

# ADVERSE CLINICAL AND PUBLIC HEALTH CONSEQUENCES OF LIMITED ANTI-RETROVIRAL LICENSING

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Within twelve years of its identification as the cause of Acquired Immune Deficiency Syndrome (AIDS), the human immunodeficiency virus (HIV) was effectively cured. By 1995, scientific innovation produced nine medicines to suppress the virus, transforming HIV into a chronic condition. Mortality from AIDS plummeted, yet these advances did not span the globe. Drug costs prevented any expansion of treatments within resource-limited settings, where the vast majority of patients lived. Since 2003, governmental, non-governmental and multilateral agencies, and impacted countries, drastically scaled-up the provision of HIV medicines—over four million more patients now receive at least some therapy. This global “scale-up” of HIV treatment depends on mass production of generics, manufacture of which requires patent licensing, expiration or unavailability. The majority of therapies on which patients rely are in the public domain; most generic production exists because of patent expiration or unavailability, and not licensure. Because HIV drug development is so recent, drugs in the public domain are not simply older, but are also considerably less valuable in suppressing HIV and considerably more costly in terms of their extensive side effects. Drugs available in the public domain are less effective and frequently toxic to patients. Additionally, the newer, safe treatments that define the domestic standard of care are mostly unavailable in child- and fixed-dose and formulations. Whether excluded by price or technology, many low- and middle-income (LMI) countries cannot adopt modern treatments to treat their own, more substantial epidemics. These trends create significant deviations in the standard of care for HIV around the world.

Part I of this Note explores the epidemic’s spread, discusses the medical community’s subsequent response, and finally concentrates on governmental efforts to treat infected persons and the effect of legal regulations. Part II considers how these legal systems differently impact particular patient populations, specifically examining disparities in the standard of care for HIV patients. Part III concludes by surveying recent trends within the field.

## I. THE AIDS EPIDEMIC

### A. CURRENT TREATMENTS AND THE EFFECTS OF HIV AND AIDS IN THE DEVELOPING WORLD

In 2008, HIV infected 2.7 million new patients and killed an estimated 2 million people.<sup>1</sup> Since its identification in 1981, AIDS killed 25 million patients; nearly 35 million more currently live with HIV.<sup>2</sup> HIV infects the immune system, destroying the cells that fight infection. Lacking these cells, patients develop AIDS and eventually die from opportunistic secondary infections, such as tuberculosis or pneumonia.<sup>3</sup> Without treatment, HIV almost always causes AIDS.

Most new HIV infections and related deaths occur in sub-Saharan Africa. Greater than 65 percent of infected persons live there. Moreover, new pediatric infections (91 percent) and deaths (72 percent) occur disproportionately in this region.<sup>4</sup> The epidemic's impact is concentrated where governments cannot respond with effectively targeted health interventions<sup>5</sup> and patients are overwhelmingly impoverished. Lacking resources to create commercial demand or even afford the marginal costs of treatment, these populations fail to attract medicines and formulations specific to local needs. Because of their extreme impoverishment, sub-Saharan communities cannot effectively express demand. Limited domestic

1. UNAIDS & WORLD HEALTH ORG., AIDS EPIDEMIC UPDATE 2009 6 (2009), available at [http://data.unaids.org/pub/Report/2009/2009\\_epidemic\\_update\\_en.pdf](http://data.unaids.org/pub/Report/2009/2009_epidemic_update_en.pdf) [hereinafter AIDS EPIDEMIC UPDATE].

2. *Id.*

3. CENTER FOR DISEASE CONTROL, 1993 REVISED CLASSIFICATION SYSTEM FOR HIV INFECTION AND EXPANDED SURVEILLANCE CASE DEFINITION FOR AIDS AMONG ADOLESCENTS AND ADULTS (1992). The World Health Organization authored its own guidelines for resource-limited settings, where diagnostics are rare. See WORLD HEALTH ORG., WHO CASE DEFINITIONS OF HIV FOR SURVEILLANCE AND REVISED CLINICAL STAGING AND IMMUNOLOGICAL CLASSIFICATION OF HIV-RELATED DISEASE IN ADULTS AND CHILDREN 5–6 (2007), available at [http://www.who.int/hiv/pub/guidelines/HIV\\_staging150307.pdf](http://www.who.int/hiv/pub/guidelines/HIV_staging150307.pdf).

4. AIDS EPIDEMIC UPDATE, *supra* note 1, at 21.

5. COMMISSION ON MACROECONOMICS AND HEALTH, WORLD HEALTH ORG., MACROECONOMICS AND HEALTH: INVESTING IN HEALTH FOR ECONOMIC DEVELOPMENT 57 (2003), available at <http://whqlibdoc.who.int/publications/2001/924154550x.pdf>. The Commission noted,

Even if poor countries allocated more domestic resources to health, such measures would still not resolve the basic problem: poor countries lack the needed financial resources to meet the most basic health needs of their populations. At \$30 to \$40 per capita for essential interventions, these costs would represent more than 10 percent of GNP of the least developed countries, far above what can in fact be mobilized out of domestic resources.

health budgets in the region cannot finance substantial HIV interventions. Consequently, staggering mortality characterized the developing world's first twenty years of AIDS, as a vanishingly small number of patients received any care before death.

The treatment landscape changed dramatically in 1995 with the innovation of the triple-cocktail, or highly-active anti-retroviral therapy (HAART). Prior to HAART, HIV almost always led to death. Because only one class of antiretroviral (ARV) drugs—nucleoside reverse transcriptase inhibitors (NRTI)—existed prior to 1995, therapies were incapable of suppressing HIV's rapid replication. HIV copies itself quickly and inaccurately, creating drug-resistant strains within a single patient when she is treated with a single agent. As new classes of therapies<sup>6</sup> entered the clinic in 1995, researchers recognized the potential of using multiple agents against HIV.<sup>7</sup> U.S. and E.U. patients experienced 70 percent declines in mortality following introduction of these new classes of drugs, protease and non-nucleoside reverse transcriptase inhibitors (PI and NNRTI, respectively), in 1995 and 1996.<sup>8</sup> When paired with a backbone of two NRTIs,<sup>9</sup> these new drugs produced potent cocktails that ended the death sentence of AIDS for well-resourced patients.

In the mid-1990s, per-patient costs for cocktail therapies exceeded \$10,000 per year.<sup>10</sup> These costs prevented any mortality declines in LMI countries<sup>11</sup> and for uninsured patients in the developed world.<sup>12</sup> A 1998

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6. Currently, there are five classes of action: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors (II), CCR5 antagonists, and fusion inhibitors (FI).

7. Scott Hammer et al., *A Trial Comparing Nucleoside Monotherapy With Combination Therapy in HIV-Infected Adults With CD4 Cell Counts From 200 to 500 Per Cubic Millimeter*, 335 NEW ENG. J. MED. 1081 (1996); Scott Hammer et al., *A Controlled Trial of Two Nucleoside Analogues Plus Indinavir in Persons With Human Immunodeficiency Virus Infection and CD4 Cell Counts of 200 Per Cubic Millimeter or Less*, 337 NEW ENG. J. MED. 725 (1997); Roy Gulick et al., *Treatment With Indinavir, Zidovudine, and Lamivudine in Adults With Human Immunodeficiency Virus Infection and Prior Antiretroviral Therapy*, 337 NEW ENG. J. MED. 734 (1997).

8. *See id.*

9. Such as NRTI+NRTI+PI, or NRTI+NRTI+NNRTI.

10. John. Bartlett, Plenary Address at 13<sup>th</sup> Conference on Retroviruses and Infectious Diseases: 10 Years of HAART: Foundations for the Future (Feb. 8, 2006), available at <http://cme.medscape.com/viewarticle/523119?src=mp>.

11. "Low- and middle-income," like "developing country," is a term of art. For simplicity, LMI are generally non-OECD countries, while Least Developed Countries are the poorest states on earth. The World Bank uses precise metrics to classify countries as low-, middle-, and high-income based on per capita gross national income. *See* WORLD BANK, COUNTRY CLASSIFICATION, <http://web.worldbank.org/WBSITE/EXTERNAL/DATA STATISTICS/0,,contentMDK:20420458~menuPK:64133156~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html> (last visited October 7, 2010) ("[L]ow income, \$975 or

analysis of U.S. and LMI country GNP indicated that ARVs cost 300 times more in the developing world, where most patients live.<sup>13</sup> In the same year, another analysis showed the cost of HAART in Haiti, relative to U.S. health care expenditures, was 225 times more expensive.<sup>14</sup> Developing world price points for ARVs resulted in near-total inaccessibility of the drugs. Donations and scaled pricing mechanisms did little to change these circumstances.<sup>15</sup> Because the most at-risk populations in the world typically cannot pay *anything* for medicines, potential revenues for worldwide distribution were (and remain) trivial, and neither manufacturers nor purchasers reached patients.

In the absence of effective production and distribution mechanisms to reach the majority of the world's infected population, predictable results followed: in 2000, fewer than 10,000 patients in Africa received HAART.<sup>16</sup> By 2003, treatment coverage crawled to 2 percent,<sup>17</sup> and reached 10 percent by 2005.<sup>18</sup> The long-term consequences of delaying introduction of HAART to LMI countries are overwhelming demographically—infections in sub-Saharan Africa outnumber U.S. and E.U. infections by a factor of 20:1, but life-years saved in the United States and European Union continue to outnumber life-years saved in sub-Saharan Africa by 3:1.<sup>19</sup> Delays in bringing therapy to South Africa between 2000 and 2005 killed over 330,000 people,

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less; lower middle income, \$976–\$3,855; upper middle income, \$3,856–\$11,905; and high income, \$11,906 or more.”).

12. See Marsha Lillie-Blanton et al., *Association of Race, Substance Abuse, and Health Insurance Coverage With Use of Highly Active Antiretroviral Therapy Among HIV-Infected Women 2005*, AM. J. PUB. HEALTH. (forthcoming 2010); William D. King, *Factors Associated with HIV Viral Load in a Respondent Driven Sample in Los Angeles*, 13 AIDS & BEHAVIOR 1573 (2009); Michael J. Mugavero, *Missed Visits and Mortality among Patients Establishing Initial Outpatient HIV Treatment*, 48 CLINICAL INFECTIOUS DISEASES 248 (2008).

13. Robert S. Hogg et al., *One World, One Hope: the Cost of Providing Antiretroviral Therapy to All Nations*, 12 ACQUIRED IMMUNE DEFICIENCY SYNDROME 2203 (1998).

14. Julio S.G. Montaner et al., *The Costs of Triple-Drug Anti-HIV Therapy for Adults in the Americas*, 279 J. AM. MED. ASS'N. 1263 (1998).

15. Barton Gellman, *An Unequal Calculus of Life and Death; As Millions Perished in Pandemic, Firms Debated Access to Drugs; Players in the Debate Over Drug Availability and Pricing*, WASH. POST, Dec. 27, 2000, at A1; Barton Gellman, *A Turning Point That Left Millions Behind*, WASH. POST, Dec. 28, 2000, at A1; Bill Brubaker, *The Limits of \$100 Million; Epidemic's Complexities Curb Impact of Bristol-Myers's Initiative*, WASH. POST, Dec. 29 2000, at A1.

16. See Mark A. Wainberg, *Generic HIV Drugs – Enlightened Policy for Global Health*, 352 NEW ENG. J. MED. 747, 747 (2005).

17. AIDS EPIDEMIC UPDATE, *supra* note 1, at 25.

18. John A. Bartlett & Eva P. Muro, *Generic and Branded Drugs for the Treatment of People Living with HIV/AIDS*, 6 J. INT'L ASS'N PHYSICIANS AIDS CARE 15 (2007).

