evaluate the different quality assurance processes or independently determine the comparative quality of the products.

To compare the prices of different ARV products provided under the Emergency Plan and the other initiatives, we obtained price information from selected manufacturers of ARV products that are generally available to the focus countries.⁷ We report prices for the focus countries quoted to us during June and July 2004 by 13 manufacturers. We asked ARV manufacturers to quote prices according to a standard set of terms. Because the price information we requested is proprietary to each manufacturer, we could not directly assess the reliability of the price data given to us. However, we checked the price data against several published sources and determined that they are sufficiently reliable.

To determine what the Coordinator's Office is doing to provide an expanded selection of ARV products at the lowest prices possible, we interviewed officials from the Coordinator's Office regarding their efforts to address potential barriers to providing additional ARV products under the Emergency Plan. Because the Coordinator's Office is working with the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) to support the ability of additional ARV manufacturers to meet the Emergency Plan's quality assurance requirement, we also interviewed officials from FDA regarding these efforts. Aspects of implementing treatment programs other than purchasing ARVs, such as human resources and supply chain management, and treatments other than ARVs, such as medications to treat opportunistic infections, are outside the scope of this report. We conducted our work from January 2004 through January 2005 in accordance with generally accepted government auditing standards. For more details on our scope and methodology, see appendix I.

⁷We selected the manufacturers from which major organizations that support treatment initiatives in the focus countries told us they consider purchasing ARVs.

Results in Brief

The Emergency Plan provides a smaller selection of ARV products than the selection provided under the initiatives funded by the World Bank, UNICEF, and the Global Fund. Under the Coordinator's Office's application of the Emergency Plan's quality assurance requirement, the ARV products the plan provides must have approval from either FDA or another acceptable regulatory authority. Because six original ARV products have met this requirement, the plan provides these six in its selection. Although this selection includes one double-ARV FDC that can be used in two of the four regimens recommended by WHO as first-line treatments in countries with limited resources, it does not include the triple-ARV FDCs preferred by the majority of the focus countries. In contrast, the other initiatives provide a selection of ARV products that includes not only those that meet the plan's quality assurance requirement but also generic ARVs and one of the preferred triple-ARV FDCs that have met the quality assurance requirements of these initiatives.

The Emergency Plan's selection of ARV products results in higher prices for most of the first-line treatment regimens. At the prices quoted to us during June and July 2004, the differences in price between the original version of an ARV provided under the Emergency Plan and the lowest-priced generic version of the corresponding ARV provided under the other initiatives ranged from \$11 less per person per year to \$328 more for the original version. At these prices, three of the four first-line regimens could be built for a lower price with the generic ARV products provided under the other initiatives than with the original ARV products provided under the Emergency Plan; there was no difference in price for the remaining regimen. For the three regimens that could be built for a lower price, which include WHO's first-choice for rapid implementation of large-scale treatment programs, the difference in the price of the regimens ranged from \$40 to \$368 less per person per year. Such differences in the price of a regimen per person per year could translate into millions of dollars of additional expense when considered on the scale of the Emergency Plan's goal of treating 2 million people by the end of 2008. For example, for every 100,000 patients on WHO's first-choice regimen for 5 years, the plan could pay over \$170 million more than the other initiatives to purchase the ARVs.

The Coordinator's Office has taken steps to expand the selection of quality-assured ARVs—including FDCs and lower-priced generics—that it provides to the focus countries under the Emergency Plan, but a statutory patent requirement may pose a barrier to expansion efforts. Currently, the selection of ARV products available under the plan is primarily limited by the quality assurance requirement. The Coordinator's Office has worked with FDA to expand the plan's selection of quality-assured ARV products,

particularly FDCs. The Coordinator's Office has encouraged manufacturers to seek FDA approval for their ARV products—and thereby satisfy the plan's quality assurance requirement—and several manufacturers told us that they intended to do so. However, if generic ARVs receive FDA approval, the patent requirement—a statutory prohibition on the purchase of any medication manufactured outside the United States if the manufacture of that medication in the United States would be covered by a valid U.S. patent—could become a barrier to expansion. The Emergency Plan may not be able to provide lower-priced generic ARVs and FDCs unless the Coordinator's Office addresses this potential barrier. The Coordinator's Office has the authority to provide ARVs notwithstanding the patent requirement. If applications proceed as anticipated by ARV manufacturers and FDA, we expect that FDA-approved generic ARVs will be available early in 2005. However, unless the patent holders for these ARVs give permission or the Coordinator's Office exercises its authority to purchase these products notwithstanding the patent requirement, the selection of ARVs provided under the Emergency Plan may not expand rapidly enough to address the AIDS emergency.

In commenting on a draft of this report the Department of State, responding on behalf of itself, HHS, and USAID, expressed concern about how we addressed the issue of ARV quality. In the draft report we described the quality assurance processes used by the Emergency Plan and the other initiatives, specified which process applied to each ARV product, and stated that quality is the primary factor determining the selection of products provided under each. However, as the draft report stated, evaluating the quality assurance processes used by each initiative was beyond the scope of our work.

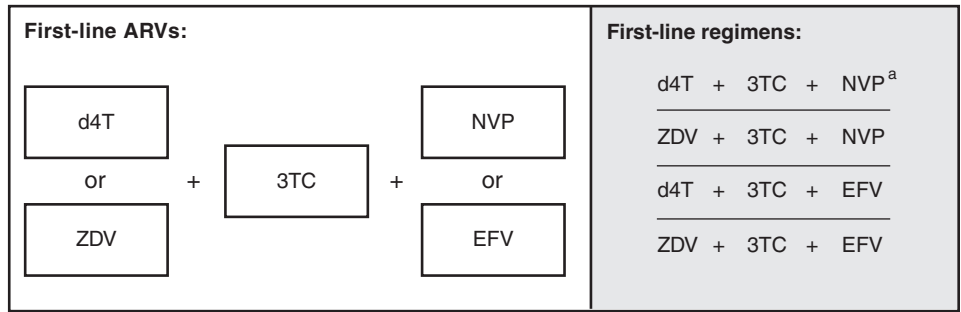
Background

Although no cure exists for HIV/AIDS, the use of multiple ARVs in combination has been shown to suppress the virus and slow the progression of the disease. Twenty distinct ARV medications can be used to treat people living with HIV/AIDS. The standard treatment is a regimen that combines three or more ARVs. People receiving ARV treatment can develop strains of HIV that are resistant to some or all of their ARVs, and as a result their treatment regimens become ineffective and they must switch to a different regimen. The risk of developing resistance decreases when patients are able to adhere to their recommended treatment by taking the prescribed ARVs, the right number of times each day, and without missing doses.

Recommended ARV Treatment Regimens

WHO has recommended certain regimens for settings in which resources are limited.⁸ For people receiving ARVs for the first time in such settings, WHO recommends one of four regimens, known as first-line regimens. These regimens are built from combinations of the following five first-line ARVs: stavudine (d4T), zidovudine (ZDV),⁹ lamivudine (3TC), nevirapine (NVP), and efavirenz (EFV).¹⁰ (See fig. 1.) Of the four first-line regimens, WHO recommends d4T + 3TC + NVP as the first-choice regimen for rapid implementation of large-scale treatment programs in resource-limited settings because, for example, it is expected that most people will be able to tolerate it without developing side effects that would require switching to another regimen. Each of the focus countries highlighted in the Emergency Plan has selected one or more of these first-line regimens for its national treatment strategy, and most have selected d4T + 3TC + NVP as their first-choice regimen.

Figure 1: WHO Recommendations for First-Line ARVs and Treatment Regimens for Resource-Limited Settings



Source: WHO.
^aWHO recommends d4T + 3TC + NVP as the first-choice regimen for rapid implementation of large-scale treatment programs in settings with limited health care resources.

