

Obstacles and Opportunities to Improve Antiretroviral Regimen Access in Low-Income Countries

Jennifer Cohn · Brook Baker

Published online: 8 June 2010
© Springer Science+Business Media, LLC 2010

Abstract Increasing evidence suggests that dramatically increasing access to effective and well-tolerated antiretroviral medications is key to reversing the HIV pandemic. Currently used first-line therapies in developing countries have multiple toxicities that cause significant morbidity and mortality. New World Health Organization HIV treatment guidelines support earlier treatment initiation and the use of less toxic first-line therapies. Adoption of these guidelines requires political and financial commitment from multiple stakeholders including country governments and donors. This review summarizes the major adverse effects associated with commonly used ARV regimens in low-income countries and also analyzes some of the barriers and potential solutions that affect the ability of low-income countries to implement the new World Health Organization guidelines.

Keywords Antiretroviral medication · Low-income countries · Medication pricing · Universal access

Introduction

Despite significant advances in scaling up antiretroviral treatment in low- and middle-income countries, HIV

continues to be a crisis of global proportions [1]. More and more, HIV is becoming two separate epidemics. In high-income countries, HIV is becoming a chronic disease with relatively low prevalence, steady incidence, and dramatically decreasing mortality [2]. The situation in poor countries is markedly different. In these countries, HIV prevalence and death rates continue to be high, although incidence peaked in 1996 and has declined slightly since [1]. In highly affected countries, not only is personal and population health affected, economic and educational development have slowed or reversed [3].

Driving these divergent epidemics is differential access to affordable and well-tolerated antiretroviral (ARV) treatment. As of 2008, global health initiatives like the Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund), and the President's Emergency Plan for AIDS Relief (PEPFAR) have succeeded in putting approximately 4 million people on treatment in the developing world [1]. However, even using older World Health Organization (WHO) treatment standards, this represented only 42% of all adults and 38% of children in the developing world who were in immediate clinical need of ARV treatment [1]. At current rates of HIV treatment funding, the gap between those receiving treatment in low-income countries and those in need of treatment will grow even larger because of new infections, recent evidence supporting starting HIV treatment at higher CD4 levels [4], and the fact that people on ARV regimens are living longer [1].

In addition to a persistent need for scaling up treatment, there is also an immediate need to improve the ARV regimens used in low-income countries. The majority of people living with HIV in poor countries are taking a regimen of stavudine, lamivudine, and nevirapine, typically as a fixed-dose combination. This regimen has benefits, including a low pill burden and simple dosing schedule,

J. Cohn (✉)
Hospital of the University of Pennsylvania,
3400 Spruce Street, 3rd Floor Silverstein Building, Suite D,
Philadelphia, PA 19104, USA
e-mail: Jennifer.Cohn@uphs.upenn.edu

B. Baker
Faculty of Law (Honorary Research Fellow), Northeastern
University School of Law, University of KwaZulu Natal,
400 Huntington Avenue,
Boston, MA 02115, USA

and at \$80 per patient per year, this is the least costly, effective triple therapy available. This economic savings loses much of its attraction, however, when the human impacts of adverse effects and costs of regimen failure are considered.

Adding to direct effects of adverse drug effects on morbidity and mortality, intolerance to medications has been shown to strongly affect drug adherence [5•]. This adverse effect on adherence may be particularly severe for drugs with a negative impact on appearance and that cause adverse effects such as lipodystrophy [6]. In low-income countries with limited formularies, second-line or salvage regimens may not be available. When available, even the cheapest second-line regimens are nearly eight times more costly than first-line and involve more complex dosing schedules and monitoring, and third-line regimens are 30 times more expensive [7••]. Thus, ensuring the tolerability, durability, and efficacy of first-line regimens is of utmost importance. Similarly, there is evidence that investing in adherence is cost effective [8].

Effective treatment is also a crucial component of comprehensive prevention efforts. ARV mediations have been shown to dramatically reduce viral load on both the individual and population level, leading to decreased rates of both vertical and horizontal transmission [9]. Observational studies and more recently expert modeling have shown that with regular adult testing and prompt initiation of optimal regimens, the HIV reproduction ratio could drop to less than one, leading to an eventual prevalence rate of less than 1%, even in a high-prevalence country such as South Africa [9]. Universal access to potent regimens with acceptable side-effect profiles thus becomes an important tool in stemming the pandemic.

