Antiviral Therapy 2014; **19 Suppl 3:**117–123 (doi: 10.3851/IMP2906)

Review

Scaling-up the use of generic antiretrovirals in resource-limited countries: generic drugs for health

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The number of people living with HIV (PLHIV) continues to increase around the world because of the increasing number on antiretroviral therapy (ART) and their associated increase of life expectancy, in addition to the number of people newly infected with HIV each year. Unless a 'cure' can be found for HIV infection, PLHIV can anticipate the need to take antiretroviral drugs (ARVs) for the rest of their lives. Because ARVs are now being used for HIV prevention, as well as for therapeutic purposes, the need for effective, affordable ARVs with few adverse effects will continue to rise. It is important to note that the dramatic growth in treatment coverage of PLHIV seen during the past decade has been primarily due to the increased use of generic ARVs. Thus, there will be a need to scale-up the research and development, production, distribution and access to generic ARVs and ART regimens. However, these processes must occur within national and international regulated free-market economic systems and must deal with increasingly multifaceted patent issues affecting the price while ensuring the quality of the ARVs. National and international regulatory mechanisms will have to evolve, which will affect broader national and international economic and trade issues. Because of the complexity of these issues, the Editors of this Supplement conceived of asking experts in their fields to describe the various steps from relevant research and development, to production of generic ARVs, their delivery to countries and subsequently to PLHIV in low- and middle-income countries. A main objective was to highlight how these steps are interrelated, how the production and delivery of these drugs to PLHIV in resource-limited countries can be made more effective and efficient, and what the lessons are for the production and delivery of a broader set of drugs to people in low- and middle-income countries.

Introduction

Since 1987, more than 25 different antiretroviral drugs (ARVs) have been developed, comprising 6 classes of drugs [1], that can now be used to ensure that people living with HIV (PLHIV) will attain near-normal life-expectancies in high-, middle- and low-income countries [2,3]. At the end of 2013, 11.7 million PLHIV in low-and middle-income countries across the world were on antiretroviral therapy (ART) [4]. The number of PLHIV worldwide on ART continues to rise and these people are now living longer. However, the incidence of HIV transmission in many regions of the world still exceeds the number of PLHIV initiating ART [5]. The combination of continuing high incidence and the prolonged life expectancy of PLHIV on ART are contributing to the increasing number of PLHIV around the world.

An important reason for the rise in PLHIV on ART is the increased use of generic ARVs in low- and middle-income countries. In countries that have access to generic drugs, the market size of generic ARVs increased by 33% from 2011 to 2012 where it amounted to USD1.4 billion in 2012 [6]. 'Generic' drugs are bioequivalent versions of 'originator' drugs that can be produced after the originator's patent has expired, when a voluntary or compulsory license has been granted, when exceptions exist, like the bolar exception, or when no patent exists. 'Originator' or 'branded' drugs are those that have been developed by commercial companies, often based on government-funded research as the foundation of drug discovery [7]. Once developed, the company can patent the new drug and these patents provide a minimum of 20 years of market exclusivity in terms of

their production, pricing and sales. However, the public sector continues to contribute to drug development through the life cycle of the new drugs [7].

Generic drugs must contain the same active ingredient(s) as the originator drug, be identical in strength, dosage form and route of administration, and have the same indications for use [8]. In addition to being 'bioequivalent' and to release active ingredient(s) at the same rate as the originator product, they must meet the same batch requirements for identity, strength, purity and quality. They must be manufactured under the same strict standards of Good Manufacturing Practice (GMP) required for innovator products [8]. Furthermore, the process from research and development, to production, distribution and finally access to ARVs, must occur within national and international economic systems. This involves increasingly multifaceted patent issues, affecting the price and quality of the ARVs.

National and international drug regulatory agencies need to be strengthened in order to increase the national capacity to control and regulate the quality of drugs as they come on the market, aspects that involve broader national and international economic and trade issues. Because of the complexity of these issues, experts in their field have described in this Supplement the various steps, from relevant research, to the production of generic ARVs, their delivery to countries and subsequently to PLHIV in low- and middle-income countries. One aim of this Supplement was to highlight how these steps are interrelated, how the production and delivery of these drugs to PLHIV in low- and middle-income countries can be made more effective and efficient, and what the lessons are for the production and delivery of other drugs to people in these countries. In addition to the need for ARVs for therapeutic purposes, ARVs now are also used in HIV prevention programmes for HIV discordant couples [9], prevention of mother-to-child transmission, post-exposure prophylaxis, pre-exposure prophylaxis and vaginal microbicides [10]. Biomedical interventions, together with behavioural and structural interventions, constitute the basis for combination prevention [11].