For people who have developed strains of HIV that are resistant to their initial treatment regimen, WHO recommends one of four second-line

⁸WHO states that its recommendations are based on considerations including a regimen’s potency, potential side effects, the need for laboratory monitoring, anticipated patient adherence, treatment of coexisting conditions, treatment of pregnant women, and the availability and cost of the medications.
⁹Also commonly known as azidothymidine (AZT).
¹⁰These five ARVs are produced in multiple forms—such as capsule, tablet, or liquid—and in several different doses (for example, 100 mg and 300 mg). The pill form is generally used for adolescents and adults, and liquid forms are primarily used for children.

regimens. The second-line regimens use a different set of five ARVs. Second-line regimens can have disadvantages, which may be magnified in resource-limited settings. The disadvantages include the need to take more pills, the potential for additional side effects, the need for refrigeration during transportation and storage, and prices that are generally higher than those for first-line regimens. WHO emphasizes that promoting better adherence to a first-line regimen, thereby reducing the occurrence of resistance and delaying the need to shift to a second-line regimen, is particularly important in resource-limited settings because of these disadvantages.

The Coordinator's Office, FDA, and the Institute of Medicine, as well as the Global Fund, the World Bank, UNAIDS, and WHO, have endorsed the use of FDCs, which combine two or more ARVs into one pill, as an important strategy to promote adherence to ARV regimens.¹¹ These organizations have determined that the benefits of FDCs include promoting adherence, by reducing the number of pills a person has to take at one time, reducing the time and costs associated with procurement and distribution of ARVs, and simplifying the selection and prescribing of ARVs.

Funding for HIV/AIDS Treatment in the Focus Countries

Both national initiatives—such as the Emergency Plan—and multinational initiatives provide funding for HIV/AIDS treatment in the focus countries. In general, these initiatives provide their funding through grants, cooperative agreements, and contracts with governments and NGOs. The NGOs provide technical assistance and support the implementation of treatment programs by, for example, purchasing medications. In recognition of the fact that several initiatives may be active in any one country, the U.S. government and the multinational initiatives have agreed to promote coordination across their initiatives in order to use resources efficiently and effectively and to ensure rapid expansion of treatment programs.

The Emergency Plan is the largest national initiative to combat the global HIV/AIDS epidemic. Through the Emergency Plan, the U.S. government both provides direct technical assistance through field offices and funds NGOs that support HIV/AIDS treatment programs in the focus countries. Under the direction of the Coordinator's Office, USAID and HHS's Centers

¹¹See, for example, Institute of Medicine, *Scaling Up Treatment for the Global AIDS Pandemic: Challenges and Opportunities* (Washington, D.C.: 2004).

for Disease Control and Prevention have primary responsibility for implementing the Emergency Plan, with USAID responsible for overseeing the purchase of medications.¹²

Multinational organizations, including the Global Fund and agencies within the UN system, also provide funding to HIV/AIDS programs in the focus countries. The Global Fund, which was initiated in 2002, expects disbursements to total \$1 billion by the end of 2004, over half of which are intended to fund HIV/AIDS programs. Within the UN system, the World Bank represents the largest source of funding for HIV/AIDS activities in developing countries. Since 1986, the World Bank reports that it has invested \$2 billion in HIV/AIDS prevention, care, and treatment services in developing countries.

Requirements Related to the Purchase of ARV Products

All HIV/AIDS treatment programs must comply with the laws—including patent and drug registration laws—that apply in the country for which they are purchasing ARV products, as well as the requirements that pertain to the source of funding they are using. The purchase of ARVs under the Emergency Plan is subject to USAID quality assurance requirements and a statutory patent requirement.¹³ To assure quality, USAID requires that ARV products purchased under the plan have either FDA approval or the approval of another acceptable regulatory authority.¹⁴ Because the Emergency Plan is largely funded under the Foreign Assistance Act of 1961, the purchase of ARVs with these funds is subject to a provision of

¹²Several other federal entities—including the Departments of Commerce, Defense, and Labor and the Peace Corps—also have responsibilities under the program. For additional information on the structure and operation of the Coordinator’s Office, see GAO, *Global Health: U.S. AIDS Coordinator Addressing Some Key Challenges to Expanding Treatment but Others Remain*, [GAO-04-784](#) (Washington, D.C.: July 12, 2004).

¹³Medications purchased under the Emergency Plan are also subject to rules pertaining to source, origin, and nationality for commodities that USAID finances, unless USAID issues a waiver to allow otherwise. *See*, 22 C.F.R. Part 228. These include a requirement that pharmaceutical products must be manufactured in the United States in order to be eligible for USAID financing. 22 C.F.R. § 228.13(c). The Coordinator’s Office confirmed that USAID can issue a specific waiver of these rules, has already done so for ARVs purchased under the Emergency Plan, and will continue to issue waivers for the purchase of ARVs to carry out the plan.

¹⁴The Coordinator’s Office defined “acceptable regulatory authority” in guidance issued to field staff on March 24, 2004. *See also*, USAID Automated Directives System, § 312.5.3c, for USAID’s internal regulations and guidance regarding the purchase of pharmaceutical products.

the act that prohibits the purchase of any medication manufactured outside the United States if the manufacture of that medication in the United States would be covered by a valid U.S. patent, unless the patent owner gives its permission.¹⁵ The purchase of ARV products with funds from the other initiatives must meet the quality assurance requirements that the World Bank, UNICEF, and the Global Fund have in common. Specifically, these organizations require that all ARV products either be approved by an acceptable regulatory authority such as FDA or be prequalified through WHO's Prequalification Project. WHO's Prequalification Project includes a process for assessing the quality of products that have not been subject to review by an acceptable regulatory authority. Prequalification relies on review of product information and manufacturing site inspections to determine if the product meets WHO standards.

Emergency Plan Provides Smaller Selection of ARV Products Than Other Initiatives

The Emergency Plan provides a smaller selection of ARV products than the other initiatives. Because the plan provides only ARV products that have been approved by FDA or another acceptable regulatory authority, it provides six ARV products, all of which are original versions. In addition to ARV products that have met the Emergency Plan's quality assurance requirement, other initiatives also provide generic ARVs that have been prequalified by WHO. While the plan does not provide the FDCs preferred by the focus countries, these products are available through the other initiatives.

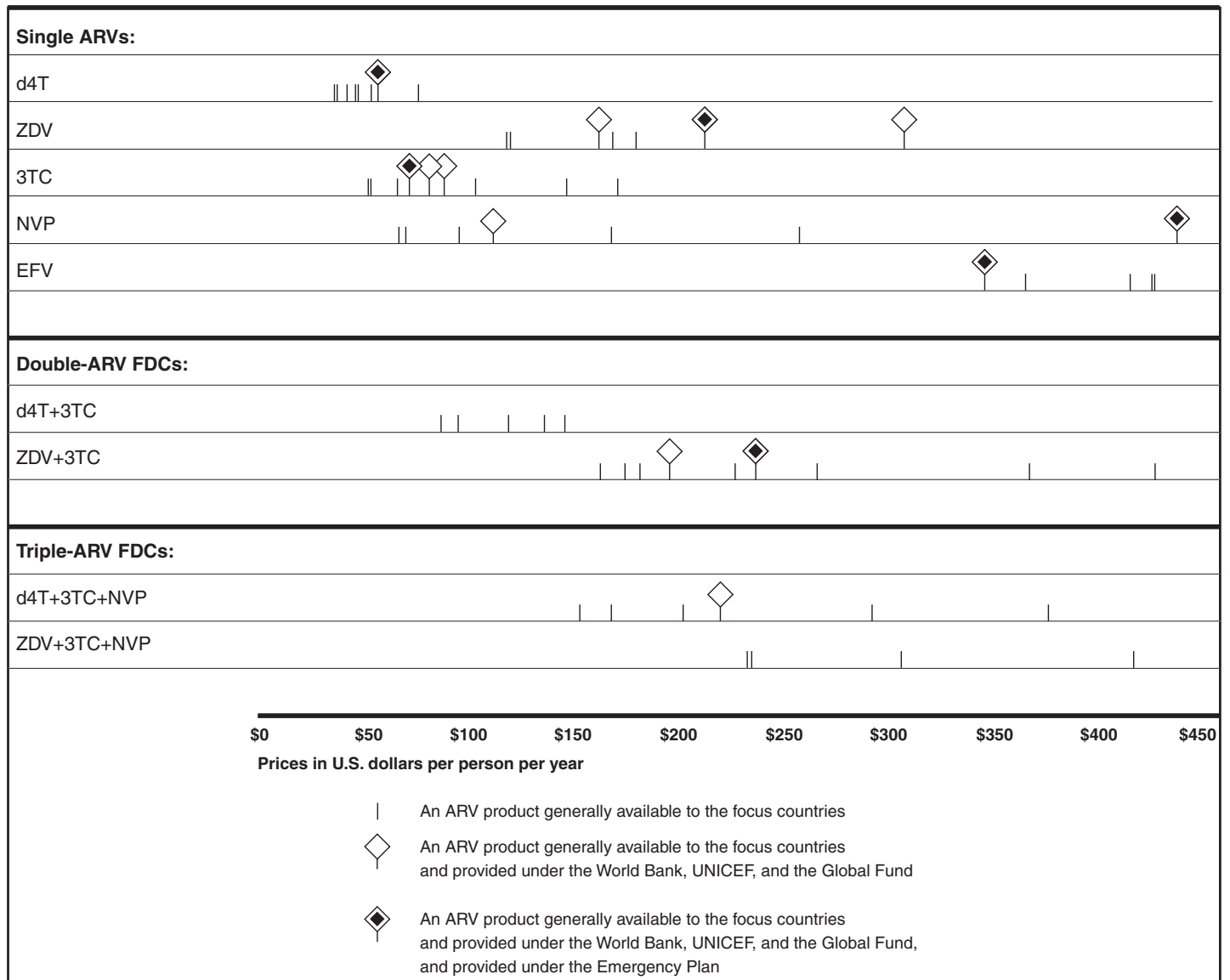
Emergency Plan Provides One Version of Each First-Line ARV and a Double-ARV FDC