In late 2009, following a study showing that treatment should be initiated earlier in resource-limited settings [10], the WHO released new HIV treatment guidelines that reflect the need to scale up treatment and improve tolerability of medications. The guidelines recommend that first-line ARV regimens now contain tenofovir as opposed to stavudine and recommend treatment be initiated at a CD4 count of 350 as opposed to 200 [11]. However, there is a long road from recommendations on paper to actual country-based policy change and implementation. This review summarizes the major adverse effects associated with the commonly used ARV regimens in low-income countries and also analyzes some of the barriers and potential solutions that affect the ability of low-income countries to implement the new WHO guidelines.

Adverse Effects of Commonly Used ARVs in Low-Income Countries

Stavudine, zidovudine, and nevirapine, all commonly used ARVs in low- and middle-income countries, have multiple

adverse effects that are often potentiated by underlying factors affecting the population, including hepatitis B and malnutrition [12•]. High rates of adverse drug reactions have led to morbidity, mortality, and increased rates of nonadherence and regimen change [13].

Stavudine has been most commonly associated with lipodystrophy, peripheral neuropathy, and lactic acidosis. The most fatal complication, lactic acidosis, disproportionately affects women, those with higher body mass index, and those with better adherence. Unfortunately, lactic acidosis has a protean presentation and a high case mortality of 29% to 57% [14, 15].

Peripheral neuropathy and lipodystrophy are more common, with prevalences in low-income countries ranging from 20% to 56% and 4% to 24%, respectively [16, 17]. Peripheral neuropathy not only causes significant discomfort, it may also be economically crippling for patients in low-income countries whose livelihoods depend on the ability to perform rigorous manual labor [12•]. Lipodystrophy's effect on visible areas of the body, including the face and abdomen, is quite stigmatizing for patients. The combination of these two common and difficult-to-manage adverse effects likely significantly contributes to the high rates of regimen change for stavudine-based highly active antiretroviral therapy (HAART) of 24.6% [18]. Although some of stavudine's toxic effects may be decreased by WHO-recommended dose reduction to the 30-mg strength, this dose may be unavailable in fixed-dose combination tablets available on national formularies [19].

Treatment with isoniazid as an anti-tuberculosis (TB) medication may amplify stavudine's propensity to cause peripheral neuropathy. A recent study in South Africa showed patients started on stavudine-containing HAART and isoniazid-containing anti-TB therapy had greatly increased rates of peripheral neuropathy and a hazard ratio for stavudine substitution that was seven times higher than those not on anti-TB medications [20]. This result was statistically significant. When considering the overall HIV-TB co-infection rate of 65% to 80% in sub-Saharan Africa, this treatment interaction becomes even more important [21].

Zidovudine is also poorly tolerated in low-income countries, with one study noting 31.2% of those on zidovudine-containing regimens required a regimen change [18]. This major adverse effect of zidovudine is anemia. Anemia may be more severe in countries where malnutrition is common [22]. Although zidovudine has much lower rates of lipodystrophy, peripheral neuropathy, and lactic acidosis than stavudine, these adverse effects are still more common with zidovudine than with newer nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir [23].

The most commonly used non-nucleoside reverse transcriptase inhibitor (NNRTI) backbone, nevirapine, is associated with serious hepatotoxicity and rash. In many high-income countries, nevirapine is relatively contraindicated for those with high CD4 counts. However, cost-containment measures and simplified national regimens do not allow for this restriction in most low-income countries. Thus, rates of serious hepatotoxicity have been reported to be as high as 17% to 50% [24].

Pricing and Price Reduction Measures

The price of less toxic medications has prohibited most low-income countries from including them as first line ARVs. But one must ask the questions: what are the major drivers of this cost and are there interventions that may be taken to reduce the cost?