Lessons learned

The article by Lange and Ananworanich [1] reminds us that developments in science are not necessarily linear, given that zidovudine or AZT, the first drug to undergo clinical trials as an anti-HIV agent, was first developed as a cancer drug. The progression of going from mono- to dual- to triple-therapy ensured that by the mid-1990s effective ARVs were available that changed the lives of PLHIV, initially in high-income countries and for those in low- and middle-income countries who could afford it. Currently, 6 classes of ARVs are available comprising more than 25 ARVs, with more in the pipeline, although most new ARVs are improvements on pre-existing ARVs. Many of these ARVs are now in generic form but most of the more recently developed ARVs are still single-source drugs. The authors also remind us that many of the successes in bringing down the price of treatment have been achieved due to the direct and active involvement of civil society groups in high-, middle- and low-income countries [12].

The increased production of different generic ARVs has been associated with a dramatic reduction in the annual price of ART regimens. Perriëns *et al*. [13] discuss the marked reduction in annual price for ART that has occurred over the past decade and potential future developments. They quote 2012 annual median prices for different regimens available in low- and middle-income countries as USD122 for first-line ART and USD497 for second-line therapy. A major reason for achieving such reductions has been the increased use of generic ARVs and a concomitant reduction in the use of branded or originator ARVs in first-line therapy. Conversely, fewer generic drugs are currently available compared with branded or originator drugs for second-line, third-line or salvage therapy, resulting in higher prices for these regimens. Similarly, although price decreases have also occurred among paediatric formulations, these have not occurred to the same extent as for adult ARVs and the production and pricing of paediatric ARVs remains a major area to be addressed. The aim of a recent partnership between UNITAID, the Drugs for Neglected Diseases initiative (DNDi) and the Medicines Patent Pool (MPP) is to improve treatments for children with HIV or AIDS. A major concern is the current lack of specific single-dose combinations of drugs for infants, children and adolescents [14].

Fortunak *et al*. [15] describe why the active pharmaceutical ingredients (APIs) are major cost-drivers for the production of ARVs. APIs are developed through chemical processes involving raw materials and comprise between 50% and 80% of the production costs of ARVs, depending on the local economy where they are produced. Apart from the availability and costs of the primary compounds, chemicals and other raw materials, other factors that affect their production costs include the availability of a labour force with the required professional skills, their wage structure and the existence of the industrial infrastructure to perform these specific chemical processes. These authors also provided projections of the population costs based on the number of PLHIV estimated to be in need of ART. These scenario-analyses included estimated costs of covering all PLHIV with $CD4^+$ T-cell counts ≤ 500 cells/mm^3 and a 'test-and-treat' scenario, when ART is started irrespective of $CD4^+$ T-cell count, and demonstrated that newer forms of drugs may not

necessarily be more expensive than older versions of similar drugs.

Vitoria *et al*. [16] remind us how the changing regimens also have been associated with substantial reductions in pill-load for PLHIV on ART: while in the late 1990s some people were taking 28 pills per day, currently many PLHIV are on a fixed-dose combination (FDC) and need only to take one pill a day. The reduction in the number of pills that need to be taken improves adherence, reduces disease progression and the need to use hospital services, resulting in reduced health-care costs [17], increased life expectancy and improved quality of life [16]. They also refer to the important role that the World Health Organization (WHO) consensus-based guidelines have come to play since the recognition of the HIV pandemic. One of these guidelines refers to when to start ART. While in 2002 a cutoff point of $CD4^+$ T-cell counts ≤200 cells/mm^3 was recommended as the time to start ART, this increased to $CD4^+$ T-cell counts ≤350 cells/mm^3 in 2010 and to $CD4^+$ T-cell counts ≤500 cells/mm^3 in 2013. Whether future recommendations will include starting ART irrespective of $CD4^+$ T-cell count, as is currently practiced in some parts of the US [18], remains to be seen. It is the specific aim of the START study [19] to assess whether starting ART at $CD4^+$ T-cell counts >500 cells/mm^3 will limit HIV-associated organ damage due to chronic inflammation [20]. Starting ART earlier also contributes to a reduction in the transmission of HIV. The normative guidelines provide guidance for countries on which ARV regimens to use, based on the best available evidence. National guidelines have been produced in different countries – like the US [21] and the UK [22] – but for many countries the WHO guidelines remain very influential as they take a 'public-health' as opposed to an 'individual' strategic approach. Simplification of regimens not only assists countries in deciding which regimens to use, it promotes scaling-up of services by simplifying drug procurement and distribution, and can reduce stock-outs [16].

