By Kartik K. Venkatesh, Kenneth H. Mayer, and Charles C.J. Carpenter

Low-Cost Generic Drugs Under The President's Emergency Plan For AIDS Relief Drove Down Treatment Cost; More Are Needed

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ABSTRACT **The President's Emergency Plan for AIDS Relief (PEPFAR) was originally authorized in 2003 with the goal of supporting HIV prevention, treatment, and care within fifteen focus countries in the developing world. By September 2011 nearly 13 million people around the world were receiving HIV/AIDS-related care through PEPFAR, and 3.9 million were receiving antiretroviral treatment. However, in the early years of the program, access to antiretroviral drugs was hampered by the lack of a licensing process that the US government recognized for generic versions of these medications. Ultimately, the obstacle to approval of generic antiretroviral drugs was removed, which led to PEPFAR's considerable success at making these treatments widely available. This article outlines PEPFAR's evolving use of generic antiretroviral drugs to treat HIV in the developing world, highlights ongoing initiatives to increase access to generic antiretrovirals, and points to the need for mechanisms that will speed up the approval of new generic drugs. The striking decline in antiretroviral treatment costs, from $1,100 per person annually in 2004 to $335 per person annually in 2012, is due to the availability of effective generic antiretrovirals. Given growing resistance to existing drugs and the planned expansion of treatment to millions more people, access to newer generations of generic antiretrovirals will have to be expedited.**

Kartik K. Venkatesh (kartik_venkatesh@brown.edu) is a medical student at the Alpert Medical School, Brown University, in Providence, Rhode Island.

Kenneth H. Mayer is the director of HIV prevention research at Beth Israel Deaconess Medical Center and medical research director of Fenway Health, in Boston, Massachusetts.

Charles C.J. Carpenter is a professor of medicine at the Alpert Medical School, Brown University.

The President's Emergency Plan for AIDS Relief (PEPFAR) was authorized by Congress in May 2003 with the goal of supporting the prevention of HIV infection, the treatment of people living with HIV, and the care of families affected by HIV in fifteen focus countries in the developing world. The focus countries are among those that are most severely affected by HIV (Exhibit 1); the program also includes limited activities and investments in other countries. Twelve of the focus countries are in sub-Saharan Africa.[1]

To carry out this program, President George W. Bush requested $15 billion over a five-year period for PEPFAR. The funding was primarily focused on HIV/AIDS, but it also covered tuberculosis and malaria. PEPFAR's initial goals were to support the care of ten million of the people then living with HIV/AIDS; provide antiretroviral treatment for two million of the people infected with HIV; and support efforts to prevent seven million new HIV infections.[2] Those goals were exceeded, and in 2008 PEPFAR was reauthorized by Congress with a five-year allocation of $48 billion.[3,4]

By September 2011 nearly 13 million people around the world were receiving HIV/AIDS-related care through PEPFAR, and 3.9 million were receiving antiretroviral treatment.[5] AIDS-related

EXHIBIT 1

Characteristics Of The Focus Countries In The President's Emergency Plan For AIDS Relief (PEPFAR)

Country	HIV prevalence (percent)	Number of people receiving treatment in 2010	Treatment provision rate[a] (percent)	Funding in 2011 (millions of dollars)
Botswana	24.8	12,200	93	84.4
Côte d'Ivoire	3.4	61,200	37	105.2
Ethiopia	1.1	207,900	—[b]	293.0
Guyana	1.8	3,000	84	14.9
Haiti	1.9	27,900	51	158.5
Kenya	6.3	410,300	61	517.3
Mozambique	11.5	138,800	40	268.8
Namibia	13.1	80,300	90	102.6
Nigeria	3.6	334,700	26	488.6
Rwanda	2.9	53,800	88	115.4
South Africa	17.8	5,600,000	55	548.7
Tanzania	5.6	255,500	42	357.2
Uganda	6.5	207,900	47	323.4
Vietnam	0.4	31,000	52	84.8
Zambia	13.5	286,000	72	306.7