As of December 2004, the Emergency Plan provides one version—the original version—of each of the five ARVs necessary to build all of the first-line regimens. The plan also provides a double-ARV FDC (ZDV + 3TC) that can be used in half of those regimens, but not the regimen that is recommended by WHO as the first choice for rapid implementation of large-scale HIV/AIDS treatment programs in resource-limited settings (d4T + 3TC + NVP). These six products, flagged with filled diamonds in figure 2, are the only first-line ARVs that have been approved by FDA or another acceptable regulatory authority and thus comply with the plan's quality assurance requirement. Because no generic ARVs currently meet the plan's quality assurance requirement, the Emergency Plan does not provide

¹⁵Foreign Assistance Act of 1961, Pub. L. No. 87-195, § 606, 75 Stat. 424, 440 (1961) (codified, as amended, at 22 U.S.C. § 2356 (2000)).

generic versions of any of the first-line ARVs or the double-ARV FDC provided under the plan. In addition, the Emergency Plan does not provide any version of three other FDC products that are generally available to the focus countries, including the triple-ARV FDC (d4T + 3TC + NVP) that is preferred by the majority of the focus countries.

Figure 2: Selection of First-Line ARV Products Provided under the Emergency Plan and Selection Provided under Other Initiatives



Source: GAO.

Notes: Data from GAO survey of ARV manufacturers during June and July 2004, the Coordinator's Office, USAID, WHO, the World Bank, UNICEF, and the Global Fund. As of December 2004, the ARV products flagged with a filled diamond have been approved by FDA or another acceptable regulatory authority; those flagged with an unfilled diamond have been prequalified by WHO; and those not flagged with a diamond have been neither approved by FDA or another acceptable regulatory authority nor prequalified by WHO. We did not determine whether the different quality assurance processes result in ARV products of differing quality. Because laws of a country may affect whether a particular ARV product is available there, not all ARV products are available in all of the focus countries.

Other Initiatives Provide Generic as Well as Original ARVs

The other initiatives provide not only the original versions of the first-line ARVs but also generic versions that meet their quality assurance requirements. In addition to ARVs that have been approved by FDA or another acceptable regulatory authority, the other initiatives also accept those that have been prequalified by WHO. Thus the other initiatives provide generic versions of most of the first-line single ARVs, as well as a double-ARV FDC (ZDV + 3TC) and a triple-ARV FDC (d4T + 3TC + NVP), flagged with unfilled diamonds in figure 2, that are not provided under the plan. Other generic versions of all ARV products are available to the focus countries but are not provided under the Emergency Plan or under the other initiatives. The additional generic ARVs generally available to the focus countries, shown in figure 2 as vertical lines without diamonds, have been neither approved by FDA or another acceptable regulatory authority nor prequalified by WHO.

Emergency Plan's Selection of ARV Products Results in Higher Prices for Most First-Line Treatment Regimens

At the prices quoted to us during June and July 2004, most first-line regimens could be built for a lower price with the generic ARV products provided under the other initiatives than with the original ARV products provided under the Emergency Plan. (See table 1.) The difference in price between the original ARVs provided under the Emergency Plan and the lowest-priced generic ARVs provided under the other initiatives ranged from \$11 less per person per year for original 3TC to \$328 more for original NVP. (See fig. 2.) At these prices, three of the four first-line regimens could be built for a lower price with the generic ARV products provided under the other initiatives than with the original ARV products provided under the Emergency Plan. The difference in price for these three regimens when built with the lowest-priced ARVs provided under the other initiatives and when built with the lowest-priced ARVs provided under the Emergency Plan ranged from \$40 less per person per year for the regimen ZDV + 3TC + EFV to \$368 less for the regimen ZDV + 3TC + NVP. There was no difference in price for the regimen d4T + 3TC + EFV because the lowest-priced ARVs provided under the Emergency Plan and the other initiatives are the same. All of the first-line regimens could be

built for a lower price using the lowest-priced generic ARVs that are generally available to the focus countries but not provided under either the Emergency Plan or the other initiatives.

Table 1: Prices for the First-Line Regimens

Regimen	Price in U.S. dollars per person per year (difference compared to the Emergency Plan)		
	Using lowest-priced ARVs provided under the Emergency Plan	Using lowest-priced ARVs provided under the World Bank, UNICEF, and the Global Fund	Using lowest-priced ARVs generally available to focus countries
d4T + 3TC + NVP	\$562	\$219 (-343)	\$150 (-412)
ZDV + 3TC + NVP	675	307 (-368)	225 (-450)
d4T + 3TC + EFV	471	471 (-0)	433 (-38)
ZDV + 3TC + EFV	584	544 (-40)	506 (-78)

Source: GAO.

Notes: GAO calculations based on price survey of ARV manufacturers. Calculated using prices quoted during June and July 2004. The lowest price for each regimen could consist of three single ARVs, a double-ARV FDC plus a single ARV, or a triple-ARV FDC. See app. II for more detailed information on prices.

Differences in the price of a regimen per person per year can translate into millions of dollars of additional expense when considered on the scale of the Emergency Plan's goal of treating 2 million people by the end of 2008. For example, the price for the regimen that WHO recommends as the first choice for rapid scale-up in settings with limited health care resources (d4T + 3TC + NVP) is \$343 more per person per year under the Emergency Plan. Thus for every 100,000 patients on this regimen for 5 years, the plan could pay over \$170 million more than the other initiatives for purchase of these ARVs. The overall impact of these price differences over the life of the plan and on the treatment goal is difficult to estimate precisely because, for example, the mix of ARVs and treatment regimens that will be used as the Emergency Plan expands is unknown and product prices may change.

Coordinator's Office Has Taken Steps to Expand Selection of ARV Products It Provides, but Patent Requirement Is Potential Barrier

The Coordinator's Office has taken steps to expand the selection of quality-assured ARV products it provides to the focus countries to include the preferred FDCs and lower-priced generics. However, the patent requirement could present a barrier to expanding the selection.