The production and distribution of generic ARVs are important factors affecting their availability. Globally, 80% of APIs and final formulations for generic ARVs are produced in India and China and exported to other countries, including sub-Saharan Africa. Some countries have developed their own local production of generic ARVs. Local in-country productions of generic APIs and ARVs has become an increasingly important issue, as the demand for ARVs, required for therapeutic and prevention services, continues to increase. Pinheiro *et al*. [23] provide a detailed discussion on the requirements for countries to develop a successful local generic ARV industry. These include a supportive and consistent government policy, adequate and appropriate technological infrastructure, available technical and managerial expertise, a good production and distribution system, and the existence of a national drug regulatory agency. While some countries have developed and are expanding national production mechanisms, others are considering the development of regional production systems, an African example of which is described by Rägo *et al*. [8]. Local production requires the development of a sound strategy with clear priorities to reduce production costs, increase efficiency and thereby reduce the cost of ARVs while maintaining or improving their quality.

Pinheiro *et al*. [23] also highlight the importance of addressing the issue of patents when developing local production capacity. Pascual [24] describes some of the issues around intellectual property rights and patents. A patent is an exclusive right given by law to inventors to make use of, and exploit, their inventions for a limited period of time. Generally speaking, a patent provides the patent owner with the right to decide how – or whether – the invention can be used by others. The inventor is granted this temporary monopoly in exchange for a full description of how to perform the invention which is made publicly available in the published patent document. Patents are granted by national authorities, mostly patent offices. In some cases patents are granted by a regional organization. Based on the 1995 World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), patents should be available in WTO member states for any invention in all fields of technology, and the protection should be available for a minimum of 20 years. However, what exactly constitutes 'patentable products' varies from country to country, as Haddad recently pointed out [25].

TRIPS also has flexibilities that enable countries to override some of these patent rights, especially if they are addressing a specific public health issue as stated in the 2001 Doha Declaration on TRIPS and Public Health [26]. The transition time for countries to become compliant with the TRIPS provisions is one of its flexibilities and has been recently extended from 2016 to 2021 for the 33 WTO least developed countries. However, the political options for low-income countries to make use of those flexibilities are being reduced, as countries are being pressured to enter into free-trade agreements that enforce intellectual property rights beyond those provided within the TRIPS agreement [27]. Other solutions that have been used to ensure that an adequate quantity of ARVs were available for low- and middle-income countries included the use of tiered pricing, where the same drug is sold at different prices in different countries, or the use of voluntary licensing, when a company receives royalties from a licensee that can produce or sell patented ARVs. Pascual [24] describes some of the uses and short-comings of these methods and the development

of the MPP. This is a collaborative effort supported by UNITAID, in which negotiations with representatives of originator and generic pharmaceutical companies aim to develop innovative drugs and access to these drugs by low- and middle-income countries. The MPP negotiates with patent holders, like pharmaceutical companies in high-income countries that make their patent available to generic pharmaceutical companies or small biotechnology firms [28]. The success of the MPP depends on the nature of the products pursued in terms of their high- or low-market potential, and the participation of a critical mass of originator and generic pharmaceutical companies [28]. To date the MPP has successfully secured licenses with five companies for eight WHO preferred first- and second-line treatments for adults and children and has six sublicense agreements with generic manufacturers. While the licenses that the MPP pursues are based on voluntary collaboration, governments can grant compulsory licenses or make government use of patents. The MPP has no such competence but a refusal to license to the MPP may strengthen the case for a non-voluntary, compulsary license. Pascual [24] furthermore points out that with the development of global markets the nature of some of the generic companies is likely to change, and that originator companies need to start working together with generic companies in new, collaborative ways.

