

Statement of Peter Lurie, MD, MPH
Public Citizen's Health Research Group
Before the Committee on Government Reform
Subcommittee on Criminal Justice, Drug Policy, and Human Resources
US House of Representatives
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Recently, the pharmaceutical industry has questioned compulsory licensing¹ and parallel imports² on the grounds that these measures might 1. lead to the development of strains of the human immunodeficiency virus (HIV) that are resistant to currently available medications; and 2. result in decreased pharmaceutical company research and development (R&D). This testimony will address these two claims in turn.

The Viral Resistance Argument

Tom Bombelles, Assistant Vice President International for the Pharmaceutical Research and Manufacturers of America (PhRMA) has recently asserted: "Just giving people drugs without the proper treatment can create drug-resistant strains of HIV. It can make people sicker, not better. And that threatens AIDS patients everywhere around the world."³

The potential development of resistance to anti-HIV drugs is a serious public health concern, one that threatens to undermine the enormous gains that have been made in treatment for HIV infection in this country. But before one can address the validity of the HIV-resistance argument directly, one must acknowledge the following aspects of compulsory licensing and parallel importing that transcend viral resistance:

- The compulsory licensing and parallel import proposals do not *require* any country to engage in these practices. Rather countries are left to decide for themselves if they wish to use these mechanisms. But preventing compulsory licensing and parallel imports in blanket fashion robs developing countries of that choice.
- The compulsory licensing and parallel import mechanisms proposed by South Africa, for example, do not only involve AIDS drugs or those for infectious diseases. The "resistant strain" argument is thus being used to prevent improved access to lifesaving drugs even for non-infectious diseases such as heart disease and cancer. Drugs like simvastatin, to lower cholesterol, and ranitidine, for ulcers, could be substantially reduced in price.
- Fluconazole is a drug that treats an often-fatal complication of HIV infection, cryptococcal meningitis, rather than HIV itself. Its price could be dramatically reduced by either compulsory licensing or parallel importing. Two 150 mg fluconazole tablets sell for \$23.50 in Italy, where its patent is protected, compared to \$0.95 in India where the patent is not recognized.

Let me now turn to the HIV-resistance argument directly.

- For a patient to be worse off due to the development of viral resistance, one would have to believe that a patient who is partially adherent to anti-HIV therapy and who consequently develops a resistant HIV strain is worse off than one who is not treated with anti-HIV drugs at all. But there is no evidence to support that assertion. First, many patients who are not fully adherent with anti-HIV therapy do not develop drug resistance. Second, even for those who might develop resistance, the change to the viral genetic material that confers resistance is likely to be different than one that would confer greater aggressiveness. Mutant microorganisms generally reproduce less efficiently than non-mutants. A recent review in the *Journal of the American Medical Association* points out that, in the absence of therapy, strains from untreated people (which are primarily non-resistant) are likely to reproduce more rapidly than resistant strains and so will come to dominate the resistant strains over time.⁴ There is also some evidence that HIV strains resistant to zidovudine are more difficult to transmit to uninfected people.⁵
- The decision to prescribe or not prescribe effective medication should be a matter between a patient and his or her doctor. Two authors, writing in the *American Journal of Public Health*, have argued that, "it would be very difficult to justify denial of access to protease inhibitors [specific drugs for HIV infection] in the face of expressed patient preference for treatment except in the presence of clear and compelling evidence that a patient could not or would not be adherent."⁶ But opposing compulsory licensing and parallel imports is a blunt instrument indeed: because of high costs, physicians and patients would be unable to make that case-by-case assessment⁷ and patients would instead be denied drug simply on the basis of their residence. Assuming that all residents in developing countries are incapable of adherence is both insulting and historically inaccurate.
- Developing countries are also not monolithic when it comes to public health capacity, and it is condescending to lump them all together in order to justify withholding effective treatments. Clearly there are enormous differences between developing countries and within them. For example, very impoverished African countries such as Zimbabwe, Zambia, Uganda, Botswana, Senegal and Cote d'Ivoire are planning to provide anti-HIV drugs for HIV-positive women to prevent HIV transmission to their infants.⁸ Other countries, such as Brazil, already provide complex anti-HIV drug regimens to their HIV-positive populations.
- The solution to the development of drug resistance due to patient difficulty in adhering to the often-complex AIDS drug regimens is not denial of drug, but rather interventions to improve adherence. (In fact, high drug prices are one of the causes of non-adherence, as poor patients may take partial drug courses to save money.) Such interventions have had substantial success with tuberculosis in developing countries,⁹ including with HIV-infected populations.¹⁰ Has anyone suggested leaving developing country tuberculosis or malaria patients untreated to prevent the development of resistance?