Coordinator's Office Has Made Efforts to Expand the Selection of Quality-Assured ARV Products It Provides

The Coordinator's Office has worked with FDA to expand the selection of quality-assured ARV products, particularly the preferred FDCs, that the Emergency Plan provides to the focus countries. The selection of ARV products provided is currently limited primarily by the plan's quality assurance requirement. The Coordinator's Office has been encouraging manufacturers to seek FDA approval for their ARV products, and thereby satisfy the plan's quality assurance requirement.¹⁶ FDA officials told us that the agency has been helping existing and potential manufacturers of ARV products, particularly FDCs, to prepare applications for submission to FDA. Several manufacturers told us that they have been working with FDA to develop applications. One of the manufacturers we spoke with announced in October 2004 that it had submitted an application, and the others told us that they intended to do so. FDA officials said that these applications would have priority for review and that they expect to be able to act on complete applications within several months of submission. In addition, the Coordinator's Office has worked with FDA to clarify that FDCs are eligible for expedited review and to assemble into a single guidance document several sets of regulations and guidelines that pertain to this expedited review.¹⁷ As part of this guidance, FDA has included a list of combinations of ARVs for which FDA believes there are sufficient

¹⁶ A generic manufacturer may seek FDA approval for a U.S. patented medication if marketing of the generic version in the United States would occur after expiration of that patent. *See*, 35 U.S.C. 271(e)(1). FDA may issue tentative approval for such a product that is shown to be safe and effective for its intended use but may not yet be marketed in the United States due to the unexpired patent.

¹⁷ Regulations that give FDA greater flexibility to rapidly review and approve medications intended to treat certain severe diseases are contained in 21 C.F.R. Part 312 and 21 C.F.R. Part 314.

publicly available safety and effectiveness data that an application would not need to include additional clinical studies.

Emergency Plan May Not Be Able to Provide Generic ARVs Unless Patent Barrier Is Addressed

The Emergency Plan may not be able to expand the selection of ARV products it provides to include lower-priced generic ARVs unless the Coordinator's Office addresses a potential barrier presented by the applicable patent requirement in the Foreign Assistance Act of 1961. Although the selection of ARV products available under the plan is currently limited primarily by the quality assurance requirement, if generic ARVs receive FDA approval, the patent requirement could be a barrier to expansion. Because all five of the first-line ARVs are currently under U.S. patents,¹⁸ even if a generic ARV were to receive FDA approval, thus meeting the plan's quality assurance requirement, the patent requirement would prevent its purchase unless the patent holder had granted permission. If such permission is not granted, this requirement could prevent the purchase of generic ARVs, including generic FDCs, that have met the plan's quality assurance requirement.

The Coordinator's Office has the authority to provide ARV products notwithstanding the patent requirement.¹⁹ We asked officials from the Coordinator's Office whether the Coordinator would use this authority in order to purchase an FDA-approved generic ARV for which permission could not be obtained from the patent owner. Officials from the Coordinator's Office told us that they could not address hypothetical situations but that the Coordinator would consider using his authority to make funds available to purchase these products notwithstanding this requirement if the ARV in question is critical to the plan's treatment responsibilities and no readily available substitute exists. It may not be possible for most generic ARVs to meet these conditions because generics are by definition substitutes for existing products. In addition, a

¹⁸The patent on ZDV is due to expire on September 17, 2005. The patents on the remaining first-line ARVs are scheduled to expire between December 2008 and May 2013.

¹⁹This authority is provided in the foreign operations appropriation, which largely funds the Emergency Plan. For each of the last 3 years, the foreign operations appropriation has made funds available for the prevention, treatment, and control of HIV/AIDS "notwithstanding any other provision of law." Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, 118 Stat. 3, 175 (appropriation for fiscal year 2004) (specifies exemptions unrelated to the patent requirement); Consolidated Appropriations Resolution, 2003, Pub. L. No. 108-7, 117 Stat. 11, 187 (appropriation for fiscal year 2003); and Foreign Operations Export Financing, and Related Programs Appropriations Act, 2002, Pub. L. No. 107-115, 115 Stat. 2118, 2146 (appropriation for fiscal year 2002).

representative of one of the generic manufacturers we spoke with told us that the company is concerned and is hesitating to apply to FDA because it has sought, but not yet obtained, assurances from the Coordinator's Office that once its products have met the plan's quality assurance requirement these products will be eligible for purchase under the Emergency Plan.

Concluding Observations

During its first year, the Emergency Plan has provided a limited selection of ARV products that does not fully support the treatment strategies of the focus countries and is not optimally coordinated with other multinational initiatives because it does not include the FDCs and lower-priced generics that the majority of these countries prefer. Better coordination with the focus countries and with other treatment initiatives could facilitate more rapid implementation of the Emergency Plan. Moreover, given the intended scale of the plan, lower prices for ARVs could result in savings of hundreds of millions of dollars, which could be used to treat additional patients or to support other aspects of the program. The Coordinator's Office has taken steps to expand the selection of ARV products that meet its quality assurance requirement—with special focus on FDCs—by working with manufacturers and FDA to increase the number of products that have FDA approval. If applications proceed as anticipated by ARV manufacturers and FDA, we expect that FDA-approved generic ARVs will be available early in 2005. However, unless the patent holders for these ARVs give permission or the Coordinator's Office exercises its authority to purchase these products notwithstanding the patent requirement, the selection of ARVs provided under the Emergency Plan may not expand rapidly enough to address the AIDS emergency.

Agency Comments and Our Evaluation

We provided a draft of this report to the Department of State, HHS, and USAID. Written comments submitted by the Department of State on behalf of itself, HHS, and USAID are reprinted in appendix III. In its comments, the Department of State expressed concern about how our report addressed the issue of ARV quality and urged us to mention prominently in the report recent changes in the list of products that are prequalified by WHO. However, we stated in the draft report that concern about quality is the primary factor limiting the selection of ARVs provided under the Emergency Plan and the other initiatives. Our draft report recognized that quality assurance is a critical concern, and provided background information on the quality assurance requirements of the Emergency Plan and the other initiatives and specified the quality assurance processes applied to each ARV product. However, as the draft report stated, evaluating the quality assurance processes used by each initiative was

beyond the scope of our work. We have updated the draft report to reflect all changes in the availability of ARV products, including those highlighted by the Department of State.

The Department of State also characterized figure 3 (see app. II) in the report as misleading because not all of the generic ARV products are sold on the market in all 15 focus countries. However, the draft report explained that the laws of individual countries may not allow for the purchase of some products. In response to the agency's concerns, we clarified this further in notes to figure 3.

In addition, the agency expressed confusion over our use of the term "generic" and offered the more formal term, "therapeutic equivalents," used by FDA. In the draft report, we used the word "generic" broadly to mean a copy of an original product, regardless of whether FDA or another national regulatory authority has determined the generic product to be a therapeutic equivalent to an original product. We have further clarified our use of the term in the report.

We agree with the agency's comment that it is important to distinguish between issues of quality assurance and intellectual property, and these issues were treated separately in the draft report. In addition, our concern about the patent requirement being a potential barrier to expanding the selection of ARV products provided under the Emergency Plan is only with respect to those generic products that have first met the plan's quality assurance requirement.

Lastly, the Department of State highlighted that the patent requirement is a statutory restriction under the Foreign Assistance Act of 1961, as we noted throughout the draft report. We revised the draft to further clarify the source of the patent requirement. The Department also said that the Coordinator's Office has decided to exercise its authority with respect to the patent requirement "as necessary." However, because the comments did not clarify when it might be necessary for the Coordinator's Office to use its authority to make funds available to purchase products notwithstanding the patent requirement, it remains unclear if all generic products that have met the quality assurance requirement will be eligible for purchase under the Emergency Plan.

In its comments, the agency also provided additional information on the Emergency Plan's outreach activities and plans for bulk purchasing of ARV products. The Department of State, HHS, and USAID individually submitted technical comments, which we incorporated where appropriate.

As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of this letter. We will then send copies to the Secretary of State, the Secretary of Health and Human Services, and the Administrator of the U.S. Agency for International Development and make copies available to others who request them. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report, please call me at (202) 512-7119. Another contact and key contributors are listed in appendix IV.

A handwritten signature in black ink that reads "Janet Heinrich". The signature is written in a cursive style with a large, stylized "J" and "H".

