TWO PILLS A DAY SAVING LIVES: FIXED-DOSE COMBINATIONS (FDCS) OF ANTIRETROVIRAL DRUGS

MSF BRIEFING NOTE

If recent initiatives to scale up antiretroviral (ARV) treatment in developing countries are to succeed in reaching the poorest and most vulnerable people at the community level, several key issues must be addressed. Chief among these is the need to simplify and standardize treatment protocols so that people with HIV/AIDS can access treatment, even in areas where there are few hospitals, few doctors, and few laboratories[1].

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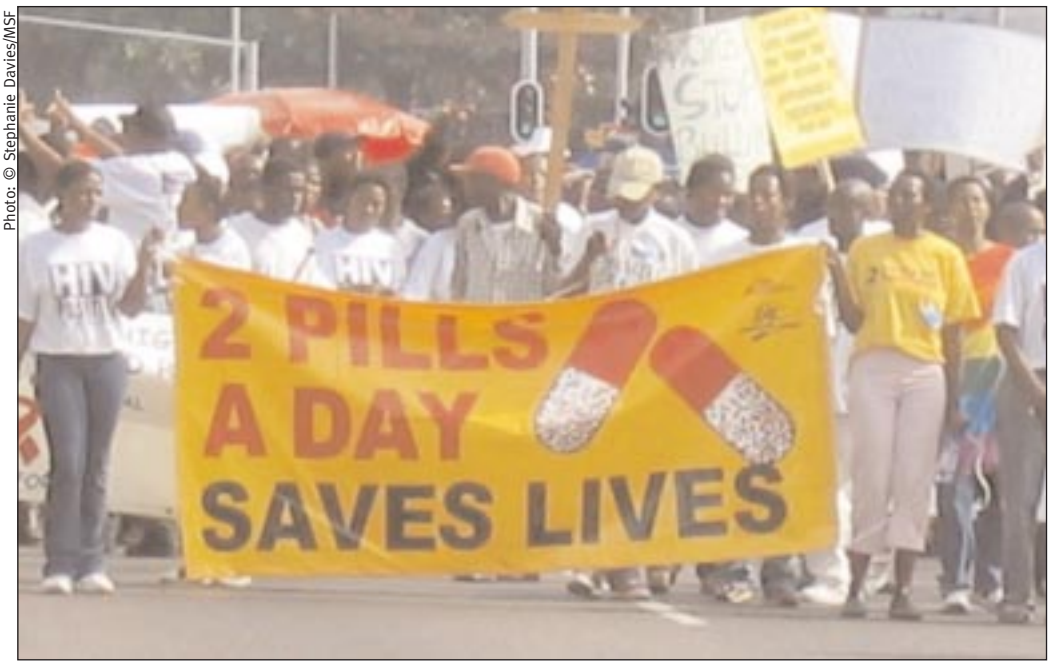

Advocating for FDCs during a march in Durban, August 2003

Fixed-dose combinations (FDCs) of ARVs – that is, pills containing two or three AIDS drugs in one tablet – are widely recognized as being a key element in efforts to scale up AIDS treatment in developing countries. FDCs are recommended in the World Health Organization (WHO) treatment guidelines and several generic FDCs have been pre-qualified by WHO (see overleaf).

Based on its own experience delivering ARV treatment in resource-poor settings, Médecins Sans Frontières (MSF) has become a strong advocate of triple FDCs. MSF is currently providing ARV treatment to more than 11,000 people living with HIV/AIDS in over 20 countries in Africa, Asia, Latin America, and Eastern Europe, and expects the total number of patients on ARVs to reach 25,000 in 25 countries by the end of 2004.

Advantages of FDCs

Compared to ARV drugs used as separate products, triple FDCs have clear advantages, such as:

- **Ease of use:** Patients need to take fewer tablets containing the full triple therapy: one in the morning, one in the evening. This helps adherence and leads to better clinical results. This has been widely documented with, for example, hypertension drugs[2].

- **Reduced risk of drug resistance:** Minimizing the pill burden reduces the risk of resistance not only because it facilitates adherence, but also because it limits the risk of taking only one or two of the three drugs.

One pill, many patents

With the exception of GlaxoSmithKline's (GSK) Trizivir (AZT/3TC/ABC), which combines three GSK products but is not included on the WHO list of recommended first-line triple therapies, no originator company currently produces triple FDCs.

