Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?

Amir Attaran, DPhil, LLB
Lee Gillespie-White, LLB

Public attention and debate recently have focused on access to treatment of acquired immunodeficiency syndrome (AIDS) in poor, severely affected countries, such as those in Africa. Whether patents on antiretroviral drugs in Africa are impeding access to lifesaving treatment for the 25 million Africans with human immunodeficiency virus infection is unknown. We studied the patent statuses of 15 antiretroviral drugs in 53 African countries. Using a survey method, we found that these antiretroviral drugs are patented in few African countries (median, 3; mode, 0) and that in countries where antiretroviral drug patents exist, generally only a small subset of antiretroviral drugs are patented (median and mode, 4). The observed scarcity of patents cannot be simply explained by a lack of patent laws because most African countries have offered patent protection for pharmaceuticals for many years. Furthermore, in this particular case, geographic patent coverage does not appear to correlate with antiretroviral treatment access in Africa, suggesting that patents and patent law are not a major barrier to treatment access in and of themselves. We conclude that a variety of de facto barriers are more responsible for impeding access to antiretroviral treatment, including but not limited to the poverty of African countries, the high cost of antiretroviral treatment, national regulatory requirements for medicines, tariffs and sales taxes, and, above all, a lack of sufficient international financial aid to fund antiretroviral treatment. We consider these findings in light of policies for enhancing antiretroviral treatment access in poor countries.

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IN RECENT MONTHS, THERE HAS BEEN a great deal of controversy about access to antiretroviral medicines to treat human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) in poor countries, where tens of millions have HIV infection and face certain death without antiretroviral treatment. A dramatic, often heated element of this debate has focused on the role of intellectual property law—specifically, patents—which activists blame for creating monopolies that keep drugs inaccessible or unaffordable, and which pharmaceutical companies extol as necessary incentive for expensive research and development. This has led to highly organized campaigns, critiques of the international patent law system, White House executive orders, and calls to limit the scope of pharmaceutical patents in poor countries.[1-3]

In this article, we examine the current relationship between patents and antiretroviral drug access. We test the hypothesis that patents are a leading barrier to widespread AIDS treatment in Africa by presenting for the first time, to our knowledge, comprehensive data on whether patents for antiretroviral drugs exist on that continent. We discuss the findings of our case study in light of the current controversy regarding AIDS medicines and the legal options for enhancing access to antiretroviral treatment for the world's poor.

METHODS

Between October 2000 and March 2001, we issued written inquiries to the intellectual property divisions of major pharmaceutical companies that produce or market antiretroviral drugs, seeking disclosure and affirmation of each patent or similar legal right in Africa of which those companies had knowledge. Our inquiries captured the patent status of the antiretroviral drugs invented or marketed by the companies in question, unless a single active ingredient is marketed in multiple formulations, in which case we sought data for the first marketed (primary) formulation. All companies we contacted agreed to furnish data in response to our inquiry. We summarized the data in tabular form and then returned the data to each of the respondent companies for 1 or more rounds of clarification, verification, or correction as needed.

Our inquiries captured several different types of legal rights: product patents (covering the pharmacologically

Author Affiliations: Center for International Development and Kennedy School of Government, Harvard University, Cambridge, Mass (Dr Attaran); International Intellectual Property Institute, Washington, DC (Ms Gillespie-White).
Corresponding Author and Reprints: Amir Attaran, DPhil, LLB, Center for International Development, Harvard University, 79 JFK St, Cambridge, MA 02138 (e-mail: amir_attaran@harvard.edu).

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active chemical or formulation), process patents (covering a manufacturing process for the same), use patents (covering the use of a drug for a medical indication), and "exclusive marketing rights" (an interim legal status in international patent law that pertains only to the least-developed countries under the World Trade Organization *Agreement on Trade-Related Aspects of Intellectual Property Rights* [TRIPS][4]). For the purposes of this study, it is generally unnecessary to distinguish among these because they all confer a degree of market exclusivity (ie, an exclusive right to manufacture, import, or sell) in similar ways.

Because our method is survey based, we cannot exclude the possibility that even after verification some inaccuracies exist because of human error in reporting data to us. However, in this large crosswise scrutiny of 15 antiretroviral drugs and 53 countries (comprising 795 data points), a small number of such inaccuracies would not materially affect our broad conclusions. Although this is satisfactory for an academic study, given the serious legal consequences of patent infringement, we strongly recommend that anyone placing reliance on these findings seek independent legal advice.