Janet Heinrich
Director, Health Care—Public Health Issues

Appendix I: Scope and Methodology

This report compares the selection of antiretroviral medication (ARV) products that are being provided under the President's Emergency Plan for AIDS Relief (Emergency Plan) with that provided under other initiatives that also fund HIV/AIDS treatment programs in the focus countries, as of December 2004.¹ Our discussion is focused specifically on the ARVs that are recommended by the World Health Organization (WHO) for first-line treatment of HIV/AIDS in countries where health care resources are limited. Our report also provides price information for the ARV products provided under the Emergency Plan and under the other initiatives. We report prices quoted, during June and July 2004, by 13 selected manufacturers of ARV products that are generally available to the focus countries. Lastly, we examine the efforts of the Office of the U.S. Global AIDS Coordinator (Coordinator's Office) within the Department of State to expand the selection of quality-assured ARV products provided at the lowest possible price to the focus countries. Aspects of implementing HIV/AIDS treatment programs other than the selection and price of medications, such as human resources and supply chain management, and treatments other than ARVs, such as medications to treat opportunistic infections, are outside the scope of this report. Similarly, the HIV/AIDS prevention and care objectives of the Emergency Plan are outside the scope of this report. We conducted our review from January 2004 through January 2005 in accordance with generally accepted government auditing standards.

Comparing Selection of ARV Products the Emergency Plan Provides to That Provided under Other Initiatives

To compare the selection of ARV products provided under the Emergency Plan to that provided under the other initiatives, we reviewed the requirements that apply to the purchase of ARV products under the Emergency Plan. Specifically, we reviewed relevant laws, regulations, and guidance from which the plan's requirements arise. We also reviewed documentation from the Coordinator's Office and the U.S. Agency for International Development (USAID) to determine which products had been provided under the plan as of December 2004. In addition, we interviewed officials from the Coordinator's Office, USAID, and the Department of Health and Human Services' (HHS) Office of Global Health Affairs, Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA) about experience within federal programs

¹The focus countries are Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia.

with purchasing ARVs for developing countries. Lastly, we interviewed officials at the nongovernmental organizations (NGO) that have received funding under the Emergency Plan to purchase ARVs in the focus countries. These NGOs include Catholic Relief Services Consortium, Columbia University Mailman School of Public Health, Elizabeth Glaser Pediatric AIDS Foundation, and Harvard University School of Public Health.²

To determine the selection of ARV products provided under the other initiatives, we reviewed the requirements that apply to the purchase of ARV products under the HIV/AIDS treatment initiatives funded by the World Bank, the United Nations Children's Fund (UNICEF), and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund). Specifically, we reviewed guidance documents from the Global Fund, the World Bank, UNICEF, and WHO related to the purchase of ARVs under these initiatives. We also interviewed officials from these organizations regarding the requirements that apply to the provision of ARVs under their treatment initiatives and to confirm the accuracy of information obtained from their Web sites. In our comparison we determined the quality assurance process applied to each product, but we did not evaluate the different quality assurance processes required under the Emergency Plan as compared with those required under the other initiatives or determine the comparative quality of the products.

Our review of the ARV products provided under the Emergency Plan and the other initiatives focuses specifically on the ARVs that are recommended by WHO for treatment of HIV/AIDS in countries with limited health care resources. In order to determine the appropriate treatment recommendations to focus on in this report, we reviewed literature on the use of ARVs in general and in countries with limited health care resources in particular. Our literature review included searches of scientific publications using electronic databases, including the National Library of Medicine's PubMed, as well as the Web sites of the *New England Journal of Medicine*, the *Journal of the American Medical Association*, and *The Lancet*. We reviewed literature on ARV treatment available from the Coordinator's Office, USAID, HHS, FDA, CDC, the HHS Office of the Inspector General, the Congressional Research Service, the Congressional Budget Office, and the Institute of Medicine. We also

²As of August 2004, the Harvard program had not finalized any ARV purchases under the Emergency Plan.

reviewed treatment guidelines and related documentation from WHO, the Global Fund, the World Bank, the Joint United Nations Programme on HIV/AIDS, UNICEF, and the United Kingdom's Department for International Development. We also interviewed officials from several of these organizations. To understand the issues involved in providing ARVs in countries with limited health care resources, we interviewed officials from several NGOs that are working in these settings—including Doctors Without Borders, the William Jefferson Clinton Foundation (Clinton Foundation), the Bill and Melinda Gates Foundation, John Snow Incorporated (JSI), Family Health International (FHI), and Management Sciences for Health (MSH). We also reviewed documentation on the focus countries' national HIV/AIDS strategies and treatment guidelines, including information that we obtained from the Coordinator's Office and NGOs.³

Determining Prices of ARVs for the Focus Countries

The prices we report are prices that 13 selected manufacturers quoted to us during June and July 2004 for the focus countries. We surveyed the manufacturers from which the major organizations that support treatment programs in the focus countries have considered purchasing their ARVs. These organizations include JSI, FHI, MSH, the Clinton Foundation, the Global Fund, the World Bank, WHO, UNICEF, Doctors Without Borders, the International Dispensary Association, and MissionPharma. We selected a manufacturer for inclusion in our report if it makes at least one of the ARVs included in the WHO-recommended first-line regimens and was selling or willing to sell its ARV product to at least one of the focus countries. Thirteen of the 15 manufacturers that we considered met these criteria and were willing to quote their prices for the first-line ARVs for the focus countries. We did not select products based on registration with the focus countries' national drug regulatory authorities because information on country-level registration was incomplete or not available.

Because some of the manufacturers we surveyed offer their products at significantly lower prices to developing countries than to developed countries,⁴ we requested price quotes specifically for the focus countries. We did not attempt to determine the prices that specific purchasers are paying for these products because at the time we conducted our analysis there was limited experience in the focus countries with using the funding

³Some of the focus countries were modifying their treatment guidelines at the time of our analysis.

⁴This practice is known as differential pricing, sometimes also called "tiered pricing."

sources discussed in this report for large-scale purchase of ARVs.⁵ Because different manufacturers offer their reduced prices according to differing criteria,⁶ in some cases the lowest price offers are not available to all of the focus countries. Specifically, Guyana and Vietnam are not eligible to purchase ARVs at some manufacturers' lowest price. In addition to these two focus countries, other developing countries outside the scope of this report may not be eligible for the prices we present.

To help ensure that the manufacturers' prices we present are as comparable as possible across different manufacturers of the same ARV, we surveyed manufacturers using a standard set of questions. We developed our questions on the basis of our literature review and discussions with various officials from U.S. government agencies, officials from other initiatives, representatives from NGOs, and representatives from pharmaceutical manufacturers. These questions took into account differences in purchasing agreements, including price negotiation based on volume and length of contract, inclusion of shipping and insurance, and financing guarantees. Some of the manufacturers we spoke with told us that they offer prices that are negotiable depending on the volume of the purchase, the length of the contract for purchase, and the degree to which financing can be guaranteed. Therefore we requested prices based on the following purchase scenarios, all of which assume financing has been guaranteed: (1) purchase of enough medication to treat 500 patients for 1 year, (2) purchase of enough medication to treat 10,000 patients for 1 year, and (3) purchase of enough medication to treat 10,000 patients for 3 years. All manufacturers were given the opportunity to provide prices according to these scenarios, although some told us that their prices were not negotiable. We developed the scenarios based on estimates of the scale of existing treatment programs in the focus countries, and the potential scale of programs over the next 3 years. We verified, with officials from USAID and other experts in ARV procurement, that these scenarios represented plausible purchasing arrangements both now and over the next 3 years as treatment programs expand in developing countries. Because the price

⁵The three NGOs that have completed purchases of ARVs under the Emergency Plan reported that as of September 2004 they have received prices that were either similar to or higher than the prices presented in our report.

⁶Some manufacturers offer their lowest prices to Least Developed Countries, or to countries in Sub-Saharan Africa, while others base their discounted offers on the Human Development Index or the World Bank's rankings of country income levels, sometimes in combination with estimates of the prevalence of HIV infection among a country's adult population.

information we requested is considered proprietary by the manufacturer, we could not directly assess the reliability of the price data given to us. However, we checked the prices quoted to us against other published sources from our literature search and manufacturers' Web sites and determined they were reliable for our purposes.