All other existing triple FDCs combine drugs the patents of which are held by different originator companies. In countries where one or more of the drugs contained in an FDC are under patent, governments may need to make full use of the flexibilities in their patent law confirmed by the 2001 Doha Declaration to issue a compulsory license, which would enable the production, import, sale and use of the product.

Governments may find themselves under pressure from originator companies and other governments close to these, such as the US, to avoid FDCs produced by generic companies. But since proprietary companies do not provide this user-friendly formulation at an affordable price, developing country governments have begun buying FDCs from generic producers.

Advantages of FDCs continued

■ **Competitive prices**: These pills are generally more affordable than separate products; MSF currently pays about US$300 per patient per year for first line triple FDCs, and the price is expected to drop in the short-term to as little as US$140 or less[3].

■ **Ease pressure on supply chain**: Managing drug storage and distribution is easier when there is a smaller range of products to supply. This saves costs and helps avoid shortages of products.

	d4T 40mg/3TC/NVP FDC from generic companies	d4T 40mg + 3TC + NVP Three separate products from originator companies
PRICE	**US$ 270/year***	US$ 562/year*
PILL BURDEN	**2 pills a day**	6 pills a day

** Best prices (source: "Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries"; 5th edition, MSF, December 1st 2003)*

The triple FDCs of stavudine/lamivudine/nevirapine (d4T/3TC/NVP), which is one of the regimens recommended for first-line treatment by WHO[4], is the one most widely prescribed in MSF projects. Double FDCs like d4T/3TC or AZT/3TC are also needed when efavirenz (EFV)-containing first-line regimens are chosen, since there are no EFV-based triple FDCs available to date. Over 50% of patients in MSF programs are on the triple FDC of d4T/3TC/NVP, and over 70% of newly enrolled patients start on this combination. Clinical outcomes and adherence rates in MSF ARV programs are encouraging.

Although existing FDCs must be made available more widely as a matter of urgency because they are effective and save lives, there must be active efforts to develop new and adapted tools that are better tolerated, easier to use, and even more potent.

Pre-qualification of FDCs

Pre-qualification of ARVs by WHO has become an essential tool for drug regulatory authorities and purchasers. Evaluations carried out by the WHO pre-qualification team provide assurance that international quality standards have been applied. The WHO pre-qualification process is based on international standards, guidelines and norms that allow quality and safety assessment of medicines. These standards have been developed and approved by the WHO Expert Committee system involving all WHO member states and WHO governing bodies. The assessments include the evaluation of: active pharmaceutical ingredients (API), specifi-cations of and methods used in

"What clearly makes the best sense, if 3 by 5[5] is to succeed, is the WHO pre-qualified triple fixed-dose combination; one pill taken twice a day. The international community...has bestowed upon WHO the responsibility for approving and providing guidance in safety and efficacy for a vast array of medications. They do so with consummate science, fidelity and integrity."

Stephen Lewis, UN Special Envoy for HIV/AIDS in Africa
(Keynote Address at the 11th Annual Conference on Retroviruses and Opportunistic Infections, San Francisco, February 8-11th 2004)

analysing APIs and finished products, stability and bio-equivalence data, compliance of the manufacturing site to Good Manufacturing Practises (GMP) and the country's drug registration situation. All references used are available publicly on the WHO website (http://mednet3.who.int/prequal/hiv/hivdefault.shtml).

The WHO pre-qualification project evaluates both generic and originator products. In the case of generic drugs, WHO standards for multi-source drugs are used for both dossier assessment (including bio-equivalence studies) and Good Manufacturing Inspections.

Evaluations are carried out by a group of external experts providing support and expertise to a core team at WHO. The team assessing dossiers consists of representatives appointed by national drug regulatory authorities (NDRAs) from a wide range of countries including Brazil, Canada, Denmark, Estonia, Finland, France, Germany, Hungary, Indonesia, Malaysia, Philippines, Spain, South Africa, Sweden, Switzerland, Tanzania and Zimbabwe.

Manufacturing sites are inspected by WHO experts and members of a well-established inspector network (e.g. Pharmaceutical Inspection Convention Scheme countries) and experts from countries like Canada, France, Italy, Switzerland and the Netherlands.