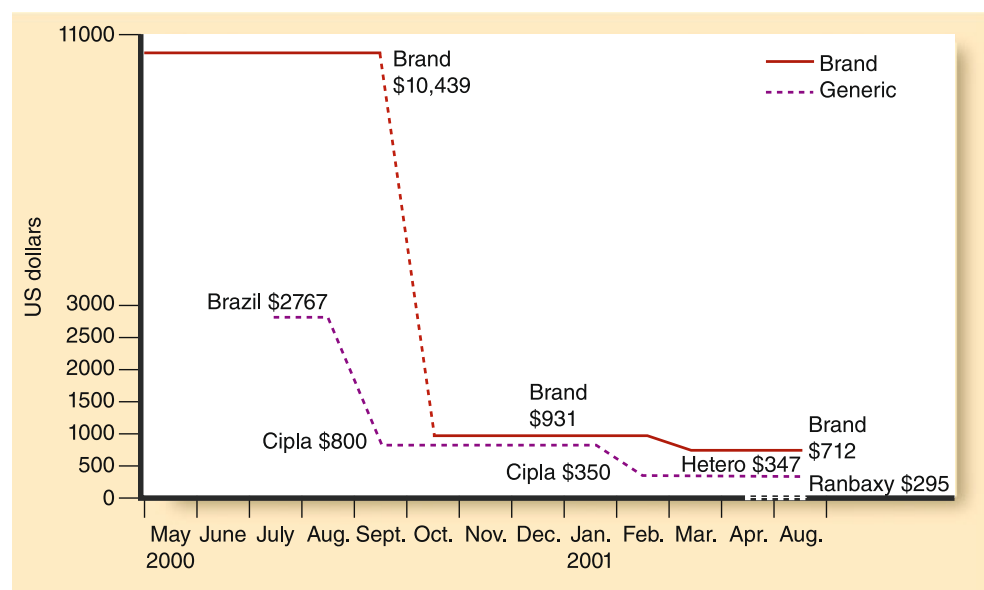
To answer these questions, a brief examination of the recent history of ARV pricing is required. The combination of stavudine, lamivudine, and nevirapine was not always an inexpensive option. In fact, in May 2000, the price of this combination was a little more than \$10,000 USD per patient per year [7••]. It was only after treatment advocates pushed for increased access to generic medications that competition between brand and generic manufacturers resulted in dramatically reduced drug costs (Fig. 1). Generic competitors were also able to combine several medications from different originators, thus creating the effective and easy-to-use fixed-dose combinations that are currently recommended in low-income countries by the WHO. Today, we have Triomune (Cipla, Mumbai, India), a single pill combining stavudine, lamivudine, and nevirapine that costs \$80 USD per patient per year [7••]. The resulting

lower costs and simplified regimens of ARVs essentially made it possible for low-income countries to treat HIV.

Unfortunately, rules regarding intellectual property rights (IPRs) continue to threaten access to generic medications in low-income countries. The 1994 World Trade Organization agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) requires nearly all World Trade Organization member countries to support minimum standards for IPRs, including a minimum duration of 20 years for patents on medications. This represented a change for the many countries that, at the time, did not grant patents for medications [25]. The major significance of the TRIPS agreement is that it may prevent the development of generic alternatives to newer, less toxic HIV medications and thus keep prices high for expanded, more effective, and better-tolerated regimens. For example, in 2005, India, which produces approximately 85% of generic antiretroviral medicines, became TRIPS-compliant, meaning that India could not make generic versions of any medications covered by valid post-1994 patents [26]. Thus far, three important new ARVs have been patented in India: etravirine, maraviroc, and raltegravir [7••].

Data exclusivity is another important IPRs barrier to reducing ARV costs through robust generic competition. Although TRIPS only requires protection of undisclosed data involving new chemical entities from unfair commercial use, the United States and Europe have tried to impose TRIPS-plus data exclusivity rules to prohibit drug regulatory authorities in developing countries from referencing or relying on clinical trial and other data in order to assess the safety and efficacy of a follow-on generic equivalent. Thus, data exclusivity can prevent drug registration for a fixed period of time even where a patent is not in effect, thereby requiring generic manufacturers to engage in lengthy,

Fig. 1 Effect of generic drug competition on antiretroviral prices for first-line regimen of stavudine, lamivudine, and nevirapine (D4t/3tc/NVP). (From *Medecins Sans Frontiers* [7••]; with permission.)



costly, and potentially unethical clinical trials to gain marketing approval [27]. Few companies, if any, are willing to do so; thus generic entry is delayed.