19. AIDS EPIDEMIC UPDATE, *supra* note 1, at 18.

and caused a loss of over three million life-years.<sup>20</sup> Life expectancy in Zimbabwe fell by eighteen years between 1990 and 2003.<sup>21</sup>

After years of inaction, global commitments to treating and preventing HIV grew more than 500 percent between 2002 and 2008.<sup>22</sup> Substantial funding is channeled through multi-lateral agents and non-governmental organizations (NGOs), such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; UNITAID, the U.N. initiative to scale-up access to treatments in developing countries; and the World Bank. The emergence of the Bill and Melinda Gates Foundation is equally significant—by 2007, its grant-making budget equaled the World Health Organization's (WHO) total budget.<sup>23</sup> Besides these global financing mechanisms, the most significant contributor was American legislation. In 2003, President George Bush signed the Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act.<sup>24</sup> The Act created the five-year, fifteen-billion-dollar President's Emergency Plan for AIDS Relief (PEPFAR), the largest global health intervention ever. In 2008, the Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act tripled the intervention to \$48 billion.<sup>25</sup> PEPFAR buys and coordinates distribution of therapies, operates testing and treatment clinics, and supports extensive research and health interventions. The aggregate global commitment to HIV/AIDS raised the number of LMI patients on HAART by four million since 2003.<sup>26</sup> This collective expansion of care cannot be overestimated.

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20. Pride Chigwedere et al., *Estimating the Lost Benefits of Antiretroviral Drug Use in South Africa*, 49 J. ACQUIRED IMMUNE DEFICIENCY SYNDROME 410 (2008).

21. E. GOMO, HIGHLIGHTS OF THE ZHDR 2003: REDIRECTING OUR RESPONSES TO HIV AND AIDS 3 (2004), available at [http://www.sarpn.org.za/documents/d0000805/P925-Zimbabwe\\_HDR\\_Intro\\_Gomo.pdf](http://www.sarpn.org.za/documents/d0000805/P925-Zimbabwe_HDR_Intro_Gomo.pdf). Similar reductions—erasing post-war gains in life expectancy—were observed in Botswana and South Africa, where life expectancy by 2005 was reduced to 34, from 60, and 47, from 62, respectively. NANA K POKU AND ALAN WHITESIDE, *THE POLITICAL ECONOMY OF AIDS IN AFRICA* 12 (2004); Fantu Cheru, *Debt, Adjustment and the Politics of an Effective Response to HIV/AIDS in Africa*, 23 THIRD WORLD Q. 299, 300 (2002).

22. Eran Bendavid & Jayanta Bhattacharya, *The President's Emergency Plan for AIDS Relief in Africa: An Evaluation of Outcomes*, 150 ANN. OF INTERNAL MED. 688, 688 (2009).

23. David McCoy et al., *The Bill & Melinda Gates Foundation's Grant-Making Programme for Global Health*, 373 THE LANCET 1645 (2009).

24. United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003, Pub. L. No. 108-25, 117 Stat. 711 (2003) (codified at 22 U.S.C. § 7601 (2006)).

25. Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008, Pub. L. No. 110-293, 122 Stat. 2918 (codified as amended at 22 U.S.C. § 7601 et seq. (2006)).

26. UNAIDS ET AL., *TOWARDS UNIVERSAL ACCESS, SCALING UP PRIORITY HIV/AIDS INTERVENTIONS IN THE HEALTH SECTOR, PROGRESS REPORT 2009* 57, available at [http://data.unaids.org/pub/Report/2009/20090930\\_tuapr\\_2009\\_en.pdf](http://data.unaids.org/pub/Report/2009/20090930_tuapr_2009_en.pdf).

Despite historic increases in funding for therapies and other interventions, most patients still receive no treatment.<sup>27</sup> Patients receiving treatment, however, almost exclusively receive medicines strongly disfavored by the WHO and U.S. Department of Health and Human Services. HIV patients in the United States and Europe no longer receive these antiquated therapies for reasons of toxicity, inefficacy, and tolerability. At the same time President Bush created PEPFAR, U.S. and E.U. physicians removed its components from prescription lists. In the United States and European Union, a variety of small-molecule drugs are combined into cocktails, offering particular side effect profiles based on a patient's tolerance, allergies, co-morbidities, and other factors. In LMI countries, there is a single cocktail. The foundation of the scale-up is a single pill: Triomune.

Recent increases in funding for global HIV treatment represent an unrivaled public health intervention that is plagued by serious side effects because the pool of accessible medicines is so small. Limited licensing and production of effective, modern compounds hamper efforts to universalize proper care. Additionally, limited licensing of safe and effective compounds prevents appropriate treatments from reaching particular patient groups, notably children. Even if every patient received a timely and accurate diagnosis, the unavailability of modern therapies precludes most patients from receiving adequate treatment. While American and European patient populations receive many iterations of triple-cocktail therapy, *most* patients, and nearly every LMI patient, receive Triomune exclusively.

#### B. SOURCING THE SCALE-UP

HAART transformed HIV into a chronic, non-fatal infection.<sup>28</sup> The "scale-up" most significantly brought HAART to more than 4,000,000 people in LMI countries.<sup>29</sup> The majority of these patients receive life-saving

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27. AIDS EPIDEMIC UPDATE, *supra* note 1, at 9. Others put the figure at 37 percent. Rochelle P. Walensky & Daniel R. Kuritzkes, *The Impact of the President's Emergency Plan for AIDS Relief (PEPFAR) beyond HIV and Why It Remains Essential*, 50 CLINICAL INFECTIOUS DISEASES 272, 274 (2010).

28. See F. Palella et al., *Declining Morbidity and Mortality Among Patients With Advanced Human Immunodeficiency Virus Infection*, 338 NEW ENG. J. MED. 853 (1998).

29. More than money was required: many initially opposed any scale-up of complex HAART therapies, but every argument against the scale-up proved groundless. See Edward J. Mills et al., *Adherence to Antiretroviral Therapy in sub-Saharan Africa and North America: A Meta-analysis*, 296 J. AM. MED. ASS'N. 679 (2006); Edward J. Mills et al., *Adherence to HAART: A Systematic Review of Developed and Developing Nation Patient-Reported Barriers and Facilitators*, 3 PLOS MED e438 (2006); Olivia Keiser et al., *Public-Health and Individual Approaches to Antiretroviral Therapy: Township South Africa and Switzerland Compared*, 5 PLOS MED e148 (2008); Paul Farmer & Jim Yong Kim, *Community-based Approaches to the Control of Multidrug-Resistant Tuberculosis: Introducing 'DOTS-Plus'*, 317 BRIT. MED. J. 671 (1998); Jonathan Mermin et al.,

treatment because generic production emerged as the most powerful mechanism for producing ARVs at prices enabling widespread distribution.<sup>30</sup> Over 80 percent of ARVs prescribed in the developing world originate in India's generic plants.<sup>31</sup> Manufacturers there compete with one another, invest in bulk manufacturing processes, and drive prices toward marginal cost. This competition occurs optimally when patent holders sign multiple licenses, or patent rights do not exist because of expiration or ineligibility.<sup>32</sup> Generic manufacturers "have neither patents nor a costly approval process to deter potential competitors [and] quickly face competition from other companies producing identical drugs. That intense competition forces . . . much lower prices than the innovator firm."<sup>33</sup> The results of such competition are clear—generic ARVs cost between 3 and 33 percent of branded sales prices.<sup>34</sup>

An example illustrates these observations: six manufacturers sell the developing world's most common ARV to PEPFAR (Triomune, co-formulated Stavudine, Nevirapine, and Lamivudine). In 2000, the originator

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*Mortality in HIV-Infected Ugandan Adults Receiving Antiretroviral Treatment and Survival of Their HIV-Uninfected Children: A Prospective Cohort Study*, 371 THE LANCET 703 (2008).

30. Sarah Lueck, *Generics Fuel AIDS Program*, WALL ST. J., Jul. 31, 2008. The President's Emergency Plan for AIDS Relief (PEPFAR) relied on a "tentative approval" process for the regulation of generically-made ARVs.

31. Colleen V. Chien, *HIV/AIDS Drugs for Sub-Saharan Africa: How Do Brand and Generic Supply Compare?*, 2(3) PLOS ONE e278 (2007).

32. Principal manufacturers are Alkem, Aurobindo, Cipla, Emcure, Hetero, Macleods, Matrix, Ranbaxy, and Strides. Barr (now Teva), Huahai (China), and Aspen Pharmcare (South Africa) are non-Indian producers of relevance. Aspen Pharmcare, in South Africa, is the only African producer. The others are Barr Pharmaceuticals, of New York, and Zhejiang Huahai Pharmaceutical Co. Ltd, of Zhejiang, China. See Nicholas Zamiska, *U.S. Opens the Door to Chinese Pills*, WALL ST. J., Oct. 9, 2007. Barr's tentative approval for didanosine, in December 2004 (ANDA no. 077167), was the first ARV approved under the Food and Drug Administration's (FDA) new Guidance, but it was a Paragraph IV ANDA and unique to the remaining 103. Aspen's first approval was the second drug approved under the new Guidance; its second followed in seventeen months. Ninety-nine percent of subsequent tentative approvals originate in India. See FOOD AND DRUG ADMINISTRATION, PRESIDENT'S EMERGENCY PLAN FOR AIDS RELIEF. APPROVED AND TENTATIVELY APPROVED ANTIRETROVIRALS IN ASSOCIATION WITH THE PRESIDENT'S EMERGENCY PLAN, <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm> (last visited December 29, 2009) [hereinafter FDA].

33. CONGRESSIONAL BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 2–3, 35 (1998), available at <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf> (finding Americans saved \$8–10 billion in 1994, with generic competition reducing average brand-name price (\$37.40) by \$20 (to \$17.40)).

34. Chien, *supra* note 31.

price for one year of these drugs approximated \$10,439.<sup>35</sup> By October 2009, the median price across manufacturers reached \$83.<sup>36</sup> These price declines directly affect the number of patients served, because most patients in resource-limited settings resources to buy pharmaceuticals. As a result, most treatment budgets come from fixed multilateral and non-governmental sources, such that the number of patients served is a function of drug cost.

PEPFAR encouraged the use and development of generic ARVs. Within a year of the Act's passage, the Food and Drug Administration (FDA) issued a Guidance Document elaborating a review pathway for international distribution of generic ARVs.<sup>37</sup> After establishing safety, efficacy, and quality standards, a foreign producer can attain "tentative" FDA approval to sell ARVs to PEPFAR, even while domestic patent protection persists.<sup>38</sup> Tentative approval qualifies a drug for PEPFAR distribution, and often qualifies a product for WHO, UNITAID, and Global Fund distribution.<sup>39</sup> Tentative approvals, therefore, can generate clearance for the world's largest ARV buyers, a circumstance creating economies of scale for producers. Global AIDS Coordinator Mark Dybul observed the effects of U.S. procurement policies before the House Foreign Affairs Committee in 2007:

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35. MÉDECINS SANS FRONTIÈRES, UNTANGLING THE WEB OF ANTIRETROVIRAL PRICE REDUCTIONS 6 (11th ed. 2008), *available at* [http://www.msface.org/fileadmin/user\\_upload/diseases/hiv-aids/Untangling\\_the\\_Web/Untanglingtheweb\\_July2008\\_English.pdf](http://www.msface.org/fileadmin/user_upload/diseases/hiv-aids/Untangling_the_Web/Untanglingtheweb_July2008_English.pdf).

36. WORLD HEALTH ORG., TRANSACTION PRICES FOR ANTIRETROVIRAL MEDICINES AND HIV DIAGNOSTICS FROM 2008 TO OCTOBER 2009 6 (2009), *available at* <http://www.who.int/hiv/amds/GPRMsummaryReportNov2009.pdf>; MÉDECINS SANS FRONTIÈRES, *supra* note 35, at 6.