RESULTS

A total of 15 antiretroviral drugs patented by 8 pharmaceutical companies were screened for patent status in 53 African countries. TABLE 1 and the FIGURE summarize the data and record every patent in force at the time we were notified. We do not present data on expired or withdrawn patents, which are of no legal force, or pending patent applications, since it cannot be presumed that these will be granted or rejected. Where a patent is shown, some form of market exclusivity exists, although this exclusivity may not preclude all uses of the pharmacologically active ingredient (eg, in the case of a formulation patent).

The data in the Table and Figure can be interpreted as disclosing 1 general rule and 2 specific exceptions. The rule is that among antiretroviral drugs, most are patented in few African countries (median, 3; mode, 0 countries) and that among the subset of countries where 1 or more patents exist, the number of patented antiretroviral drugs is typically few (median and mode, 4 drugs). The exceptions are South Africa, where a comparatively large number of antiretroviral drugs are patented (13/15), and Agouron, Boehringer Ingelheim, and GlaxoWellcome (now GlaxoSmithKline) products, which are patented in a large number of countries (up to 37 of 53 countries). Overall, of a theoretically possible 795 instances of patenting that we might have identified (assuming generously that all countries offer pharmaceutical patents, which is not true), only 172 (21.6%) actually exist.

While patents do limit the use of some highly active antiretroviral therapy regimens on a "no patent" basis (especially those using zidovudine, lamivudine, or both), the US Department of Health and Human Services (DHHS) clinical guidelines list several "strongly recommended" regimens for which there are encouraging clinical trials and which are unpatented in up to 52 of 53 African countries. In addition, other regimens are available on a "1 patent" basis, where that patented drug may be available at discounted prices. Examples of regimens recommended by the DHHS and their patent statuses are provided in TABLE 2.

COMMENT

This study demonstrates that patent protection for antiretroviral drugs in Africa is not extensive. This is surprising since earlier studies have shown that patent applications were filed in many African countries.[13] We now infer that most of these applications were probably abandoned because it is common practice to name a large number countries on an international patent application, given the option of establishing a patent later on, and later abandon many or most of them when the patent fees are due.[14] Therefore, it is not surprising that the number of applications is large while the number of patents in force is few.

These results rely on patent self-reporting and may contradict isolated press reports.[15] However, we believe there are 2 independent reasons that patent holders and licensees are the most reliable source for these data when queried systematically.

First, the relationship between a patent and a product is not always self-evident to anyone other than the patent holder or a licensee. A patent may not refer explicitly to the name of a product or the formula of the pharmacologically active chemical (eg, a process patent for a synthetic intermediate). As such, even a highly skilled observer searching the records of a national patent office (an extremely difficult or impossible undertaking in much of Africa) could easily overlook patents pertaining to a product of interest. This problem is avoided when the patent holder or licensee self-reports the data, and to the limited extent that our data were verifiable against those obtained directly from 1 national patent office (Kenya), the results match perfectly.[16]

Second, companies that self-report the lack of a patent probably would do so truthfully because there is no incentive to conceal the existence of a patent. Concealment would invite unwanted competition from generic drug suppliers. While theoretically companies may benefit from exaggerating the extent of their patent protection, there is no plausible commercial benefit in denying the existence of valid patents they own.

As most of the antiretroviral drugs we studied are infrequently patented in Africa, is this situation likely to persist in coming years? Most national patent systems follow the *Paris Convention*, which stipulates a 1-year grace period during which all patent applications ordinarily are filed.[17] This period elapsed long ago for the antiretroviral drugs we studied, meaning that the opportunity to file further patent applications and obtain future patents generally has expired. It is conceivable that "afterthought" applications could be still filed to patent incidental features of these drugs (eg, a drug's crystalline form or its

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Table 1. Patent Coverage in Africa for Antiretroviral Drugs, by Country*

