

# HATiP

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## Getting antiretrovirals to where they are needed

"Before the epidemiologists count up the AIDS deaths yet again this year, perhaps it is the time to take more drastic measures before time runs out for yet another three million people."

Julian Fleet, UNAIDS

Drug prices, trade and intellectual property issues are directly related to clinical outcomes in the developing world, according to Julian Fleet, senior adviser, Care and Public Policy, at UNAIDS. Fleet, who was instrumental in establishing the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), described some of the non-medical, non-clinical issues that affect treatment access during a session on the scale up of antiretroviral treatment at the 12<sup>th</sup> Conference on Retroviruses and Opportunistic Infections.

According to Fleet, providing greater access to antiretrovirals (ARVs) requires simultaneous efforts in four areas:

- Rational ARV selection and use (13 ARVs are now on the WHO essential medicines list and others are under consideration)
- Sustainable Financing - The World Bank, the Global Fund, and the US President's Emergency Plan for Aids Relief (PEPFAR) are bringing unprecedented funding for treatment. Some countries such as South Africa, are using local funds to buy ARVs.
- Reliable health and supply systems
- Affordable prices

### Reducing prices

"For resource-constrained governments in poor countries, the purchase price for pharmaceutical compounds directly affects the number of patients that can be put on treatment," said Fleet.

He listed a number of strategies to get more affordable pricing of ARVs and other medicines:

- Differential Pricing - Virtually all of the innovator pharmaceutical companies manufacturing ARVs offer them at lower prices in low-income countries.
- Generic competition has played a key role in making ARVs more affordable, although a few brand name drugs are more competitively priced than generics. Fleet reported "a recent study by the US Accountability Office found that price differences between brand name and generic ARVs could translate into hundreds of millions of dollars of additional expense when considered in terms of the PEPFAR goal of treating two million people with HIV by the end of 2008." PEPFAR doesn't allow its funds to be used to purchase drugs without FDA approval but the recent approval by the FDA of a generic blister-packed ARV combination from South Africa opens up opportunities for PEPFAR to procure generics as well.
- Voluntary licensing (VL) - In South Africa and Kenya generic manufacturers have negotiated voluntary licenses from patent holders and for the local production of ARVs.
- Tariffs and Taxes can account for a significant amount of the overall price of HIV medicines. Many countries have eliminated tariffs and taxes on pharmaceuticals, but very recently, Kenya has imposed a 10% tariff on medicines, including ARVs.
- Local production of ARVs can make a big difference where it is economically feasible (Brazil, China, India and Thailand). Presently eight developing countries are exchanging technology

and expertise for the production of ARVs with a million dollar grant from the Ford Foundation.

### Flexibility in trade-related aspects of intellectual property rights (TRIPS)

International trade and intellectual property rules are intended to promote both innovation and access to pharmaceuticals. There are three key international trade agreements with reference to ARV access:

- TRIPS: TRIPS sets out the minimum patent protection requirements for countries that want to be members of the World Trade Organization (WTO). But while patents in industrialised countries may be necessary to spur innovation, intellectual property rights need to be considered in the context of other social interests, such as the human right to health. To protect patent rights, TRIPS contains a provision in Article 31 for compulsory licensing. Compulsory licensing allows a government to authorize the production, sale and import of generic medicines that would otherwise be precluded if there were a valid patent in that country. In situations of a "national emergency" or "circumstances of extreme urgency," countries have the right to issue compulsory licenses to provide ARVs for free or at no commercial gain through their public health systems. Countries like Brazil, Ethiopia, Senegal, South Africa, India and Thailand could authorise the use of generics, not withstanding local patents, should they so chose.
- The Doha Declaration on Trips and Public Health (negotiated in Doha, Qatar, November 2001): The Doha declaration reaffirms the primacy of public health in the application of international trade rules and takes it a little bit further. It allows the least developed countries not to offer any patent protection in the pharmaceutical sector until 2016.
- The August 30, 2003, WTO decision: Expands access rights by allowing the export of generic drugs to countries without their own manufacturing capacity.

### Limited uptake of TRIPS flexibility

But to date, few countries have taken advantage of these public health safeguards.

"This raises questions about whether they go far enough, whether something isn't wrong that countries aren't using them," said Fleet.

There are some exceptions. Zimbabwe, Malaysia, Mozambique and Zambia have issued licenses for the use of patented products in their countries. Some prospective exporting countries like Canada and Norway have amended their national laws to help supply generics to poor countries.

But a number of regional and bi-lateral free trade agreements could limit access to generics as some of the provisions in these agreements actually undermine rights granted under TRIPS.

### WHO prequalification & concerns about quality

In addition to more affordable pricing, donors and national governments want to be certain that what they are buying meets accepted standards of quality, safety and efficacy. National drug regulatory authorities are responsible for regulating the quality of pharmaceuticals in their respective countries - however, developing countries have variable capacity to ensure the quality of imported medicines. To assist regulatory efforts in resource-limited countries,

WHO with UNICEF have established a limited quality assessment programme known as the Prequalification project.

To be prequalified, generic drugs must:

- 1 Contain the same active ingredients as the innovator drug
- 2 Be identical in strength, dosage form and route of administration
- 3 Have the same use indications
- 4 Be bio-equivalent
- 5 Meet the same batch requirements for identity, strength, purity and quality
- 6 Be manufactured under the same strict standards of GMP required for innovator products

To date around 100 HIV related pharmaceutical products have been approved, the majority of which are antiretroviral formulations. About half are from originator companies and half from generic manufacturers.

But recently there have been concerns about the quality of generic ARVs, largely because of the removal of a number of generic ARVs from the WHO quality approved lists.

