Editorial

Universal access to HIV/AIDS treatment: Challenges ahead

The World AIDS Day theme for 2009 ‘Universal Access and Human Rights’, underscores the need for and the urgency to provide live saving treatment, care and support to millions people living with HIV/AIDS (PLHA), especially in poor countries. This is also a grim reminder of the twin failures - lack of universal access and denial of fundamental right to health. More so, as universal access does not mean 100 per cent coverage but a desire to move to a high level of access for the most effective interventions that are ‘equitable, accessible, affordable, comprehensive and sustainable over the long-term’.

The UN World Summit (2005) had resolved to work towards achieving universal access to HIV/AIDS prevention, treatment and care by 2010. The ‘All by 2010’ target is also part of Millennium Development Goal 6 which includes the goal of halting and beginning to reverse the spread of HIV/AIDS by 2015. However, by 2008 the WHO conceded that few of the 100 countries would achieve the 2010 Universal Access targets.

HIV/AIDS exemplifies the complexities of access to health care for chronic life-threatening diseases. With no known cure and need for life long treatment, HIV/AIDS has caused unprecedented distress and deaths among the poor countries with a total death toll of over 25 million people since 1981. AIDS continues to be the leading cause of death in the ten highest HIV prevalence countries – with a two million death toll in 2008, a sixth being under-five children. The coverage of treatment is equally worrying with 90 per cent of 2.1 children and over 75 per cent of HIV-positive pregnant women waiting for treatment. Overall, of the total 9.5 million requiring treatment, about five million are currently awaiting treatment, over 2.3 million from India (See Ref. 3). With current rates of transmission, and when the new WHO’s recommendations of early initiation of treatment are accepted, 18-22 million PLHA may well require treatment on both existing and new generation drugs. As Peter Piot said: “The implications of HIV prevention failures are clear: unless we act now, treatment queues will get longer and longer and it will become more and more difficult to get anywhere near universal access to antiretroviral therapy”.

The mainstay of treatment of HIV/AIDS continues to be antiretroviral drugs (ARVs) which can significantly delay the progression from HIV to AIDS. Most PLHA would die within three years if remain untreated with ARVs. When the highly active antiretroviral treatment (HAART) - an effective combination therapy became available in 1996 to PLHA in rich countries, death rates plummeted by 84 per cent in just four years. Also, earlier initiation of ART (CD4 cell threshold of 350) can reduce the incidence of TB and other deadly opportunistic infections, improve survival rates thus reducing the need for costly and complex acute care underscoring the need for prompt and sustained treatment with ARVs.

Currently, over 30 FDA approved ARVs available under six categories viz., NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors), Protease inhibitors, the new Fusion inhibitors, Entry inhibitors-CCR5 co-receptor antagonists and HIV integrase strand transfer inhibitors. The major originator companies for these ARVs are: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Pfizer, Roche and Tibotec – both as single drug and fixed dose combinations (FDCs). But ever since their introduction in the developed countries, access of ARVs for the poor countries has been a serious problem (See Ref. 9). Of the factors that impact the initiation and continuation of treatment of PLHA in developing countries, cost of ARVs continues to be
important for both patient retention and mortality levels\textsuperscript{10}. And the high cost of the drugs is due to strong intellectual property rights (IPR) protection. For example, the cost of a year’s treatment that was US\$ >US\$ 10,000 per patient per year (ppp), is now available for US\$ 87\textsuperscript{11}. This was possible only because these drugs were sourced mainly from India that became fully TRIPS-complaint in 1995\textsuperscript{3,9}. Some estimates suggest that ARV cost reductions could fund an additional one million people every year, even without new resources\textsuperscript{12}.

The HIV mutates constantly in the human body eventually becoming resistant to the drug being administered. In resource-poor settings, the drug resistance becomes more complex with poor compliance of the patients coupled with irregular supply of drugs. With PLHA needing lifelong treatment, the widely used first-line ARVs could also develop problems like drug intolerance and treatment failure\textsuperscript{13-15}. For example, data from Africa show that over a five year period 22 per cent people needed such a switch-over from d4T based regimens, also recommended by the WHO in 1996\textsuperscript{13,16}. Therefore, drugs outside the currently available first line and strong second line drugs are required as otherwise the PLHA could well lose out the benefits of ARV therapy. Worse still, they may transmit the drug-resistant virus to others. “Sustaining” may well soon surpass “scaling up” of antiretroviral therapy as a new major challenge\textsuperscript{17}. Children are worst hit as of the 22 ARVs approved by the US FDA for adults, 8 are not cleared for use in children while 9 do not have any pediatric formulations\textsuperscript{17}.

How then should we grapple with the target of universal access? The first major problem is funds for ARVs - both first line drugs (mercifully cheap generics) and for procuring the second line drugs (mostly under patent protection). The cheapest second line regimen is $590 ppp, seven times costlier than the cheapest first line generic regimen\textsuperscript{17}. Even if one of the drugs in the second line regimen is under patent protection, the costs could well be 17 times the price of first line drugs\textsuperscript{11}. The overall coverage of ARVs is about 42 per cent\textsuperscript{12}. With the current rate of drug resistance noticed, eventually there would be need for third line and fourth line treatments, which, with the current funding for drug procurement, R&D for new drugs and IP-regimes, does not look bright. To meet the universal targets, at least US\$ 35 billion is required in 2010 and US\$41 billion in 2015\textsuperscript{1}. An investment of $7 billion will be required in 2010 for treatment and care alone that is part of the estimated $25 billion needed to achieve all targets\textsuperscript{2}. With less than $14 billion invested in 2008, a funding shortfall looks real\textsuperscript{2}. What is more, with the Global Fund, PEPFAR etc., reporting shortage of funds\textsuperscript{2} compounded by the current global financial meltdown in the major donor countries, things look pretty gloomy.