	NRTIs							NNRTIs			Protease Inhibitors					
	Lamivudine-zidovudine (Combivir) [GSK]	Lamivudine (Epivir) [GSK]	Zalcitabine (Hivid) [Roche]	Zidovudine (Retrovir) [GSK]	Didanosine (Videx) [BMS]	Stavudine (Zerit) [BMS]	Abacavir (Ziagen) [GSK]	Delavirdine (Rescriptor) [Pharmacia]	Efavirenz (Stocrin) [Merck]	Nevirapine (Viramune) [BI]	Amprenavir (Agenerase) [GSK]	Indinavir (Crixivan) [Merck]	Saquinavir (Fortovase) [Roche]	Ritonavir (Norvir) [Abbott]	Nelfinavir (Viracept) [Agouron]	Total
Algeria																0
Angola																0
Benin	X	X								X					X	4
Botswana	X	X		X			X			X	X					6
Burkina Faso	X	X								X					X	4
Burundi	X			X												2
Cameroon	X	X								X					X	4
Cape Verde																0
Central African Republic	X	X								X					X	4
Chad	X	X								X					X	4
Comoros	X	X		X												3
Congo (Republic)	X	X					X			X					X	5
Congo (Democratic Republic)	X											X				2
Côte d'Ivoire	X	X								X						3
Djibouti																0
Egypt	X	X														2
Equatorial Guinea																0
Eritrea																0
Ethiopia																0
Gabon	X	X								X					X	4
Gambia	X	X		X			X			X	X				X	7
Ghana	X	X		X			X				X				X	6
Guinea										X					X	2
Guinea Bissau															X	1
Kenya	X	X		X			X			X	X				X	7
Lesotho	X	X					X			X	X				X	6
Liberia																0
Libya																0
Madagascar	X	X														2
Malawi	X	X		X						X	X				X	6
Mali	X	X								X					X	4
Mauritania	X	X								X					X	4
Mauritius																0
Morocco	X	X														2
Mozambique																0
Namibia																0
Niger	X	X													X	3
Nigeria	X	X		X									X			4
Rwanda	X			X												2
Sao Tome and Principe																0
Senegal	X	X								X					X	4
Seychelles	X	X		X			X									4
Sierra Leone	X			X			X									3
Somalia										X						1
South Africa	X	X		X	X	X	X	X	X	X	X	X	X		X	13
Sudan	X	X		X			X			X	X				X	7
Swaziland	X	X					X			X	X				X	6
Tanzania	X	X		X			X			X						5
Togo	X	X													X	3
Tunisia	X	X														2
Uganda	X	X		X			X			X	X				X	7
Zambia	X	X		X			X			X	X					6
Zimbabwe	X	X		X			X			X	X		X		X	8
Total	**37**	**33**	**0**	**17**	**1**	**1**	**15**	**1**	**1**	**25**	**12**	**2**	**3**	**0**	**24**	**172**

*NRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; GSK, Glaxo SmithKline; BMS, Bristol-Myers Squibb; and BI, Boehringer Ingelheim.

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metabolite), but such claims may be regarded skeptically by courts outside the United States.[18-20] We think it is unlikely that the observed omissions to patent in Africa could now be reversed, meaning that current antiretroviral drugs will remain largely unpatented in Africa (future antiretroviral drugs, of course, may be another matter).

It is an interesting question why there are not more antiretroviral drug patents in Africa. Certainly, it is not simply because the option to patent has been lacking. Although the laws of some African countries do not permit pharmaceutical patents, or did not when applications to patent these antiretroviral drugs were filed, most have allowed pharmaceutical patents for years.[21] The 15 member countries of Francophone West Africa in OAPI (the Organisation Africaine de la Propriété Intellectuelle) have offered a system of pharmaceutical product and process patents since the *Bangui Agreement* of 1977.[22] Similarly, pharmaceutical patent protection has been available in most of the 15 Anglophone countries of ARIPO (the African Regional Industrial Property Organization) since at least 1984.[16]

