

effects that are considered socially undesirable, such as a manufacturer's development of a new formulation of a product to extend patent life, can be seen as one cost that is incurred to collect the very large benefits of the law. The policy question then becomes what the net benefits of addressing the legislation's side effects might be.

Recent congressional debates have focused on regulating author-

ized generic drugs and limiting the ability of brand-name manufacturers to settle patent litigation through payments to generic manufacturers. In these cases, Congress seems to be directing its attention sensibly to areas in which modification of the law may reduce problematic conduct without undermining the law's benefits.

An interview with Dr. Frank can be heard at www.nejm.org.

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Closing the Affordability Gap for Drugs in Low-Income Countries

Robert Steinbrook, M.D.

The cost of treating human immunodeficiency virus (HIV) infection is decreasing. Nonetheless, tenofovir–emtricitabine–efavirenz, the standard first-line treatment in North America and Europe, is prescribed rarely in low- and middle-income countries. The lowest annual cost for a generic formulation of this regimen is still hundreds of dollars more than the \$100 annual cost of generic stavudine–lamivudine–nevirapine, an effective but less safe alternative that has been largely abandoned in Western countries (see Figure 1).¹

Unfortunately, many medications remain unaffordable in low- and middle-income countries. In the public sector, medicines are often provided free of charge, but essential drugs may be unavailable.² If they were less expensive, governments could provide them to more patients and international drug aid would benefit more people. In the private sector, medicines are more available but not more affordable. One

way to estimate affordability is to calculate the number of days the lowest-paid government employee would have to work to purchase a 1-month treatment regimen.² The affordability of standard treatment for coronary heart disease in the private sector varies from less than 2 days' wages in Bangladesh and Sri Lanka to about 5 in Brazil, Nepal, and Pakistan to more than 18 in Malawi (see Figure 2). The affordability range of standard asthma and diabetes treatments is similar.³

Medicines may be unavailable because of bureaucratic factors that delay licensure and discourage manufacturers from introducing drugs into low-income countries. Manufacturers' prices are an important cause of unaffordability, but there are many other factors, including import tariffs and taxes, distribution costs, a lack of comparative price data, and markups by distributors, pharmacies, and doctors who dispense medications.

The affordability of generic

drugs may be improved by increasing the efficiency and volume of production, prescribing the lowest effective dose, clarifying treatment guidelines so that manufacturers can focus on fewer drugs, stimulating competition, negotiating with manufacturers, and publicizing the lowest prices.¹ However, it may take years to streamline production and maximize volume-related efficiencies. Without robust competition, generic manufacture does not lead to the lowest prices; retail prices may dwarf production costs. A credible threat of government action may also encourage price reductions.

Drug companies have issued nonexclusive licenses for manufacturers to produce generic versions of patented medicines for sale in low-income countries and have established differential pricing for countries of various income levels. Voluntary licenses, however, may limit the countries in which the drugs can be sold and impose conditions that some