37. *See* CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION, FIXED DOSE COMBINATIONS AND CO-PACKAGED DRUG PRODUCTS FOR TREATMENT OF HIV, DRAFT GUIDANCE (2004), *available at* <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125278.htm>; CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY: FIXED DOSE COMBINATIONS, CO-PACKAGED DRUG PRODUCTS, AND SINGLE-ENTITY VERSIONS OF PREVIOUSLY APPROVED ANTIRETROVIRALS FOR THE TREATMENT OF HIV (2006), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf>.

38. Manufacturers file Abbreviated New Drug Applications (ANDA), as per the Drug Price Competition and Patent Restoration Act, Pub. L. No. 98-417 (1984) (codified at 21 U.S.C. § 355(j) (2006)). ANDA applicants provide bioequivalence, safety, efficacy, and other criteria, and indicate the future expiration of the patent, as per § 355(j)(2)(A)(vii)(III) (2006).

39. OFFICE OF THE U.S. GLOBAL AIDS COORDINATOR, BRINGING HOPE: SUPPLYING ANTIRETROVIRAL DRUGS FOR HIV/AIDS TREATMENT 6 (2006); Press Release, U.S. Food and Drug Administration, FDA Grants Tentative Approval for 50<sup>th</sup> and 41<sup>st</sup> Anti-Retroviral Drugs Under President's Emergency Plan for AIDS Relief (Aug. 15, 2007), *available at* <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108964.htm>. The FDA also synchronized its approval process with the WHO's process, accelerating some WHO approvals ("prequalification") immediately on a tentative basis.



PEPFAR also has increased the availability of safe, effective, low-cost generic antiretroviral drugs (ARVs) in the developing world . . . . [T]here was a significant increase in the use of generic products, and in 2007 we will continue to work with partners to utilize the safest, cheapest drugs whenever possible. As a side benefit, the process has also expedited the availability in the United States of six generic versions of ARVs whose U.S. patent protection had expired. . . [PEPFAR's supply chain system] increased its share of ARV purchases that are generics from 72 percent in April to September 2006, to 88 percent (by volume) in January to March 2007.<sup>40</sup>

No FDA process, however, affects a patent-holder's ability to enforce patent rights in any country where the patent is registered.<sup>41</sup> PEPFAR does nothing to abate patent rights.

The FDA's tentatively approved PEPFAR ARVs provide a dataset of 104 generic formulations that constitute the backbone of HAART in LMI countries.<sup>42</sup> These 104 formulations include 165 active ingredients, some of which are combined into co-formulations. Of the 164 medicines, 135 (82.3%) were unpatented in India, where the vast majority of generic production facilities exist. Only 17.7% of PEPFAR-purchased ARVs result from voluntary license exchanges between patent owners and generic producers. It is likely that the ratio of generic-to-licensed volume actually exceeds these figures, because the majority of procured drugs are for "first-line" patients, all of which were registered before 1995. The pharmaceutical industry largely eschews licensing to manufacturers in India that would then sell generic drugs to PEPFAR. Instead, PEPFAR relies mostly on

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40. PEPFAR: *An Assessment of Progress and Challenges: Hearing Before the H. Comm. on Foreign Affairs*, 110th Cong. 16 (2007) (testimony of Honorable Mark R. Dybul, U.S. Global AIDS Coordinator, U.S. Dept. of State); see Sarah Lueck, *supra* note 30.

41. Chien, *supra* note 31, at 3, notes evidence of de facto non-assertions for the importation of generically (and legally, in India) produced drugs delivered to countries where patent protection exists (South Africa). Additionally, Kapczynski et al. describe Bristol-Myers Squibb's express non-assert position for one drug in South Africa. Amy Kapczynski et al., *Addressing Global Health Inequities: An Open Licensing Approach for University Innovations*, 20 BERKELEY TECH. L.J. 1031, 1034–08 (2005).

42. The data includes strength, dosage, supplier, manufacturer, and date of approval. The author coded the data and performed all calculations, as of November, 2009. FOOD AND DRUG ADMINISTRATION, APPROVED AND TENTATIVELY APPROVED ANTIRETROVIRALS IN ASSOCIATION WITH PRESIDENT'S EMERGENCY PLAN, <http://www.fda.gov/internationalprograms/fdabeyondourbordersforeignoffices/asiaandafri ca/ucm119231.htm>.

compounds in India's public domain, as a result of the timing of India's TRIPS obligations.<sup>43</sup> Table 1 illustrates these trends.

**Table 1 All PEPFAR Formulations, by Active Substance**

<b>Drugs Registered After 1995<sup>44</sup></b>	<b>PEPFAR Iterations<sup>45</sup></b>
Abacavir (Ziagen ®)	11
Atazanavir (Reyataz ®)	1
Emtricitabine (Emtriva ®)	5
Lopinavir/ritonavir (Kaletra ®)	3
Tenfovir disoproxil fumarate (Viread ®)	9
Total	29 (17.68%) <sup>46</sup>
<b>Drugs Registered Before 1995</b>	<b>PEPFAR Iterations<sup>47</sup></b>
Didanosine (Videx ®)	4
Efavirenz (Sustiva ®)	16
Nevirapine (Viramune ®)	22
Lamivudine (Epivir ®)	46
Stavudine (Zerit ®)	20
Zidovudine (Retrovir ®)	27
Total	135 (82.3%)

43. Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299, 333 I.L.M. 1197 (1994)[hereinafter TRIPS]. Art. 27 required India to protect products; arts. 65-6 and 70.8-9 concern the transition period and mailbox procedure. January 1, 2005. Post-1995 registrations are evaluated as per India's 2005 Patents (Amendment), see *infra* note 54.

44. UNAIDS & WORLD HEALTH ORG., PATENT SITUATION OF HIV/AIDS-RELATED DRUGS IN 80 COUNTRIES (2000), <http://www.who.int/3by5/en/patentshivdrugs.pdf>.

45. FDA, *supra* note 42.

46. Calculated by summing the number of ingredients in the 104 formulations, *supra* note 42, and adding priority dates from Chien, *supra* note 31, and UNAIDS & WORLD HEALTH ORG, PATENT SITUATION OF HIV/AIDS-RELATED DRUGS IN 80 COUNTRIES, *supra* note 44, at 11-16.

47. FDA, *supra* note 42.

## C. UNDERLYING LEGAL SYSTEMS

Patent law varies by country, though the TRIPS Agreement informs the laws of each member country.<sup>48</sup> TRIPS requires WTO Members enforce patent rights for most pharmaceutical products.<sup>49</sup> Passed in conjunction with the establishment of the World Trade Organization (WTO), it binds all member states with time-phased exceptions. For example, the Least Developed Countries must fully implement TRIPS by January 2016.<sup>50</sup> Additionally, the Doha Declaration of Ministers in 2001 affirmed the ability of states to consider the public health impact of compliance and reiterated the legality of compulsory licenses in public health emergencies.<sup>51</sup> These exceptions, however, do not inform the current analysis because pharmaceutical production occurs mainly in middle-income countries with substantial production facilities—primarily, this production occurs in fully TRIPS-compliant India.<sup>52</sup> Flexibilities for Zimbabwe, for example, cannot help patients there because the country lacks the infrastructure to synthesize or manufacture medicines.<sup>53</sup> Additionally, the phase-in flexibilities of TRIPS excludes middle-income countries, like South Africa.

India's entry into the WTO required TRIPS compliance. The country amended its Patent Act, effective in 2005, to provide protection for

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48. See TRIPS, *supra* note 43.

49. *Id.* art. 27 requires patent protection “for any inventions, whether products or processes, in all fields of technology” that are “new, involve an inventive step, and are capable of industrial application.”

50. The U.N. Committee for Development Policy reviews its list of Least Developed Countries every three years, and focuses on income (below \$745 per capita), human capital status (nutrition, health, education, and adult literacy), and economic vulnerability (population size, remoteness, export concentration, share of agriculture in GDP, and instability of exports). UNITED NATIONS OFFICE OF THE HIGH REPRESENTATIVE FOR THE LEAST DEVELOPED COUNTRIES, LANDLOCKED DEVELOPING COUNTRIES AND SMALL ISLAND DEVELOPING STATES, CRITERIA FOR LDC, <http://www.unohrrls.org/en/ldc/related/59/>.

51. TRIPS, *supra* note 43, art. 31, describes compulsory licensing procedures. See Frederick Abbott & Jerome H. Reichman, *The Doha Round's Public Health Legacy: Strategies for the Production and Diffusion of Patented Medicines Under the Amended TRIPS Provisions*, 10 J. INT'L ECON. L. 921 (2007). This Note does not address the possibility of India or any other country issuing a compulsory license. The use of compulsory licenses in health contexts is a substantial topic in its own, and countries have considered, and some implemented, compulsory licenses for ARVs.

52. John H. Barton, *TRIPS and The Global Pharmaceutical Market*, 23 HEALTH AFFAIRS 146 (2004).

53. See MÉDECINS SANS FRONTIÈRES, NEITHER EXPEDITIOUS, NOR A SOLUTION: THE WTO AUGUST 30TH DECISION IS UNWORKABLE (2006). This trend is not static. Brazil aims to build an antiretroviral factory in Mozambique that will produce eight antiretrovirals. Charles Mangwiro, *Brazil Offers Drug Factory to AIDS-Ravaged Mozambique*, REUTERS, May 29, 2007.

pharmaceutical products.<sup>54</sup> Before 2005, India did not grant medicines product patents—India only granted patent rights to innovative processes. After 2005, products registered in the country after 1995 were eligible for patent protection. Drugs registered before 1995 were “not [to] be substantially affected” by the transition<sup>55</sup> and producers continue to manufacture them without licensing. By coincidence, HAART transformed modern medicine in 1995. Thus the earliest HIV drugs remain in India’s public domain; more advanced, safe, effective, and tolerable drugs remain protected by patents.

While “generics fuel [the] AIDS program,”<sup>56</sup> voluntary licensing does not provide much fuel and the generics that reach PEPFAR patients are low-octane.<sup>57</sup> For reference, of the thirty-two ARVs approved in the United States, only seven received approval before 1995.<sup>58</sup> Post-1995 innovations include almost all protease inhibitors, and three new classes of drugs—integrase inhibitors, fusion inhibitors and CCR5 antagonists. Even the most basic post-1995 therapies are newer, safer, more effective, and less toxic than the compounds PEPFAR distributes. A majority of HIV patients, therefore, suffer a substandard of care. For these patients, medical science did not progress after 1995.

PEPFAR procurement and the subsequent worldwide therapy uptake demonstrate that widespread drug availability is closely linked to generic manufacture, which relies on either sublicensing efforts or patent term expiration. The status quo of scarce voluntary licensing, thus, effectively sequesters recent therapies from LMI patients for the length of their Indian patent terms. The 1995 patentability cutoff date in India—created by TRIPS—and the paucity of voluntary licenses preclude uptake of the HAART compounds that characterize successful HIV treatment in the

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54. See The Patents (Amendment) Act, 2005, No. 15, Acts of Parliament, 2005. The Indian government evaluated applications filed after January 1, 1995 in 2005.

55. Frederick Abbott, *The WTO Medicines Decision: World Pharmaceutical Trade and the Protection of Public Health*, 99 AM. J. INT’L L. 317, 321 (2005).