The major impediment towards the objective of universal access continues to be the strong global IP regimes that have pushed up the costs of ARVs\textsuperscript{5,11}. Simply put, even the existing access of 42 per cent is primarily due to availability of cheap generics from countries like India that became fully TRIPS-complaint in 1995 as most of the drugs were then not under IP protection\textsuperscript{3,9}. The current harmonization of global patent rules has adversely impacted access to drugs in developing countries and the battle on IPRs and access to life-saving drugs is likely to get more intense\textsuperscript{4,11,18-19}.

In addition to the IP regimes that impact access, new trade-related barriers are also being erected to stifle the pipeline of drugs to the African countries. In November 2008, Dutch authorities seized 49 kg of abacavir sulphate – a second line antiretroviral drug-bound for treatment of HIV/AIDS patients in Nigeria sourced by the UNITAID and Clinton Foundation - on the grounds that the drug was counterfeit and infringed IPRs\textsuperscript{20}. The seized drug was actually a generic version of a patented product of GlaxoSmithKline manufactured by Aurobindo Pharma Ltd. in India. This step, widely criticized as an example of rising protectionism in the economic crisis that hampers access\textsuperscript{20}, is being strongly contested by the Government of India\textsuperscript{21}.

There are two main means of manufacturing the ARVs viz., voluntary licensing (VL) or compulsory licensing (CL). In the former, the originator company chooses to licences one or more manufacturers for a set royalty as done by Gilead and Boehringer for some of their ARVs. VL, if executed on fair terms, can be an effective means of improving access as costs would significantly come down. CL, on the other hand, primarily works on the terms set by the originator company including the number of licensees etc., that determine the final cost of the drug\textsuperscript{17}. CL essentially overrides patent rights of the originator company to serve health needs of a country in an entirely lawful manner (See Ref. 22). Like, Thailand issued CL for two patented AIDS drugs – efavirenz and lopinavir/ritonavir for importing from an Indian company at a
fraction of the cost of patented drug\textsuperscript{12}. However, CLs are fiercely fought in courts and countries run the risk of retaliatory measures from the originators’ companies and countries\textsuperscript{22}. Not surprisingly, few poor countries have enforced CL.

Analysis of the IP landscape on ARVs shows that the major originator companies filed 93 patents at the USPTO:- Gilead (25), Abbott (20), GSK (17) and Tibotec (5), Merck (5), Agouron (5), BI (5), BMS (4), Roche (4) and Pfizer (3) for single drugs, formulations etc.\textsuperscript{3}. With so many patents from different companies on the ARVs, it is very difficult to devise licensing agreements to manufacture affordable ARVs. A broader form of voluntary licensing as patent pool for ARV drugs that was debated for long, has just been approved by the UNITAID\textsuperscript{23}. Willing originator companies voluntarily put their ARV patents into a single pool in return for royalty. Any manufacturer wishing to use the relevant patents can do so for a set negotiated fee. The Patent pool can also potentially create a system of competition among the licensees that can drive the price down while the originator companies are assured of royalty with minimum hassle. Patent pool for ARVs can also help in the development of pediatric formulations, less toxic FDCs, and significantly help in the target of universal access through cheap generics (See Ref. 3). The ARV patent pool initiative has been widely welcomed by various stakeholders from all over the world\textsuperscript{24}. The UNITAID has meanwhile approached the various originator companies and the National Institutes of Health, USA for 19 drugs (Table) (Ellen t’ Hoen, UNITAID, Personal communication). The UNITAID patent pool is expected to be operational by the end of 2010 with agreements yet to be worked out with the originator companies. But in the absence of details, there are several apprehensions like reports of reluctance of some originator companies to allow the benefit of the patent pool to middle income countries-especially China, India, Brazil and Thailand\textsuperscript{25-27}. Patent pool is voluntary and its success essentially depends upon the willingness of originator companies.

The negotiating strength of the UNITAID is rather limited\textsuperscript{25} that could impact access to cheap ARVs to poor countries. Almost all the ARVs - single drug and FDCs covering both the first line and second line are supplied by Indian generic companies at a fraction of the cost of patented drugs to all major global drug providers like MSF, Clinton Foundation, PEPFAR for distribution in African countries\textsuperscript{11,28}. The originator companies have also been aggressively patenting and enforcing the patents in countries like India, Brazil and Thailand (See Ref. 3). Keeping India out of the Patent pool therefore could be detrimental to the primary objective of universal access.

But emerging economies- China, India, Brazil and South Africa (BASIC countries) which currently sit at the high table in global negotiations alongside the G8 countries (like the Copenhagen meeting) seeking concessions at par with less developed countries may find the going tough. Even traditional allies like the MSF, CPTech etc. appear to be having a rethink on support to the BASIC countries vis-à-vis African countries.

In fine, a crude scale up suggests that the PLHA would be about 55 million by 2030\textsuperscript{12}. With the current rigid and relenting patent-regimes, the future battles for access could well be tough and nasty. Several resource-poor countries may be compelled to resort to the full use of the public health safeguards and flexibilities under the TRIPS Agreement including compulsory licensing provisions (See Ref. 18,19) even to sustain the present levels of treatment with the first line drugs\textsuperscript{17}. There are other challenges as well beyond access to ARVs – related products for co-infectons, diagnostics, better drugs to prevent mother-to-child infection\textsuperscript{12}, all of which have a strong IP linkage. Universal Access may well remain a mere mirage in the near future.

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<tr>
<th>Compound</th>
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References