In some cases a manufacturer's prices include costs that other manufacturers do not include—such as shipping and insurance charges. We note where these differences exist, and have determined that they do not undermine the essential comparability of the prices presented in our report. In making this determination, we first requested specific information from each manufacturer about what is included in its price and the terms of the purchase agreements it uses. The manufacturers we surveyed for this report used one of six standard agreements to cover shipping and insurance (see table 2). We also asked multiple purchasers about the shipping and insurance costs they have incurred when purchasing ARVs. While systematic evidence was not available, the organizations we spoke with provided estimates ranging from 3 to 15 percent additional cost for shipping and insurance for large-scale ARV purchases. One NGO that was purchasing ARVs under the Emergency Plan told us that purchasing the same ARV product through two different distribution channels—one directly from the manufacturer with shipping and insurance costs included in the price and one through a distributor that added those costs to its price—made no appreciable difference in the final cost of the product. We also found, after reviewing responses to our survey, that manufacturers of both original and generic products used a range of purchase agreements, both more and less inclusive of shipping and insurance costs. Other factors that may contribute to the total cost of ARVs to a specific treatment program, such as taxes and distribution surcharges, are beyond the scope of this report.

Table 2: Standard International Terms for the Shipping and Insurance Conditions of Purchase Agreements

International commercial term ^a	Shipping and insurance conditions
Ex-Works (EXW)	The seller transfers the goods to the buyer at the seller's named place of business (the factory, warehouse, etc.). The buyer is responsible for the full risk of loss of or damage to the goods, clearing the goods for export, and any costs related to transport. EXW places the minimum obligation on the seller.
Free on Board (FOB)	The seller clears the goods for export and is responsible for the risks and costs of delivering the goods past the "ship's rail" (that is, off the dock onto the ship) at the domestic port of shipment. The risks and costs related to transport are transferred to the buyer when the goods pass the ship's rail. This term is exclusively for maritime transport.
Free Carrier (FCA)	The seller clears the goods for export and delivers them to a carrier selected by the buyer (at the domestic port, terminal, etc.). The buyer is responsible for the full risks and costs related to transport.
Cost, Insurance, and Freight (CIF)	The seller clears the goods for export and is responsible for the risks and costs of delivering the goods past the "ship's rail" at the domestic port of shipment. The seller is also responsible for paying the costs of transport and insurance of the goods to the port of destination. Any additional risks or costs related to transport, including applicable import tariffs, are transferred to the buyer when the goods pass the ship's rail. This term is exclusively for maritime transport.
Carriage Paid To (CPT)	The seller clears the goods for export and is responsible for paying for carriage through to the named port of destination, including applicable import tariffs. The buyer assumes all risks once the seller has delivered the goods to the carrier at the port of shipment.
Carriage and Insurance Paid To (CIP)	The seller clears the goods for export and is responsible for paying for carriage and insurance through to the named port of destination, including applicable import tariffs. The buyer assumes all risks once the seller has delivered the goods to the carrier at the port of shipment.

Source: International Chamber of Commerce.

^aManufacturers offer prices for their medications in accordance with an international system of shipping and handling terms—known as international commercial terms, or incoterms—that describe various possible purchase agreements. These incoterms are published by the International Chamber of Commerce.

Examining the Efforts of the Coordinator's Office to Expand the Selection of ARVs It Provides

To examine the efforts of the Coordinator's Office to expand the selection of quality-assured ARV products provided under the Emergency Plan to the focus countries, we reviewed relevant laws, regulations, and guidance from which the plan's quality assurance and patent requirements arise. We interviewed officials from the Coordinator's Office and USAID regarding how they interpret these laws, regulations, and guidance and how they apply these requirements to the provision of ARVs under the plan. We also interviewed officials from the Coordinator's Office regarding their efforts to address potential barriers to expansion. Lastly, because the Coordinator's Office is working with FDA to support the ability of additional ARV manufacturers to meet the Emergency Plan's quality assurance requirement, we interviewed officials from FDA regarding these efforts.

Appendix II: Price Information from Survey of ARV Manufacturers

We surveyed the following 13 manufacturers during June and July 2004 to obtain price quotes for the focus countries for the ARVs used to build the WHO-recommended first-line regimens:

- Aurobindo Pharma Limited (Aurobindo)
- Boehringer Ingelheim (BI)
- Bristol-Myers Squibb Company (BMS)
- Cipla Limited (Cipla)
- Combino Pharm
- Cristalia Produtos Quimicos Farmaceuticos LTDA (Cristalia)
- Far-Manguinhos FIOCRUZ Ministry of Health (Far-Manguinhos)
- GlaxoSmithKline (GSK)
- Government Pharmaceutical Organization Thailand (GPO)
- Hetero Drugs Limited (Hetero)
- Merck & Co., Inc. (Merck)
- Ranbaxy Laboratories Limited (Ranbaxy)
- Strides Arcolab Limited (Strides)

The price per person per year for each ARV product—stavudine (d4T), zidovudine (ZDV), lamivudine (3TC), nevirapine (NVP), and efavirenz (EFV)—is shown in figures 3 and 4. Figure 3 shows prices quoted for single-ARV products, and figure 4 shows prices quoted for fixed-dose combination (FDC) ARV products. For each product we indicate the type of standard agreement used to cover shipping and insurance charges and whether the manufacturer indicated that the price quoted was negotiable or based on a specific purchase scenario (see figure notes a, b, and c). Both figures also show which ARV products are provided under the Emergency Plan, which additional products are provided under the other initiatives, and which products are generally available to the focus countries but not provided under either the Emergency Plan or the other initiatives, as of December 2004.

**Appendix II: Price Information from Survey of
ARV Manufacturers**

Figure 3: Manufacturers' Prices for First-Line ARV Products for the Focus Countries (prices per person per year in U.S. dollars)

ARVs:

d4T: 40 mg	Price	ZDV: 300 mg	Price	3TC: 150 mg	Price	NVP: 200 mg	Price	EFV: 600 mg	Price
GPO (FCA/FOB) ^a	77	Combino Pharm (EXW) ^b	307	GPO (FCA/FOB) ^a	171	BI (CIP/FCA) ^a	438	Ranbaxy (FOB) ^c	427
BMS (FCA) ^a	55	GSK (CIP) ^a	212	Cristalia (CIF) ^c	146	GPO (FCA/FOB) ^a	256	Cipla (FOB) ^c	426
Strides (FOB) ^b	51	Ranbaxy (FOB) ^c	180	Ranbaxy (FOB) ^c	100	Ranbaxy (FOB) ^c	166	Hetero (FOB) ^b	414
Cipla (FOB) ^c	47	Strides (FOB) ^b	168	Cipla (FOB) ^c	88	Cipla (FOB) ^c	110	Aurobindo (FOB) ^c	364
Ranbaxy (FOB) ^c	47	Cipla (FOB) ^c	161	Strides (FOB) ^b	80	Strides (FOB) ^b	95	Merck (CIF) ^a	347
Hetero (FOB) ^b	42	Hetero (FOB) ^b	118	GSK (CIP) ^a	69	Far Manguinhos (CPT) ^c	69		
Far Manguinhos (CPT) ^c	38	Aurobindo (FOB) ^c	118	Hetero (FOB) ^b	64	Aurobindo (FOB) ^c	66	EFV: 200 mg	Price
Aurobindo (FOB) ^c	36			Aurobindo (FOB) ^c	50			Strides (FOB) ^b	730
		ZDV: 100 mg	Price	Far Manguinhos (CPT) ^c	50			Merck (CIF) ^a	500
		Combino Pharm (EXW) ^b	394					Cipla (FOB) ^c	462
		GSK (CIP) ^a	346					Ranbaxy (FOB) ^c	427
		GPO (FCA/FOB) ^a	307					Hetero (FOB) ^b	418
		Cristalia (CIF) ^c	263					Aurobindo (FOB) ^c	383
		Cipla (FOB) ^c	197						
		Strides (FOB) ^b	164						
		Hetero (FOB) ^b	145						
		Far Manguinhos (CPT) ^c	140						

International Commercial Terms:
 (EXW) Ex-Works
 (FOB) Free on Board
 (FCA) Free Carrier
 (CIF) Cost, Insurance, and Freight
 (CPT) Carriage Paid To
 (CIP) Carriage and Insurance Paid To

- An ARV product generally available to the focus countries
- An ARV product generally available to the focus countries and provided under the World Bank, UNICEF, and the Global Fund
- An ARV product generally available to the focus countries and provided under the World Bank, UNICEF, and the Global Fund, and provided under the Emergency Plan

Source: GAO.