SOURCES For HIV prevalence, Note 47 in text. For people receiving treatment, Note 5 in text. For treatment coverage, World Health Organization. Global health observatory data repository: antiretroviral therapy coverage, 2010 [Internet]. Geneva: WHO; [cited 2012 Jun 6]. Available from: http://apps.who.int/ghodata/?vid=23300. For funding, President's Emergency Plan for AIDS Relief. Fiscal year 2011: PEPFAR operational plan [Internet]. Washington (DC): PEPFAR; 2011 Dec [cited 2012 Jun 6]. Available from: http://www.pepfar.gov/documents/organization/183974.pdf. [a]Treatment provision rate is the percentage of people infected with HIV and in need of treatment who are receiving antiretroviral therapy. Therapy is funded by several sources. Although PEPFAR is the largest donor, the relative contributions of donors vary considerably across countries. [b]Not available.

mortality in countries that received PEPFAR-funded assistance decreased by more than 10 percent between 2004 and 2007, compared to countries without PEPFAR funds; this achievement translated into 1.2 million lives saved.[6]

Because HIV tends to develop resistance to antiretroviral drugs rapidly when the virus is not fully suppressed, a successful antiretroviral therapeutic regimen requires the use of three different drugs that target at least two distinct steps in the virus's life cycle.[7] Over the past fifteen years, there have been remarkable advances in the development of better-tolerated therapeutic regimens that are also more convenient to follow, some of which now require as few as one to three pills once a day.[8] However, these therapeutic advances—which offer increased efficacy, greater acceptability, and more convenient dosing schedules, which in turn improve medication adherence—resulted in extremely expensive regimens.[9]

When PEPFAR was conceived, an immediately recognized hurdle was the cost of providing antiretroviral therapy to the target population of two million people by the end of 2008. The initial PEPFAR guidelines established by the Office of the Global AIDS Coordinator stated that all antiretrovirals purchased by PEPFAR must have received at least tentative approval by the Food and Drug Administration (FDA).[1] Such approval indicated that a generic drug met all of the FDA's requirements for approval but could not be marketed in the United States until the brand-name drug's patent protection expired.

In 2003, when PEPFAR was initiated, no generic antiretrovirals had received this approval, so only brand-name antiretrovirals were approved for purchase through PEPFAR. The cost of brand-name antiretrovirals has generally been ten to forty times higher than that of the corresponding generic medications. Initially, this restriction severely limited the number of patients who could receive antiretroviral treatment through PEPFAR.[10]

Recognizing the need to rapidly expand access to generic antiretroviral medications, the FDA developed an expedited review and inspection process for generic antiretrovirals. By the end of 2007 more than 90 percent of antiretrovirals provided in eleven of the PEPFAR focus countries were generic. This article outlines the evolving use of generic antiretrovirals as a critical element in providing HIV treatment in the developing world through PEPFAR. It also highlights the continuing need for effective expedited mechanisms for generic drug approval.

Competing Quality Assurance Requirements For Antiretrovirals

TENTATIVE APPROVAL BY THE FOOD AND DRUG ADMINISTRATION Since the earliest days of

PEPFAR, critics have voiced concern about the limited and costly brand-name drug formulary. As noted, initially only brand-name antiretrovirals, which were produced by multinational pharmaceutical companies, could be obtained by PEPFAR, and the cost was more than $10,000 per year for each triple-drug regimen.

To address access issues, the FDA initiated an expedited review process in May 2004 for tentative approval of essential generic antiretrovirals.[11] The agency used outreach activities to encourage manufacturers worldwide to submit US marketing applications for single-entity, fixed-dose-combination, and copackaged versions of previously approved antiretrovirals.[12]

Initially, the tentative approval process was slow. By the end of 2004 only two generic antiretrovirals had been approved. But by 2006, 27 percent of PEPFAR's purchases of antiretrovirals were of generics tentatively approved by the FDA, and by 2011, the figure was 92 percent.[13] By 2012 more than 140 generic antiretroviral formulations had received tentative FDA approval.[12] The generic antiretroviral drugs that have been tentatively approved by the FDA are shown in Exhibit 2.