In addition to patent issues, a number of other regulatory issues exist to ensure the quality of originator and generic drugs produced. Rägo *et al*. [8] describe the contextual factors required for regulation to be successful, including the existence of the political will and commitment to good governance in regulation, the adequate availability of medicines to avoid smuggling and illegal use, strong public support for drug regulation, effective cooperation across national authorities, and sufficient qualified and experienced professionals. The need for national medicine regulatory agencies (NMRAs) was raised by Pinheiro *et al*. [23] and these are required for local production and to examine imported drugs. Rägo *et al*. [8] highlight some of the required characteristics of a strong NMRA. The quality of originator drugs are currently approved and monitored by regulatory authorities according to the harmonized requirements of the *International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use* (ICH). This is a forum that brings together representatives of national and international regulatory authorities and the pharmaceutical industry to make new products available to patients more quickly while protecting international public health. At a national level, monitoring the quality of generics is also based on ICH principles and predominantly performed by a country's NMRA.

In the absence of an effective national regulatory system, countries can use the WHO Prequalification Program (WHO PQP) or the US Food and Drug Administration Tentative Approval Mechanism (US FDA TAM) to monitor the quality of branded and generic drugs. The US FDA TAM was put in place to allow PEPFAR to pay for generic drugs that were not available on the US market because of patents. WHO PQP was first started in 1987 to review vaccine developments and its remit was extended in 2001 to monitor the quality of generic drugs [8]. It became and remains a very important mechanism in the scale-up of ART services in resource-limited countries and the authors provide a fascinating account of how the need to provide generic ARVs has influenced the development and workings of such regulatory systems. For example, the MPP requires generics to go through the WHO PQP in order for them to be included in the MPP. WHO does not only provide regulatory support but also facilitates the development of national, regional, continental and global regulatory systems and assesses their quality. The development of an African Medicines Regulation and Harmonization (AMRH) initiative may be a long-term project, but regional regulatory frameworks are being set up, potentially intermediary steps towards developing an AMRH. The WHO also played an important role in paving the regulatory way for the production of ARV FDCs for which originator versions did not exist [12].

In the last thematic article, Ripin *et al*. [29] describe selected relevant issues of procurement and supply chain management. Drugs are moved from the manufacturer to the facility where patients are seen, and this process should be governed by the following underlying principles: *take the right product, in the right quantities that are available under the right conditions, deliver it to the right place and person, at the right time and cost.* The main stakeholders in this process include manufacturers, donors, beneficiaries and operational agents. The operational agents include governments, procurement agents, freight forwarders – either air or sea freight – custom brokers and carriers. Different procurement and supply chain models are discussed by the authors, including a distributed model, which is a predominantly country-led process, as opposed to an integrated model, where procurement and distribution is carried out on behalf of countries. The supply of the drugs involves both strategic and operational processes. Having selected the product and supplier, the next step is that of forecasting current and future quantities of drugs needed, followed by the procurement, distribution, use of the drugs, all associated with good inventory management. Trade policies and regulations heavily affect the process, especially when tariffs and import fees are charged. Other challenges include shelf-life, quality control and traceability of the products [29].

The final two articles are descriptive analyses of how a low- and middle-income country, respectively, deals with their HIV epidemic, as they are situated within different socio-economic contexts and have differing resources available to them. As Rouzier *et al*. [30] reminds us, Haiti's epidemic was first recognized when it was one of the four 'H' risk factors for US citizens living with AIDS early in the history of the pandemic. Since then, the country, in addition to dealing with its epidemic, has had to deal with great social and economic inequity and major environmental problems, including the 2010 earthquake. Despite these challenges, a sustainable response to their HIV epidemic is being developed that is integrated with other health and social services and general infrastructure development. One issue is the difference in annual costs of ART across drug regimens, ranging from USD138 for first-line, USD235 for second-line and USD2,006 for third-line regimens. As more PLHIV will eventually fail first-line regimens, prices will need to come down for second- and subsequent lines of ART, employing some of the mechanisms that have been mentioned in the thematic papers, including developing new collaborative working methods between innovator and generic companies.