Beyond data exclusivity, other registration-related barriers exist that reduce access to affordable, quality generics. Originator or generic companies must register their drugs on a country-by-country basis, and the registration procedures may be complex, costly, and time consuming. In countries where companies do not see a significant profit margin, there is little incentive to initiate registration [27]. Many important ARVs have not been widely registered in poor countries with high HIV burden [27].

A number of useful tools have been developed to reduce costs of antiretroviral medications for low-income countries. The WHO has attempted to streamline drug registration procedures by creating the Prequalification Programme. The Prequalification Programme provides a stringent international standard for assessing medications for quality, safety, and efficacy [27]. This stamp of approval can be used by aid agencies and countries wishing to fast-track access to generic medicines of assured quality. At this time, however, the information from the Prequalification Programme has not been fully used by countries, as many countries' drug regulatory bodies do not yet use fast-track mechanisms to expedite registration of prequalified drugs [27].

IPR holders have two mechanisms whereby they can voluntarily increase access to more affordable medicines. The first is by offering price discounts and the second is by granting voluntary licenses allowing others to manufacture and sell the medicine in select territories. There is now an established practice of tiered or discount pricing by companies that hold patents on older antiretroviral medicines, but these prices rarely if ever match the prices offered by generic companies [7•]. Voluntary licenses are granted at the discretion of originator pharmaceutical companies and may not be granted in a timely fashion, if at all [25].

A clarification to the WTO TRIPS Agreement, called the Doha Declaration on TRIPS Agreement and Public Health, states that the TRIPS agreement should not interfere with the ability of countries to protect the health of the public and to assure access to medicines for all [28]. Included in this declaration was a clarification about the rights of countries to issue involuntary or compulsory licenses and to comparison shop for cheaper medicines via parallel importation. A compulsory license allows a government authority to declare a public health need to access an affordable generic version of a medication and to license one or more generic manufacturers to produce it. Compulsory licensing has the potential to be a powerful tool to ensure the availability of generic ARVs and to allow generic competition to reduce prices. For example, when Brazil and Thailand issued compulsory licenses for generic

efavirenz, the cost per unit rapidly fell by 77% and 58%, respectively [29].

However, issuing compulsory licenses is relatively complicated, especially for countries that need to import a medicine because of their lack of domestic pharmaceutical capacity [25]. Moreover, attempts by countries to issue compulsory licenses have been met by hostility and retaliation from pharmaceutical companies and from trade authorities. For example, in 2007 when Thailand issued a compulsory license on Abbott's drug Kaletra, Abbott retaliated by withdrawing registration applications not only for heat-stable lopinavir/ritonavir tablets, but for seven other medications, thus making these medications unavailable in Thailand [30]. Similarly, the United States Trade Representative immediately placed Thailand on its 2007 Special 301 Priority Watch List [31].

Recently, UNITAID has led the way to develop the idea of a patent pool. Originator companies would voluntarily enter their patents, data reference rights, and possibly even their proprietary know-how into such a pool and generic manufacturers would be able to license these rights to create generic medications [32]. Importantly, medications from multiple patent holders in this pool could be combined into new fixed-dose combinations for first-line and second-line use in low-income countries. Generics could also produce new pediatric formulations and combinations. The terms and conditions of establishing the patent pool as a separate legal entity are currently under discussion. One important area of future negotiations with patent holders is the ability of the patent pool to be used to supply middle-income countries. It is important that generic manufacturers have access to middle-income country markets to provide financial motivation for the production of generic medications, especially second-line medicines for which there is currently only limited demand in low-income and sub-Saharan countries. By the same token, it is important for originator companies to protect these markets by maintaining patents in middle-income countries [33•]. Although the patent pool is a powerful concept, it is yet to be seen if negotiations will reach a useful conclusion.

In addition to patent and regulation issues, assured purchasing power and economies-of-scale can theoretically play an important role in price reductions. Large funding mechanisms such as PEPFAR and the Global Fund provide for favorable market conditions, including bulk purchasing and predictable demand, that have all helped to decrease prices of commonly used first-line medications such as stavudine, lamivudine, nevirapine, and zidovudine [34].