56. Lueck, *supra* note 30.

57. There are exceptions. Gilead signed thirteen licenses for production of its best-selling ARV Tenofovir. GlaxoSmithKline signed eight voluntary licenses for its anti-retrovirals, including Abacavir. Press Release, GlaxoSmithKline, GSK Announces New Commitment to Right HIV/AIDS in Sub-Saharan Africa (July 14, 2009), *available at* [http://www.gsk.com/media/pressreleases/2009/2009\\_pressrelease\\_10073.htm](http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10073.htm). Tibotec collaborated with Aspen (of South Africa) to manufacture Darunavir. Press Release, Tibotec, Tibotec and Aspen Collaborate on Prezista (TM), *available at* [http://www.tibotec.com/news/detail.jhtml?action=view&itemname=news\\_31](http://www.tibotec.com/news/detail.jhtml?action=view&itemname=news_31). The execution of a single license, however, often fails to create optimal competition between producers.

58. U.S. Food and Drug Administration, Antiretroviral Drugs Used in the Treatment of HIV Infection, <http://www.fda.gov/ForConsumers/byAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118915.htm> (last visited December 16, 2009).

developed world. Though four million LMI patients received HAART since 2003, a comparison of HAART in LMI countries and in the United States reveals significant and deleterious disparities in toxicity, efficacy, and safety.<sup>59</sup> Patients in the developing world ingest drugs of far lower quality than those used by American and European patients. What's acceptable to U.S. patients and physicians differs markedly from what is acceptable for Kenyan patients.

Reauthorization of PEPFAR in 2008 tripled the program's size and produced new statutory language ensuring ARVs "are purchased at the lowest possible price at which such pharmaceuticals may be obtained in sufficient quantity on the world market . . . approved, tentatively approved, or otherwise authorized for use by [FDA]."<sup>60</sup> Substantial gaps in technology and availability of therapies persist around the world, partially because of insufficient licensing. While progress continues toward treating most of the world's infected population, a highly stratified standard of care grows between patients in the developing and the developed world.

## II. TREATMENT LINES AND FORMULATIONS

### A. FIRST- AND SECOND-LINE THERAPIES

Patients in the developed world rarely use the drugs and treatment schedules offered to similar patients in developing countries. Developed world patients rely on newer, more effective, and less toxic drugs that are generally subject to patent protection in India. Based on geography and income, and not clinical progression or status, more than 80 percent of AIDS patients rely on inadequate therapies, in part because of scarce voluntary licensing to PEPFAR suppliers.<sup>61</sup> Because LMI formulations develop as a result of competition between generic manufacturers, a patent holder's refusal to license her property effectively sequesters it from PEPFAR purchase and LMI uptake. In other words, because PEPFAR purchases most of its input from Indian generic companies, the originator retains the prerogative to refuse PEPFAR distribution by not licensing to manufacturers in India. Relying on India's public domain alone, despite augmentation of manufacturing capacity and accelerated FDA/WHO approval, ARVs in LMI countries fall into one of two categories: old or malformed.

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59. AIDS EPIDEMIC UPDATE, *supra* note 1, at 9.

60. Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008, Pub. L. No. 110-293, § 301(c)(4)(C), 122 Stat. 2918 (2008); *see* Letter from Congresswoman Barbara Lee and Congressman Henry Waxman to Dr. Eric Goosby, U.S. Global AIDS Coordinator (Dec. 11, 2009) (on file with author).

61. Globally, approximately 4.7 million patients access HAART, with over 4 million users in LMI countries. UNAIDS, *supra* note 26.

The disparity between developed-world science and developing-world use is stark and well-known. Former Executive Director of UNAIDS, Dr. Peter Piot, and World Health Organization Director of HIV/AIDS, Dr. Kevin de Cock, observe, “[t]he overwhelming majority of patients are receiving first-line regimens that have significant issues of toxicity.”<sup>62</sup> Two questions follow: (1) how widely does the standard of care for HIV diverge between the developed and developing world; and (2) what divergence in Western-tolerated and LMI-tolerated toxicity and inefficacy is reasonable?

1. *LMI Standard of Care*

The standard of care for patients in LMI settings depends entirely on therapy availability. Therapy schedules are functions of licensing behavior: public-domain medications are super-abundant, and medications requiring licensing are scarce. While patients in developed settings select therapies based on efficacy, safety, and side effects, patients in LMI countries rely overwhelmingly on a single cocktail, the components of which existed prior to patent protections in India. Almost every LMI patient begins HAART on the “first-line” therapy Triomune.<sup>63</sup> This regime abounds because it is inexpensive; its competitive manufacture, and high-volume procurement by bi- and multi-lateral purchasers, creates enormous downward pressure on cost. Triomune costs \$83 yearly for patients in low-income countries, and \$97 in middle-income countries.<sup>64</sup> The cost of procurement for license-dependent treatments, however, impedes their clinically-indicated use. For

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62. Debrework Zewdie et al., *Sustaining Treatment Costs: Who Will Pay?*, 21 ACQUIRED IMMUNE DEFICIENCY SYNDROME S1 (2007).

63. Anthony D. Harries et al., *Scaling Up Antiretroviral Treatment in Resource-poor Settings*, 367 THE LANCET 1870, 1870 (2006) (indicating 95 percent of patients in Malawi hospitals are on Triomune); Lauren Ferradini et al., *Scaling Up Highly Active Antiretroviral Therapy in Rural District of Malawi: An Effectiveness Assessment*, 367 THE LANCET 1335, 1338 (2006) (indicating 78 percent of patients in Malawi hospitals use Triomune); WHO HIV DEPARTMENT WORKING GROUP, *PRIORITIZING SECOND-LINE ANTIRETROVIRAL DRUGS FOR ADULTS AND ADOLESCENTS: A PUBLIC HEALTH APPROACH 2007*, available at [http://www.who.int/hiv/pub/meetingreports/second\\_line\\_art\\_report\\_2008.pdf](http://www.who.int/hiv/pub/meetingreports/second_line_art_report_2008.pdf) (indicating almost all patients in low- and middle-income countries are on d4t-containing regimen); Françoise Renaud-Théry et al., *Use of Antiretroviral Therapy in Resource-Limited Countries in 2006: Distribution and Uptake of First- and Second-Line Regimens*, 21 ACQUIRED IMMUNE DEFICIENCY SYNDROME S89, S95 (Supp. 4) (2007) (indicating the ratio of first to second line therapy prescriptions is 97:3, with a majority of adults and children on Stavudine).

64. WORLD HEALTH ORG., *TRANSACTION PRICES FOR ANTIRETROVIRAL MEDICINES AND HIV DIAGNOSTICS FROM 2008 TO OCTOBER 2009 6* (2009), available at <http://www.who.int/hiv/amds/GPRMsummaryReportNov2009.pdf>.

example, the most common “second-line” therapy, a co-formulation of Abacavir, Didanosine, and Lopinavir/ritonavir, costs \$1134 a year.<sup>65</sup>

Distinguishing “lines” is simple: price, safety and efficacy are the most significant characteristics separating U.S. therapies and LMI “first-line” therapies. Treatment guidelines, and treatment decisions, in the United States are functions of safety and efficacy, but LMI guidelines sacrifice safety and efficacy to stretch budgets. LMI treatment decisions are rare, because Triomune is often the single agent available to patients and providers. Were safer and more effective compounds available, undoubtedly LMI providers would offer these treatments and LMI patients would demand them. The reality, however, is that the rationale behind “current treatment guidelines for antiretroviral therapy is rationing—limiting the number of people who must be treated, providing the cheapest available drugs, and delaying shifts to more expensive drugs for as long as possible.”<sup>66</sup> Although the absolute number of patients for whom Triomune fails to achieve viral suppression is unknown, some observe that 30 percent of patients on Stavudine (a common “first-line” therapy) require switching within twelve months of initiation.<sup>67</sup> The switches rarely occur, however, because the patient in need cannot afford the second treatment. While a Western patient would discontinue a toxic or ineffective therapy, treatment decisions in LMI settings depend on the particular drugs that reach the public domain in India, rather than patient need.

The world’s most abundant formulation of HAART is the “first-line” therapy Triomune, a formulation combining Stavudine, Nevirapine, and Lamivudine. It is overwhelmingly the predominant treatment for patients in LMI countries and the world’s most common HIV treatment.<sup>68</sup> The combination’s low price stretches PEPFAR, UNITAID, and Global Fund dollars to millions of patients.<sup>69</sup> But the consequences of its prevalent use also include widespread toxicity, ineffectiveness, and medical expenses because of side effects. Patients react differently to the same therapies, necessitating individualized drug iterations, but in LMI settings, HAART is

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65. *Id.* at 20. The price differential for “second-line” drugs including protease inhibitors remains significant. See N. Kumarasamy, *Generic Antiretroviral Drugs – Will They Be the Answer to HIV in the Developing World?*, 364 *THE LANCET* 9428, 3 (2004) (observing a ten-fold price differential in 2004).

66. Nathan Ford et al., *Rational Antiretroviral Therapy in Africa – Treating Too Few, Too Late*, 360 *NEW ENG. J. MED.* 1808, 1810 (2009).

67. L.W.Y. Tam et al., *Performance of a World Health Organization First-Line Regimen (Stavudine/lamivudine/Nevirapine) in Antiretroviral-Naïve Individuals in a Western Setting*, 8 *HIV MED.* 267, 269 (2008).

68. Renaud-Théry et al., *supra* note 63, at S91.

69. See generally Dyubl, *supra* note 40.

reduced to a single regime containing compounds of limited efficacy. In contrast to this one-size-fits-millions approach, one clinician in Birmingham, Alabama, reported his clinic administered over 800 unique iterations of HAART.<sup>70</sup> Compared to this single clinic, an entire district in Malawi placed 97 percent of patients on just a single iteration (Triomune).<sup>71</sup> Thus, about one eight-hundredth as much diversity-in-therapy exists in an entire district in Malawi as in a single clinic in Alabama, a situation resulting from the license-dependent costs of drugs.

Treatment in LMI countries starts with “first-line” therapies because of their price. U.S. and E.U. patients change therapies because HIV mutates quickly and develops resistance. Notably, U.S. guidelines do not advocate rigid “lines” of treatment, whereas the guidelines for LMI patients consistently refer to such “lines.”<sup>72</sup> On the contrary, Western therapies are individualized, with some clinicians reporting as many as eight different HAART iterations per 100 patients starting therapy.<sup>73</sup> With effective access to all thirty-two ARVs, patients in the United States commonly initiate therapy on a once-daily fixed-dose combination or a regime containing a protease inhibitor. Treatment-naïve patients in the United States and Europe do not ingest Stavudine, while almost every LMI patient does. Reflecting on the disparities between first-world and “first-line” therapies, one commentator observed, “[t]he increased toxicity associated with these agents is well documented in industrialized nations, data that are increasingly echoed by mounting evidence from resource-limited settings.”<sup>74</sup>

## 2. *Stavudine*

Stavudine exemplifies the clearest disconnect between developed- and developing-world standards of care for HIV patients. An NRTI,<sup>75</sup> Stavudine

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70. Charles Flexner, *HIV Drug Development: The Next 25 Years*, 6 NATURE REVIEWS DRUG DISCOVERY 959 (2007).

71. Ferradini, *supra* note 63, at 1338.

72. See generally US DEPARTMENT OF HEALTH AND HUMAN SERVICES, PANEL ON CLINICAL PRACTICES FOR THE TREATMENT OF HIV INFECTION (2009), <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>; WORLD HEALTH ORGANIZATION, HIV/AIDS PROGRAMME ANTIRETROVIRAL THERAPY FOR HIV INFECTION IN ADULTS AND ADOLESCENTS (2006) <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>; WORLD HEALTH ORGANIZATION, RAPID ADVICE, ANTIRETROVIRAL THERAPY FOR HIV INFECTION IN ADULTS AND ADOLESCENTS (2009) [http://www.who.int/hiv/pub/arv/rapid\\_advice\\_art.pdf](http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf).