The initially slow pace of the FDA's tentative approval of generic drugs was a major focus of criticism during the first three years of the PEPFAR program.[14] The first director of the Office of the US Global AIDS Coordinator, Ambassador Randall Tobias, had served as CEO of the major pharmaceutical manufacturer Eli Lilly prior to his government service, and critics suggested that the office was not making a good-faith effort to facilitate tentative approval of generic antiretrovirals because that threatened the market share of brand-name pharmaceuticals. They charged that PEPFAR's initial modus operandi was inconsistent with the program's mandate, "to fund the purchase of the lowest cost ARVs [antiretrovirals] from any source, regardless of origin, whether copies, generic or branded, as long as these drugs are proven safe, effective and of high quality and their purchase is consistent with international law."[14(p158)]

PEPFAR's quality assurance requirement of tentative FDA approval also initially prevented the program from fully coordinating with other antiretroviral programs in the focus countries, as detailed further below.

PREQUALIFICATION BY THE WORLD HEALTH ORGANIZATION These in-country programs, as well as other early major antiretroviral donors—including the World Bank; the multinational Global Fund to Fight AIDS, Tuberculosis, and Malaria; and agencies of the United Nations—relied on the World Health Organization Prequalification of Medicines Program to ensure the quality of antiretrovirals for local purchase.[1] The World Health Organization prequalification process includes multiple levels of quality assurance, such as tracking the product from its origin and inspecting manufacturing sites.[15] Since its inception in 2001, this process has prequalified more than 240 medicines for priority diseases, including HIV, tuberculosis, and malaria. However, PEPFAR could not purchase antiretrovirals until they obtained FDA tentative approval, limiting the program's ability to purchase the focus countries' generic antiretrovirals of choice.

In 2007 an Institute of Medicine review of PEPFAR[1] strongly endorsed a single, rigorous, standardized international mechanism to support national quality assurance programs for antiretrovirals. Most PEPFAR focus countries already required World Health Organization prequalification for the generic antiretrovirals that they purchased. Therefore, the Institute of Medicine recommended that the Office of the US Global AIDS Coordinator evaluate the World Health Organization prequalification process and—unless the office had substantive concerns about it—accept it and support it as the single accepted global standard for assuring the quality of generic medications.[1] A single standard might have enabled more rapid access to antiretrovirals within PEPFAR focus countries.

However, the Office of the US Global AIDS Coordinator decided to continue to require FDA tentative approval of all generic antiretrovirals as a prerequisite for PEPFAR purchase of the drugs, given the scope of the planned investment in HIV treatment and the explicit aim of demonstrating that drugs supplied by PEPFAR

EXHIBIT 2

Generic Antiretroviral Drugs Tentatively Approved By The Food And Drug Administration (FDA)

Drug	Drug class	Year of tentative FDA approval
Didanosine	NRTI	2004
Lamivudine	NRTI	2005
Nevirapine	NNRTI	2005
Efavirenz	NNRTI	2005
Stavudine	NRTI	2005
Zidovudine	NRTI	2005
Abacavir	NRTI	2006
Tenofovir	NRTI	2007
Atazanavir	PI	2008
Emtricitabine	NRTI	2008
Lopinavir	PI	2009

SOURCE Note 12 in text. **NOTES** Year of tentative approval is first time a given drug was approved for generic manufacture. Combined and coformulated antiretrovirals are not included. NRTI is nucleoside reverse transcriptase inhibitor. NNRTI is nonnucleoside reverse transcriptase inhibitor. PI is protease inhibitor.