Despite these and other opportunities to patent antiretroviral drugs in Af-

Figure. Patent Coverage by Country

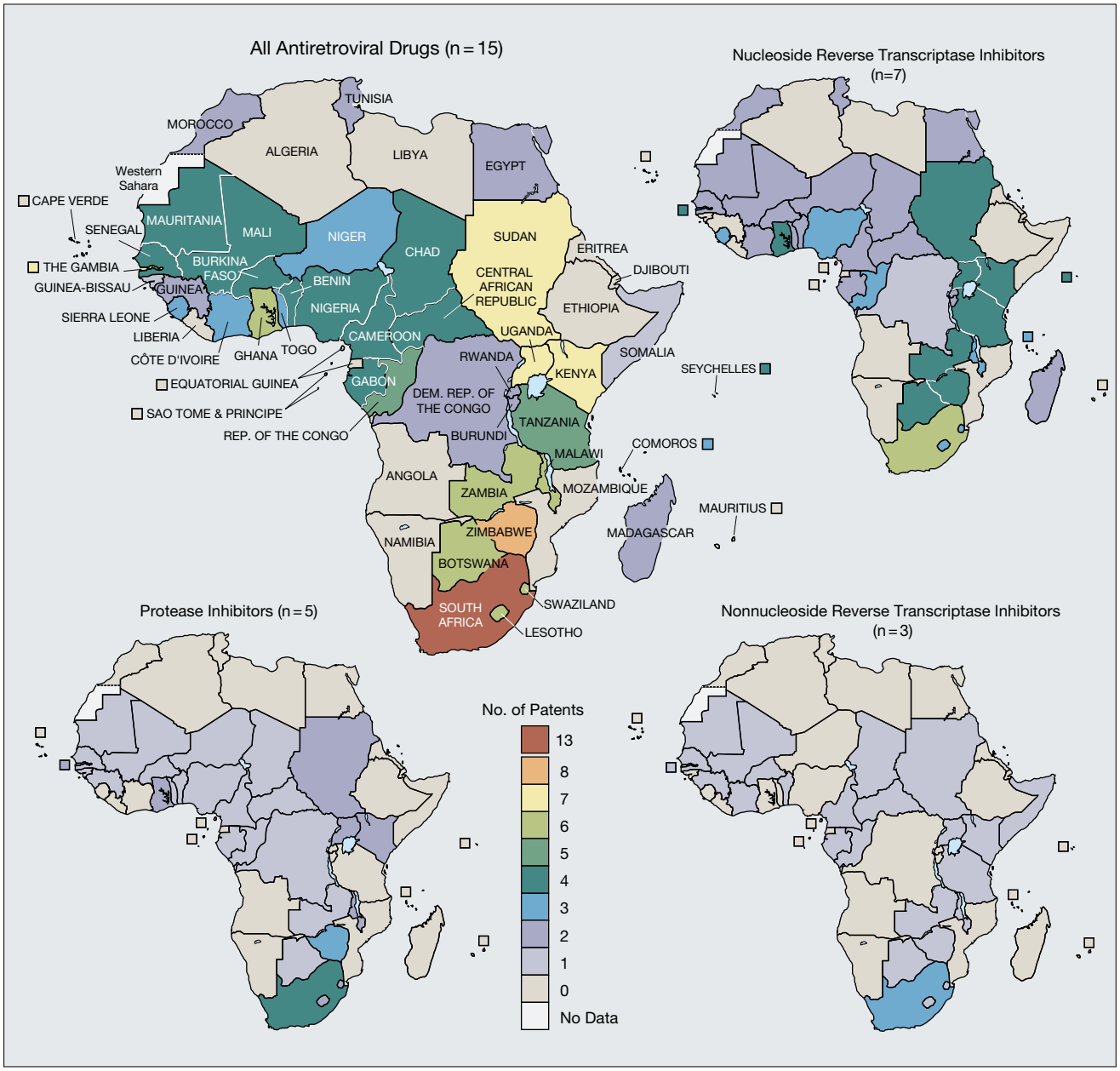

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Table 2. Patent Status of Antiretroviral Drugs Used in Selected Highly Active Antiretroviral Therapy Regimens (N = 53)*

Regimen	DHHS Assessment[5]	No. (%) of Countries With		Multiarm Clinical Trial?
		0 Patents	0 or 1 Patents	
Stavudine-didanosine-indinavir	Strongly recommended	51 (96.2)	52 (98.1)	Yes[6]
Stavudine-didanosine-ritonavir-indinavir	Strongly recommended	51 (96.2)	52 (98.1)	Yes[7]
Stavudine-lamivudine-indinavir	Strongly recommended	19 (35.8)	52 (98.1)	Yes[8]
Zidovudine-lamivudine-nelfinavir	Strongly recommended	15 (28.3)	25 (47.2)	Yes[9]
Stavudine-didanosine-efavirenz	Strongly recommended	52 (98.1)	52 (98.1)	No[10]
Lamivudine-stavudine-nevirapine	Recommended as alternative	18 (34.0)	30 (56.6)	No[11]
Didanosine-stavudine-nevirapine	Recommended as alternative	28 (52.8)	52 (98.1)	Yes[12]

*DHHS indicates US Department of Health and Human Services.

rica, patents were not often sought, suggesting 2 important conclusions.