73. James A. McKinnel et al., *Antiretroviral Prescribing Patterns in Treatment-Naïve Patients in the United States*, 24 AIDS PATIENT CARE AND STDs 79, 79 (2010).

74. James H. Willig et al., *Durability of Initial Antiretroviral Therapy in a Resource-Constrained Setting and the Potential Need for Zidovudine Weight-Based Dosing*, 53 J. ACQUIRED IMMUNE DEFICIENCY SYNDROME 215, 218 (2010).

75. NRTIs were the original class of ARV drugs.



reaches over 75 percent of patients in developing countries.<sup>76</sup> It does not, however, appear on the list of therapies recommended by the WHO or Department of Health and Human Services.<sup>77</sup> Domestically, physicians replaced Stavudine years ago, when superior, safer, and more effective NRTIs entered the market. Explaining the omnipresence of Stavudine in resource-limited settings is simple: the Clinton Foundation's 2009 Antiretroviral Price List records Stavudine, at \$0.036/unit, as the cheapest ARV on earth. Tenofovir, Stavudine's domestic replacement, sells at \$0.280/unit.<sup>78</sup>

Approved in 1995, Stavudine toxicities were soon reported; peripheral neuropathy (loss of nervous system functions in extremities),<sup>79</sup> lactic acidosis (life-threatening acidification of the blood),<sup>80</sup> and lipodystrophy (body fat migration) affected many Stavudine recipients.<sup>81</sup> In 2002, clinical guidelines first detailed methods for substituting Stavudine with more effective prescriptions.<sup>82</sup> In 2003, U.K. guidelines downgraded Stavudine. Usage of the drug among Dutch patients declined from nearly 50 to fewer than 3 percent between 1996 and 2004.<sup>83</sup> The U.S. List of Recommended Components removed Stavudine in 2004 because of its side effects (peripheral neuropathy, elevated lipids, pancreatitis, and hepatic enzyme abnormalities), and new clinical data indicated other drugs in its class achieved nearly complete viral suppression.<sup>84</sup> In the same year, data from a three-year, eighty-one center, randomized, double-blind study comparing Tenofovir and Stavudine indicated that Tenofovir had comparable benefits, but lacked Stavudine's

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76. Renaud-Théry et al., *supra* note 63, at S92; Omar Galárraga et al., *Forecast of Demand for Antiretroviral Drugs in Low and Middle-Income Countries: 2007–8*, 21 ACQUIRED IMMUNE DEFICIENCY SYNDROMES S97, S101 (Supp. 4) (2007).

77. US DEPARTMENT OF HEALTH AND HUMAN SERVICES, *supra* note 72 at 22–35.

78. CLINTON FOUNDATION, ANTIRETROVIRAL PRICE LIST (2009), <http://www.clintonfoundation.org/files/chairvpricelistaugust2009english.pdf>.

79. Charles C.J. Carpenter et al., *Antiretroviral Therapy in Adults, Updated Recommendations of the International AIDS Society – USA Panel*, 283 J. AM. MED. ASS'N. 381 Appendix (2000).

80. US DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDELINES FOR THE USE OF ANTIRETROVIRAL AGENTS IN HIV-INFECTED ADULTS AND ADOLESCENTS 50 (Feb. 4, 2002) <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL04232001006.pdf>.

81. C.J. Carpenter et al., *Antiretroviral Therapy in Adults, Updated Recommendations of the International AIDS Society – USA Panel*, 283 J. AM. MED. ASS'N. 381, Appendix 1 (2000); T. Saint-Marc et al., *Fat Distribution Evaluated by Computed Tomography and Metabolic Abnormalities in Patients Undergoing Antiretroviral Therapy: Preliminary Results of the LIPOCO Study*, 14 ACQUIRED IMMUNE DEFICIENCY SYNDROME 37, 48 (2000).

82. Patrick G. Yeni et al., *Antiretroviral Therapy in Adults, Updated Recommendations of the International AIDS Society – USA Panel*, 288 J. AM. MED. ASS'N. 222, 229 (2002).

83. Kees Brinkman, *Stavudine in Antiretroviral Therapy: is This the End?*, 23 ACQUIRED IMMUNE DEFICIENCY SYNDROME 1727, 1727 (2009).

84. Patrick G. Yeni et al., *Antiretroviral Therapy in Adults, Updated Recommendations of the International AIDS Society – USA Panel*, 292 J. AM. MED. ASS'N. 251, 258 (2004).

toxicity.<sup>85</sup> In 2006, U.S. guidelines reiterated that Stavudine, in comparison to other drugs in its class, was “more commonly associated” with lipodystrophy and highly associated with lethal lactic acidosis.<sup>86</sup> In 2008, Stavudine was completely removed from U.S. lists of recommended therapy components.<sup>87</sup>

Despite its drawbacks, Stavudine still remains the bedrock drug with which the scale-up treats more than four million HIV patients in LMI nations. In short, juxtaposing U.S. and LMI uptake patterns reveals LMI patients—and therefore most HIV patients—remain unaffected by developments in HIV care since 1995, dependent on compounds in the public domain, and generally treated as if side effects, toxicity, and tolerability were inconsequential. Resource-limited countries with “fixed and limited healthcare resources to treat epidemics, [decide] whether to treat more patients with the cheapest HAART regimes, or whether to use more expensive combinations which might prevent others from accessing HAART at all.”<sup>88</sup> While Stavudine’s low upfront cost seems beneficial for massive worldwide treatment efforts, the costs of toxicity, eventual switching, side effects, efficacy,<sup>89</sup> and the overall cost-effectiveness of treatments suggest otherwise.<sup>90</sup> Additionally, comparisons of Stavudine-containing and Tenofovir-containing regimes indicate that patients on the latter regime remain alive for at least ten months longer.<sup>91</sup> While Stavudine is undoubtedly better than nothing, evidence shows its use is detrimental to patient adherence and its side effects debilitating. The drug’s cheap upfront price mask its true costs.

ARV side effects reduce adherence in patients and lead to mutations, treatment failure, and death. Side effects are the most common reason to switch therapies, and when one lacks a medication to which she could switch,

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85. See generally Joel E. Gallant et al., *Efficacy and Safety of Tenofovir DF v. Stavudine in Combination Therapy in Antiretroviral-Naïve Patients*, 292 J. AM. MED. ASS’N. 19 (2004).

86. Scott M. Hammer et al., *Antiretroviral Therapy in Adults, Updated Recommendations of the International AIDS Society – USA Panel*, 296 J. AM. MED. ASS’N. 827, 834 (2006).

87. See generally Scott M. Hammer et al., *Antiretroviral Therapy in Adults, Updated Recommendations of the International AIDS Society – USA Panel*, 300 J. AM. MED. ASS’N. 555 (2008); Brinkman, *supra* note 83, at 1728.

88. Andrew Hill & Evan Wood, *Balancing Effectiveness and Access to HIV Treatment in The Developing World*, 21 ACQUIRED IMMUNE DEFICIENCY SYNDROME 361, 362 (2007).

89. See generally Melissa A. Bender et al., *Cost-Effectiveness of Tenofovir as First-Line Antiretroviral Therapy in India*, 50 CLINICAL INFECTIOUS DISEASES 416 (2010).

90. See generally Sydney Rosen et al., *Cost and Cost-Effectiveness of Switching From Stavudine to Tenofovir in First-Line Antiretroviral Regimens in South Africa*, 28 ACQUIRED IMMUNE DEFICIENCY SYNDROME 334 (2008).

91. Melissa A. Bender et al., *Cost-Effectiveness of Tenofovir as First-Line Antiretroviral Therapy in India*, 50 CLINICAL INFECTIOUS DISEASES 416, 422 (2010).

the result is cessation of therapy.<sup>92</sup> Administering intolerable therapies to greater than four million patients is inherently unsustainable. Properly treating patients in the United States and European Union led to mortality declines and the adjustment of HIV from a death sentence to a chronic condition. Improperly treated patients, lacking safe and effective medicines, cannot enjoy the successes of properly treated domestic patients. At present, LMI treatments attempt to replicate domestic successes with toxins.

### 3. Demand, and Failure, to Switch off Stavudine

The inability of patients and practitioners to suspend Stavudine administration leads to several interrelated observations. Firstly, patients *not switching*, or staying on Stavudine, are often treated inadequately to suppress HIV. Median time to switching from first- to second-line therapies is between sixteen and twenty-one months.<sup>93</sup> Current data indicate that only 3 percent of patients in the developing world rely on second-line therapies,<sup>94</sup> and experts predict 5 percent of such patients *should* rely on second-line therapies by 2011.<sup>95</sup> Over four million patients in LMI countries received HAART in 2009, and normal clinical progression indicates that all will eventually switch regimes. Combining these data, of all patients on first-line therapy, nearly one-third *should* switch *today* but lack access to second-line therapies,<sup>96</sup> another indication that the Indian public domain cannot sustain the therapeutic demands of millions of LMI patients. While the previous section showed the abundance of Stavudine in LMI regimes complicates the scale-

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92. Paula Braitstein et al., *Sustainability of First-Line Antiretroviral Regimens: Findings From a Large HIV Treatment Program in Western Kenya*, 52 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES 254, 256 (2010) (“[T]he most common reason for change or discontinuation in [HAART] is toxicity.”).

93. Patients in the developed world monitor drug effects with regular viral load and CD4 monitoring, but these expensive diagnostics often are neither designed nor priced for resource-limited settings. See generally ART-LINC of IeDEA Study Group, *Switching to Second-Line Antiretroviral Therapy in Resource-Limited Settings: Comparison of Programmes With and Without Viral Load Monitoring*, 23 ACQUIRED IMMUNE DEFICIENCY SYNDROME 1867 (2009). Stavudine is also associated with mutations outside of its own class, complicating eventual switches. See Joel E. Gallant, *Drug Resistance after Failure of Initial Antiretroviral Therapy in Resource-Limited Countries*, 44 CLINICAL INFECTIOUS DISEASES 453 (2007).

94. Francoise Renaud-Théry et al., *supra* note 63, at S89 (indicating ratio of first- to second-line therapy prescriptions is 97:3, with majority of adults and children on Stavudine).

95. Anil Soni & Rajat Gupta, *Bridging the Resource Gap: Improving Value for Money in HIV/AIDS Treatment*, 28 HEALTH AFF. 1617, 1621 (2009).

96. See generally John Bartlett & John Shao, *Success, Challenges, and Limitations of Current Antiretroviral Therapy in Low-Income and Middle-Income Countries*, 9 THE LANCET INFECTIOUS DISEASES 637 (2009); Olivia Keiser et al., *supra* note 29; Habib O. Ramadhani et al., *Predictors of Incomplete Adherence, Virologic Failure, and Antiviral Drug Resistance Among HIV-Infected Adults Receiving Antiretroviral Therapy in Tanzania*, 45 CLINICAL INFECTIOUS DISEASES 1492 (2007); Laurent Ferradini et al., *supra* note 63.

up's effectiveness, these data demonstrate "first-line" therapies are, at best, inadequate.