- Lack of adherence to anti-HIV drugs is a problem in the United States as well. Even in the controlled setting of a clinical trial, non-adherence rates of 25% have been observed.¹¹ Should we therefore apply the same logic to some populations in the United States? Imagine if someone tried to make that argument with respect to all drug users or particular socioeconomic sectors of the United States.
- Is the real concern that resistant strains from the developing world will enter the United States? If so, is the pharmaceutical industry really arguing that Africans should remain untreated so that Americans can live longer?
- It is true that pharmaceutical company pricing practices are not the only reason that anti-HIV drugs are unavailable in most developing countries. The lack of health care infrastructure is a very important impediment to drug delivery. But pricing is an important, and in this case partially correctable, part of the problem. One reason that the HIV counseling and testing infrastructure in developing countries is weak is that, in the absence of affordable therapies, there are only limited reasons to improve it. But, if effective therapy were more widely available, there would be an incentive to improve the infrastructure to detect undiagnosed HIV infection.

In sum, on both policy and virological grounds, the possible emergence of drug-resistance strains provides no support for arguments against compulsory licensing and parallel imports.

The R&D Scare Card

Tom Bombelles of PhRMA has also asserted that “compulsory licensing creates an active disincentive to research-based pharmaceutical industry involvement in the international effort to improve public health in developing countries, as companies will choose not to develop medicines which will not be patent-protected. Such disincentives are more likely to drive patients and the availability of medicines further apart.”¹² This seems to argue that patients in developing countries should wait patiently without existing drugs because of prohibitively high prices while companies develop other drugs that may eventually be affordable in developing countries. The history of international drug development teaches us that this is likely to be an empty promise.

Once again, the pharmaceutical industry is playing its R&D Scare Card. This is an empty threat: pharmaceutical company R&D expenditures almost doubled between 1990, when Congress imposed price restraints on Medicaid drugs, and 1995.¹³ R&D represented a median of 11.4% of sales for the top 10 pharmaceutical companies (ranked by revenue) in 1998.¹⁴ In contrast, profit (net income) represented a median of 18.6% of sales by those same companies in 1998.

Furthermore, the pharmaceutical industry is the most profitable in the United States, whether measured by return on sales, assets or equity.¹⁵ Since 1989, pharmaceutical company return on equity has been at least 1.7 times the median of all U.S. industries.¹⁶

Given the extraordinary profits generated by the pharmaceutical industry, and its failure to make many critical medications affordable for developing country patients, we urge you to call the R&D Scare Card bluff.

Conclusion

Neither the viral resistance nor the R&D scare card arguments provides support for opposing legal trade measures such as compulsory licensing and parallel importing. Furthermore the sub-Saharan African market represents a scant 1.4% of the global pharmaceutical market. The explanation for the pharmaceutical companies' opposition to compulsory licensing and parallel importing is to be found elsewhere: in their desire to not have their irrational pricing practices exposed. We suggest that providing potentially lifesaving drugs to residents of developing countries should have a higher priority.

