Emerging Retroviral Regimens for the Developing World - “Stop AIDS; Keep the Promise”

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December 1st is observed as the World AIDS Day globally with the 2006 year’s theme being – “Stop AIDS; Keep the Promise – Accountability”. For many years, World AIDS Day was organised by UNAIDS, who chose the theme after consultation with other organisations. However, in 2005 UNAIDS handed over responsibility for World AIDS Day to an independent organisation known as The World AIDS Campaign (WAC). The WAC’s theme for their campaign is “Stop AIDS: Keep the Promise”. This theme is however not specific to World AIDS Day alone but to the work the WAC does throughout the year. It will also remain the focus until 2010. “Keep the Promise” is an appeal to governments and policy makers to ensure they meet the targets they have agreed to in the fight against HIV and AIDS. This change in the way that World AIDS Day is organised has caused some confusion among HIV & AIDS organisations. Some chose to adopt “Stop AIDS; Keep the Promise” as their theme for World AIDS Day 2005. Others, for the first time, picked their own topic for the events they held last year on the 1st of December. Whatever you decide to do for World AIDS Day however, the most important thing is that you follow its basic principals by raising awareness and understanding where you live and by remembering the millions living with HIV or suffering because of AIDS.

The World Trade Organization made a ministerial declaration on the TRIPS Agreement (Trade Related Aspects of Intellectual Property Rights) and public health on 14 November, 2001, in Doha, Qatar. The declaration emphasized that trade rules should support countries’ right to protect public health, particularly “access to medicines for all”. The declaration recognized concerns about the effect of the TRIPS Agreement on prices of medicines, but today new medicines continue to be priced exorbitantly high. The declaration reaffirmed the right of governments to use the flexibilities of TRIPS, but now some countries are using new bilateral and regional trade agreements specifically to remove these flexibilities. The declaration called for a solution that would allow medicines made under compulsory licences to be exported to countries without manufacturing capacity but despite claims that this has been solved, so far no one has managed to do this. In 2005 the G8 meeting and UN World Summit committed to scaling up HIV prevention, treatment, care and support services, “with the aim of coming as close as possible to the goal of universal access to treatment by 2010 for all those who need it.” This promise was reaffirmed by all member states at the UN High level AIDS Meeting in New York on June 2, 2006. “Access to medicines for all can only be reached by starting to keep the promise of the Doha Declaration on TRIPS and Public Health and the production of generic medicines”. Principles that have been implemented from the Doha Declaration that have led to reductions in first line ARVs, for example, have benefited countries. However, the access to generics competition of ARVs and other essential medicines needed by people living with AIDS are under serious threat by additional provisions in bilateral and regional trade agreements, particularly with the US. In addition, newer medicines come from single sources, and without competition, the price of second generation ARVs is prohibitive. Limitations imposed by companies to accessing the lowest price has led to huge discrepancies among developing countries. Middle-income countries are still paying 1.5 times the price paid in low-income countries for first-line ARVs and even up to nine times more, for new ARVs such as Lopinavir (LPV)/Ritonovir (r), according to data published by the World Health Organisation.

Currently the Indian estimates of HIV/AIDS are a matter of debate between the official government and global agencies; still anywhere the figure could be from 6 to 12 million. It may appear that the epidemic may be reaching the plateau but the number of HIV people is rapidly increasing. Soon a large pool of cases will be eligible for retroviral therapy. The Association of Physicians of India (API) came out this year with its own guidelines which are now well accepted. However the ever-changing nature of the virus will mandate regular update and Guideline modifications similar to global guidelines. The guidelines will now be revised every year. The Indian HIV virus is subtype C and AC variant clade, but precious little work is done in this area. Also clade specific drug sensitivity patterns from the Indian populations are scant and the wild type strains in the
Indian cohorts are not well elucidated. However both public and private sectors are treating retroviral disease with low cost options without systematic uniform guidelines and universal lack of resistance testing. This augurs very ominous for we are sitting on an iceberg of an MDR HIV bomb. This could spell disaster for our Antiretroviral (ARV) protocols and organisations like National AID Control Organisation (NACO) which have done excellent work in prevention should immediately rationalize their ill structured free ARV program. The so-called Free ARV program with economic drugs with potential fatal side effects will spell dangers both now and later. Just like MDR TB we shall be soon plagued of MDR HIV. After Tuberculosis (TB) and Multi-Drug Resistant TB (MDR-TB), the Extensively Drug-Resistant TB (XDR-TB) has come to haunt the health officials. The chronic manifestations of TB have recently been defined by the World Health Organization as the condition where the person becomes resistant to even the second line of treatment. This manifestation of TB does not have any cure and the condition is grim for India where there are no official figures to ascertain the reach of XDR-TB. According to the world estimates, two percent of the TB population is suffering from this type and if the same benchmark is applied to India, about two lakh patients may be in the grip of the deadly XDR-TB. Soon after HIV we will have MDR HIV and later XDR HIV if scientists and physicians to not use antiretroviral therapy rationally guided by sound resistance assays.