Secondly, it is only very recently that individual LMI countries began to switch off Stavudine for Tenofovir. This switch is the result of Tenofovir's developer, Gilead Sciences, sub-licensing manufacture with thirteen producers in India. Most patients cannot switch off, however, because alternative drugs are unaffordable or unavailable. This indicates the mechanisms on which the scale-up depends are inadequate to sustain existing patient demand. Were HIV infections declining, and patient rosters not increasing continuously, remedies might exist to augment existing mechanisms. But the scale-up, itself an enormous health intervention, expands daily: for every patient beginning HAART, another 2.5 people are infected elsewhere.<sup>97</sup> Global HIV incidence trends are flat, or sloping downward slightly, but this stasis includes 2.7 million new infections yearly,<sup>98</sup> and a projected global burden exceeding 50 million patients by 2030.<sup>99</sup> Swelling need, and known deficiencies in scaling-up appropriate treatment, shows a substantial number of patients continue to receive ineffective treatments.<sup>100</sup> These first-line treatments increasingly fail to achieve meaningful viral suppression or immunological benefit. Because new patients acquire strains resistant to existing medicines, Stavudine's efficacy can only decline. Even the relatively ineffective treatment interventions that reach LMI patients cannot sustain the current infected populations because the treatments must eventually be switched. Consider the LMI-rarity and U.S. preference for Atazanavir (Reyataz ®, one of two preferred protease inhibitors in the United States).<sup>101</sup> As of December 2009, Bristol-Myers Squibb and a single generic sub-licensee, Emcure, sell Atazanavir to PEPFAR.<sup>102</sup> Atazanavir sells at a median price of \$4353 per patient-year in LMI countries.<sup>103</sup> As a result, the drug is rarely used in the developing world,

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97. Peter Piot, Executive Director, UNAIDS, Speech at Tsinghua University (Sept. 17, 2008), *available at* [http://data.unaids.org/pub/SpeechEXD/2008/20080917\\_sp\\_pp\\_tsinghuauni\\_en.pdf](http://data.unaids.org/pub/SpeechEXD/2008/20080917_sp_pp_tsinghuauni_en.pdf).

98. AIDS EPIDEMIC UPDATE, *supra* note 1, at 7.

99. Colin D. Mathers & Dejan Loncar, *Projections of Global Mortality and Burden of Disease from 2002 to 2030*, 3(11) PLOS MED. e442, 2017 (2006); Joshua A. Salomon et al., *Integrating HIV Prevention and Treatment: From Slogans to Impact*, 2 PLOS MED e16, 0054 (2005).

100. On possible effects, see Davey Smith & Roger Shooley, *Running With Scissors: Using Antiretroviral Therapy Without Monitoring Viral Load*, 46 CLINICAL INFECTIOUS DISEASES 141(2008). *See also* Frederick K. Sawe & James A. McIntyre, *Monitoring HIV Antiretroviral Therapy in Resource-Limited Settings: Time to Avoid Costly Outcomes*, 49 CLINICAL INFECTIOUS DISEASES 463 (2009).

101. HEALTH AND HUMAN SERVICES, *supra* note 72, at 39.

102. FDA, *supra* note 42.

103. UNAIDS, *supra* note 36, at 10.

despite domestic awareness of its superiority and efficacy. Convergence between LMI and U.S. treatment schedules remains elusive as the number of Atazanavir producers constrains use of the drug in LMI countries.

As current patients on Stavudine develop resistance, or require switching off of it because of toxicity, licensing post-1995 compounds increases in import.<sup>104</sup> These observations complicate the successes of the scale-up, as analysts are compelled to ask “with what” when confronted with celebrations of “total patients treated.”<sup>105</sup>

Finally, Stavudine is not unique—Triomune, the developing world’s most prescribed HAART co-formulation, also includes Azidothymidine (AZT). Like Stavudine, doctors in the developed world do not recommend AZT, which suffers from significant toxicities and decreased efficacy when compared with other nucleoside reverse transcriptase inhibitors.<sup>106</sup> As early as 2000, the drug was associated with neutropenia, anemia, nausea, vomiting, headache, myopathy, and nail pigmentation.<sup>107</sup> Providers choosing between Stavudine or nothing face a Hobson’s Choice, and their patients suffer the consequences of inadequate treatment.

## B. MISSING FORMULATIONS

### 1. *Licensing and Co-Formulations*

An active pharmaceutical ingredient is formulated into a particular dosage for a particular patient population. The paucity of licensing prevents creation of formulations appropriate to resource-limited settings. Due to variations in the epidemic’s effects, and differences in infrastructure and local capacity, resource-limited countries need formulations different from the formulations used in developed settings. Developing successful LMI formulations by PEPFAR suppliers requires an increase in voluntary licensing, as the Indian public domain does not contain sufficient therapies to synthesize new formulations. The lack of particular formulations significantly hampers efforts to globalize treatment for HIV infections, and is related to the unwillingness of originators to license their compounds for PEPFAR-sale, reformulation, and distribution.

Early HAART cocktails required dozens of pills dosed at distinct times, leading to diminished adherence and accelerated mutations. Ideal formulations now combine medicines into a once-daily “co-formulation.”

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104. See generally Lawrence Long et al., *The High Cost of Second-Line Antiretroviral Therapy for HIV/AIDS in South Africa*, 24 ACQUIRED IMMUNE DEFICIENCY SYNDROMES 1, 2 (2010) (“[T]he number of second-line patients will increase steadily.”).

105. See generally UNAIDS Progress Report, *supra* note 61.

106. Braitstein et al., *supra* note 92, at 256.

107. Carpenter et al., *supra* note 79, at Appendix 1.

Synthesizing multiple therapies into single tablets requires the acquisition of many patent rights, each with distinct expiration dates.<sup>108</sup> With dozens of approved HIV medicines, manufactured by more than half-a-dozen producers, the inherent difficulty and cost of these acquisitions is substantial. Co-formulation demands licensing, typically from competitors, each of whom can “block” the end product. The downstream product could include “upstream” technologies—for example, Merck’s Raltegravir, Gilead’s Tenofovir, and Glaxo’s Lamivudine—owned by numerous separate entities. Any interested party with associated patent rights may prevent the creation of such a downstream product. Because these co-formulations often involve distant producers, the high costs of negotiations can also prevent the creation of downstream products.<sup>109</sup> This may explain the existence of a single once-daily formulation in the United States and European Union. Atripla is the developed world’s first once-daily co-formulation,<sup>110</sup> consisting of NRTIs Tenofovir and Emtricitabine and the NNRTI Efavirenz. With a minimal pill burden, no need for refrigeration, and a minimal side-effect profile, it is the standard of care for new patients in the United States.<sup>111</sup>

The high transaction costs associated with the licensing efforts that occur between competitors complicates successful development of co-formulations.<sup>112</sup> Given the diversity of actors and producers, and the number

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108. Abbott, *supra* note 55, at 321 n. 35, describes these complexities. Often, several patents are linked to a New Drug Application. Additional patents on improvements lengthen protections. Frederick Abbott shows that the first patent for Abbott Laboratories’ Lopinavir/ritonavir (Kaletra®) expires on December 13, 2005, yet twenty-one additional patents on the drug, in two formulations, extend effective protections until November 7, 2017. Eleven Lopinavir patents expirations span seven years, 2013–2020 (U.S. Patent Nos. 5,541,206 and 7,364,752). Nine Ritonavir patents expire in 2012–2020 (U.S. Patent Nos. 5,541,206 and 7,432,294). *Id.*

109. Heller and Eisenberg considered a biomedical “anti-commons,” a reflection of which may be found in the instant circumstances. Michael Heller, *The Tragedy of the Anticommons: Property in the Transition from Marx to Markets*, 111 HARV. L. REV 621, 668 (1998); Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698 (1998).

110. Triumune actually predates Atripla, and its existence is arguably the result of allowing producers to co-formulate chemicals in the public domain.

111. PANEL ON ANTIRETROVIRAL GUIDELINES, DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDELINES FOR THE USE OF ANTIRETROVIRAL AGENTS IN HIV-1-INFECTED ADULTS AND ADOLESCENTS 37, 39 (2009), available at <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>; McKinnel et al., *supra* note 73, at 79.

112. Abbott was, and remains, unwilling to co-formulate its protease inhibitor booster Ritonavir (Norvir®) with rival protease inhibitors. It did the opposite, raising the price of Ritonavir 400 percent to customers purchasing it without Abbott’s protease inhibitor, Lopinavir. Abbott survived multiple rounds of antitrust litigation. The company exempted Medicaid, Medicare, and the AIDS Drug Assistance Programs from the price hike, but also considered re-formulating the therapy (for those intending to use Ritonavir as a booster for

of manufacturers required for efficient generic competition, generic co-formulations are generally limited to drugs lacking patent protection. A generic producer wishing to re-produce Atripla faces high transaction costs, involving at least seventeen sets of licenses from at least two companies: Gilead Sciences (for Tenofovir and Emtricitabine) and Merck (for Efavirenz).<sup>113</sup> Additionally, mass producing a drug of known efficacy and safety, like Atripla, is cheaper than creating an innovative cocktail. New co-formulations, due to associated costs of development and testing, cost significantly more. A manufacturer might desire to co-formulate (1) Atazanavir, a protease inhibitor made by Bristol-Myers Squibb; (2) Ritonavir, made by Abbott, and two more drugs not contraindicated for tuberculosis (TB) therapy;<sup>114</sup> (3) Tenofovir, made by Gilead; and (4) Emtricitabine, manufactured by Gilead. Such a combination would implicate dozens of patents. Licensing costs would become prohibitive for a single manufacturer to complete the acquisition of rights. Refusal of any patent holder, or simply the high costs of entry, could block development of the product.

Within the PEPFAR dataset, more than 80 percent of the 164 active ingredients that appear in 104 formulations are unprotected and therefore do not require licenses. Among co-formulations within the PEPFAR dataset, public domain therapies also predominate. The FDA, for PEPFAR, approved forty-two formulations containing more than one compound—twenty are triple-therapy, and twenty-two are dual-therapy. Of these co-formulations, twenty-eight (66 percent) contain only license-independent compounds.<sup>115</sup> Compounds—the acquisition of which does not require a license—are two times more likely to appear in a co-formulation. Whereas limited licensing caused the omnipresence of toxic and ineffective Stavudine, limited licensing similarly prevents the creation of safe and effective formulations for impoverished populations.

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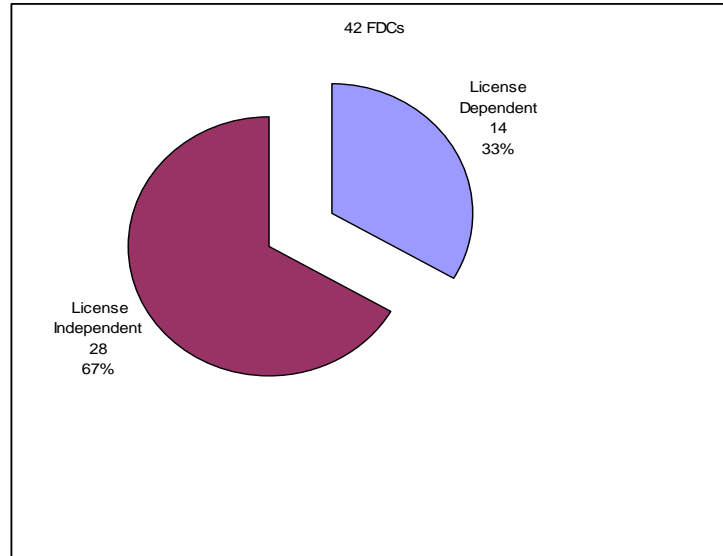
another company's protease inhibitor) to make it less palatable—one observer reported the therapy “tasted like vomit.” See John Carreyrou, *New Regimen: Inside Abbott's Tactics to Protect AIDS Drug*, WALL ST. J., Jan. 3, 2007, at A1; Vanessa Fuhrmans, *Abbott Lifts Price of Norvir 400%—Costs of Lifetime HIV Drug Jumps, Reigniting Debate Over Drug Pricing Policies*, WALL ST. J., Dec. 19, 2003; In re Abbott Labs Norvir Anti-Trust Litigation, 442 F. Supp. 2d 800 (N.D. Cal. 2006), *rev'd* John Doe 1 v. Abbott Laboratories, 571 F.3d 930 (9th Cir. 2009).