would be of equal quality to those provided to US patients. As a result, some critics[16] argued that antiretroviral prices may have been artificially high for years longer than necessary. In comparison, the Global Fund accepted World Health Organization certification for the same generic antiretrovirals that were later approved by the FDA. The Global Fund's policy meant that as early as 2002, the fund was paying considerably less for antiretrovirals than PEPFAR was.[17]

Subsequently, the World Health Organization accepted FDA tentative approval of antiretrovirals as equivalent to its own prequalification.[11] Most manufacturers of generic drugs now pursue the FDA tentative approval route.[12]

PEPFAR's Supply Chain Management System To further accelerate the procurement of generic antiretrovirals, in 2006 PEPFAR established the nonprofit Supply Chain Management System, a partnership of thirteen member organizations—including organizations in recipient countries, private-sector corporations, and academic institutions[18]—that was created to provide a cost-effective and secure supply of products for HIV/AIDS programs in PEPFAR-supported countries.

The Supply Chain Management System helps countries forecast local antiretroviral needs; procure and distribute the drugs; and provide other services needed for the reliable supply of antiretrovirals. By 2009, 50 percent of the antiretroviral drugs used in PEPFAR programs were purchased via the Supply Chain Management System.[10] In its first year of operation, the system increased the share of generic antiretrovirals procured to 88 percent—up from 72 percent the year before—saving more than $30 million. Coupled with the accelerated FDA tentative approval process, this system allowed PEPFAR to greatly expand access to generic antiretrovirals.

Generic Antiretrovirals

Multiple studies conducted in settings with limited resources have shown that fixed-dose combinations of generic antiretrovirals are as clinically efficacious in treating HIV disease as their brand-name equivalents.[19–21] However, as discussed above, the broad use of generic drugs was initially hampered by PEPFAR's quality assurance standards.

Several major manufacturers of generic antiretrovirals stated that both the cost and the time frame for obtaining FDA approval were prohibitive during the first several years of the PEPFAR program, especially in comparison to the process of World Health Organization prequalification.[11] As already noted, the Office of the Global AIDS Coordinator and the FDA worked to speed up the approval process, and by 2011 the average time for FDA evaluation and tentative approval of generic antiretrovirals had been reduced to two months.[22]

By 2011 almost all antiretrovirals purchased by PEPFAR were generic equivalents that had received FDA tentative approval.[10] Thus, despite access issues in the early years of the program, the current process for the approval and purchase of antiretrovirals appears to be both clinically and operationally sound.

Reduced Cost of Drugs The cost to manufacturers of generic drugs for the FDA approval process has not proven to be prohibitive, as shown by the fact that more than 140 generic antiretroviral formulations have now been tentatively approved. Between 2004 and 2012 the annual cost of antiretrovirals per patient in the PEPFAR program fell from $1,100 to $335. By 2011 the estimated mean total cost per patient-year of treatment, including financial and in-kind contributions from all sources, was $768. Excluding the contributions of partner governments and other donors, the estimated PEPFAR cost per patient-year of treatment was $335. These decreases in the cost of treatment are partly because of increased contributions from national partners in moderate-income countries and ongoing efficiency gains in the treatment programs under way in various countries.[22]

In countries supported by PEPFAR, the availability of generic antiretrovirals allowed for greatly increased drug procurement at substantial estimated cost savings. In a recent review of the PEPFAR program,[10] its leaders noted that although antiretroviral expenditures increased from $116.8 million in 2005 to $202.2 million in 2008, procurement nearly quadrupled—increasing from 6.2 million to 22.1 million monthly medication packs during the same period.