Finally, innovative approaches such as those taken by the Clinton HIV/AIDS Initiative (CHAI) combine with economies-of-scale to further lower ARV prices. CHAI works with generic companies to negotiate lower prices and with country partners to ensure prompt payment while

providing direct technical assistance to manufacturers to help reduce production costs [35]. Since 2006, when CHAI partnered with UNITAID to harness the power of bulk procurement, drug prices obtained through this partnership have fallen by 43% for commonly used adult ARVs and 64% for commonly used pediatric formulations [36]. Thus, in mid-2009, CHAI announced a newly negotiated price for a regimen of tenofovir, lamivudine, and efavirenz of \$210 USD per patient per year, making a tenofovir-based regimen almost as affordable as a zidovudine-based regimen

Given the reduced cost of tenofovir-based regimens, new cost-effectiveness data have emerged supporting the use of tenofovir in first-line therapy. A study from India took into account ARV efficacy, toxicity, and adjusted for quality of life for regimens that included stavudine, zidovudine, or tenofovir as first-line therapy. It was found to be most cost effective to use tenofovir as first-line therapy, with a cost-effective ratio of \$670 USD per quality-adjusted year of life saved [37••]. A study from South Africa also supported that it would be cost-effective to use tenofovir as first line therapy when considering quality-adjusted life years [38]. This analysis might need to be recalibrated to take into account new evidence of tenofovir-related declines in kidney function [39].

Given these data, it is becoming favorable for countries to move toward less toxic regimens that include tenofovir. However, in order to meet the new WHO guidelines including initiation of therapy at CD4 counts of 350 and plan for expanded formularies to care for patients with increasingly resistant HIV, all of the aforementioned tools must be utilized to ensure access to affordable and safe HIV regimens.

Funding for Global HIV: A Discouraging Future

Despite new calls for expanded treatment access and improved first-line regimens, important funders, such as the Global Fund and PEPFAR, show signs of donor fatigue and stalled funding commitments, which in turn negatively impact developing country ambition and scale-up plans [40•]. The Global Fund's donors, primarily wealthy countries including the United States, have not responded to resource needs, resulting in a growing funding gap. As a result, the Global Fund Board had to impose a 10% efficiency cut on its phase-one Round 8 grants, which face a 25% cut in phase-two renewals [41]. The efficiency and shortfall cuts in Round 9 are even more egregious, and there are discussions about delaying or rationing funding in Round 10 [42].

Similarly, funding for PEPFAR has been stagnating. Although the incoming Obama administration and other

Congressional leaders had promised to strengthen PEPFAR and commit \$48 billion over 5 years [43], the fiscal year 2009, 2010, and proposed 2011 budget are essentially flat-funded for global HIV programs [44, 45]. In order to support scale up to achieve universal access to life-saving ARVs and provide global leadership, the United States would need to increase its contribution in fiscal year 2011 to approximately \$7.5 billion [46].

At the same time that external aid is decreasing, the reverberations of the global economic crisis are leading national governments down a dangerous road of selectively cutting health and HIV budgets. Thirty-nine of the poorest countries in the world faced a \$216 billion balance-of-payment shortfall in 2009. Fiscal stimulus to reverse the recession would have required another \$41 billion. More broadly, there was an estimated \$1 to 2 trillion shortfall in external financing in developing countries (remittances, export earnings, foreign direct investment, official development assistance) at the same time that growth rates had fallen from 8.7% percent in 2007 to 1.6% in 2009 [47].

As a result of the economic crisis, the World Bank estimated that 1.7 million people living with HIV/AIDS worldwide and receiving treatment were under threat of treatment interruption because of the economic downturn and that 22 countries would face hurdles in providing ARV treatment [48]. Already, spending is being capped in some of the countries with the highest HIV burdens, including Botswana, Swaziland, and Tanzania [49]. Flat-lined spending in the US PEPFAR program has resulted in treatment waiting lines in Uganda and Zambia [50]. Although there is a modest commitment to increase treatments supported by the United States to reach at least 4 million people, this commitment, when combined with faltering commitments from Europe, will fall far short of universal access even by 2015. It is troubling that the wealthiest countries are finding it difficult to meet long-standing commitments to universal access to comprehensive HIV/AIDS prevention, treatment, and care.

