

## Editorial

### ‘Getting to Zero’: a steep path ahead

It is December again and another World AIDS Day but with a new theme “Getting to Zero”<sup>1</sup>. This slogan, to be used until 2015, is expected to project the vision of the Joint United Nations Programme on HIV/AIDS (UNAIDS) of achieving “Zero new HIV infections, Zero discrimination, Zero AIDS-related deaths”<sup>1</sup> underscoring the need to sustain and push forward the progress achieved over the last decade. This year also marks 30 and 25 years since first AIDS report from the world and India respectively. It is perhaps time to reflect over where we have reached in addressing the twin failures – lack of universal access and continued denial of the fundamental right to health for people living with HIV/AIDS (PLHA). More importantly, assess the current status of the global commitment, especially the UN World Summit (2006) resolution to work towards achieving Universal Access, the desire to move to a higher level of access for the most effective interventions that are ‘equitable, accessible, affordable, comprehensive and sustainable over the long-term’, the first major step towards HIV/AIDS control prevention, treatment and care by 2010<sup>2,3</sup>.

The last decade has seen extraordinary achievements with both lower new infections and deaths in major part of the world. In 2010 there are about 2.7 million new infections, down from 3.1 million in 2001<sup>2</sup>. People receiving ARVs rose 16 fold from a mere 0.4 million in 2005 to about 6.65 million at the end of 2010, 50 per cent of pregnant women receiving ARVs to prevent mother-to-child transmission and rise in the number of children receiving therapy (71,500 in 2005; 456,000 in 2010)<sup>2</sup>. PLHA are living longer and deaths due to AIDS-related causes plummeted from 2.2 million in 2005 to 1.8 million in 2010. Over 2.5 million deaths were averted in low- middle- and upper middle-income countries (LICs, MICs, UMICs - classification based on World Bank <http://go.worldbank.org/K2CKM78CC0>) since 1995<sup>2</sup>. Overall, the number of deaths prevented

has doubled in the past two years<sup>2</sup>. This decrease has been reported from almost all across the globe – 26 per cent from the sub-Saharan Africa from the peak levels in 1997, about 33 per cent from South Africa and the Caribbean and over 40 per cent in South and South-East Asia<sup>3</sup>. This has happened due to various factors including the unprecedented progress in science coupled with enhanced access to treatment, awareness through advocacy *etc*<sup>2</sup>. The estimated adult HIV prevalence in India in 2009 was 2.39 million (0.31%) down from 0.32 per cent in 2008 in both men and women, and in the young population (15-24 yrs)<sup>4</sup>.

The estimated coverage of HIV testing and counseling among pregnant women exceeded 50 per cent in 13 of the 22 priority countries for eliminating mother-to-child transmission<sup>2</sup>. Spurred by this positive development, a new *Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive* has since been launched as universal coverage of pregnant women and children looks quite feasible<sup>3</sup>. Surely, 2011 is the first game changing year for HIV/AIDS control.

The progress in morbidity and mortality is due to, among other reasons, the dramatic rise in the access to antiretroviral therapy (ART) in LICs, MICs and UMICs from 400000 (2003) to 6.65 million (2010) covering over 47 per cent of people eligible to treatment. In 2010 alone, ARVs have averted about 700000 deaths in low- and middle-income countries. There is thus adequate scientific evidence suggesting that increased access to ART since 1995 has significantly contributed to both declining number of new infections as well as deaths<sup>2</sup>.

Despite the euphoria, there are concerns. Universal Access is still sometime away. As of December 2010, only ten LMICs, including three countries with generalized epidemics (Botswana, Namibia and

Rwanda), have achieved universal access to ART, (defined as providing antiretroviral therapy to at least 80 per cent of the people eligible for treatment) from 109 reporting countries<sup>2</sup>. Seven additional countries, including two with generalized epidemics (Swaziland and Zambia), had estimated coverage levels between 70 and 79 per cent<sup>3</sup>. If the current recommendations of the WHO on the treatment on the basis of CD4 count<sup>5</sup> are followed, there will be over 9 million still waiting for ARVs<sup>6</sup>.

There are other worrying signs too. In 2010 there are an estimated 34 million PLHA up 17 per cent from 2001. About 2.7 million new infections in 2010, including 390 000 children, largely due to new cases from the Eastern Europe and Central Asia, Oceania and Middle-East and North Africa<sup>2</sup>. Even with increased coverage, the treatment gap, therefore, continues to be 53 per cent in adults with lowest recording of 39 per cent in East, South and South-East Asia. India, that accounts for almost half the PLHA of Asia, continues to be a laggard with an ARV coverage of an estimated 30-38 per cent - much less than Brazil (65-75%), South Africa (52-58%), Thailand (55-85%) or even Kenya (56-66%) and Mozambique (36-46%)<sup>2</sup>.