The following first-line regimen drugs recommended in WHO guidelines have been pre-qualified by the WHO (latest updated list of January 28th 2004):

Three triple FDCs:
- d4T 40mg/3TC/NVP from Cipla (Triomune 40)
- d4T 30mg/3TC/NVP from Ranbaxy (Triviro LNS 30)
- d4T 40mg/3TC/NVP from Ranbaxy (Triviro LNS 40)

Six double FDCs:
- d4T 40mg/3TC from Ranbaxy (Coviro LS 40)
- d4T 30mg/3TC from Ranbaxy (Coviro LS 30)
- 3TC/AZT from Ranbaxy (Avocomb)
- 3TC/AZT from Cipla (Duovir)
- 3TC/AZT from GSK (Combivir)
- 3TC/AZT from Hetero (Zidolam).

The Role of National Drug Regulatory Authorities

The final responsibility for drug evaluation and approval is in the hands of the NDRA of each country, not international organisations or donors. It is the NDRA's role to guarantee the quality, safety and efficacy of the drugs it allows on the market, as well as their ongoing quality assurance and pharmacovigilance. Depending on their human and financial resources, and considering the difficulty to assess new products, countries can either conduct their own dossier assessment and GMP inspection or rely on the WHO pre-qualification list to decide whether or not to grant national approval.

Some countries have put in place fast-track registration procedures for products that are included on the WHO pre-qualification list.

The d4T/3TC/NVP triple FDCs have to date been registered by NDRAs in Burundi, Central African Republic, Cameroon, Congo Brazzaville, Ghana, Guinea, Honduras, India, Ivory Coast, Kenya, Liberia, Macao, Malawi, Nigeria, Peru, Sierra Leone, Tanzania, Uganda, Ukraine, Zambia and Zimbabwe.

The AZT/3TC double FDCs are now registered in more than 40 developing countries including Brazil, South Africa, Uganda, Ukraine, Burundi and India.

The d4T/3TC double FDCs are registered in Burundi, Cameroon, Congo Brazzaville, Gabon, Honduras, India, Ivory Coast, Liberia, Malawi, Macau, Nigeria, Sierra Leone and Zimbabwe.

"My health has improved drastically, tremendously, as has my wife's. I don't get the coughs and the infections I was getting. The bad feeling of taking too many pills is not there. The mere fact that you have to take just one pill in the morning and one in the evening is fantastic."

James Kamau, beneficiary of MSF ARV treatment program in Kenya

[1] ARV Simplification for High-Prevalence Countries. Report from a workshop organised by MSF, Nairobi, September 20th 2003.

[2] http://www.medscape.com/viewarticle/465716

[3] In October 2003, the Clinton Foundation announced that it had negotiated prices with several generic companies and producers of raw materials, making the cheapest available announced price for triple therapy as low as US$140 per person per year (for the fixed-dose combination of d4T40mg/3TC/NVP).

[4] WHO treatment guidelines published on December 1st, 2003 recommend one of the following as the preferred first-line regimen: d4T/3TC/NVP, d4T/3TC/EFV, AZT/3TC/NVP, or AZT/3TC/EFV. http://www.who.int/3by5/publications/guidelines/en/arvguidelines.pdf

[5] The initiative, launched by the World Health Organization (WHO) in 2003, aiming to put three million people in developing countries under antiretroviral (ARV) treatment by the year 2005.

Premature, avoidable deaths

- Over 40 million people are living with HIV/AIDS in developing countries.
- Of the more than six million people in urgent clinical need of antiretroviral (ARV) treatment, only 400,000 have access to it, and one-third of them live in one country, Brazil.
- An estimated 8,000 people die each day of AIDS-related complications.

MSF supports the professional evaluations carried out by the WHO pre-qualification team. The project has been supported by other UN agencies including UNICEF, UNAIDS and UNFPA as well as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Columbia University MTCT-Plus Initiative and the World Bank. At a recent WHO meeting (Geneva, December 15–17th, 2003), the project was lauded by the participants including experts from the US Food and Drug Administration (FDA), the Australian Therapeutic Goods Administration (TGA) and Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS).

MSF is an international medical humanitarian organization providing assistance through over 500 medical relief programs in 80 countries worldwide. MSF was awarded the 1999 Nobel Peace Prize.

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