

## Generic HIV Drugs — Enlightened Policy for Global Health

Mark A. Wainberg, Ph.D.

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 7000 people in Africa had access to effective combination antiretroviral regimens. Though 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 2003, 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 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 possibility brought demands by some funders of the initiative that the generic drugs first be shown to be the bioequivalents of the drugs that are produced by major pharmaceutical companies and are approved by the Food and Drug Administration (FDA). However, international agencies such as the World Bank and the Global Fund to Fight AIDS, Tuberculosis, and Malaria have argued that delays owing to the imposition of very high standards of bioequivalence will result in needless deaths.

Much of the past two years has been consumed by a debate on whether generic antiretroviral drugs are truly the equivalent of their "Big Pharma" cousins and whether they should be approved by a regulatory agency before being used in developing countries. In the context of this debate, the WHO recently listed a number of generic antiretroviral drugs as suitable for its programs and then removed five of

them from the list because equivalence had not been established. Two of the five drugs were recently reinstated, after their manufacturer conducted new bioequivalence studies.<sup>1</sup>

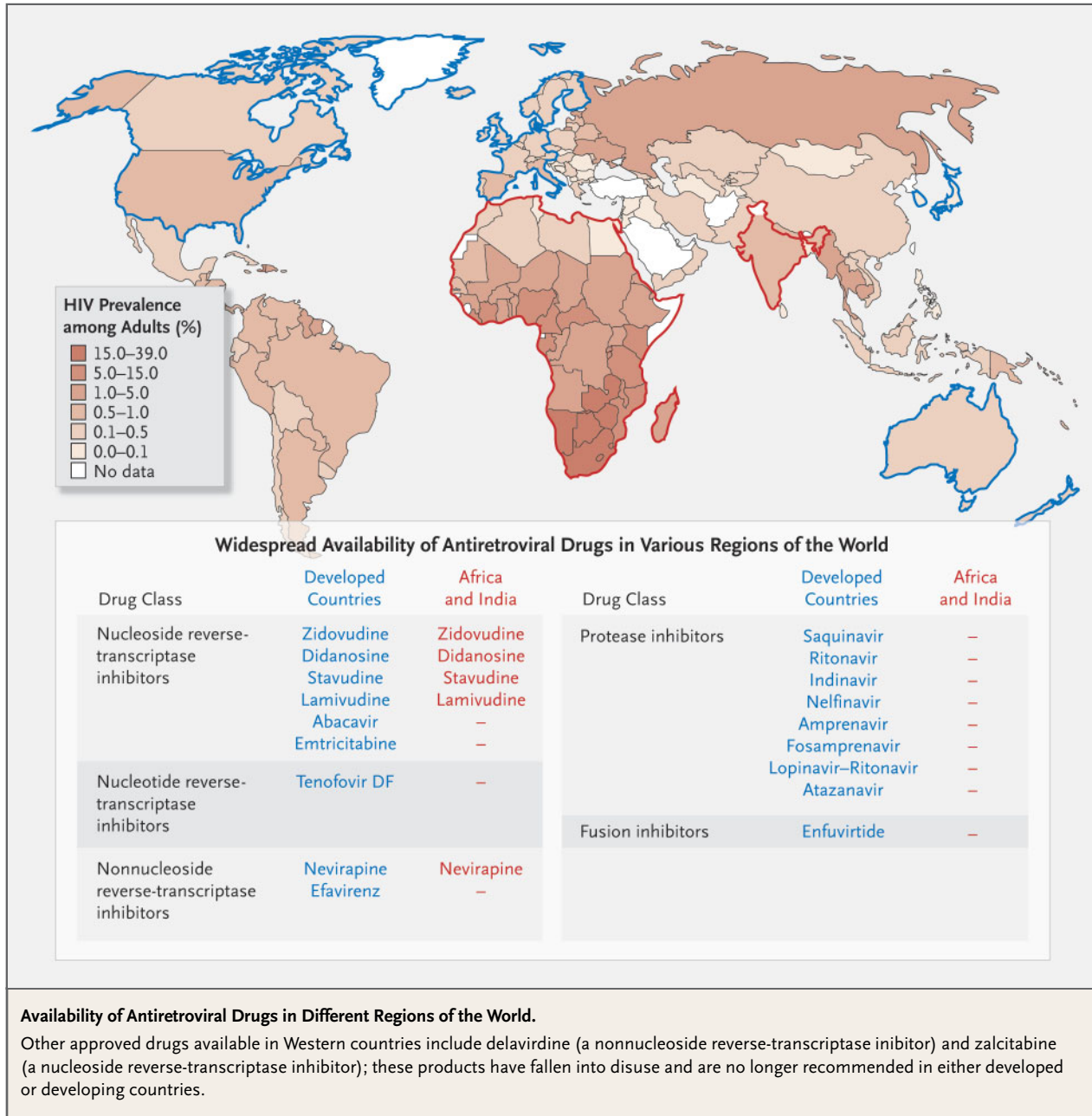
An obvious question is what means should be used to document bioequivalence, given that the WHO is not a regulatory authority and does not have the resources with which to conduct clinical trials. Some take the extreme position that no generic compound should be used in developing countries until a successful randomized clinical trial directly comparing it with its brand-name counterpart has been conducted. 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 many deaths from AIDS in the interim.

Rather than permit the indiscriminate use of generic drugs, however, we could follow a few commonsense rules. For example, equivalence could be determined with the use of stringent chemical tests that are readily available. Generic drugs could also be shown to be effective and nontoxic by means of studies in animals and tissue culture, biochemical studies, and short-term clinical trials that would include demonstrations of equivalence with regard to such outcomes as the plasma levels and half-lives of the drugs. 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 national sovereignty.