Coverage of ARVs for two major most vulnerable sections of populations (pregnant women and children) continues to be another problem area. Of the pregnant women eligible for ART in 2010, only about 35 per cent (197000) could access even in priority countries with specific programmes for eliminating mother-to-child transmission<sup>2</sup>. Significantly, a mere 100 000 (4%) of the 2.5 million averted deaths were children younger than 15 years. Only 10 of the 109 reporting countries have achieved universal coverage<sup>2</sup>. This despite reports of proven benefits of ART both in human and economic terms. Consequent upon the ARV coverage, there has been enhanced economic activity and labour force productivity in several LMICs resulting in an estimated economic gains of US\$ 34 billion and 18.5 million life-years by 2020, more than the money spent on ARV roll out<sup>7</sup>.

This significant turn-around was possible largely due to enhanced global ART coverage primarily due to affordable generics. Significantly, Indian generic companies accounted for over 80 per cent of global ARV supply to 96 of the 100 countries including high HIV-burden sub-Saharan African countries for many adult formulations<sup>8</sup>. When paediatric ARVs and adult nucleoside and non-nucleoside reverse transcriptase inhibitor markets were also considered, generics

manufactured by Indian companies, accounted for 91 and 89 per cent of total purchases in 2008<sup>8</sup>. Thus, India continues to remain the 'pharmacy of the developing world'.

Availability of affordable generics also helped coverage of more people due to the plummeting cost of ARVs. The cost of the most commonly used first-line adult regimen from India (lamivudine/nevirapine/stavudine), for example, dropped from \$414 per person per year (ppp) in 2003 to \$74 ppp in 2008<sup>8</sup>. More importantly, the prices of non-Indian generics were twice as expensive while the innovator prices for this first-line regimen were 4.5 and 7.7 times higher than Indian generic prices underscoring the importance of Indian manufacturers<sup>8</sup>.

Several steps have been initiated or being proposed to reach Zero status. At a broad level, keeping civil society groups in the loop would be very beneficial in view of their path breaking contributions ever since the first battle in 1996 in Bielefeld, Germany<sup>6</sup>. The UNAIDS<sup>2</sup> has a clear agenda for the future that include preparing health systems for reaching and sustaining universal access that needs to be supported. There are other challenges too outlined below.

Despite the lowered costs of first line ARVs, funding continues to be a major challenge. An estimated US\$ 22-24 billion would be needed in 2015<sup>2</sup> while the international assistance actually declined from US\$ 8.7 billion in 2009 to US\$ 7.6 billion in 2010<sup>2</sup>. This despite significant reduction in the prices of second line ARVs as well as several other cost cutting measures initiated globally<sup>2</sup>. The Global Fund and the United States President's Emergency Plan for AIDS Relief continue to be the two major international sources of funding for antiretroviral therapy programmes in LMIC covering about 4.7 million people at the end of 2010<sup>2</sup>. In LICs, the prices of the six most frequently used first-line regimens recommended by WHO declined between 2 and 53 per cent during 2009 and 2010 despite the wider adoption of more expensive tenofovir-based regimens due to scaling up of the programme, increased volumes and competition among manufacturers<sup>2</sup>. The median price paid for first-line regimens in LICs in 2010 ranged from US\$ 64 ppp for the most widely used fixed-dose combination (stavudine + lamivudine + nevirapine) to US\$ 242 for the most expensive FDC of tenofovir + emtricitabine + efavirenz. In 2010, the median reported cost of the most commonly used second-line regimen, lamivudine + tenofovir + ritonavir-boosted lopinavir, was US\$ 554 ppp in LICs, US\$ 692 ppp in LMICs

and US\$ 601 in UMICs<sup>2</sup>. Other second line FDCs was US\$ 701 ppp in LICs, US\$ 908 ppp in LMICs and US\$ 970 in UMICs, with some variation<sup>2</sup>. Though the prices of second-line drugs declined between 2006 and 2010, mainly due to off-patent didanosine, scaling up of treatment programmes *etc.* could be tough as the number of people requiring second-line regimen is likely to grow. What is more, the costs of ARVs are unlikely to see any significant decline. The days of dramatic 99 per cent drop<sup>9</sup> seen for the currently used first-line ARVs - from >\$10,000 ppp in 2000 to \$87 in 2008 is all but history.

For UMICs like India, it is going to be much tougher with the national HIV/AIDS control programmes already impacting the health system. Public sector spending for HIV control is under strain since 2007 and by 2020 India may well have to spend 7 per cent of its health budget on AIDS control<sup>2,4</sup>. Governments of UMICs may also have to take a tough call either to treat more number of patients on affordable existing fixed drug combinations (FDCs) or put fewer people on less toxic but more expensive new combinations. For example, switching over from the most commonly used d4T-based first-line ARV combination to a less toxic option would be twice expensive<sup>10</sup>. Switching over to a TDF-based ARV regimen would mean a 4-11 fold price increase<sup>10</sup>. Unless there are overall price reductions, the budget for cost for ARVs in some middle-income countries would go as high as 17 times<sup>10</sup>.

