

Generic HIV Drugs *Enlightened Policy for Global Health*

Mark Wainberg, PhD

The debate

The 2000 International AIDS Conference in Durban, South Africa, focused the world's attention on disparities between rich and poor countries with respect to access to antiretroviral drugs. At that time, an estimated 7,000 people in Africa had access to proper combination antiretroviral regimens. Although the number exceeds 100,000 today, it is still a far cry from the 8 million who are thought to require such therapy. In response, in 2002, the World Health Organization (WHO) launched an ambitious program termed "3 by 5" in an attempt to treat at least 3 million infected people by the end of 2005.

Sadly, the WHO initiative ran into trouble almost from the start. First, it quickly became clear that the only way to mass produce and stockpile the amount of medication required would be to turn to the manufacturers of generic drugs that could produce these compounds at low cost. This reality has inspired demands by some funders of the initiative that the generics first be shown to have bioequivalence to the versions that are produced by major pharmaceutical companies and approved by the U.S. Food and Drug Administration.

Much of the past two years has been consumed by a debate over whether generic antiretroviral drugs are truly the equivalent of their "Big Pharma" cousins and whether or not they should gain approval by a regulatory agency before being used in developing countries. In this context, the WHO recently listed a number of generic antiretrovirals as suitable for its programs and then removed five of them from the list because equivalence had not been proven. The drugs were two different coformulated versions of lamivudine, stavudine, and nevirapine (Ranbaxy, India), two versions of coformulated lamivudine and zidovudine (produced by both Ranbaxy and Cipla, India) and one version of lamivudine alone (Cipla).

An obvious question is what means should be used to document bioequivalence, given that the WHO is not a regulatory authority and does not have the resources to conduct clinical trials. Some take the extreme position that no generic compound should be used in developing countries until a successful randomized clinical trial directly comparing it with its brand-name counterpart has been performed. Such a process, however, would be inordinately expensive, would detract from the goal of making as much medication as possible available to people in need, and would result in millions of deaths from AIDS in the interim.

Bioequivalence

Rather than permitting the indiscriminate use of generics, however, we could follow a few common-sense rules. For example, one could determine equivalence using stringent chemical tests that are readily available. Generic drugs could also be shown to be effective and nontoxic through studies in animals and tissue culture, biochemical studies, and short-term clinical trials. And ultimately, individual countries should be the arbiters of which drugs their citizens should be denied or permitted to take. A country that desperately wants to import or produce generic drugs might well interpret an attempt by the WHO or another party to impose its own rules on the process as an infringement of its national sovereignty.

This debate has put the WHO on the defensive, since it has been accused of a willingness to treat people in developing countries with medicines that would not be used in western countries. But this is a spurious argument that ignores the realities of common practices in the use of other generic drugs in developing countries. For example, the use of generic statin drugs to control hypertension is widely accepted in many countries, although it is unclear that these compounds have formally proven themselves in long-term clinical trials involving head-to-head comparisons with their brand-name counterparts.

So why the delisting by the WHO of generic drugs that are components of its 3 by 5 regimen? The official reason given is that some of the independent contract-research organizations that had been tasked with testing for bioequivalence were not able to deliver information on a timely basis and that good clinical and laboratory practices might not have been followed. Although this may certainly be the case, it begs the question of whether such standards ought to be applied in the first place—for the imposition of unrealistically high standards for proving bioequivalence might result in unacceptably long delays in bringing drugs to the people who need them the most.

Facing the challenges

The benefits of providing antiretroviral drugs to HIV-infected patients in developing countries will extend far beyond the direct effects on the health of the patients. Such access would almost certainly reduce the overall rates of HIV transmission: high viral loads represent the most important correlate of HIV transmission, and antiretrovirals greatly diminish the levels of HIV in plasma and the viral burden in fluids such as semen—often to below the limit of detection. Hence, the public health benefits of widespread access to HIV drugs constitute an important rationale for the immediate pursuit of universal treatment programs.