1. Compulsory licensing allows local production of patented medications with a royalty to be paid to the patent holder.
2. Parallel importing allows countries to find the lowest price for a particular drug on the international market, rather than being required to purchase from the manufacturer at a higher price.
3. World News Tonight with Peter Jennings (6:30 PM Eastern Time), July 8, 1999 (rush transcript).
4. Hirsch MS, et al. Antiretroviral drug resistance testing in adults with HIV infection: implications for clinical management. *JAMA* 1998;279:1984-91.
5. Wahlberg J, et al. Apparent selection against transmission of zidovudine-resistant human immunodeficiency virus type 1 variants. *J Infectious Disease* 1994;169:611-4.
6. Bayer R, Stryker J. Ethical challenges posed by clinical progress in AIDS. *Am J Public Health* 1997;87:1599-602.
7. Bangsberg D, et al. Protease inhibitors in the homeless. *JAMA* 1997;278:63-5.
8. Lurie M, et al. Denying effective antiretroviral drugs to HIV-positive pregnant women -- the national government's flawed decision. *S Afr Med J* 1999;89:621-3.
9. Wilkinson D, et al. Directly observed therapy for tuberculosis in rural South Africa, 1991 through 1994. *Am J Public Health* 1996;86:1094-7.
10. Davies GR, et al. Twice-weekly, directly observed treatment for HIV-infected and uninfected tuberculosis patients: cohort study in rural South Africa. *AIDS* 1999;13:811-7.
11. Kastrissios H, et al. The extent of non-adherence in a large AIDS clinical trial using plasma dideoxynucleoside concentrations as a marker. *AIDS* 1998;12:2305-11.
12. Bombelles T. Remarks before Presidential Advisory Council on HIV/AIDS, Washington, DC, June 7, 1999.
13. Pharmaceutical Research and Manufacturers Association. *Pharmaceutical Industry Profile 1999*, Washington, DC 1999.
14. Based on 1998 Annual Reports.
15. Fortune 500. *Fortune Magazine*, April 26, 1999, p. F-27.
16. Sager A, Socolar D. Winning affordable prescription drugs for all Americans: problems, causes and solutions. Boston University School of Public Health, 28 June, 1999.



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August 20, 1999

Representative John L. Mica
Chairman
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Dear Representative Mica:

Thank you for the opportunity to testify before your committee on the global HIV/AIDS epidemic on July 22 of this year. That hearing was one of the first occasions on which the U.S. Congress afforded the international dimensions of the epidemic significant attention.

In this letter, I respond to the three follow-up questions you mailed to me on July 28, 1999.

1. *Do you feel that it is futile to attempt to treat large numbers of infected persons in developing countries due to insufficient medical professionals and infrastructures? Is this a reason for not expanding drug treatment to those nations?*

Any consideration of the gravity of the AIDS epidemic must begin with the recognition that over 95% of current HIV infections are believed to be in the developing world. To in effect write off the developing world as somehow not appropriate for benefiting from the recent advances in anti-HIV therapy is to resign ourselves to having almost no global impact in treating this now-treatable disease.

In addition, there are important differences between developing countries in both their abilities and their desires to make anti-HIV drugs available. Argentina, Brazil, Colombia and Mexico have all begun to make anti-HIV drugs available to their populations. Other even poorer countries such as Botswana, Cote d'Ivoire, Senegal, Uganda, Zambia and Zimbabwe have focused on providing anti-HIV drugs to HIV-positive women to prevent transmission to their infants. Clearly, these countries believe that they have infrastructures adequate to support the administration of these drugs. Rather than using the grossly inadequate infrastructures of many

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developing countries to justify not providing needed therapies, we should be greatly increasing our investment both in the infrastructural needs of the countries, which would have beneficial effects throughout the health system, and in paying for the drugs themselves.

But even if funding were not to be increased, the U.S. government could act today to increase access to these critical medications without spending a penny. Compulsory licensing and parallel imports, discussed extensively at your hearing, represent a no-cost method for the U.S. government to expand access to much-needed medications in developing countries. Instead, we have seen a sustained effort by the Clinton administration to put pressure on developing countries to not implement compulsory licensing or parallel importing mechanisms, even though these are perfectly legal under World Trade Organization rules. In so doing, the administration has placed the profit motives of multinational drug companies over the public health needs of desperately ill patients in developing countries.