The Politics of Regimen Change

Signals from donors are having a dramatic chilling effect on countries' plans to scale up HIV treatment and care and discouraging efforts to meet with new WHO treatment guidelines, both with respect to an earlier start-point and utilization of a higher-cost but more tolerable and effective treatment regimen. The authors' own experience in Kenya illustrates this point. Kenya's current guidelines date from 2006 and recommend treatment initiation at a CD4 of 200 or WHO clinical stage 4 disease with stavudine. Monitoring of treatment response is via clinical response and CD4 trends.

When the new WHO guidelines came out, Kenya was already in the process of revising their guidelines. As the WHO guidelines were fully supported by the clinicians working on the new guidelines, the fear of diminishing donor support became a primary driving force in decisions on which of the WHO recommendations to support. There is much concern among Kenyan leaders in the HIV field that these recommendations may become unfunded mandates if donors do not make bold moves to support them. At the time of writing, the new guidelines are still to be made and may in large part be determined by the posture of major donors such as PEPFAR.

Uganda, an early PEPFAR focus country, succeeded in incorporating many of the WHO recommendations into their updated national treatment guidelines only to face major financial constraints when PEPFAR capped their donations to Uganda. As PEPFAR is the major source of support for AIDS care and treatment in Uganda, this action prevented implementation of their new guidelines

Conclusions

Rapid and robust scale up of high-quality global HIV treatment while patients' immune system is still strong is the key to stopping the AIDS pandemic, both in terms of stemming morbidity and mortality and providing effective prevention. Making ARV medications affordable and tolerable is one crucial component to achieving universal access. In light of expanded IPRs, AIDS advocates, governments, donor organizations, and other stakeholders must maximize the available tools to ensure important drug prices remain within reach of low-income countries. Although drug pricing is likely the make-or-break issue, other challenges also exist, such as strengthening health systems, expanding human resources for health, and incentivizing research for treatments and diagnostics that will primarily be used in the developing world, including pediatric formulations, heat-stable formulations, and dried blood spot viral load testing.

Starting treatment earlier and with better, but more expensive medicines and reaching the vast majority of those in need of antiretroviral therapy cannot occur if donors and countries backtrack on their commitments to expand resources. Donor governments, including the United States, must partner with governments and civil society in low- and middle-income countries to ensure that the promise of universal access is not an empty one. Only by fully providing the financial and technical support needed to effectively scale up good, quality treatment can we end the AIDS epidemic.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. UNAIDS: 2009 AIDS Epidemic Update. Available at http://data.unaids.org/pub/Report/2009/JC1700_Epi_Update_2009_en.pdf. Accessed January 28, 2010.
 2. Bhaskaran K, Hamouda O, Sannes M, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* 2008, 300:51–59.
 3. Bell C, Lewis M: The Economic Implications of Epidemics Old and New. Center for Global Development Working Paper 54, 2005.
 4. The HIV-CASUAL Collaborative: The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS* 2010, 24:123–137.
 5. • Nacheha J, Trotta M, Nelson M, et al.: Impact of metabolic complications on antiretroviral treatment adherence: clinical and public health implications. *Curr HIV/AIDS Rep* 2009, 6:121–129. *This is a comprehensive review that includes major effects of commonly used antiretroviral medications used in low-income countries.*
 6. Lenert L, Feddersen M, Sturley A, et al.: Adverse effects of medications and trade-offs between length of life and quality of life in human immunodeficiency virus infection. *Am J Med* 2002, 113:229–232.
 7. •• Medecins Sans Frontiers: Untangling the web of antiretroviral price reductions (12th edition) 2010. Available at <http://utw.msfacecess.org/background/challenges>. Accessed February 2, 2010. *This is an excellent resource for current drug prices and updates on policies affecting drug pricing.*
 8. Nacheha J, Leisengang R, Bishai D, et al.: Spending more to save more: interventions to promote adherence. *Ann Intern Med* 2010, 152:18–25.
 9. Granich R, Crowley S, Vitoria M, et al.: Highly active antiretroviral treatment for the prevention of HIV transmission. *AIDS* 2010, 13:1. Available at <http://www.jiasociety.org/content/13/1/1>. Accessed January 13, 2010.
 10. Carter M: HIV treatment should be started earlier in resource-limited settings, shows trial. *Aidsmap news* 2010. Available at <http://www.aidsmap.com/en/news/B4BEE942-4347-4FBB-87AC-38C654774959.asp>. Accessed November 30, 2009.
 11. World Health Organization: Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents 2009. Available at http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf. Accessed February 9, 2010.
 12. • Subbaraman R, Chuguturu S, Mayer K, et al.: Adverse effects of highly active antiretroviral therapy in developing countries. *Clin Infect Dis* 2007, 45:1093–1101. *This review focused on adverse effects of antiretrovirals in the context of low-income countries.*
 13. Murphy R, Sunpath H, Kuritzkes D, et al.: Antiretroviral therapy-associated toxicities in the developing world: the challenge of a limited formulary. *J Infect Dis* 2007, 196(Suppl 3):449–456.
 14. Falco V, Rodriguez D, Ribera E, et al.: Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: Report of 12 cases and review of the literature. *Clin Infect Dis* 2002, 34:838–846.
 15. Geddes R, Knight S, Moosa Y, et al.: A high-incidence of nucleoside transcriptase inhibitor-induced lactic acidosis in HIV-infected patients in a South African context. *South African Med J* 2006, 96:722–724.
 16. Van Griensven J, Zachariah R, Rasschaert F, et al.: Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigale, Rwanda. *Transactions R Soc Trop Med Hygiene* 2009 (in press).