The utility of local production was brought out in the South Africa context [31]. This middle-income country currently has the greatest number of PLHIV living within its borders and Bekker *et al*. [31] poignantly remind us that strong government support is required in order for a country's HIV response to be effective and brought up-to-scale. This needs to be augmented by strong civil society activism as exemplified by the Treatment Action Coalition and other South African non-government organizations, especially if government support is weak or hinders the development of an effective response. The importance of civil society community groups was also seen in the 1980s and 1990s in the US and ensured that HIV and AIDS issues were brought high onto the US Government's agenda.

Haiti and South Africa are following technical guidance from the WHO and other agencies to determine who should be started on ART, when and with what regimen. However, both are grappling with the recent WHO guidance change in CD4$^+$ T-cell count cut-off from starting ART at CD4$^+$ T-cell counts ≤350 to starting when CD4$^+$ T-cell counts ≤500 cell/mm^3; this change requires additional resources to accommodate the increased number of PLHIV requiring life-long ART. Currently, Haiti remains predominantly funded for its ART programme through external sources while South Africa is able to increasingly draw on national resources to fund its ART programme. Many other countries around the world are now struggling with sustaining their HIV response and will need additional resources especially if 'test-and-treat' strategies are going to be adopted and global guidelines adopt the recommendation that treatment should be started irrespective of CD4$^+$ T-cell count.

South Africa has diverted more funding to finance its own HIV response, something that Haiti is unlikely to be able to do for the foreseeable future. South Africa is also developing its local production of generic ARVs, though currently not on such a scale that it is self-sufficient and able to cover its requirement for generic ARVs. However, its industry can be scaled-up and influence both national, regional and African production of generic ARVs as well as developing the respective necessary regulatory frameworks, including the AMRH. These developments, when successful, could lead to further reductions in prices of generic ARVs and reduced reliance on importing generic ARVs from outside Africa. In the short-term, projects like the MPP and other mechanisms that deal with intellectual property-related issues, will be important in devising mechanisms to ensure generic competition, including voluntary license agreements or by making use of TRIPS flexibilities. These foster the possibility that new innovative drugs can also be used in low- and middle-income countries, without having to wait until patents have expired.

Apart from the national and international regulatory mechanisms that are required to be created or extended, the developments of the WHO PQP and the US FDA TAM are examples that where there is a political will, things can change rapidly within national and international contexts to ensure that the right product, in the right quantities are available under the right conditions, delivered to the right place and person, at the right time and cost. However, Haiti and South Africa, like many other countries, have issues concerning the testing of PLHIV, linking them with the appropriate treatment and care, retaining them in care and ensuring that they are virologically suppressed and immunologically stable. Being 'lost to follow-up' in a particular facility may be due to patients changing treatment facilities, stopping treatment and care or due to the death of the person [31]. As Bekker *et al*. [31] comment, to ensure the success of these ART programmes the development and implementation of National Health Identifiers will be important in conjunction with the development of national health service information systems, linked to vital statistic and social service systems [32]. Such systems are important infrastructure components that need to be developed, implemented and maintained in countries in order to develop longitudinal records for people using services provided at health facilities and using this individual-level information in a de-identified format to monitor and evaluate the use, cost, outcome and impact of

these programmes or services [33]. This in turn will require the development and implementation of guidelines to protect the confidentiality and security of personal health information [34].

Conclusions

As PLHIV are living longer, they are likely to develop comorbidities [20], requiring access to integrated health care, including those for non-communicable diseases (NCDs) [35]. Furthermore, NCDs in their own right are major causes of morbidity and mortality in low- and middle-income countries and many of these countries therefore require the development and scale-up of their health systems including access to specific cancer, cardiovascular, diabetic and other drugs. For local production of generic ARVs to be successful, the production portfolio of generic companies will need to be extended to include a broader range of drugs, in order for them to be profitable and sustainable companies in the long term. These portfolio's need to be tailored to the specific requirements of the country or region in question, in terms of which communicable disease and NCD generic drugs are produced. However, recent discussions at the Global Commission on HIV and the Law indicated the limitations of the current patent system to promote innovation within the pharmaceutical sector that addresses the health needs of low- and middle-income countries [36]. Moreover, the WHO Consultative Expert Working Group (CEWG) is promoting demonstration projects that pursue innovative financing mechanisms for research and development within the pharmaceutical sector that are not dependent exclusively on granting patents [37]. WHO members, based on the advice of the CEWG, agreed in May 2014 on a plan to find alternative financing for diseases predominantly afflicting poor populations. The decision includes the possibility of establishing 'a pooled fund for voluntary contributions towards research and development' by delinking research and development costs from product prices [38].