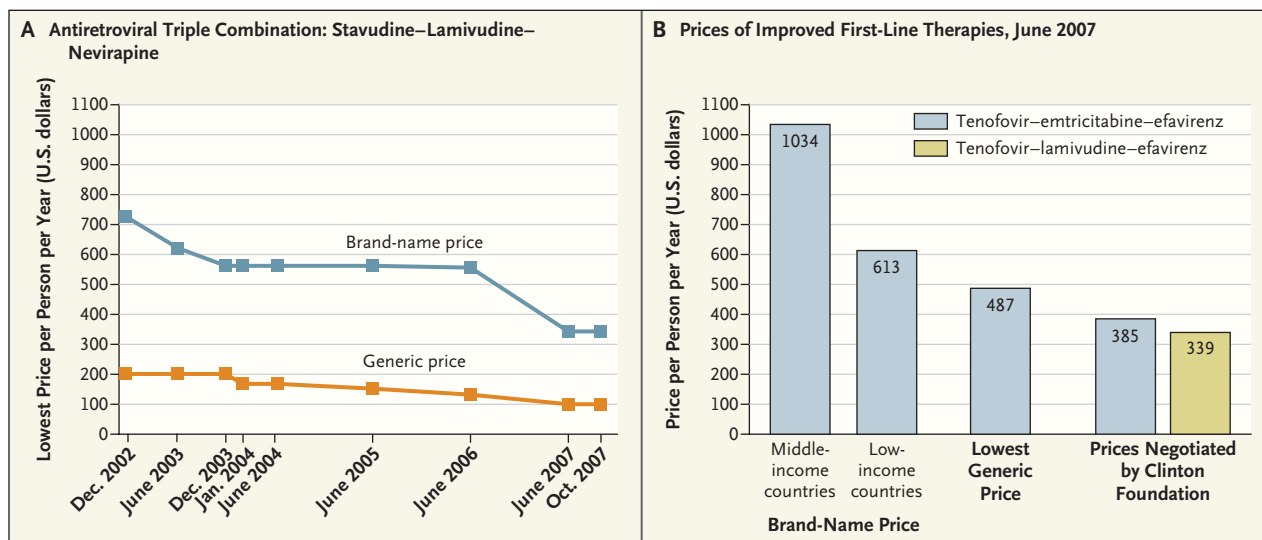


Figure 1. Annual Cost of Three First-Line Treatment Regimens for HIV Infection.

Panel A shows the annual price per patient of an older treatment — 30 mg of stavudine, 150 mg of lamivudine, and 200 mg of nevirapine, administered as one pill twice daily (760 mg of active pharmaceutical ingredients [API] per day). Panel B shows the annual price per patient of two newer treatments: 300 mg of tenofovir, 200 mg of emtricitabine, and 600 mg of efavirenz (1100 mg of API) and 300 mg of tenofovir, 300 mg of lamivudine, and 600 mg of efavirenz (1200 mg of API), a fixed-dose combination that will probably be marketed within the next several months. Both regimens are administered as one pill once daily. According to the World Health Organization's 2006 treatment guidelines, emtricitabine and lamivudine are interchangeable. The lower of the two prices for brand-name tenofovir–emtricitabine–efavirenz is also available in middle-income countries with an HIV prevalence of 1% or greater among adults. The generic tenofovir–lamivudine–efavirenz will be available at the \$339 annual price to the approximately 70 countries participating in the Clinton Foundation HIV–AIDS procurement consortium; the product will not be available in North America or Europe. Data are adapted from Médecins sans Frontières.¹

manufacturers find unacceptable. Although there is wide support for tiered pricing for HIV, malaria, and tuberculosis medications, there is disagreement about how to apply this mechanism to other drugs, how to determine which countries qualify, how to set price differentials, and how to prevent price spillovers to wealthier countries.⁴ Differential pricing schemes vary widely among manufacturers, creating confusion for purchasers.¹ Moreover, in countries such as China and India, there are many people with high incomes who can afford Western prices, although most people cannot.

Compulsory licensing, a legal means for allowing the use of a patent without the patent holder's permission, has been used

in various health care contexts. For example, in 2001, Tommy Thompson, then the secretary of Health and Human Services, threatened to authorize imports of generic ciprofloxacin without the permission of the patent holder, Bayer, so that the antibiotic could be stockpiled for use against anthrax.

Under World Trade Organization (WTO) rules, a country can issue compulsory licenses for patented drugs to protect public health or increase access to essential medicines. Although prices may fall and access may improve, such licenses are controversial because they affect intellectual property rights and the revenues of pharmaceutical companies, which maintain that strong patent protection is an impor-

tant incentive for the investments in research and development that lead to improved therapies.

In November 2006, Thailand issued a compulsory license for efavirenz, a nonnucleoside reverse-transcriptase inhibitor and a critical component of several first-line HIV treatment regimens.⁵ The license permits the Thai Government Pharmaceutical Organization to import generic efavirenz from India, where the drug is not patented, and to make the drug itself — though Merck still holds a patent on it in Thailand. Merck is to receive a royalty payment.