17. van Oosterhout J, Bodasing N, Kumwenda J, et al.: Evaluation of antiretroviral therapy results in a resource poor setting in Blantyre, Malawi. *Trop Med Intl Health* 2005, 10:464–470.
18. Amoroso A, Sheneberger R, Edozien A, et al.: Antiretroviral-associated drug toxicities leading to a switch in medication: experience in Uganda, Kenya and Zambia. Presented at 14th Conference on Retroviruses and Opportunistic Infections. Los Angeles, CA; February 25–28, 2007.
19. Collins S: Pharmacokinetic study of Triomune-40 in Malawi: higher d4T exposure suggests importance of using lower dose formulations of d4T. Available at <http://i-base.info/htb/2773>; <http://i-base.info/htb/2773>. Accessed January 9, 2010.
20. Westreich D, Sanne I, Maskew M, et al.: Tuberculosis treatment and risk of stavudine substitution in first-line antiretroviral therapy. *Clin Infect Dis* 2009, 48:1617–1623.
21. Lalloo U, Pillay S: Managing tuberculosis and HIV in sub-Saharan Africa. *Curr HIV/AIDS Rep* 2008, 5:132–139.
22. Wills T, Nadler J, Somboonwit C, et al.: Anemia prevalence and associated risk factors in a single-center ambulatory HIV cohort. *AIDS Reader* 2004, 14:313–315.
23. Gallant J, DeJesus E, Arribas J, et al.: Tenofovir DF, emtricitabine and efavirenz vs zidovudine, lamivudine and efavirenz for HIV. *N Engl J Med* 2006, 354:251–260.
24. Sanne I, Mommeja-Marin H, Hinkle J, et al.: Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis* 2005, 191:825–829.
25. Baker B: Arthritic Flexibilities for Accessing Medicines, Analysis of WTO Action Regarding Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health. *Ind Intl Comp L Rev* 2004, 14:613–715.
26. Baker B: *India's 2005 Patent Act: Death by Patent or Universal Access to Second- and Future-Generation ARVs?* *Global AIDSLink* 2005, 93:17.
27. Baker B: Ending drug registration apartheid—taming data exclusivity and patent/registration linkage. *Am J Law Med* 2008, 34:303–344.
28. World Trade Organization: Declaration on the TRIPS Agreement and Public Health 2001. Available at http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm. Accessed February 2, 2010.
29. International Center for Trade and Sustainable Development: Brazil issues a compulsory license for efavirenz 2007. Available at <http://ictsd.org/i/ip/38960/>. Accessed February 2, 2010.
30. Medical News Today: Abbott To Stop Launching New Drugs In Thailand In Response To Country's Compulsory License For Antiretroviral Kaletra 2007. Available at <http://www.medicalnewstoday.com/articles/65274.php>. Accessed on January 28, 2010.
31. US Trade Representative: 2007 Special 301 Report. Available at <http://ictsd.org/i/ip/38960/>. Accessed February 2, 2010.
32. UNITAID: UNITAID Approves Patent Pool 2009. Available at <http://www.unitaid.eu/en/20091215237/News/UNITAID-APPROVES-PATENT-POOL.html>. Accessed February 2, 2010.
33. • Morris K: HIV drug patents in the spotlight. *Lancet Infect Dis* 2009, 9:39–40. *This article offers an explanation of certain intellectual property restrictions on medication access.*
34. Dionisio D, Khanna A, Nicolaou S, et al.: For profit policies and equitable access to antiretroviral drugs in resource-limited countries. *Future HIV Therapy* 2008, 2:25–36.
35. Waning B, Kaplan W, King A, et al.: Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. *Bull World Health Organization* 2009, 87:520–528.