By 2008 generic antiretrovirals represented 76.4 percent of treatment expenditures, and the proportion of generic packs used was 89.3 percent.[23] In 2008 eight PEPFAR-funded programs procured at least 90 percent of their antiretroviral packs in generic form. As a result, estimated yearly savings from the use of generic antiretrovirals increased dramatically, from $8 million in 2005 to $24 million in 2006, $75 million in 2007, and $214 million in 2008.[10,22] By 2012 the cost of treatment per patient-year to PEPFAR is estimated to have declined 23 percent from the previous year.[22]

These reduced costs reflect more than just a switch to generic antiretrovirals, however. The Office of the US Global AIDS Coordinator has documented that per patient costs tend to drop

as sites become more adept at managing HIV disease treatment.[24]

EXPANDED DELIVERY OF SERVICES PEPFAR also has rapidly expanded its service delivery. In 2011, in addition to providing antiretroviral treatment for more than 3.9 million people, it provided HIV testing and counseling to more than 9.8 million pregnant women and antiretroviral prophylaxis to more than 660,000 HIV-infected pregnant women, resulting in the prevention of more than 200,000 infant HIV infections.[2] PEPFAR is also increasingly supporting evidence-based prevention activities, including male circumcision.[25] However, PEPFAR's greatest single expenditure continues to be for the provision of antiretrovirals, accounting for almost 40 percent of its annual budget. With the recent demonstration that earlier initiation of treatment decreases heterosexual HIV transmission in resource-limited settings,[26] it is clear that the increased availability of antiretrovirals should also reduce the future spread of the pandemic.

Access To Newer Generic Antiretrovirals

NEED FOR NEWER DRUGS The increased availability of generic versions of older antiretrovirals constitutes a major success for PEPFAR. However, newer second- and third-line drug regimens are prohibitively expensive.

PEPFAR currently projects that up to 10 percent of people receiving antiretrovirals will develop resistance to their treatment regimen each year. Thus, the use of effective alternative regimens—which are usually more complex and expensive than the initial treatment—for those who have developed resistance to a first- or second-line antiretroviral regimen has become a major priority.[27,28] Preliminary surveillance data collected by the World Health Organization suggest that the transmission of HIV that is resistant to all drug classes in parts of the developing world where antiretroviral therapy is widely available is less than 5 percent.[29]

However, in some places these rates are much higher. For example, drug resistance in Kenya and South Africa has been shown to exceed 80 percent in people with unsuppressed virus—that is, a high concentration of HIV RNA in plasma, known as the "viral load."[30,31]

LACK OF GENERIC VERSIONS OF NEWER DRUGS Unlike first-generation drugs, which are now available from a wide range of manufacturers, newer generations of antiretrovirals are mainly provided by a few multinational pharmaceutical corporations. Additionally, although "preferential pricing" mechanisms are in place with manufacturers to reduce the costs of drugs in the developing world, there are still large price variations across countries.[32]

One major barrier to the development of generic formulations of newer antiretrovirals has been the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), established in January 1995.[33] This agreement protects intellectual property rights in international trade and ensures that profits from any new product are distributed exclusively to the patent holder for the duration of the patent, which is usually seventeen years from the issue date.[11] Thus, generic manufacturers could not market a drug until proprietary patents expire. This continuing issue involves the balance of interests between the major patent-holding pharmaceutical companies in developed countries and the public health needs in developing countries.

Because of the magnitude of the HIV/AIDS pandemic in the developing world, World Trade Organization members—some of which, such as India, export generic drugs—approved a decision in Doha, Qatar, in 2001 that offered an interim waiver under the Agreement on Trade-Related Aspects of Intellectual Property Rights. The waiver allows member countries to export pharmaceutical products made under compulsory licenses (licenses granted by a government or governments that allow someone else to produce a patented product without the consent of the patent owner) to least-developed countries.[34] As a result, more than two-thirds of the world's generic antiretrovirals are currently manufactured in India. In addition, there generic drug manufacturers in Thailand, Brazil, and South Africa now also provide antiretrovirals to developing countries.[35,36]

However, these waivers are available only for drugs that were already on the market at the time of the agreement. Major pharmaceutical companies can refuse to allow generic manufacturers to make versions of compounds developed after the agreement's 2001 date, which raises concerns about access to affordable medication for patients unable to use first-line antiretroviral therapy.

