

TENOFOVIR DISOPROXIL FUMARATE (TDF)

GENERAL INFORMATION

- Therapeutic class: Nucleotide reverse transcriptase inhibitor (NtRTI).
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.²⁴
- World sales of originator product: 2010: US\$ 732 million; 2009: \$667 million; 2008: \$621 million; 2007: \$613 million; 2006: \$689 million; 2005: \$778 million; 2004: \$783 million.^{128, 129, 130, 131, 132, 278, 279}
- Patents: The basic patent on tenofovir was applied for by the Academy of Sciences of the former Czechoslovakia in 1986. It has now expired in most countries.²⁸⁰ Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997²⁸¹ and to the fumarate salt of tenofovir disoproxil in 1998.²⁸² These are due to expire in 2017 and 2018, respectively. In addition, Gilead and BMS have applied for patents on fixed-dose combinations of TDF/FTC and TDF/FTC/EFV which will not expire before 2024 and 2026 respectively,^{120, 121} in countries where granted.
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.^{6, 22}
- Originator company and product brand name: Gilead, Viread.
- First approval by U.S. Food and Drug Administration (FDA): October 2001.²³

PRICE INFORMATION

Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

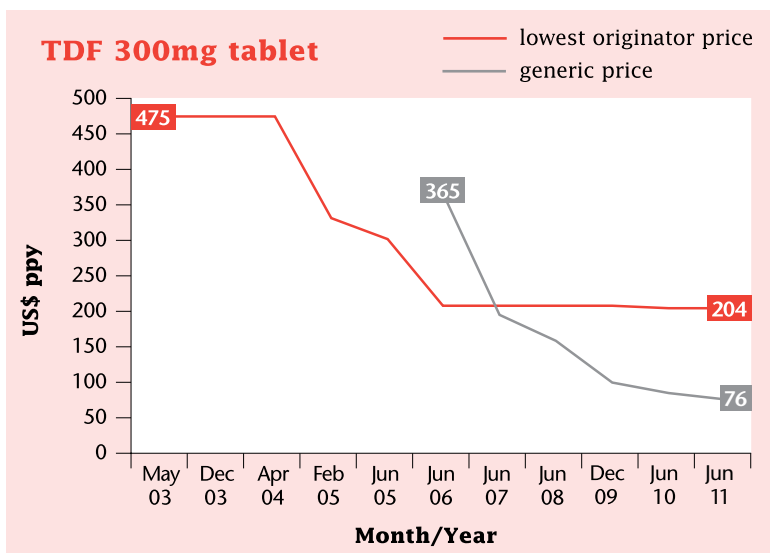
	Daily dose	Gilead		Aspen	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)	Strides
		Category 1 countries	Category 2 countries							
Who can access this price?		See annex 2 & annex 9			See annex 2					
TDF 300mg tablet	1	204 (0.559)	360 (0.986)	87 (0.237)	88 (0.242)	83 (0.227)	103 (0.283)	76 (0.208)	97 (0.267)	79 (0.217)

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

Evolution of the lowest price quoted for developing countries since 2003:

As of May 2011, five generic sources of TDF 300mg tablet were quality-assured by US FDA and WHO prequalification. The one with the lowest price is shown here.

Since 2003, the originator price has decreased by 57%, while generic prices have dropped by 79%.



Continued overleaf ❖

SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T has played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which is one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.⁷

TDF is also used in second-line treatment as the NRTI backbone – in combination with either lamivudine (3TC) or emtricitabine (FTC), to which a boosted protease inhibitor (PI) should be added – if d4T or AZT have been used in first-line treatment.

TDF is also active against the hepatitis B virus (HBV) and therefore plays an important role in co-infected patients. The latest WHO 2010 guidelines recommend using TDF with either FTC- or 3TC-containing antiretroviral

regimens in all HIV/HBV co-infected individuals needing treatment.⁷

Patents

Gilead has applied for patents related to TDF in many developing countries, including Brazil, India and China.

