

Briefing Note

GILEAD'S TENOFOVIR 'ACCESS PROGRAM' FOR DEVELOPING COUNTRIES

*Doctors Without Borders/Médecins Sans Frontières (MSF)
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Doctors Without Borders/Médecins Sans Frontières (MSF) is alarmed at the lack of availability of a key antiretroviral to treat HIV/AIDS, Gilead Science's tenofovir disoproxil fumarate (TDF), marketed as Viread®. TDF is emerging as an important option of antiretroviral treatment for both patients starting therapy for the first time, and those that require access to newer drugs as they develop resistance to prior first-line regimens. Although Gilead claims that it offers this vital drug at a preferential price in 97 low-income countries, the reality is that TDF is registered for use in only six of these. The only way to get access to TDF in many countries is through a burdensome and resource-intensive set of procedures that Gilead imposes. In short, Gilead's Access Program promises access to TDF for millions of people living with AIDS in developing countries, but fails to deliver.

Because there are fewer known side effects associated with the use of TDF in adults, it is commonly prescribed as part of a first-line treatment regimen in the US and Europe, where the drug is widely available. The updated World Health Organization (WHO) treatment guidelines recognize the importance of TDF and recommend TDF for first and second-line regimens.¹ MSF would like to be able to provide TDF to some of its patients, but accessing TDF in the countries in which MSF operates has proven very difficult and sometimes impossible. Because Gilead is the sole producer of TDF and no generic versions have been internationally validated, MSF and others are dependent on the willingness of the company to make this urgently needed drug widely available.

GILEAD'S PROMISES

In December 2002², Gilead first announced its Access Program for TDF, which was supposed to be available in 68 developing countries at preferential prices. The preferential price for TDF has been \$208 per patient per year since August 2005³, which represents a significant discount compared to prices in developed countries, e.g. in Spain the drug costs \$4,934 per year. In March 2005⁴, the number of countries benefiting from the reduced prices was extended from 68 to 97, but some middle-income countries like Brazil, China and Thailand, are still not included.

THE REALITY NEARLY THREE YEARS LATER:

Price Reductions on Paper Only – TDF Remains Unavailable

The availability of a drug in a particular country depends on several factors. The most direct means of assuring availability is for a company to file for registration. This means submitting required safety and efficacy data to national drug regulatory authorities. The authority considers the submission and decides whether or not to register the drug. If a drug is not registered in a country, special authorization to use and/or to import a drug can sometimes be requested. Rules governing this process vary widely and are often very complex and only available to institutions, not individual doctors.

¹ Summary is available for consultation at <http://www.who.int/3by5/mediacentre/news51/en/>

² Gilead announcement available at http://www.gilead.com/wt/sec/pr_1040081128

³ Gilead announcement available at http://www.gilead.com/wt/sec/pr_750303

⁴ Gilead announcement available at http://www.gilead.com/wt/sec/pr_686106

In the case of TDF, Gilead has failed to file for registration in most of the countries eligible for its Access Program. As of October 2005, TDF was registered in only six of 97 eligible countries according to the WHO/AMDS registration database.⁵ It is possible that additional countries have registered TDF since October 2005, but MSF direct experience is that the drug is not registered in most of the countries where we work.⁶

Delays in registration can be caused by the national drug regulatory authorities that review a company's file, but if a company does not fulfill filing criteria or does not submit its file for consideration, national authorities cannot be blamed for delays. Other companies have managed to overcome these delays. Bristol-Myers Squibb/Merck, the producer of efavirenz, which is marketed as Sustiva® and was registered in the US in 2002, has registered the drug in 49 developing countries, and registration is pending in a further eleven countries. Similarly, ddI enteric-coated, marketed as Videx EC® by Bristol-Myers Squibb and registered in the US in 2002, is now registered in 24 countries and pending in a further thirteen, out of 51 countries on the company's access list. Four years after the launch of Abbott Laboratory's Access Program for lopinavir/ritonavir, marketed as Kaletra®, the original formulation of this drug was registered or pending in all 68 of the countries eligible for its access program.

Getting TDF to Southern Africa: Jumping Through Hoops and Fighting Stock-outs

Because of the need for TDF, MSF has tried to overcome the registration barrier in South Africa. In its projects there, MSF has diagnosed a significant level of hyperlactemia and lactic acidosis due to toxicities associated with d4T – a drug included in MSF's standard first-line regimen. Patients that experience these side effects need to be taken off of d4T and ideally placed on a TDF-based regimen. Gilead did not complete its filing for TDF in South Africa until November 2005. That is, their request to market the drug in South Africa was made three years after they announced that they would offer discounts on the drug in developing countries.

To obtain TDF for patients that need it in South Africa, MSF has been procuring TDF directly from Gilead in California. But this procedure is burdensome, involving extensive paperwork that requests information on the history of the treatment program, source of funding, catchment area, the type and number of employees, protocols initiating treatment, the first and second-line regimens used, laboratory monitoring and other program details. Additionally, due to South Africa's regulations, MSF must apply for special authorization to use TDF on a patient-by-patient basis. The significant time required to overcome the lack of registration in South Africa makes the use of TDF impossible for most care-providers.

Although special authorization can serve as an intermediate measure to access TDF and other drugs, there can be a risk of stock-outs associated with this procedure. In South Africa and Zimbabwe, the special authorization hurdles make it impossible to store a buffer stock, a standard operating procedure, in case there are drug delivery delays. This process also introduces the possibility of delay at many levels because of the complexity of the supply chain.