In addition, since 2005 developing countries have had to adhere to the international intellectual property standards of the Agreement on Trade-Related Aspects of Intellectual Property Rights, which limits their flexibility in producing new generic antiretrovirals based on newly developed proprietary compounds.[37] Until 2016, least-developed countries have a waiver from these obligations on patents and protection from prosecution for producing drugs that are still

under patent.[17,32]

STATUS OF CERTAIN NEW THERAPIES Some new therapies are available in generic versions. Eight generic nucleoside reverse transcriptase inhibitor drugs, two generic nonnucleoside reverse transcriptase inhibitor medications, and three generic protease inhibitors have received FDA tentative approval.[24]

The newer agents include generic darunavir, a highly potent and well-tolerated protease inhibitor that is currently available only in India; and generic etravirine, a nonnucleoside reverse transcriptase inhibitor that can be used in some patients who cannot use first-line nonnucleoside reverse transcriptase inhibitors but that is currently available only in South America.

At present, there are no generic forms available of antiretroviral integrase inhibitors or of entry inhibitors, which target HIV replication at different points in the virus's life cycle. Both will be critical in future responses to increasing levels of antiretroviral resistance in patients who do not respond to first—or second-line regimens or who are newly infected by a drug-resistant strain of HIV.

Monitoring Drug Resistance

Essential components of the clinical management of long-term effective antiretroviral therapy include periodic monitoring of the immune function—using counts of patients' CD4+ lymphocytes, which are white blood cells that play a role in the immune system's defenses against tumors and infections—and assessing whether HIV is fully suppressed by, for example, monitoring the viral load.[7,37] Lack of virologic suppression indicates that the patient is not responding to the medication, because of either nonadherence or the development of resistance to the drug.

A survey of PEPFAR sites in 2006–07 showed that fewer than a third offered viral load monitoring as a component of care.[38] The current cost of viral load assays is $20–$100 per test in the developing world. As a result, the World Health Organization does not currently recommend viral load monitoring.[8]

However, measuring the CD4+ count alone may not indicate treatment failure promptly. Patients who remain on regimens that fail to suppress HIV run the risk of developing mutations of the virus that are resistant to multiple drugs, which makes the selection of a new regimen more challenging.[39] In addition, changing treatment regimens based on CD4+ counts without viral load monitoring raises the concern that clinicians may change therapy too early—because the counts can decline despite adequate viral load suppression—or too late—because the counts can remain stable despite inadequate viral suppression.[40] Strains of HIV that are resistant to multiple drugs can then be transmitted to other people, resulting in the need for more-expensive treatment regimens for the patient as well as his or her partners. Thus, there is an urgent need for effective point-of-care viral load assays that can be utilized in resource-limited settings.

As an increasing number of people infected with HIV in PEPFAR's focus countries receive antiretroviral therapy, it is important not only to provide generic antiretroviral drugs, but also to regularly monitor viral load and provide resistance testing when needed.

Health Care Service Delivery Within PEPFAR

Nearly one-half of PEPFAR's resources have been spent on antiretrovirals and treatment-related infrastructure, and about one-fifth on prevention programs.[22] Some policy makers have advocated alternatives to further expansions of HIV treatment through PEPFAR, such as the proposed Mother and Child Campaign. The goal is to invest more broadly in maternal and child health because early treatment of respiratory and diarrheal disease could save more lives at a lower cost than is now the case.[41]

Although PEPFAR originally focused on HIV/AIDS treatment, care, and prevention, the program's 2008 reauthorization also supports ancillary services including nutrition, access to safe water and sanitation, and certain income-generating activities.[4] Additionally, from 2005 through 2009 PEPFAR increased its direct bilateral funding (from the United States to a foreign country, as distinct from multilateral funding channeled through the Global Fund) for tuberculosis and HIV programs (from $26 million to $150 million per year), supporting tuberculosis treatment for more than 308,000 HIV-infected people in 2009.[42] Because many countries do not have enough trained health care workers to address the expanding HIV pandemic, PEPFAR has also supported the strategic shifting of tasks to health care personnel with relatively less clinical training.[39,43]