Despite the fact that many of these factors are not necessarily mutually supportive, significant successes have been achieved in the areas of research and development, production, pricing, regulation and distribution of generic ARVs to PLHIV. However, there is little room for complacency, as requirements are increasing to cover the rising therapeutic and preventive use of ARV drugs. This need to scale-up production and delivery of ARVs could also provide an important impetus for developing the successful production, regulation and distribution of affordable generic drugs for other communicable diseases and NCDs in low- and middle-income countries.

Disclosure statement

The authors declare no competing interests.

References

1. Lange JMA, Ananworanich J. The discovery and development of antiretroviral agents. *Antivir Ther* 2014; **19 Suppl 3**:5–14.
2. May MT, Gompels M, Delpech V, *et al*. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS* 2014; **28:**1193–1202.
3. Mills EJ, Bakanda C, Birungi J, *et al*. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. *Ann Intern Med* 2011; **155:**209–216.
4. WHO. People most at risk of HIV are not getting the health services they need. Geneva, Switzerland 2014. (Accessed 11 July 2014.) Available from http://www.who.int/mediacentre/news/releases/2014/key-populations-to-hiv/en/
5. UNAIDS. Report of the global AIDS epidemic 2013, Geneva, Switzerland. (Accessed 11 July 2014.) Available from http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf
6. Camponeschi G, Fast J, Gauval M, *et al*. An overview of the antiretroviral market. *Curr Opin HIV AIDS* 2013; **8:**535–543.
7. Field RI. How the government created and sustains the private pharmaceutical industry. *St Louis Univ J Health Law Policy* 2012; **6:**12–68. (Accessed 11 July 2014.) Available from http://www.slu.edu/Documents/law/SLUJHP/Field_Article.pdf
8. Rägo L, Sillo H, 't Hoen E, Zweygarth M. Regulatory framework for access to safe, effective quality medicines. *Antivir Ther* 2014; **19 Suppl 3:**69–77.
9. Cohen MS, Chen YQ, McCauley M, *et al*. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:**493–505.
10. Cohen MS, Smith MK, Muessig KE, Hallett TB, Powers KA, Kashuba AD. Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here? *Lancet* 2013; **382:**1515–1524.
11. Hankins CA, de Zalduondo BO. Combination prevention: a deeper understanding of effective HIV prevention. *AIDS* 2010; **24 Suppl 4:**S70–S80.
12. 't Hoen EF, Hogerzeil H, Quick J, Sillo H. A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme. *J Public Health Policy* 2014; **35:**137–161.
13. Perriëns JH, Habiyambere V, Dongmo-Nguimfack B, Hirnschall G. Prices paid for adult and paediatric antiretroviral treatment by low- and middle-income countries in 2012: high, low or just right? *Antivir Ther* 2014; **19 Suppl 3:**39–47.
14. Saez C. New initiative to address lack of paediatric-specific HIV treatments. Intellectual Property Watch. (Accessed 11 July 2014.) Available from http://www.ip-watch.org/2014/05/19/new-initiative-to-address-lack-of-paediatric-specific-hiv-treatments/
15. Fortunak JM, de Souza ROMA, Kulkarni AA, King CL, Ellison T, Miranda LSM. Active pharmaceutical ingredients for antiretroviral treatment in low- and middle-income countries: a survey. *Antivir Ther* 2014; **19 Suppl 3:**15–29.
16. Vitoria M, Ford N, Doherty M, Flexner C. Simplification of antiretroviral therapy: a necessary step in the public health response to HIV/AIDS in resource-limited settings. *Antivir Ther* 2014; **19 Suppl 3:**31–37.
17. Beck EJ, Mandalia S, Sangha R, *et al*. Lower healthcare costs associated with the use of a single-pill ARV regimen in the UK, 2004–2008. *PLoS ONE* 2012; **7:**e47376.