113. Bristol-Myers Squibb distributes Efavirenz domestically, and Merck internationally.

114. Twenty-five percent of HIV/AIDS deaths are caused by tuberculosis (TB) infection, making TB the most common cause of death for persons with HIV. HIV-positive persons represent 15 percent of all active infections; HIV diagnosis increases the odds ratio of developing TB by 20 percent. WORLD HEALTH ORG., GLOBAL TUBERCULOSIS CONTROL REPORT 2009 10 (2009), available at [http://www.who.int/tb/publications/global\\_report/2009/en/index.html](http://www.who.int/tb/publications/global_report/2009/en/index.html).

115. See *supra*, note 42.

Figure 1: Fixed Dose Combinations



## 2. Pediatric AIDS Failures

The world's two million pediatric HIV patients may provide the best illustration that LMI markets may not effectively manifest demand or produce incentives to innovate.<sup>116</sup> Developed countries have nearly eliminated mother-to-child-transmission of HIV with comprehensive prenatal testing and administration of ARVs shortly before, during, and after birth.<sup>117</sup> Developing countries remain highly burdened, and 90 percent of pediatric HIV patients live in sub-Saharan Africa. Globally, HIV infected approximately 370,000 children and infants in 2007,<sup>118</sup> six times the number of Americans infected in that year (56,300).<sup>119</sup> Scaling-up prophylaxis for pregnant women has reduced the incidence of pediatric infections—33 percent of pregnant women in need of ARV prophylaxis received it in 2007,

116. See generally COMM'N ON INTELLECTUAL PROP. RIGHTS, INTEGRATING INTELLECTUAL PROPERTY RIGHTS AND DEVELOPMENT POLICY (2002).

117. See generally Edward M. Conner et al., *Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type-1 with Zidovudine Treatment*, 331 NEW ENG. J. MED. 1173 (1994); Mary Lou Lindegren et al., *Trends in Perinatal Transmission of HIV/AIDS in the United States*, 282 J. AM. MED. ASS'N, 531, 535 (1999) (observing an 80 percent decline in mother-to-child transmissions associated with increase in zidovudine to reduce perinatal transmission).

118. UNAIDS, EXECUTIVE SUMMARY OF UNAIDS REPORT ON THE GLOBAL HIV/AIDS EPIDEMIC 2009 8, [http://data.unaids.org/pub/GlobalReport/2008/JC1511\\_GR08\\_ExecutiveSummary\\_en.pdf](http://data.unaids.org/pub/GlobalReport/2008/JC1511_GR08_ExecutiveSummary_en.pdf).

119. H. Irene Hall et al., *Estimation of HIV Incidence in the United States*, 300 J. AM. MED. ASS'N 520, 524 (2008).



a 400 percent increase from 2004.<sup>120</sup> Despite improvement in reducing pediatric infections,<sup>121</sup> the pediatric epidemic rages, and HAART reaches only 15 percent of infants in need, almost all of whom live in sub-Saharan Africa.<sup>122</sup>

Given the prevalence of pediatric HIV infections, one might predict the existence of appropriate therapies, if the patients were not impoverished children with impoverished parents. In fact, HAART contains tools almost entirely for adults—dosing and treatment schedules are optimized for adult body sizes and medicines are formulated as pills, with complex timing and food requirements. Because adults can swallow pills, palatability is rarely considered. Dissolving drugs in water is a common means of pediatric administration, but many pills designed for adults are insoluble. Crucial data for pediatric patients is rare. Pediatric clinical, bioavailability, and medicinal chemistry data are largely non-existent, making safe and effective pediatric dosing speculative.<sup>123</sup> The WHO's Treatment Guidelines for Children reflects the inadequacy of existing ARVs: when an HIV-infected infant resists Nevarapine, the authors recommend a protease inhibitor, but “recognize. . . that currently, in many resource limited settings, lopinavir/ritonavir is not available, affordable, or, due to cold chain requirements, not feasible for [pediatric] use. . . . [This recommendation] compromises the potential to construct a potent second line regime.”<sup>124</sup>

Although high demand for pediatric medicines in LMI settings reflects patent constraints, the non-existence of appropriate treatments for pediatric patients cannot be solely tied to patents. Inadequate prenatal and antenatal testing, weak health care infrastructures, and other factors prevent effective scale-ups of pediatric HIV interventions. Yet the non-existence of pediatric co-formulations is a highly significant independent variable in the analysis of high pediatric HIV mortality. The US Global AIDS Coordinator indicated as

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120. UNAIDS, *supra* note 118, at 15.

121. Antenatal prophylaxis in Botswana increased to 91 percent, from zero, in five years, averting 10,000 pediatric infections. John Stover et al., *Estimated HIV Trends and Program Effects in Botswana*, 3 PLOS ONE e3729, 3 (2008).

122. UNAIDS, *supra* note 118, at 25.

123. Synthesizing co-formulations for children is complex. As with any pediatric medicine, clinical trials are more challenging, and these circumstances are even more challenging because most HIV-infected children succumb to AIDS and death early in their lives. Additionally, many more steps are involved beyond simply shrinking the pill by the ratio of a child's weight. Michael Dunne, *Antiretroviral Drug Development: The Challenge of Cost and Access*, 21 ACQUIRED IMMUNE DEFICIENCY SYNDROME S73, S74-5 (2007).

124. WORLD HEALTH ORGANIZATION, REPORT OF THE WHO TECHNICAL REFERENCE GROUP, PEDIATRIC HIV/ART CARE GUIDELINE GROUP MEETING 6 (2008), [http://www.who.int/hiv/pub/paediatric/WHO\\_Paediatric\\_ART\\_guideline\\_rev\\_mreport\\_2008.pdf](http://www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf).

much to Congress: “[a] lack of formulations for pediatric regimens appropriate for resource-limited regions of the world has posed a significant barrier to reaching the millions of children impacted by HIV/AIDS.”<sup>125</sup> The single pediatric co-formulation in existence<sup>126</sup> is not heat-stable, contains medicines no longer recommended for use in the United States, and suffers from substantial resistance in pediatric patients.<sup>127</sup> For infants that cannot tolerate the side effects of that therapy, survival requires impractical acquisition and use of second-line solid pills. This is complicated by “poor palatability, high pill burden or liquid volume, frequent dosing requirements, dietary restrictions and side effects [that] hamper the regular intake of required medication.”<sup>128</sup> The swiftness of disease progression in infants<sup>129</sup> demands stringent and unrealistic adherence to dosing schedules, making these contingency plans unfeasible. Producers wishing to synthesize therapies for PEPFAR-assisted pediatric patients have few compounds from which to choose. Lacking license to develop new formulations of newer medicines, producers cannot provide clinics with therapies to sustain pediatric AIDS patients.

Pediatric AIDS patients in developing countries face a difficult reality—few medicines exist to keep them alive. Whereas effective public health interventions have largely eradicated the incidence of pediatric infections in the United States and European Union, millions of pediatric patients in LMI countries continue to suffer the fates of patients before HAART. Pediatric co-formulations, like heat-stable formulations, are so-called missing

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125. OFFICE OF THE U.S. GLOBAL AIDS COORDINATOR, BRINGING HOPE: SUPPLYING ANTIRETROVIRAL DRUGS FOR HIV/AIDS TREATMENT 3 (2006).

126. A single pediatric co-formulation exists. Indicating the willingness of generic producers to invest in, and develop, new formulations, Cipla received tentative approval for a small-dose Lamivudine/Stavudine/Nevirapine co-formulation in 2007. See Letter from FDA to Cipla Ltd. Regarding Lamivudine/Stavudine/Nevirapine (Aug. 13, 2007), [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2007/021972s000taltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2007/021972s000taltr.pdf).

127. Jean-Chrysostome Gody et al., *High Prevalence of Antiretroviral Drug Resistance Mutations in HIV-1 Non-B Subtype Strains from African Children Receiving Antiretroviral Therapy Regimen According to the 2006 Revised WHO Recommendations*, 49 J. ACQUIRED. IMMUNE DEFICIENCY SYNDROME 566, 566 (2008) (observing that 77 percent of infants presenting at a hospital in the Central African Republic were infected with virus resistant to at least one ARV).

128. WORLD HEALTH ORG. & UNICEF, SCALE-UP OF HIV-RELATED PREVENTION, DIAGNOSIS, CARE AND TREATMENT FOR INFANTS AND CHILDREN 22 (2008), [http://www.who.int/hiv/pub/paediatric/paediatric\\_program\\_fmwk2008.pdf](http://www.who.int/hiv/pub/paediatric/paediatric_program_fmwk2008.pdf).

129. UNAIDS, ET. AL., CHILDREN AND AIDS, SECOND STOCKTAKING REPORT 12 (2008), [http://data.unaids.org/pub/Report/2008/childrenandaidssecondstocktakingreport\\_en.pdf](http://data.unaids.org/pub/Report/2008/childrenandaidssecondstocktakingreport_en.pdf); Taha E. Taha et al., *Morbidity Among Human Immunodeficiency Virus-1-Infected and –Uninfected African Children*, 106 PEDIATRICS e77, 4 (2000) (observing 89 percent mortality rate for HIV-positive children in Malawi, by age three).

formulations. Pills that do not require refrigeration are highly preferred to those requiring cold-chains of refrigerators, electricity, and infrastructure.

Given the ability of the U.S. and E.U. biomedical community to effectively cure HIV fifteen years after the first patient presented, the continued failure of pediatric ARV therapy reflects poorly on mechanisms developed to abate disease burdens. Within fifteen years of presentation, medical science ended the scourge of AIDS among a subgroup of patients, but the world's most vulnerable patients remain largely unassisted. This outcome is related to the burdened group's ability to incent creation of pharmaceuticals particular to its needs. A manufacturer's costs of developing and producing appropriate pediatric formulations may be recoverable from high-volume sales to PEPFAR, UNITAID, and UNAIDS, but this scenario still brings us back to square one: without a license from an originator, the product cannot exist. Whether they seek an adult co-formulation, or a pediatric dispersible, the most cost-effective producers can only tinker with compounds in the public domain.

### III. TRENDS & PROJECTIONS

The number of patients in need of HAART will increase an order of magnitude by 2031. Currently, almost half of LMI patients needing HAART receive it (four million of nine million);<sup>130</sup> by 2030, the projected number in may pass 55 million.<sup>131</sup> Given the inability of existing licensing and manufacturing arrangements to meet current demand, the projections for heightened demand suggest current mechanisms will fall even further short in the future. To date, only eleven<sup>132</sup> of the thirty-two FDA-approved ARVs<sup>133</sup> are sold to PEPFAR, a 60-billion-dollar buying facility. The opportunity cost for these decisions is high, as one-third of Stavudine-receiving patients should switch off it immediately but cannot access a replacement.<sup>134</sup>

Some licensing behavior indicates that the future availability of effective treatments will improve. In 2006–07, Gilead Sciences, the manufacturer of two preferred NRTIs (Tenofovir and Emtricitabine), entered negotiations with generic producers in India. Gilead, a highly successful but small company, executed thirteen licenses with these producers, which allow it to earn royalties on high-volume sales. Given the company's finite

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130. AIDS EPIDEMIC UPDATE, *supra* note 1, at 21.

131. ALL-PARTY PARLIAMENTARY GROUP ON AIDS, THE TREATMENT TIMEBOMB 6 (2009), [http://www.ghet.org.uk/userfiles/file/APPG\\_TreatmentTimebomb\\_09.pdf](http://www.ghet.org.uk/userfiles/file/APPG_TreatmentTimebomb_09.pdf).