WHO requires that a generic drug meet strict criteria including bioequivalence studies in humans. A number of Indian generics manufacturers retained independent contract research organizations (CRO) to do their bioequivalence studies and last year some WHO inspectors made some site visits to these CROs and found discrepancies in the bioequivalence data. This prompted WHO to remove ARVs from one manufacturer from its list and subsequently two other manufacturers voluntarily withdrew some of their products.

See:

<http://www.aidsmap.com/en/news/2F72C8D5-3F24-4B7B-BE71-68B3518F83AC.asp> ,

<http://www.aidsmap.com/en/news/52ADD62D-4FA3-4E7A-A3ED-980FC68ABF20.asp> ,

<http://www.aidsmap.com/en/news/8C9E93F2-8B01-4EBC-8E1C-50FDF758EFDC.asp> ,

<http://www.aidsmap.com/en/news/62C85222-7FE2-4029-A64E-87134D989FA8.asp>

"There has been a lot of misinformation swirling around quality issues in the last couple of months," said Fleet. The withdrawal of these products from prequalification "caused confusion and worries for patients and undermined public confidence in generic medicines and perhaps ARVs generally, but those of you who work in the pharmaceutical industry or in drug regulatory agencies will know it didn't mean that the products were substandard or deadly as in some of the spin that has appeared in the media. It meant that there were problems with the data. Some of these bioequivalence studies have been rerun, and one of these products, a fixed dose combination, has already been returned to the WHO list. Arguably the controversy around this issue did not come because the prequalification process was flawed but because it was more rigorous. Carrying out these site visits to CROs went beyond what was required even then by some European regulatory agencies."

## Current coverage and challenges to expanding access

Fleet presented the following estimate of the current coverage of antiretroviral treatment before describing obstacles limiting expansion of access.

ARV therapy coverage in developing and transitional countries, December 2004

WHO Region Number of People Receiving ARV Therapy (Range)  
Estimated need Coverage

Africa 310 000 (270 000-350 000) 4 000 000 8%

Americas 275 000 (260 000-290 000) 425 000 65%

Europe

(including

Eastern Europe,

Central Asia) 15 000 (13 000-17 000) 150 000 10%

Eastern

Mediterranean 4 000 (2 000-6 000) 77 500 5%

South-East Asia 85 000 (70 000-100 000) 950 000 9%

Western Pacific 17 000 (15 000-19 000) 200 000 9%

All WHO regions 700 000 (630 000-780 000) 5.8 million 12%

## Challenges - access for children

- Pediatric formulations: In 2004, more than 500,000 children died of AIDS and few children globally are currently able to access treatment, largely because of problems diagnosing problems soon enough, lack of suitable formulations, and insufficient advocacy on behalf of children with HIV.
- Affordability of antiretrovirals in middle-income countries and for second-line regimens: The Global Fund recently issued its Purchase Price Report, which is the first time that a significant amount of real transactions data for the purchase of ARVs has been made public. The report is primarily based upon procurement transactions by UNICEF and the international dispensary organization, IDA. It suggests that prices in low income countries are broadly consistent with the lowest possible price mentioned above. But in middle-income countries, prices varied considerably and were often very high, a levels that seem unreasonable given the income levels of these countries. Prices of second-line regimens, in some cases, elements of second line regimens, in particular, Kaletra, are also high.

"Sometimes, even for low-income countries, there is a disconnect from global discourse and the ability for buyers to procure product at these prices on the ground," Fleet added. Additionally, generic companies, sometimes even small research companies do not always have sufficient international infrastructure to register their drugs throughout the developing world where they are needed.

(During the question and answer session following Fleet's lecture, Daniel Berman of MSF noted that Gilead Sciences, maker of tenofovir, emtricitabine and the co-formulation Truvada has not registered its products in most developing countries, that Gilead has informed MSF that it only intends to pursue registration in countries that receive PEPFAR funding.)

- Procurement and supply systems in countries: Improving procurement involves more than just affordable prices. Supply distribution systems need to be strengthened in almost all income-poor countries, from inventory tracking and ordering, to warehousing and security of supplies.
- Equity for women, children, underserved populations
- National financing systems and fees for service: The inability of patients to pay for treatment remains a barrier in many countries. In some countries, HIV treatment is increasingly free to patients at the point of delivery but in not in all.

Fleet noted that recently, more than 500 eminent scientists, and economists, public health experts launched the Free by Five Declaration in which they make a compelling case for universal free access to ARVs and a minimum package of care.

- Stigma & Discrimination
- Lack of HIV testing Services
- Human Resource Crisis: Finally, human resources in the health and social sectors in the hard hit countries are in a state of crisis. Africa has nearly 25% of the global burden of disease, 69% of the treatment burden and yet it has less than 2% of the world's healthcare workers. The region with the greatest need has the fewest available health workers and AIDS is taking its toll among them.

"In Mozambique, over 20% of the staff in a hospital we visited had a reduced workload," said Fleet. "The human resource utilization in many resource-poor countries is characterized by public sector spending caps, by the damaging impact of immigration to greener-backed pastures of industrialized country health services and by poor pay and conditions at home."

### Developing countries are actually undeveloping

"AIDS is a threat to human security in many countries," concluded Fleet. "My boss, Peter Piot, said earlier this month at a speech at the London School of Economics that many developing countries are no longer developing, they are undeveloping on account of AIDS. When a million refugees show up on a border, most heads of state take notice. When natural disasters strike, like the recent Tsunami, international relief workers stream into the region, as they should - but a dramatic exceptional response for AIDS has not yet been mounted."

### Reference

Fleet J. *Getting Antiretrovirals to Where They're Needed*. 12<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, Boston, abstract 4, 2005.

## about HATIP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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