In January 2007, Thailand issued a compulsory license for lopinavir–ritonavir, the most commonly used protease inhibitor in the United States. This cofor-

lation is available from Abbott Laboratories as both a capsule (Kaletra) that requires refrigeration and a heat-stable tablet (Aluvia). Although both had been considerably more expensive in many countries, they are currently available for between \$500 and \$1,000 per patient per year in many low- and middle-income countries. Kaletra is sold in Thailand; Aluvia is not. The Clinton Foundation HIV–AIDS Initiative has announced a price of \$695 for generic versions of the heat-stable tablet. Thailand also issued a compulsory license for clopidogrel, an antiplatelet agent. In May 2007, Brazil issued its first compulsory license, for efavirenz. It would not be surprising if Brazil, Thailand, or other countries issued additional compulsory licenses, the objections of the United States and pharmaceutical manufacturers notwithstanding.

Brazil, Thailand, and India all have substantial capacity to produce generic medicines. In-

dian generic drugs are among the world's least expensive, because India has a thriving com-

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petitive pharmaceutical industry and did not grant patents on medicines until 2005, when it was required to do so by the WTO. India exports two thirds of the drugs it makes and is the

main supplier of essential medicines for developing countries. Eventually, however, enhanced patent protection is likely to drive prices up. In August 2007, the Chennai High Court rejected a patent application from Novartis for imatinib mesylate, a treatment for chronic myeloid leukemia. However, applications are pending for many medicines, including tenofovir, lopinavir–ritonavir, and atazanavir, another protease inhibitor. It is likely that India will eventually grant some patents, in which case generic-drug manufacturers would require voluntary or compulsory licenses to continue production.

For HIV — the realm where the affordability gap has received the most attention — costs may continue to fall, as long as multiple generic versions of key medications remain widely available in developing countries and innovative strategies are used. When it is marketed, the fixed-dose combination of tenofovir–lamivudine–efavirenz will be priced at \$339 a year, a 12% savings from the \$385 annual price of tenofovir–emtricitabine–efavirenz (see Figure 1), since lamivudine is cheaper to make than emtricitabine. Both treatments contain about 50% more of their active pharmaceutical ingredients than the fixed-dose combination of stavudine–lamivudine–nevirapine, which increases manufacturing costs. Within several years, lower prices for the new regimens are likely.

Among protease inhibitors, which are essential components of second-line regimens, atazanavir–ritonavir, which is not currently made as a fixed-dose combination, is an alternative to

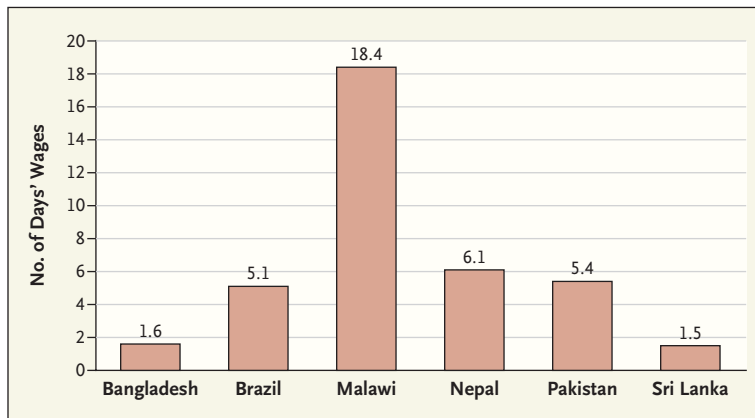


Figure 2. Affordability of Treatment for Coronary Artery Disease in Six Low- or Middle-Income Countries.

Affordability is defined as the number of days' wages required for the lowest-paid government worker to purchase a 1-month supply of generic aspirin (100 mg daily), atenolol (100 mg daily), an angiotensin-converting-enzyme inhibitor (10 mg daily), and a statin (20 mg daily). Brazil, Pakistan, and Sri Lanka are middle-income countries. Bangladesh, Malawi, and Nepal are low-income countries. Data are from Mendis et al.³

lopinavir–ritonavir. However, to compete, a generic version would have to be heat-stable. If generic fixed-dose combinations of atazanavir–ritonavir are marketed and protease inhibitors remain off-patent in India, they should be considerably less expensive options, because they are likely to contain 60% less of their active pharmaceutical ingredients.

Although there are many strategies for closing the affordability gap, each drug and dis-

ease poses unique challenges that require nuanced approaches. The experience with HIV medicines has called attention to the broader problem, but progress may come one drug at a time.

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