As a result, MSF's projects in both countries have faced the risk of stock-outs. In December 2005, the project in South Africa had only two bottles of TDF at one point due to delivery delays from Gilead. The project in Zimbabwe has had to borrow TDF from Zambia at twice the price. Similarly, in Malawi, MSF's project has requested special authorization to use TDF and orders the drug through MSF procurement centers in Europe, but it takes months for the drug to be processed for importation. There is little hope of establishing a more stable supply of TDF in the short-term, as Gilead has still not submitted its file for registration in Zimbabwe or Malawi.

⁵ Out of the 97 countries listed as eligible for Gilead's Access Program, according to the WHO <http://ftp.who.int/htm/AMDS/drugsdatabase.pdf>, TDF is registered only in the Bahamas, Gambia, Kenya, Rwanda, Uganda and Zambia.

⁶ MSF is providing ART to over 57,000 patients in over 50 projects in a total of 29 countries: Angola, Benin, Burkina Faso, Cambodia, Cameroon, China, Congo Brazzaville, Democratic Republic of Congo, Ecuador, Ethiopia, Guatemala, Guinea, Honduras, Indonesia, Kenya, Laos, Malawi, Mozambique, Myanmar, Nigeria, Peru, Rwanda, South Africa, Tanzania, Thailand, Uganda, Ukraine, Zambia and Zimbabwe.

Gilead's Deal with Aspen Pharmacare: An Additional Two-Year Delay?

Gilead has signed an exclusive marketing and distribution agreement with the South African pharmaceutical company Aspen Pharmacare for TDF. Based on this agreement, Aspen Pharmacare is responsible for registering TDF in the 97 countries in the Access Program and producing and distributing TDF for these countries. However, registration approval in South Africa for Aspen's version of TDF is not expected until mid-2007, and registration in, and distribution to, other countries will not be possible until Aspen receives this approval in South Africa. The result could be several more years without TDF in developing countries unless Gilead takes responsibility for making TDF available now.

Inclusion on WHO Essential Medicines List: Gilead Doesn't Want Essential Info Published

Gilead requested that TDF be considered for inclusion on the WHO's Essential Medicines List [EML]. However, TDF was not included in the 2005 revision of the EML because Gilead refused to authorize WHO to publish some of the data in their submission on the WHO website. Publication of these data is standard operating procedure and to our knowledge no other companies have ever refused to comply with this request

TURNING PROMISES ON PAPER INTO PILLS FOR PATIENTS

MSF urges Gilead to put an end to its empty promises and turn its virtual 'Access Program' into a reality for the millions of patients that would benefit from TDF. Gilead needs to immediately:

- **File for registration in all of the countries eligible for the reduced price;**
- **Cooperate with the WHO so that TDF can be added to the Essential Medicines List; and**
- **Work with countries to make TDF easily available while registration applications are being considered.**

NOTE:

Since Gilead has the same access policies for all its AIDS medicines, the same barriers exist to accessing the fixed-dose combination tenofovir disoproxil fumarate/emtricitabine (Truvada®). MSF is concerned that these barriers to access will exist for any new AIDS medicines marketed by Gilead.

BACKGROUND

Tenofovir disoproxil fumarate (TDF) is the first nucleotide reverse transcriptase inhibitor developed. In 1986, a Czech academic institution (the Institute of Organic Chemistry and Biochemistry or Ceskoslovenska Akademie ved) patented tenofovir after discovering some antiviral activity. In 1991, Gilead Sciences, Inc. and the Czech academic institution signed a license to allow Gilead to market TDF. In 1996, *in vivo* antiviral activity of TDF was demonstrated. Gilead developed a salt of tenofovir (disoproxil fumarate), which allowed for oral administration and received a patent for this formulation in 1997. In the late 1990s, Gilead conducted clinical studies on TDF for the treatment of AIDS.

In 2001, tenofovir disoproxil fumarate (TDF) was approved by the US Food and Drug Administration and marketed in the US as Viread®. It is indicated with other antiretroviral medicines for the treatment of HIV-1 infection in adults over 18 years of age. In 2002, TDF was authorized for marketing in Europe. TDF is available in 300mg tablets and in a fixed-dose combination tablet with emtricitabine (FTC) 200mg, marketed as Truvada®. A FDC combining FTC/TDF and EFV is being developed and may become available in the US soon.

There is no pediatric formulation of TDF. There are some pharmacokinetic data on paediatric formulations, however experts believe that there is more toxicity in children, e.g. bone malformation/maturation problems (WHO/UNICEF Pediatric consultation Nov 2004 and Advisory Committee on Safety of Medicinal Products, Oct 2004).

Patent Status:

There are currently no internationally validated generic sources of TDF, and patents on the drug could block the development of generic versions in some countries. Although Gilead has said that it will not enforce its patent in countries that are included in its Access Program, there is little capacity for generic production in these countries. They would depend on generic versions produced in countries such as Brazil, India and China, which are not included in the Access Program. TDF is patented in Brazil and Gilead applied for a patent in India. These patent barriers could effectively block generic competition for years.

MSF and HIV/AIDS Treatment:

MSF began providing HIV/AIDS prevention and care services in the 1990s. In 2000, MSF introduced antiretroviral therapy in its projects in Thailand, South Africa, and Cameroon. Currently, MSF provides antiretroviral therapy to nearly 60,000 patients in 50 projects in 29 countries.

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