18. Russell S. City endorses new policy for treatment of H.I.V. *New York Times*, April 3 2010. (Accessed 11 July 2014.) Available from http://www.nytimes.com/2010/04/04/us/04sftreatment.html?_r=0

19. Babiker AG, Emery S, Fätkenheuer G, *et al*. Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. *Clin Trials* 2013; **10 Suppl:**S5–S36.

20. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* 2011; **62:**141–155.

21. AIDS Info. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. National Institutes of Health 2014. (Accessed 11 July 2014.) Available from http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

22. British HIV Association. Current guidelines. 2013. (Accessed 11 July 2014.) Available from http://www.bhiva.org/guidelines.aspx

23. Pinheiro E, Brüning K, Macedo MF, Siani AC. Production of antiretroviral drugs in middle- and low-income countries. *Antivir Ther* 2014; **19 Suppl 3:**49–55.

24. Pascual F. Intellectual property rights, market competition and access to affordable antiretrovirals. *Antivir Ther* 2014; **19 Suppl 3:**57–67.

25. Haddad W. Pharmaceutical genocide: 'India in the Crosshairs'. *Equilibri.* (Accessed 11 July 2014.) Available from http://www.equilibri.net/nuovo/en/node/2720

26. World Trade Organization. Declaration on the TRIPS agreement and public health. WT/MIN(01)/DEC/2, 20 November 2001, Ministerial Conference, Fourth Session, Doha, 9–14 November 2001. (Accessed 11 July 2014.) Available from http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm

27. UNDP/UNAIDS. The potential impact of free trade agreements on public health, Geneva 2012. (Accessed 11 July 2014.) Available from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/JC2349_Issue_Brief_Free-Trade-Agreements_en.pdf

28. Vinayek S. Medicines Patent Pool: a primer. Development is human. (Accessed 11 July 2014.) Available from http://developmentishuman.blogspot.com/2014/04/medicines-patent-pool-primer.html

29. Ripin DJ, Jamieson D, Meyers A, Warty U, Dain M, Khamsi C. Antiretroviral procurement and supply chain management. *Antivir Ther* 2014; **19 Suppl 3:**79–89.

30. Rouzier V, Farmer PE, Pape JW, *et al*. Factors impacting the provision of antiretroviral therapy to people living with HIV: the view from Haiti. *Antivir Ther* 2014; **19 Suppl 3:**91–104.

31. Bekker L-G, Venter F, Cohen K, *et al*. Provision of antiretroviral therapy in South Africa: the nuts and bolts. *Antivir Ther* 2014; **19 Suppl 3:**105–116.

32. UNAIDS/PEPFAR. Considerations and guidance for countries adopting national health identifiers. Geneva: UNAIDS. (Accessed 8 October 2014.) Available from http://www.unaids.org/en/resources/documents/2014/name,100356,en.asp

33. Beck EJ, Santas X, DeLay P. Why and how to monitor the cost and evaluate the cost effectiveness of HIV services in countries. *AIDS* 2008; **22 Suppl 1:**S75–S85.

34. UNAIDS/PEPFAR. Interim guidelines on protecting the confidentiality and security of HIV information: proceedings from a workshop, 15–17 May 2006, Geneva, Switzerland. (Updated 15 May 2007. Accessed 11 July 2014.) Available from http://data.unaids.org/pub/manual/2007/confidentiality_security_interim_guidelines_15may2007_en.pdf

35. Justice AC. HIV and aging: time for a new paradigm. *Curr HIV/AIDS Rep* 2010; **7:**69–76.

36. Global Commission on HIV and the Law. Risks, rights & health. Secretariat UNDP HIV/AIDS Group, New York, USA July 2012. (Accessed 11 July 2014.) Available from http://www.hivlawcommission.org/resources/report/FinalReport-Risks,Rights&Health-EN.pdf

37. WHO Director-General. Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, WHO Geneva 2013. (Accessed 31 May 2014.) Available from http://apps.who.int/gb/ebwha/pdf_files/EB134/B134_26-en.pdf

38. WHO. Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, Sixty-seventh World Health Assembly A67/B/CONF./2 Rev.1, Agenda item 15.2 Geneva, Switzerland, 24 May 2014. (Accessed 11 July 2014.) Available from http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_BCONF2Rev1-en.pdf

Accepted 14 July 2014; published online 13 October 2014