It is common practice in other areas of medicine to use generic drugs in developing countries even though the drugs have not always undergone head-to-head comparisons with their brand-name counterparts. So why did the WHO remove from its list generic drugs that are components of its 3-by-5 regimen? The official reason was that some of the

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research organizations charged 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 — because the imposition of unrealistically high standards for proving bioequiv-

alence might result in unacceptably long delays in bringing drugs to those who need them the most.

The benefits of providing effective antiretroviral drugs to patients with human immunodeficiency virus (HIV) infection 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 transmission of HIV: high

Potential Problems Associated with the WHO-Preferred Regimen of Lamivudine, Stavudine, and Nevirapine.	
Problem and Drug	Comments
Toxic effects	
Stavudine	More closely associated with lipoatrophy and lipodystrophy than any other drug in its class.
Nevirapine	No longer favored in most treatment protocols in developed countries because of potential hepatotoxicity and immune-related toxic effects if therapy is commenced in patients with a relatively high CD4 count (e.g., >300 cells/mm <sup>3</sup> ).
Resistance	
Nevirapine, lamivudine	Antiviral effectiveness is severely compromised in the presence of a single point mutation in reverse transcriptase (e.g., K103N for nevirapine and M184V for lamivudine); such mutations may arise at high frequency under conditions of therapy. This “low genetic barrier” to resistance does not, in general, apply to most other antiretroviral drugs: in most cases, a single resistance-associated mutation is unlikely to occur with high frequency or is unlikely to confer high-level resistance in the absence of other resistance-associated mutations.

viral loads are the most important correlate of HIV transmission, and antiretroviral drugs greatly reduce the levels of HIV in plasma and the viral burden in fluids such as semen, often to a level below the limit of detection.<sup>2</sup> Hence, the public health benefits of wide 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 are unlikely to adhere to antiretroviral regimens and that, as a result, 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 these possibilities have been exaggerated.<sup>3</sup> Indeed, the consensus of the conference was that the public health benefits of providing immediate broad access to antiretroviral drugs outweigh all other considerations and that we should proceed accordingly. Several studies have shown that patients in developing countries are at least as likely to adhere to antiretroviral regimens as are those in North America.<sup>4</sup> And the potential problem of drug resistance is mitigated by reports showing that drug-resistant viruses are often less virulent than wild-type, drug-sensitive strains<sup>5</sup> — though the WHO, recognizing this possibility, has

now instituted a surveillance program for HIV drug resistance.

None of which suggests that the WHO-favored regimen of stavudine, lamivudine, and nevirapine is without problems (see table). Indeed, no doctor in a Western country today would choose to initiate therapy with this combination; of all the nucleoside reverse-transcriptase inhibitors, stavudine has the greatest long-term toxicity, resulting in 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. There are probably good alternatives to stavudine, the best of them possibly being 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 now allow patent protection for HIV drugs that become available in 2005 and thereafter.

Another possibility may be to take advantage of the impending expiration of the patent on zidovudine by using that drug as a cornerstone of HIV therapy. For reasons of cost, this choice may make sense in both developing and developed countries, and most studies have shown that zidovudine has less long-term toxicity than stavudine, although it has a greater toxic effect than tenofovir. Relevant here is the recent approval that the FDA granted to a South African pharmaceutical company to produce a coformulation of a combination of zidovudine, lamivudine, and nevirapine, which will permit these drugs to be purchased under President George Bush's President's Emergency Plan for AIDS Relief. In the short term, however, the problem is not only standards of bioequivalence but also the need to increase production: only the combination of stavudine, lamivudine, and nevirapine is currently produced in sufficiently large quantities to allow patients rapid access to this kind of therapy.

There have been many attempts to 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 have met. Some have gone as far as to argue that it would be immoral to treat patients in developing countries with generic drugs while patients in richer countries receive only brand-name products. Such arguments, although presumably well

intended, will serve only to deny millions of people lifesaving drugs and to deny the world the greater public health benefits of wide access. It will be interesting to see whether the opponents of generic drugs will also object to the use of generic drugs in Western countries when some of the earliest antiretroviral agents go off patent — as both zidovudine and didanosine will in 2005 — even though the use of generic drugs might translate into lower overall drug prices in the West. 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 to come.

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 financial 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. A good place for them to start would be the licensing of their products to makers of generic drugs that could manu-

facture antiretroviral agents under conditions that would pass international muster. Such collaboration could 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 programs for providing access to antiretroviral drugs that make scientific sense and are morally imperative.

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## Geriatrics in the United States — Baby Boomers' Boon?

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The graying of America, a triumph of medical and cultural advances, has caught us unprepared. Our economic system, burdened with Social Security, Medicare, and extended retirement years, is shaking. Our legal system may be overwhelmed by the choosing of surrogates to make health care and end-of-life decisions, evaluations of competence, and the issuing of advance directives. Our health

care system is challenged by the sheer number of elderly people and the demands of providing cost-effective care to those who are frail.

For the elderly, health is the foundation of a good quality of life — the obvious reason that the birth of U.S. geriatrics in the 1960s met with public and government support, media attention, and active (though defensive and at times obstructive) interest from medical schools, hospitals, and private practitioners. It was hoped that geriatrics would lead the response to this unprecedented demographic challenge.

And indeed, this specialty has enhanced clinical

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