First, and perhaps surprisingly, it is doubtful that patents are to blame for the lack of access to antiretroviral drug treatment in most African countries. Conventional wisdom has spuriously assumed that drugs patented in Europe or North America must also be patented in Africa, or that a lack of generic competition and high retail prices (sometimes in excess of those charged in developed countries) are prima facie evidence of patents, which they are not.[23,24] Determining actual patent coverage is therefore instructive, and in doing so, we observe that that there is no apparent correlation between access to antiretroviral treatment, which is uniformly poor across Africa, and patent status, which varies extensively by country and drug. We were unable to identify any evidence, systematic or anecdotal, that antiretroviral treatment is more accessible in countries with few or no antiretroviral patents (eg, Mozambique, Namibia). Similarly, we were unable to identify any evidence that the antiretroviral drugs of, for example, Abbott, patented in 0 countries, are consumed in any greater numbers than those of GlaxoSmithKline, patented in up to 37 countries. These observations are necessarily qualitative given that accurate data on African antiretroviral drug consumption do not exist, but are based on the consensus that very few of the 25 million HIV-positive Africans now receive treatment (perhaps 25 000, or just 1 in 1000, receive 1 antiretroviral drug).[25] This scarcity of treatment cannot rationally be ascribed to antiretroviral patents that are few—or nonexistent—in most African countries. Other factors, and especially the ubiquitous poverty of African countries, must be more to blame.

Second, also perhaps surprisingly, it is doubtful that pharmaceutical research and development will always require the incentive of patentability in poor countries, since the option to patent antiretroviral drugs in Africa has frequently gone unexercised. The economics and profitability of antiretroviral drug research (unlike that of, say, malaria) are driven by consumption of drugs by AIDS patients in the lucrative North American and European markets. In comparison, the entire African pharmaceutical market, at 1.1% of the global whole, is commercially negligible, as is the market share of antiretroviral drugs sold to the poorest third of the world (0.5%) (Jean O. Lanjouw, PhD, written communication, August 7, 2001).[26] Patenting in poor countries therefore yields very small financial returns, and, given the cost of patenting and the difficulty of enforcing one's patents before sometimes weak judicial systems, most companies appear to have decided that extensive patenting in Africa is not worthwhile.

Thus, the data suggest that patents in Africa have generally not been a factor in either pharmaceutical economics and antiretroviral drug treatment access (South Africa, with its larger affluent market, is an exception). This counters some of the sweeping policy arguments made for or against patents, and, within the limited scope of this study, it is no more correct to allege that "intellectual property protection [has] huge [adverse] influences on . . . access to medicines" than it is to claim that ongoing pharmaceutical research and development finds it "necessary to protect intellectual property rights on a global scale."[27,28] Although we agree that either or both of these statements may be correct in other contexts, neither is borne out as true in this case study.

Our data or conclusions should not be misinterpreted. It would be wrong to cite this study as proof that patents never affect access to medicines—that conclusion would require research well beyond antiretrovirals in Africa in 2001. Also, in reporting data on antiretroviral patent status, it must be remembered our data reflect only the existence of patents, and never their validity, which is testable only through a legal challenge. We presume that all patents reported to us are valid, as is the rule until being judicially invalidated.

What are the nonpatent barriers impeding antiretroviral treatment in Africa? Certainly, access to treatment can be impeded many ways: by insufficient finances to purchase relatively costly antiretroviral drugs; by a lack of political will among countries; by poor medical care and infrastructure; by inefficient drug regulatory procedures that exclude competing products from the marketplace; by high tariffs and sales taxes; and so on. Such barriers have been identified by others.[29-31] A comprehensive treatment access plan for Africa must overcome these nonpatent barriers and make use of expeditious strategies that combine affordability, compliance with patent laws, and sufficient finance. We consider these in turn.

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At this writing, both brand name and generic sources of antiretroviral drugs are available at reduced price, typically about 90% less than in the United States. Prices range from $350 a year for the cheapest possible 3-drug combination of stavudine, lamivudine, and nevirapine (Cipla) to perhaps $1000 for a regimen containing a more expensive protease inhibitor, which might cost $600 itself (eg, indinavir).[32]

Patent status is a central consideration when sourcing drugs. Where a drug is not patented in a given country, one may freely manufacture, import, and buy the brand-name drug or its generic equivalent (provided that both are registered for use by the local drug regulatory authorities, which is not always the case since some authorities decline to register generic products [Richard O. Laing, MD, written communication, August 7, 2001]). Therefore, competition can lead to a concurrent market for brand-name and generic antiretroviral drugs, such as exists for other medicines. Purchasing for the public or charitable sector in poor countries could be assisted by a single global brokering facility that would receive orders and put them to a competitive tender among a number of high-quality suppliers. A central, tender-based system like this has been very successful in increasing access to tuberculosis drugs for poor countries at prices near the marginal cost of production, or as much as 97% below prices in United States or Japan.[33,34] However, the risk of driving prices down while simultaneously increasing the funds available to purchase antiretroviral drugs for Africa (as the much-anticipated international trust fund for infectious disease might soon do[35]) is that it creates market conditions in which it could become lucrative to patent antiretroviral drugs more widely in the future. The TRIPS agreement will make this possible in all developing countries belonging to the World Trade Organization by no later than 2006.