The real crux of the problem in India is that antiretroviral therapy is neither systematic nor guided and directed by state of the art virology laboratories which have both expertise in viral load and Resistance assays. This will go a long way in establishing region specific resistance pattern and directed chemotherapy. Soon either due to toxicity, cost or resistance we will keep changing the drugs as first line and the therapy cost will escalate as well as it will get more complex and like a game of chess.

Non-PI based nucleoside (NRTI and NNRTI) therapies form the First line of all Indian Anti HIV regimens. Nevirapine (NVP) a drug which can cause fatal Steven Johnson’s syndrome and fatal hepatotoxicity as reported in this issue by Maniar et al form the cornerstone of Free Antiretroviral Therapy (ART) program. Also there is a shift in from nevirapine to Efavirenz (EFV) based regimens. The back bone nukes viz. Zidovudine (AZT) was first replaced by Stavudine (D4t) and now with lipoatrophy rampant this place is taken by Tenofivir. Lamivudine is still there but already Lamivudine resistance like HBV resistance strains are rapidly emerging. Patel et al report a classical NVP based regimen which is low cost with an EFV based regimen and compare their immunological potency. Even as this group report it, the API guideline has Tenofovir as the first line agent for India. This will leave the practising physicians wondering what to follow. Fatalities of NVP are idiosyncratic and need close pharmacovigilance.

Metabolic toxicities both biochemical and morphological are now recognised in India.6,7,8 The stavudine is distinctly notorious amongst Indian causing very disfiguring lipoatrophy while other cause lipodystrophies. Stavudine (D4t) is now relegated as a second line drug by the API but still is used regularly by NACO. Lipodystrophies are higher in the Asian Indians due to higher body fat in the Asian Indians. DEFA studies confirm this fact. In fact diabetes, dyslipidaemias and metabolic syndrome are now seen with most of the First and Second line regimens including and excluding protease inhibitors (PI). The Pune -Ahmedabad group as well as our group is now reporting metabolic and morphological toxicities consistently leading to proactive switching of antiretroviral treatment regimens. Biochemical abnormalities like dyslipidaemias and glucose intolerance are routine and it is now mandatory to regularly test fasting blood glucose and lipids pre and post ARV. Also both diabetes and dyslipidaemia may warrant prompt treatment as both can eventually lead to coronary artery disease which has happened in the west. The ARV treated HIV populations are now vulnerable for Acute Myocardial Infarction (AMI) via the metabolic routes. Also of concern is the high incidence of avascular necrosis of femur, osteopenia, osteoporosis and fracture in the ARV cohorts.9 Soon we will have healthy ARV treated cases which will be vulnerable for CAD, DM, dyslipidaemia, osteoporosis and fractures.

The real need of the hour is not only to develop low cost treatment models for India but they should be guided by virology and toxicity surveillance so that the national guidelines can clearly direct our physicians to use ARV rationally. Both articles from lead groups in retroviral medicine highlights this fact. Maniar et al report the fatal case of Nevirapine (NVP). Patel et al tell us the immunological robustness of Efavirenz (EFV) v/s Nevirapine (NVP) based regimen in Indian clinical cohort.

REFERENCES