36. UNITAID: UNITAID and the Clinton HIV/AIDS Initiative announce new price reductions for key drugs 2009. Available at <http://www.unitaid.eu/en/20090417198/News/UNITAID-and-the-Clinton-HIV/AIDS-Initiative-Announce-New-Price-Reductions-for-key-drugs.html>. Accessed January 23, 2010.
37. • Bender M, Kumarasamy N, Mayer K, et al.: Cost-effectiveness of tenofovir as first-line antiretroviral therapy in India. *Clin Infect Dis* 2010, 50:416–425.
38. Rosen S, Long L, Fox M: Poster presentation: Cost and cost-effectiveness of switching from stavudine to tenofovir in first-line ARV regimens in South Africa. 15th Conference on Retroviruses and Opportunistic Infections 2008. Boston, MA; February 3–6, 2008.
39. Horbery M, Tang B, Towner W, et al.: Impact of tenofovir on renal function in HIV-infected, antiretroviral-naïve patients. *J AIDS* 2010, 53:62–69.
40. • Medecins San Frontiere: Punishing success? Early signs of a retreat from commitment to HIV/AIDS care and treatment 2009. Available at http://www.doctorswithoutborders.org/publications/reports/2009/MSF_HIV-AIDS-Punishing-Success.pdf. Accessed February 9, 2010. *This article discusses the repercussions of donor fatigue with regard to HIV treatment.*
41. Aidspan: Global Fund Approves Round 8 Grants, But Cuts Budgets and Delays Round 9. *Global Fund Observer* 2008, 98. Available at <http://www.aidspace.org/index.php?issue=98&article=1&highlights=Round-8~results>. Accessed February 3, 2010.
42. Aidspace: Global Fund Board Approves Round 9 Grants Despite Financial Shortfall. *Global Fund Reporter* 2009, 110. Available at <http://www.aidspace.org/index.php?issue=110&article=1>. Accessed February 3, 2010.
43. US Congress. Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008, P.L. 110–293.
44. Kaiser Family Foundation. Budget Tracker: Status of U.S. FY10 Funding for Key Global Health Accounts 2010. Available at <http://www.kff.org/globalhealth/upload/8045.pdf>. Accessed February 3, 2010.
45. Kaiser Family Foundation. Policy Tracker: White House Releases FY 2011 Budget 2010. Available at <http://globalhealth.kff.org/Policy-Tracker/Administration/Actions/2010/February/01/FY11-Budget-Request.aspx>. Accessed February 3, 2010.
46. The Global Health Initiative: The Future of Global Health: Ingredients for a Bold and Effective Initiative 2009. Available at <http://www.theglobalhealthinitiative.org/documents/report.pdf>. Accessed on February 3, 2010.
47. International Monetary Fund: Impact of the Global Financial Crisis on Sub-Saharan Africa 2009. Available at www.imf.org/external/pubs/ft/books/2009/afrglobfin/ssaglobalfin.pdf. Accessed November 17, 2009.
48. World Bank: Averting a Human Crisis during the Global Downturn 2009. Available at <http://siteresources.worldbank.org/NEWS/Resources/AvertingTheHumanCrisis.pdf>. Accessed February 3, 2010.
49. Kilshweko O: Government may cut AIDS budget by 20%. *The Citizen*. May 25, 2009. Available at www.thecitizen.co.tz/newe.php?id=12692. Accessed May 29, 2009.
50. Allen M: War on AIDS Hangs in the Balance as U.S. Curbs Help for Africa. *Wall Street Journal* 2010. Available at http://online.wsj.com/article/SB10001424052748703906204575027442437944112.html?mod=WSJ_latestheadlines. Accessed February 2, 2010.