Several observers, however, have cited potential problems with such programs, arguing that patients in developing countries will be unlikely to adhere to antiretroviral regimens or that drug resistance will quickly emerge and an epidemic of drug-resistant strains will ensue. A series of recent articles emanating from a World Bank conference,

however, indicate that both of these possibilities have been overrated. Indeed, the consensus of the conference was that the public health benefits of providing immediate widespread access to antiretroviral drugs outweigh all other considerations and that we should proceed accordingly. Several studies have shown that patients in developing countries are likely to be at least as adherent to antiretroviral regimens as are North Americans. And the problem of drug resistance is mitigated by reports showing that drug-resistant viruses are often less virulent than wild-type drug-sensitive strains. Nonetheless, the WHO has recognized the importance of this concern and has instituted an international surveillance program for HIV drug resistance that will compile relevant information in key countries and track the sexual transmission of drug-resistant viruses.

None of this suggests that the WHO-favoured regimen of stavudine, lamivudine, and nevirapine is without problems. Indeed, no one in a western country would today initiate therapy with this combination for several reasons, including the fact that of all the nucleoside reverse-transcriptase inhibitors, stavudine has the greatest long-term toxicity, causing lipoatrophy and lipodystrophy. Yet there are currently few, if any, alternatives, and the benefits of providing stavudine, lamivudine, and nevirapine to millions of HIV-infected people over the next several years far exceed any negative consequences, such as the possibility that lean-mass redistribution associated with long-term stavudine use will result in facial and body disfigurement that may, in turn, promote stigmatization and susceptibility to cardiac and endocrine insult. There are probably good alternatives to stavudine in this context, the best of which may be tenofovir. However, a shift to this drug might require Gilead Pharmaceuticals, its manufacturer, to assist in producing a generic version and to surrender its intellectual-property rights in countries, such as India, whose laws do not allow patent protection for HIV drugs that were available before 2000.

Another possibility may be to take advantage of the impending expiration of the patent on zidovudine by using that drug as the cornerstone of HIV therapy. For reasons of cost, this may make sense in all countries, and most studies have shown that it has less long-term toxicity than stavudine, although it appears to be more toxic than tenofovir.

There have been many attempts to deliberately obfuscate issues relating to the use of generic drugs, which some portray as unsafe because they may not have met the same criteria for approval as brand-name products. Some have gone so far as to argue that it would be immoral to treat patients in developing countries with generics while patients in richer countries receive only brand-name products. Such attitudes, although presumably well-intended, will only serve to deny millions of people life-saving drugs and to deny the world the greater public health benefits of widespread access. I believe that we should support the WHO initiative and move forward, with the understanding that efforts will be made to prove the bioequivalence of generic and brand-name products as soon as possible but that lesser standards may be acceptable in the short term. I think we should also agree that the WHO will try to change its recommended regimen, although this may not be practical for several years.

The moral imperative

Finally, if we are to deal adequately with the inevitable drug resistance that will continue to occur, it should be understood that the major pharmaceutical companies must retain incentives to discover and develop novel HIV therapies. At the same time, these companies should accept their share of responsibility for finding solutions to the problems that HIV represents. The relatively enlightened, socially responsible policies that most of these companies have developed in recent years have often resulted from pressure applied by governments and international agencies. Companies can do much more, and a good place to start would be the licensing of their products to makers of generic drugs who could manufacture antiretrovirals under conditions that would pass international muster. Such collaboration might obviate the need to prove bioequivalence under conditions that western regulatory authorities find insufficiently rigorous. The world cannot afford any further delay in the implementation of antiretroviral-access programs that make scientific sense and are morally imperative.

Dr. Mark Wainberg is professor of molecular biology and virology and director of the AIDS Centre at McGill University, Montreal. Dr. Wainberg was president of the International AIDS Society from 1998 to 2000. He is co-chair of the 16th International AIDS Conference, to be held in August 2006 in Toronto.