Enhanced research and development (R&D) will be a key for the success of future HIV prevention and control programmes. Top on the agenda is to find less toxic first line ARV combinations in view of the reports of emerging drug resistance with the rise in ARV users<sup>6</sup>. Eventually there would perhaps be need for third and fourth line treatments as well. R&D is also required for finding newer and safer FDCs especially for early pregnancy, as some drugs like efavirenz are potentially teratogenic, and to find substitutes for the currently widely used nevirapine-based regimens that are unsuitable for treating early stages of HIV infection due to toxicity<sup>6</sup>. More importantly, formulations are required that are child-friendly, heat stable, require minimal monitoring and amenable to simplified dosing schedules to facilitate compliance<sup>6</sup>. Finally, the emerging HIV-TB cases which currently number about 1.4 million<sup>2</sup> demand a new formulary of TB drugs with ARVs. More R&D support would thus be needed for finding women-initiated and controlled strategies like new microbicides, especially in view of the promising results with tenofovir-based vaginal microbicides<sup>6</sup>.

Intellectual property rights (IPR) issues and global IP regimes continue to pose serious challenges. India could remain the pharmacy of developing world primarily due to two reasons. Firstly, many of the currently widely ARVs are either off patent or belong the pre-2005 period when India became fully Trade Related Intellectual Property Rights (TRIPS)-compliant<sup>12,13</sup>. The continued manufacture and export of new generic ARVs that was possible under the pre-TRIPS regime could therefore be difficult in the coming years for the Indian companies due to the new IPR regimes. That originator companies have been aggressively patenting and prosecuting in countries like India, Brazil and Thailand<sup>12</sup> is but a pointer in that direction.

There are newer impediments designed to stifle the flow of affordable generics from India. Shipments of ARVs enroute to Africa were seized on the pretext of being counterfeit medicines, an issue that was resolved with some effort from India<sup>13</sup>. The current concern UMICs also relates to attempts by developed countries seeking new IPR provisions through trade agreements, investment treaties and other WTO accession agreements<sup>14</sup>. As little headway could be made to enforce new IP obligations through multilateral treaties like the TRIPS agreement, many developed countries are increasingly entering into regional and bilateral trade agreements with LMICs and UMICs with clauses on IPR that would prevent local manufacture and export of generics<sup>14</sup>. The FTA currently being negotiated between India and the European Union (EU) is but an example where TRIPS-plus obligations<sup>14</sup> are being sought. India has been resisting such demands as extension of the patent term and data exclusivity while negotiating many other clauses that could potentially affect access to medicines<sup>14</sup>. Such TRIPS-plus clauses besides undermining the position of India as the global supplier of cheap, high quality ARVs, could significantly impede the ongoing global HIV control strategies. There have also been attempts to undermine the Indian patent law by proposing/challenging like patent linkage, questioning section 3 (d) of the Indian Patent Act *etc*<sup>12</sup> by some MNCs.

To overcome these IP-linked constraints being imposed by developed countries, LMICs that carry the significant burden of PLHA and key generics-producing UMICs like India, Brazil, and Thailand should strongly oppose any TRIPS-plus measures and make full use of the public health safeguards and flexibilities enshrined in the WTO TRIPS as reiterated in the Doha Declaration<sup>15</sup> including compulsory

licensing provisions<sup>6,12,15</sup>. Over 60 LMICs have been able to use such flexibilities including issuing of compulsory licensing or Government use provisions to provide access to ARVs<sup>6</sup>. Sovereign countries also should consider redesign or interpret national patent laws to limit the scope of patentability of new chemical entities with a clear public good focus<sup>6,12</sup>. For example, the Indian Patents Act (2005) that allows pre-grant opposition was successfully defended in the Indian courts for the pediatric syrup formulation of NVP<sup>12</sup>.

Despite years of effort, we still do not have viable models of innovation that delink R&D with market. The ongoing initiatives as open-source collaborative drug discovery, R&D treaty and other models need to be strongly pushed for global acceptance<sup>6,12</sup>. New initiatives as the Patent Pool mooted by the UNAIDS<sup>16</sup> have not much headway as despite year-long efforts as only one company - Gilead Sciences has agreed to sublicense its products to generic manufacturers for the production of lower-cost medicines<sup>16</sup>. UMICs have a reason to worry as there are reservations about inclusion of India as a beneficiary of the Patent Pool due to a rethink even among civil society groups as the MSF, CP Tech *etc.* on support to the BASIC countries *vis-à-vis* African countries<sup>11,12</sup>.

HIV/AIDS continues to exemplify the complexities of access to health care for chronic life-threatening diseases where interventions are available but out of reach for large numbers who need them. With the current rigid and unrelenting global IP regimes, the future battles for access to ARVs could well be tough and nasty. International agencies, donors, civil society would do well to create enough policy space for ARV manufacturers from the UMICs to produce and export low priced, quality-assured generic medicines to ensure sustained supply to LICs<sup>6,12</sup>. For LMICs, the journey up the therapeutic ladder from near universal access to 'Getting to Zero' is going to be a long and steep haul.

### K. Satyanarayana

Intellectual Property Rights Unit  
Indian Council of Medical Research  
Department of Health Research  
New Delhi 110 029, India  
Kanikaram\_s@yahoo.com

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