**Appendix II: Price Information from Survey of
ARV Manufacturers**

Notes: Data from GAO survey of ARV manufacturers during June and July of 2004, the Coordinator's Office, USAID, WHO, the World Bank, UNICEF, and the Global Fund. Numbers in this figure may not sum to numbers shown in table 1 due to rounding. As of December 2004, the ARV products shaded in black have been approved by FDA or another acceptable regulatory authority; those shaded in gray have been prequalified by WHO; and those without shading have been neither approved by FDA or another acceptable regulatory authority nor prequalified by WHO. We did not determine whether the different quality assurance processes result in medications of differing quality. Because laws of a country may affect whether a particular ARV product is available there, not all ARV products are available in all of the focus countries. Guyana and Vietnam are not eligible to receive the prices shown for some of the products shaded in black. Information about the 100-mg dose of ZDV and the 200-mg dose of EFV is provided in fig. 3 but not included in fig. 2 and table 1.

^aManufacturer indicated that price quoted was nonnegotiable.

^bManufacturer indicated that price quoted was based on a 1 year / 10,000 patients per year purchase scenario.

^cManufacturer indicated that price quoted was negotiable, but not based on any specific purchase scenario.

**Appendix II: Price Information from Survey of
ARV Manufacturers**

Figure 4: Manufacturers' Prices for FDC ARV Products for the Focus Countries (prices per person per year in U.S. dollars)

Double-ARV FDCs:

d4T+3TC: 40+150 mg		ZDV+3TC: 300+150 mg	
Cipla (FOB) ^a	146	GPO (FCA/FOB) ^b	426
Ranbaxy (FOB) ^a	135	Cristalia (CIF) ^a	365
Strides (FOB) ^c	120	Ranbaxy (FOB) ^a	265
Hetero (FOB) ^c	93	GSK (CIP)^b	237
Aurobindo (FOB) ^a	87	Strides (FOB) ^c	226
		Cipla (FOB) ^a	197
		Aurobindo (FOB) ^a	182
		Hetero (FOB) ^c	174
		Far Manguinhos (CPT) ^a	159

Triple-ARV FDCs:

d4T+3TC+NVP: 40+150+200 mg		ZDV+3TC+NVP: 300+150+200 mg	
GPO (FCA/FOB) ^b	375	Ranbaxy (FOB) ^a	416
Ranbaxy (FOB) ^a	292	Cipla (FOB) ^a	304
Cipla (FOB) ^a	219	Aurobindo (FOB) ^a	234
Strides (FOB) ^c	201	Hetero (FOB) ^c	231
Aurobindo (FOB) ^a	168		
Hetero (FOB) ^c	150		

International Commercial Terms:

(EXW) Ex-Works
(FOB) Free on Board
(FCA) Free Carrier
(CIF) Cost, Insurance, and Freight
(CPT) Carriage Paid To
(CIP) Carriage and Insurance Paid To

-  An ARV product generally available to the focus countries
-  An ARV product generally available to the focus countries and provided under the World Bank, UNICEF, and the Global Fund
-  An ARV product generally available to the focus countries and provided under the World Bank, UNICEF, and the Global Fund, and provided under the Emergency Plan

Source: GAO.

Notes: Data from GAO survey of ARV manufacturers during June and July of 2004, the Coordinator's Office, USAID, WHO, the World Bank, UNICEF, and the Global Fund. Numbers in this figure may not sum to numbers shown in table 1 due to rounding. As of December 2004, the ARV product shaded in black has been approved by FDA or another acceptable regulatory authority; those shaded in gray have been prequalified by WHO; and those without shading have been neither approved by FDA or another acceptable regulatory authority nor prequalified by WHO. We did not determine whether the different quality assurance processes result in medications of differing quality. Because laws of a country may affect whether a particular ARV product is available there, not all ARV products are available in all of the focus countries. Guyana and Vietnam are not eligible to receive the price shown for the product shaded in black.

^aManufacturer indicated that price quoted was negotiable, but not based on any specific purchase scenario.

^bManufacturer indicated that price quoted was nonnegotiable.

^cManufacturer indicated that price quoted was based on a 1 year / 10,000 patients per year purchase scenario.

Appendix III: Comments from the Department of State



United States Department of State

Assistant Secretary and Chief Financial Officer

Washington, D.C. 20520

Ms. Jacquelyn Williams-Bridgers
Managing Director
International Affairs and Trade
Government Accountability Office
441 G Street, N.W.
Washington, D.C. 20548-0001

DEC 6 2004

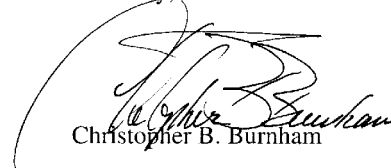
Dear Ms. Williams-Bridgers:

We appreciate the opportunity to review your draft report, "GLOBAL HIV/AIDS EPIDEMIC: Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited," GAO Job Code 290336.

The enclosed Department of State comments are provided for incorporation with this letter as an appendix to the final report.

If you have any questions concerning this response, please contact Myron Meche, Director, Office of the Global AIDS Coordinator, at (202) 663-2727.

Sincerely,



Christopher B. Burnham

cc: GAO – Chad Davenport
S/GAC – Randall Tobias
State/OIG – Mark Duda

**Department of State Comments on GAO Draft Report
GLOBAL HIV/AIDS EPIDEMIC: Selection of Antiretroviral Medications Provided under
U.S. Emergency Plan Is Limited
(GAO-05-133)**

On behalf of the United States Departments of State, Health and Human Services (HHS) and the United States Agency for International Development (USAID), we appreciate the opportunity to comment on the draft Government Accountability Office (GAO) report entitled *GLOBAL HIV/AIDS EPIDEMIC: Selection of Antiretroviral Medications Provided under the U.S. Emergency Plan Is Limited* (GAO-05-133).

The President's Emergency Plan for AIDS Relief (PEPFAR) has been committed from the beginning to providing treatment at the most cost-effective prices that can be found – but only drugs that are proved safe and effective. The Emergency Plan has moved forward with urgency to help build the human and physical capacity needed to deliver treatment, and to fund the purchase of HIV/AIDS drugs. The Administration strongly believes that persons served by the President's Emergency Plan deserve the same assurances of safety and efficacy that we expect for our own families. There should not be any double standard.

There is economic, human and ethical value in drug quality, which the draft report completely overlooks, and the significant health risks posed by poor quality anti-retrovirals (ARVs). Some drugs approved for the World Health Organization (WHO) pre-qualification list may not be equivalent to drugs approved by the Food and Drug Administration (FDA) within HHS, as they cannot be guaranteed to have undergone quality-assurance tests of the same rigor. Significantly, several generic drug manufacturers have voluntarily withdrawn their ARVs from the WHO pre-qualification list because of concerns over quality and potential risk to patients.

In early November, the Indian company Ranbaxy announced that it was withdrawing all of its generic versions of ARVs from the WHO pre-qualification list because of the company's uncertainty that their copy drugs were not bio-equivalent to the patented versions. On November 19, Hetero Drugs Limited, also of India, announced that it was withdrawing six ARVs from the WHO pre-qualification list to review data on their bioequivalence.

Though the events are recent, we have urged the GAO to mention these de-listings prominently in the report, because they go to the heart of the definition of what is "available" in these countries. Many nations make purchasing or procurement or even licensure/registration decisions on the basis of the WHO pre-qualification list: the WHO de-listings plus the voluntary withdrawal from the market and the list means that a number of products from several manufacturers in the GAO's charts are no longer "available" in the same way as before. It should be noted that the manufacturers and the WHO Secretariat are both recommending that no new patients be placed on these drugs until the manufacturers clear up the quality-assurance problems.

In addition, the chart provided on page 29 of the report is misleading, because not all of the generic ARV products listed are sold on the market in all of the 15 focus countries of the Emergency Plan. (Some, like those produced in Brazil and Thailand, might not be regularly

available in any of the 15 focus countries.) The chart therefore gives a distorted impression that the possible selection of ARVs in the 15 focus countries is wider than it actually is.