On the other hand, in African countries where antiretroviral drug patents do exist, the international community should ensure a supply of affordable drugs. An equitable balance is that countries ought to respect patent laws, but that patent holders reciprocally supply medicines to the global poor without profit, but also without loss. Various solutions to achieve this exist. Merck, Bristol-Myers Squibb, and Abbott have discounted antiretroviral drugs to prices not above their stated costs of production and distribution, and GlaxoSmithKline has taken similar steps for malaria medicines as well. These examples should be followed by other pharmaceutical companies. Alternatively, various legal proposals have been made to limit the patentability of certain medicines in poor countries without markedly affecting revenues.[36,37] Brand-name pharmaceutical companies might also consider adhering to a code of practice, in which they agree to voluntarily license patents for important medicines (antiretroviral drugs and others) to high-quality generic manufacturers willing to supply at low prices (the licenses would be geographically restricted to poor countries, and generic firms would pay a modest royalty for the privilege[38]). Arrangements like these would signify ethical business leadership and would affect revenues negligibly, given the diminutive pharmaceutical market in poor countries. Without them, poor countries have only the last resort of compulsory licensing (a governmental authorization that allows competitors to use a patent without the patent holder's consent), which both TRIPS and the Paris Convention legitimately allow them to do.[39,40]

Given these options to procure medicines at reduced prices, finance and distribution remain as impediments to treatment access. The impossibility of poor countries paying for antiretroviral treatment themselves cannot be overemphasized; countries such as Ghana, Nigeria, and Tanzania have annual national health budgets of $8 or less per capita.[41] In contrast, estimates endorsed by 140 faculty members of Harvard University for a treatment plan of diagnosis, care, and antiretroviral drugs are about $1200 per patient-year (including infrastructure development and training would cost somewhat more).[42] This vast finance gap means that even if health budgets were radically expanded and all waste or corruption banished, Africa's impoverished economies could never afford more than a few percent of the cost of treatment—and this is true even if antiretroviral drug prices continued to decline significantly, which is unlikely. Therefore, for antiretroviral treatment to take place, which it must, international aid finance is essential.

Based on these data, the extreme dearth of international aid finance, rather than patents, is most to blame for the lack of antiretroviral treatment in Africa. It is remarkable that the world's richest nations of North America, Western Europe, and Asia-Pacific together set aside only $74 million specifically for African AIDS in 1998—about $3 per HIV-infected African, or what it costs to build 3 miles (5 km) of rural freeway.[43] Such sums do not come close to financing the physicians, clinics, and infrastructure needed to administer antiretroviral therapy, much less to screen patients for HIV infection, and this has the lamentable result that even in cases in which pharmaceutical companies discount or freely donate antiretroviral drugs, poor African countries still cannot afford to use them. Lack of finance thwarts not only "expensive" AIDS treatment but even the highly cost-effective use of antiretroviral drugs in preventing pediatric HIV infection at birth (1 such drug, nevirapine, is donated by Boehringer Ingelheim but is rarely used in Africa).[44] The failure of wealthy governments to provide sufficient aid to fund these highly necessary interventions violates not only basic medical ethics but possibly international human rights laws as well.[45]

In summary, patents generally do not appear to be a substantial barrier to antiretroviral treatment access in Africa today. Activists, industry, physicians, and media who have so successfully raised public awareness of AIDS treatment issues are in a position to challenge the more important barriers. We agree that there are other patent issues of public health importance beyond the scope of this study (eg, access to new medicines after 2005, when TRIPS comes into force

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for all World Trade Organization members), but concern for the lives of those now dying of AIDS in Africa makes it necessary to unbundle those issues and proceed toward furnishing antiretroviral treatment concertedly and with speed. Acquired immunodeficiency syndrome is now the most numerically lethal pandemic since the Black Death 650 years ago—a pandemic so rare that it presents a literally unprecedented test to Western democracy, which is not 650 years old. History will not judge kindly an avoidable delay.

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