The real point is that developing countries should be allowed to decide for themselves how much emphasis they wish to place on providing access to anti-HIV treatment drugs (as opposed to HIV prevention, drugs for other diseases or infrastructure improvements, for example). But for the world's economic superpower to force developing countries to abandon perfectly legal strategies, lest they lose access to U.S. markets, is to deny developing countries that choice.

2. Do you feel that drug companies and the United States benefit from vaccine and drug treatment research conducted in developing countries? Do we conduct this research fairly and reward participants appropriately?

There is every indication that drug companies plan to expand their drug testing into developing countries. We are extremely concerned that ethical standards for conducting clinical trials that are accepted in the U.S. will not be honored when this research is conducted abroad.

Three ethical issues are of particular concern. First, will drug companies and other sponsors of clinical trials ensure that adequate informed consent has been obtained from study participants? Study after study in developing countries has documented just how inadequate informed consent often is.

Second, will drug companies or funding institutions feel obligated to provide known effective therapy in clinical trials? The evidence from recent mother-to-infant HIV transmission studies conducted or funded by the U.S. government suggests that they often do not. Thousands of HIV-positive pregnant women received placebos when effective preventive therapy existed. Pharmaceutical companies will probably not prove more likely to provide these treatments.

Third, will drug companies and other sponsors feel obligated to provide the study drug, if it is proven effective, to local populations? Researchers' track record in this area is also extremely poor. The Council for International Organizations of Medical Sciences' ethics guidelines require that any treatment proved effective "be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out." But this precept is frequently violated, leading to cries of exploitation from developing countries as the knowledge

generated by the research is used in industrialized countries and local residents fail to benefit.

The current situation with regard to the ethical conduct of clinical trials is likely to worsen. A coordinated campaign involving researchers both within the U.S. government and in the academic sector is now underway. The campaign is attempting to rewrite the major documents governing the ethical conduct of research so that informed consent requirements are relaxed and the obligation to provide known effective treatment is weakened for poor people, both domestically and abroad. A letter we published in the British medical journal *The Lancet* describing these proposed changes is attached, as is our article describing the perinatal HIV transmission trials.

3. What are some of the major problems that you see in expanding the availability of drug treatment in developing nations? How can these problems be overcome?

The pharmaceutical industry has raised two issues that they believe weigh against providing drug treatment: the potential development of strains of HIV resistant to existing drugs and the lack of health care infrastructure to actually administer the drugs. The former was the focus of my testimony before your Subcommittee, so I will not reiterate my comments in detail here. But there is no scientific basis for believing that patients will be worse off for receiving these drugs, even if drug-resistant strains emerge, compared to receiving no treatment at all. If anything, the scientific evidence is that drug-resistant strains are likely to be less aggressive than non-resistant strains.

The lack of infrastructure in many developing countries is certainly a massive public health problem. But the solution to this problem is to improve infrastructure, not to deny potentially life-saving drugs. One reason the infrastructure for HIV counseling and testing in many developing countries is so weak is that there is no incentive to improve it.

In the absence of drugs to treat those diagnosed as HIV-positive, there are only limited reasons to expand HIV testing. The real question before the Congress is what the U.S. government can do about a situation in which those most in need go without critical drugs. First, U.S. government spending on international health remains minuscule and needs to be greatly augmented.

Second, the U.S. government should not simply hand over the patents for drugs it has played a major role in developing to drug companies without exacting agreements on pricing. Third, the Clinton administration's pressure on governments seeking to employ legal mechanisms such as compulsory licensing and parallel importing to expand drug access must end. Again, some countries do have the infrastructure to provide anti-HIV drugs, particularly in the setting of mother-to-infant transmission, but the policies promoted by the administration in effect summarily group all developing countries in a single category and then deny them a legal mechanism for promoting access to medications.

Thank you once again for the opportunity to share this information with you. If I can be of any further assistance, please do not hesitate to contact me.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Peter Lurie". The signature is fluid and cursive, with a prominent initial "P" and a long, sweeping underline.

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Medical Researcher