It is important to note that PEPFAR is not the only international agency providing funds for HIV treatment in partner countries, and in certain countries it is not the first international agency to do so. Other early global players include the Global Fund, the Clinton Health Access Initiative, and UNITAID. Drug procurement activities have increasingly been coordinated between PEPFAR and these organizations.

As PEPFAR continues to move in the direction of further sustainability through individual country "ownership"—that is, management, control, and even funding—of HIV prevention, care, and treatment, the need for continued close collaboration between the US government, the Global Fund, and host countries on the broader issues of delivery of services and health care infrastructure will be crucial.[44] PEPFAR's cost savings through increased use of generic antiretrovirals, estimated at more than $320 million between 2005 and 2008 alone, have allowed the program to increase its investments in related activities—including training for health care workers and expanding the direct provision of services to patients.

PEPFAR is currently making the transition from an emergency-oriented program to one focused on sustainable long-term access to care, and it has expanded its priorities beyond increased procurement of generic antiretrovirals to emphasize health system strengthening, capacity developing, and quality of care.[45]

Conclusion

PEPFAR has made contributions of historic magnitude to address the global AIDS pandemic, providing antiretroviral therapy to nearly four million HIV-infected men, women, and children since 2003. This number constitutes more than half of the people in low- and middle-income countries estimated to be receiving HIV treatment. In addition, since its inception, PEPFAR has successfully and rapidly expanded health care service delivery.[6,46,47]

However, the sobering realities are that the global HIV pandemic continues to grow, with more than 2.5 million people infected with the virus each year,[48] and that for each person currently receiving treatment, an estimated four others in need of treatment are not receiving it.[49] PEPFAR's increasing use of generic drugs has been essential to expanding access to these medications.

The announcement by President Barack Obama on World AIDS Day, December 1, 2011, of the objective to have more than six million people receiving antiretrovirals through PEPFAR by 2013 highlights the need to double the availability of generic antiretrovirals and to increase the availability of second- and third-line antiretrovirals.[50] In addition, with the current aim of increasing access to antiretrovirals to treat 90 percent of the people in countries that receive PEPFAR funding with a CD4+ cell count of less than 350/mm^3 at a time when PEPFAR faces a 10 percent decrease in its total funding for fiscal year 2013,[51] the need for generic antiretrovirals will continue to increase sharply.

Even if the Obama administration is able to meet its stated goal, more than half of people who need antiretroviral treatment will still not be receiving it.[8] To deal with this remaining unmet need, continuing attention must be paid to expanding the availability of generic medications, as well as to the use of effective clinical monitoring and the provision of care.

It is incumbent on US policy makers to work with major multinational pharmaceutical producers, including overseas manufacturers of generic drugs, to determine how best to expedite the manufacture of essential generic versions of new antiretrovirals, to meet the emerging treatment gap—that is, the increasing number of people who need treatment but do not yet have access to it.[52] One important step to take is convening meetings of manufacturers of brand-name and generic drugs to discuss ways to solve the problem.