Poor quality drugs can add substantial cost in terms of adverse drug effects and lack of efficacy in treating HIV/AIDS. When appropriate concentrations of active drugs are not reached in the body, the human immunodeficiency virus is able more rapidly to mutate such that it becomes resistant to the drugs. This allows the virus to resume its devastation of the body's immune system more quickly. The only recourse in this situation is another combination of three or more drugs. Such "second-line" drugs, if available at all, are often several times the cost of the "first-line" drugs, which leads to a significant escalation in the cost of treatment.

It is also important to distinguish the issues of intellectual property and quality assurance. These issues are separate, but the draft report obscures the distinction between the two, and suggests that they arise in a sequential manner, which is not necessarily so. The Emergency Plan maintains that it will only use the highest-quality, safest drugs available, but that issue is separate from patent and intellectual property issues.

Clarification about Generics

The draft report uses the term "generic" throughout without defining it, and appears in certain cases to refer to drug products that are other than those manufactured by the innovator or brand-name company, and that are approved in some manner by non-U.S. regulatory bodies. At other points, the document uses the term to refer to products other than those manufactured by the innovator that HHS/FDA has approved or might approve. As this issue and the term "generics" are at the center of major controversy surrounding the fight against HIV/AIDS, it is worth spending some time to clarify the term as used in the United States compared to how it is used elsewhere in the international community.

The federal Food, Drug, and Cosmetic Act or HHS/FDA regulations do not define the term "generic drug." It is generally used informally to refer to drugs that 1) are not marketed by the brand-name company and 2) are substitutable for the brand-name product. HHS/FDA's more formal term to denote substitutable products is "therapeutic equivalents."

Therapeutic equivalents are drug products approved by HHS/FDA as safe and effective; contain identical amounts of the same active drug ingredient in the same dosage form and route of administration; meet applicable standards of strength, quality, purity, and identity; are bioequivalent; are adequately labeled; and are manufactured in compliance with Current Good Manufacturing Practice. Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

Because of the varying standards used to classify drugs as "generics" by regulatory authorities other than HHS/FDA, we do not know whether these drugs should be considered to be generic drugs (i.e., therapeutic equivalents) within the general meaning of the term as used in the United States.

To add even more complexity to the situation, many of the drug products HHS/FDA expects to approve or tentatively approve, and which will be subsequently acquired for use in the Emergency Plan, will not be drugs that are generic versions (i.e., therapeutic equivalents) of innovator products. Rather, a number of these drugs under consideration will be new fixed-dose combinations of previously approved single-entity drug products, or they will be new co-packaged products of drugs previously available only separately. These products would not be considered substitutable "generics" in the United States because they are not therapeutic equivalents to an approved brand-name product.

Outreach Under the Emergency Plan

The United States Government (USG) is reaching out to national drug regulatory agencies in the 15 Emergency Plan focus countries and providing training and technical assistance in the process of certifying the quality of ARVs. In the long run, this should increase the capabilities of these countries to manage the pharmaceutical supply chain and thereby help to reduce attendant costs.

To ensure the availability of high-quality pharmaceuticals under the Emergency Plan, HHS/FDA is reaching out to companies in the 15 focus countries as well as in other developing countries to facilitate their applications to the expedited review process. At least two generic drug companies have released press announcements that they have entered the expedited review process and are working with HHS/FDA to receive tentative approval for anti-retroviral drugs in support of the Emergency Plan.

This outreach effort will have tangible and rapid results because of procedures already in place in the Office of the Global AIDS Coordinator (OGAC). When a new combination drug for HIV/AIDS treatment receives a positive outcome (approval or tentative approval) under the expedited HHS/FDA review, OGAC will recognize that result as evidence of the safety and efficacy of that drug. Thus, the drug will be eligible to be a candidate for funding by the Emergency Plan for AIDS Relief, so long as international patent agreements and local government policies allow their purchase.

And we are already building momentum in reaching the President's treatment goals. As of July 31, 2004, the Emergency Plan is supporting ARVs for, at minimum, 24,900 HIV-infected men, women, and children in nine countries. Of this number, the Emergency Plan is directly funding ARV therapy for approximately 18,800 HIV-infected individuals at the point of service delivery. At least an additional 6,100 persons are receiving indirect treatment support through U.S. Government contributions to national, regional, or local activities, such as laboratory support, training, logistical systems strengthening, and treatment policy and protocol development. Over the next few months, numerous sites in all 15 focus countries have begun to provide ARV therapy with the goal of reaching at least 200,000 by June 2005. The Emergency Plan is well on its way to meeting that goal. By meeting this goal, the Emergency Plan will approximately double the number of persons receiving ARV therapy in sub-Saharan Africa. Outreach to national drug regulatory agencies in Emergency Plan focus countries is a key component of meeting treatment goals set by the President.

Bulk Purchasing

USG bulk purchasing will be made available in calendar year 2005 through the Emergency Plan Supply Chain Management System (SCMS) contract. The purpose of this project is to establish and operate a safe, secure, reliable, and sustainable SCMS to procure pharmaceuticals and other products needed to provide care and treatment of persons with HIV/AIDS and related infections. As described in "The President's Emergency Plan for AIDS Relief: U.S. Five-Year Global HIV/AIDS Strategy", an important focus of the Plan and a necessary tool for ensuring sustainability, is building the capacity of local providers to implement effective programs. In this regard, this project will have as a priority capacity building of essential supply chain management personnel to strengthen the quality and expand the reach of effective HIV/AIDS interventions. Emergency Plan focus countries will be able to voluntarily buy into this contract. This mechanism is expected to reduce costs significantly.

The United States Government supports several other activities as key parts of its treatment initiative. As the price of drugs continues to decrease, and individual governments and international donors purchase an increasing share of ARVs, the Emergency Plan support will shift to those elements that are supportive and necessary for effective treatment of patients:

- o Clinical guidelines and selection of ARV products;
- o Laboratory;
- o Training;
- o Counseling;
- o Adherence interventions; and
- o Supportive care, including palliative care.

Within the category of direct procurement and distribution of drugs, the Emergency Plan is also supporting an increasing array of interventions that increase the efficiency and lower the total cost of ARV distribution:

- o Shipping and attendant costs;
- o Storage and product maintenance;
- o Distribution;
- o Rational Use; and
- o Post-marketing surveillance for product defects or adverse reactions among patients.

Patent Requirement

The report repeatedly raises what it refers to as the Emergency Plan's "patent requirement." To be sure, the Emergency Plan's "patent requirement" is not a requirement that OGAC imposed upon itself. Rather, it is a statutory restriction that applies to the use of any funds subject to the Foreign Assistance Act of 1961, as amended. This section, Section 606, states the following:

Funds appropriated pursuant to this Act shall not be expended by the United States Government for the acquisition of any drug product or pharmaceutical product manufactured outside of the United States if the manufacturer of such drug product or pharmaceutical product

in the United States would involve the use of, or be covered by, an unexpired patent of the United States which has not previously been held invalid by an unappealed or unappealable judgement or decree of a court of competent jurisdiction, unless such manufacture is expressly authorized by the owner of such patent.

Because the Emergency Plans' funds are subject to the Foreign Assistance Act of 1961, as amended, the Global AIDS Coordinator must carry out the Emergency Plan consistent with Section 606. As set forth in the GAO Report, it is the case that the Foreign Operations, Export Financing Act and Related Programs Appropriations Act of 2004 provides "notwithstanding" authority that the Coordinator may use to overcome the statutory prohibition of Section 606. After careful consideration, the Office of the Global AIDS Coordinator has decided to exercise this available notwithstanding authority with respect to Section 606, as necessary.

We appreciate the opportunity to respond to this report, and we hope that this information is useful to you. Please do not hesitate to contact us if we can be further assistance.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Michele Orza, (202) 512-7119

Acknowledgments

Other key contributors to this report are George Bogart, Chad Davenport, J. Alice Nixon, Nkeruka Okonmah, and Roseanne Price.

Related GAO Products

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