Thanks to generic production that started in India in 2005 and to the patent oppositions filed by civil society groups in 2006²⁸³ and 2007²⁸⁴ to safeguard production, the price of TDF fell dramatically between 2005 and 2010. In a major victory for access to medicines, the Indian patent office rejected in September 2009 several patent applications, relating to the pro-drug,²⁸⁵ the fumarate form²⁸⁶ and the intermediate,²⁸⁷ and the use of TDF in combination with FTC and EFV. The patents were rejected on the grounds that they lack an inventive step – they do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law.^{285, 286, 287} Further, combinations of known molecules are not patentable under Indian patent law.²⁸⁸

Nevertheless, divisional applications have already been filed by Gilead for key applications covering pro-drug²⁸⁹ and fumarate salt²⁹⁰ and the combinations of TDF with FTC, EFV and LPV/r.^{290, 291} These warrant additional pre-grant oppositions.

In 2006, while the oppositions by members of Indian and Brazilian civil society to the patent applications were still pending, Gilead signed voluntary licensing (VL) agreements with key generic manufacturers in India and one in South Africa. One generic manufacturer – Cipla – did not accept the VL and instead opted to file patent oppositions to protect the manufacture and availability of

its generic TDF – both domestically and for export.

Under the terms of the VL, Gilead and participating Indian manufacturers have divided up developing country markets for TDF and TDF-based fixed-dose combinations, whereby the generic manufacturers like Matrix could only export to a limited pre-defined list of countries, against the payment of a 5% royalty.¹³⁹ The VLs also include geographic market limitations. Participating manufacturers are unable to supply countries such as Brazil, Sri Lanka and China, leaving these countries unable to benefit from competitive prices or to improve access. Following negotiations with Gilead, Brazil is today paying \$715 ppy for TDF. This is over nine times the best available generic price.⁷⁶

In Brazil, civil society groups filed an opposition contesting Gilead's patent application for TDF in December 2006.²⁹² In April 2008, the government declared TDF as a medicine of public interest for priority examination purposes, and in September 2008, the Brazilian patent office published the patent rejection. However, in January 2010, Gilead launched a legal challenge against the patent office's decision to reject the patent. Gilead also requested a divisional patent, which was opposed by civil society groups,²⁹³ and in another victory for access to medicines, rejected in May 2011.²⁹⁴

In February 2011, the Brazilian government announced the beginning of local production of TDF through a partnership between Brazilian public and private manufacturers.²⁹⁵

Continued above right ❖

☞ *Continued from below left*

The access challenges Brazil experiences today will be faced by other developing countries in coming years, and Brazil's actions to improve the accessibility and affordability of TDF¹⁴⁷ and other newer medications will have wider implications for all developing countries. Price reductions achieved by Brazil will set a target price for other countries, especially for other middle- and lower middle-income countries.

The size of Brazil's cohort is also critical. With approximately 64,000 people taking TDF,¹⁴⁷ the country could stimulate an international generic market where prices are reduced through competition and economies of scale.

Paediatrics

In March 2010, TDF was approved by US FDA for use in adolescents older than 12 years old and weighing more than 35kg.²⁹⁷ Gilead's Phase II trial involving children (aged between two and 12 years), using an oral powder formulation is still on-going. Such data, provided appropriate formulations are developed, will be crucial to address the urgent needs of this paediatric population. Having safety and efficacy data in paediatric populations would enable children to stay longer on the same treatment regimen, and would facilitate harmonisation with adult regimens, as TDF-based first-line

regimens are also the preferred option for adults.

In March 2009, US FDA granted TDF an Orphan Drug designation for treatment of paediatric HIV infections.²⁹⁸ Gilead is now entitled to seven years of marketing exclusivity for the designated paediatric indication, tax credits for clinical research and can apply for grants to defray the cost of clinical trials.²⁹⁹