Expanding mechanisms to strengthen the bargaining position of purchasing countries—for example, negotiating as a group with manufacturers, procuring material in bulk, increasing the global transparency of drug prices, and facilitating negotiations with third parties such as global nongovernmental organizations—may also help.[53] In addition, voluntary patent pools, in which pharmaceutical companies voluntarily allow the use of their patents by generic manufacturers making medicine for developing countries, may help expand the availability of generic antiretrovirals.[10,17,54]

Emerging data show that antiretrovirals may also be a means of HIV prevention. As a result, PEPFAR may need to consider new indications for the use of these drugs.[26,55]

In its first nine years, PEPFAR has made unprecedented strides and proved that a worldwide expansion of HIV treatment and prevention programs is both possible and effective, resulting in millions of lives saved and infections averted. A major factor in PEPFAR's success has been its increasing ability to use generic antiretrovirals, allowing more people to receive these lifesaving drugs as well as freeing up funding to further expand health care delivery in the developing world. For this success to continue, PEPFAR must pay attention to ensuring access to newer generations of generic antiretrovirals. ■

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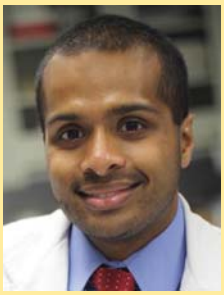
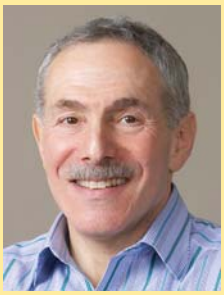
ABOUT THE AUTHORS: KARTIK K. VENKATESH, KENNETH H. MAYER & CHARLES C.J. CARPENTER



Kartik K. Venkatesh is a medical student at Brown University.

In this month's *Health Affairs*, Kartik Venkatesh and coauthors discuss the history of the President's Emergency Plan for AIDS Relief in moving to make generic antiretroviral drugs widely available in the developing world. The use of generics has led to a sharp decline in treatment costs, from $1,100 per person annually in 2004 to $335 per person annually in 2012. The authors describe how various factors, including developing resistance to existing drugs, will require new mechanisms to speed up the approval of new generations of generic antiretrovirals.

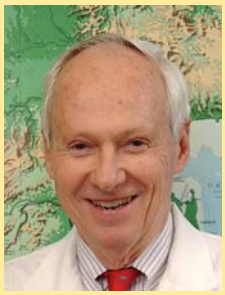
Venkatesh is pursuing his medical degree as part of a National Institutes of Health–funded medical and doctoral degree training program at the Brown University Alpert Medical School. His research, funded primarily by a training grant from the National Institute of Mental Health, has examined the natural history of HIV disease and the preventive impact of wider access to generic antiretroviral therapy in southern Africa and India. Venkatesh holds a doctorate in epidemiology from Brown University, where he focused on the impact of antiretroviral therapy in preventing HIV infection in the developing world.



Kenneth H. Mayer is director of HIV prevention research at Beth Israel Deaconess Medical Center.

Kenneth Mayer is the director of HIV Prevention Research at Beth Israel Deaconess Medical Center and a visiting professor at Harvard Medical School. He is also medical research director of Fenway Health, the largest center focusing on sexual and gender minority health in the United States. He is an adjunct professor of medicine and epidemiology at Brown University.

Previously, Mayer directed the Brown University AIDS Program. He has conducted community-based research since the start of the AIDS epidemic and has led multiple studies of biobehavioral interventions to prevent HIV transmission. Mayer is on the Governing Council of the International AIDS Society. He has a medical degree from Northwestern University.



Charles C.J. Carpenter is a professor of medicine at Brown University.

Charles Carpenter is a professor of medicine at Brown University's Alpert Medical School, where he has been involved in the clinical management of people living with HIV. He is also director of the Lifespan/Tufts/Brown Center for AIDS Research and director of the Brown University AIDS Center. He was a professor of medicine and director of the Division of Infectious Diseases at the Johns Hopkins University for several years before becoming a professor and chair of the Department of Medicine at Case Western Reserve University.

Carpenter has served as a member of the National Institutes of Health AIDS Executive Committee, the National Advisory Allergy and Infectious Diseases Council, and the US Public Health Service AIDS Task Force. He also chaired a subcommittee of the Institute of Medicine committee charged with evaluating the President's Emergency Plan for AIDS Relief during 2004–08. Carpenter holds a medical degree from the Johns Hopkins University.