132. FOOD AND DRUG ADMINISTRATION, *supra* note 42.

133. FOOD AND DRUG ADMINISTRATION, *supra* note 58.

134. Braitstein et al., *supra* note 92, at 256.

manufacturing capacity, Gilead's decision guarantees revenue streams with minimal up-front investment, serving patient needs and its own. The licenses empower generic producers to sell Tenofovir in ninety-five countries<sup>135</sup> without price floors or ceilings.<sup>136</sup> The "Licensed Territory" includes 83.5 percent of people currently living with HIV,<sup>137</sup> including the highly-burdened and middle-income countries South Africa and India, as well as Least Developed Countries, other highly-burdened and resource-limited areas. Gilead's technology transfer included know-how and involved substantial assistance from the company to speed production and ensure quality. Finally, the licenses permit development of any Tenofovir-based fixed-dose combination or pediatric formulation, and the manufacture and sale of Tenofovir's active ingredient in India with no royalty payment.<sup>138</sup>

Gilead's peers do not comprehensively license their medicines. Although other companies may refuse to license for many reasons, some may fear the transfer of generic drugs into their primary markets, a rarely observed phenomenon known as pharmaceutical arbitrage.<sup>139</sup> Some fear a lack of domestic enforcement of intellectual property protections within sub-licensing countries, but any Member State's accession to the WTO requires compliance with TRIPS. Additionally, the Dispute Settlement Board, within the WTO, exists for the purpose of protecting intellectual property when a state's efforts are insufficient. Given that many arguments in support of TRIPS indicated countries like India would benefit from technology transfers because of the agreement's intellectual property enhancements,<sup>140</sup> it is peculiar that India is not the site of more manufacturing for PEPFAR. The U.S. government is a \$60 billion buyer, but few pharmaceutical originators are willing to sub-manufacture therapies for American procurement. Although some companies contracted with individual generic producers to manufacture ARVs for LMI countries, the existence of a single generic

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135. A license between Gilead and its generic partners is on file with the author.

136. GILEAD SCIENCES, ADVANCING SUSTAINABLE ACCESS TO HIV/AIDS MEDICINES IN THE DEVELOPING WORLD (2009), [http://www.gilead.com/pdf/access\\_fact\\_sheet.pdf](http://www.gilead.com/pdf/access_fact_sheet.pdf).

137. UNAIDS, *Estimated Number of People Living With HIV by Country, 1990–2007* (July 2008), [http://data.unaids.org/pub/GlobalReport/2008/20080818\\_gr08\\_plwh\\_1990\\_2007\\_en.xls](http://data.unaids.org/pub/GlobalReport/2008/20080818_gr08_plwh_1990_2007_en.xls).

138. Gregg Alton, Executive Vice President, Gilead Sciences, Presentation at Berkeley Law HIV & Neglected Disease Patent Pool Workshop (Nov. 6, 2009), [http://www.law.berkeley.edu/institutes/bclt/patentpools/presentations/12\\_alton.pdf](http://www.law.berkeley.edu/institutes/bclt/patentpools/presentations/12_alton.pdf).

139. Kevin Outterson, *Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets*, 5 YALE J. HEALTH POL'Y L. & ETHICS 193, 198 (2005).

140. See generally Carlos A. Primo Braga & Carsten Fink, *The Economic Justification for the Grant of Intellectual Property Rights: Patterns of Convergence and Conflict*, 72 CHI. KENT. L. REV. 439 (1996) (surveying arguments for possible technology transfer benefits due to TRIPS).

partner does not predict price drops. Rather, competition between producers in the number of licenses predicts accessibility, not the existence of a single generic partner.<sup>141</sup> Gilead's efforts are likely to accelerate the end of Stavudine, but the decisions of Gilead's peers not to license their preferred compounds constrains the ability of LMI practitioners and providers to construct safe, effective, and potent anti-retroviral cocktails. The economies of scale among generic producers provides PEPFAR and other buyers with rates facilitating the scale-up, but the scale-up cannot survive on the small number of therapies within India's public domain.

In 2009, UNITAID, which has an international pharmaceutical buying facility with programming similar to PEPFAR, announced the formation of a patent pool for ARVs.<sup>142</sup> Model terms are not yet available, though some firms expressed interest in licensing their compounds to an administrator responsible for sub-licensing to generic producers and returning royalties to licensors.<sup>143</sup>

Current licensing trends alone will not abate existing inadequacies in therapy availability. Licensing of the newest ARVs, especially first-in-class integrase inhibitors<sup>144</sup> and CCR5 antagonists,<sup>145</sup> cannot be predicted. GlaxoSmithKline, in February 2009, announced price reductions on its ARV sales to LMI countries and the creation of a price ceiling for its products in the Least Developed Countries, at 25 percent of their primary market cost.<sup>146</sup> Most likely, these reductions will not pull prices to the level of competitive generic manufacture. Glaxo's Pricing Guide reflects this reality—its middle-income country prices are “set at levels that meet [Glaxo's] cost.”<sup>147</sup>

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141. *See supra* note 57.

142. Ellen 't Hoen, Special Advisor on IP, UNITAID, Presentation at Berkeley Law HIV & Neglected Disease Patent Pool Workshop (Nov. 6, 2009), [http://www.law.berkeley.edu/institutes/bclt/patentpools/presentations/1030\\_thoen.pdf](http://www.law.berkeley.edu/institutes/bclt/patentpools/presentations/1030_thoen.pdf).

143. GREGG ALTON, GILEAD SCIENCES, INC., UNITAID PATENT POOL SUMMARY STATEMENT (2009), [http://www.unitaid.eu/images/NewWeb/documents/PP\\_presentations/alton%20unitaid%20wha%20patent%20pool%20summary%20statement%20gilead%20.pdf](http://www.unitaid.eu/images/NewWeb/documents/PP_presentations/alton%20unitaid%20wha%20patent%20pool%20summary%20statement%20gilead%20.pdf); Letter from Chris Strutt, Senior Vice President GlaxoSmithKline, *GSK is in Talks on Patent Pools*, THE GUARDIAN, Sept. 10, 2009, at 35, available at <http://www.guardian.co.uk/business/2009/sep/10/glaxosmithkline-hiv-aids-patents>.

144. Indian Patent No. 212400 (filed Oct. 26, 2001).

145. Indian Patent No. 204132 (filed Dec. 2, 1999).

146. Andrew Witty, CEO, GlaxoSmithKline, Speech to Harvard Medical School: Big Pharma as Catalyst for Change (Feb. 13, 2009) (summary available at <http://www.gsk.com/media/Witty-Harvard-Speech-Summary.pdf>); *see also* GLAXOSMITHKLINE, FACING THE CHALLENGE (2008), <http://www.gsk.com/responsibility/Downloads/facing-the-challenge-feb08.pdf>.

147. *Id.* at 1. Glaxo sub-licensed its therapy Combivir (Lamivudine and Azidothymidine), and since 2006, its sub-licenses have produced more of the compound than Glaxo. GlaxoSmithKline, Preferential Pricing, <http://www.gsk.com/responsibility/>

#### IV. CONCLUSION

PEPFAR saved over 1.2 million lives and reduced AIDS mortality in target countries by ten percent.<sup>148</sup> The program and the accompanying scale-up's effects are historic. Although the scale-up occurred more quickly than any previous public health intervention, every aspect of the scale-up proceeds too slowly. It undoubtedly marks great progress that the biopharmaceutical, academic, government, and not-for-profit sectors so effectively, and speedily, developed compounds to suppress HIV. That the scientific community synthesized nine drugs within fourteen years of the first patient visit, and eleven years from identification of the virus itself, is itself a testament to scientific innovation.

Currently, the majority of HIV patients do not benefit from significant advances against HIV. Four million now benefit from the dimensions of India's public domain, and the American taxpayer's support. But outside of small, wealthy markets, price trumps side effects, toxicity, and efficacy of compounds, resulting in the "first-line" therapy now failing a third of its adherents. One Geneva-based physician described his and his patient's choices for initial anti-retroviral therapy as an "embarrassment of riches."<sup>149</sup> The normative point here is not to diminish the Geneva physician's ability to construct a safe, tolerable, and efficacious cocktail. Rather, the point is that the Geneva patient should be less exceptional. Instead, as this Note demonstrates, the vast majority of people with HIV take Stavudine-containing Triomune. While a Stavudine-containing regime is superior to none at all, the reasons to jettison Stavudine for Tenofovir are financially and medically compelling. Furthermore, administration of a chemical lacking efficacy is not superior to administration of no compound, when the impotent compound is linked to lethal, disfiguring, expensive, and disabling side effects. Stavudine will eventually fall off pharmacy shelves, and Gilead's licenses accelerate that outcome. The ongoing persistence of Stavudine in low- and middle-income patients, nonetheless, reflects a remarkable medical disparity.

Distinct standards of care for HIV treatment frequently cause great harm to patients, as the compounds used to suppress an infection in San Francisco differ markedly from those used in Kenya. In fact, the Kenyan patient suffers the toxicities, reduced efficacy, and sometimes even pill burden of a 1995-era

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preferential-pricing-performance.htm (last visited January 31, 2010). *But see* Jeffrey Stewart, *Comment on Ford et al. Sustaining Access to Antiretroviral Therapy in Developing Countries: Lessons From Brazil and Thailand*, 21 ACQUIRED IMMUNE DEFICIENCY SYNDROMES S129 (2007).

148. Walensky & Kuritzkes. *supra* note 27, at 273.

149. *See generally* Bernard Hirschel & Alexandra Calmy, *Initial Treatment for HIV Infection – An Embarrassment of Riches*, 358 N. ENG. J. MED. 2170, (2008).

San Francisco patient. That Kenyan patient, like the vast majority of similarly situated patients in the developing world, has not benefited from the last fifteen years of scientific innovation, advancement and progress. One could argue TRIPS is the single cause of this circumstance, as undoubtedly India's ascension to the WTO required protection for post-1995 products. The existence of thirteen Gilead licenses argues with this point, as the company's technology transfer is beneficial to it, the producer, and Stavudine-receiving patients.

In addition to compelling use of ineffective and toxic therapies, inadequate voluntary licensing contributes to a dearth of formulations specific to LMI settings. Timely acquisition of rights to manufacture and improve recent compounds could enable manufacturers to synthesize formulations suited to LMI populations and settings, and to co-formulate once-dailies from different originators. While there is no reason an innovator company cannot reduce prices to the level of a generic producer—thus removing any reason to sub-license manufacture—Indian, South African, and Chinese producers are demonstrably better positioned to manufacture mass quantities of low-margin ARVs. A pharmaceutical innovator producing pills for pennies could not recoup his enormous costs of research, development, and employment. Likewise, while there is no reason why a sub-manufacturer could best formulate dispersible co-formulations for pediatric patients, originators have not collaborated to do so. For whatever reasons, originators spurn the multi-billion dollar, low-margin ARV market. Consequently, old medicines are scaled-up, as are their associated side effects, toxicities, and inefficiencies.

Limited availability of non-toxic, effective medications for HIV patients in LMI settings frustrates PEPFAR and its international partners. Scarce licensing of newer compounds causes reliance on disfavored therapies, and associated side effects in LMI patients. Resulting poor adherence and sub-optimal viral suppression leads to transmission of ARV-resistant viruses, and increased mortality. HAART that is unsuitable for Western patients is no more suitable for LMI patients, but the scale-up depends on this dual-standard of care. The strategy is inherently unsustainable, as patients require switching therapies, and as existing therapies fail many patients, particularly children. PEPFAR, the Global Fund, WHO, UNITAID, UNAIDS, and thousands of other agencies and groups continue the scale-up. Reaching Universal Access remains their goal, a task that daily increases in size and complexity. Regularly, and cheaply, procuring the safest and most effective therapies is fundamental to the endeavor.