

TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE/EFAVIRENZ (TDF/FTC/EFV)

GENERAL INFORMATION

- Therapeutic class: One NtRTI + one NRTI + one NNRTI in a triple fixed-dose combination.
- WHO guidelines: Indicated for first-line for adults and adolescents.⁶
- Originator companies and product brand name: Gilead/Bristol-Myers Squibb/Merck, Atripla.
- First approval by U.S. Food and Drug Administration (FDA): July 2006.²³
- WHO Model List of Essential Medicines (EML): Included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.²⁴
- World sales of originator product: 2010: US\$ 2.927 billion; 2009: \$2.382 billion; 2008: \$1.572 billion; 2007: \$903 million; 2006: \$164 million (the product entered the market in the third quarter of the year).^{128, 132}
- Patents: Most patents related to tenofovir (TDF), emtricitabine (FTC), TDF/FTC or to efavirenz (EFV) also affect this combination. In addition, Gilead and BMS jointly applied for patents specifically related to this combination in 2006,¹²¹ which would last until 2026. Gilead pays royalties to BMS (and consequently Merck) for the EFV portion, originally owned by Dupont Merck, which was subsequently acquired by BMS.

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**.

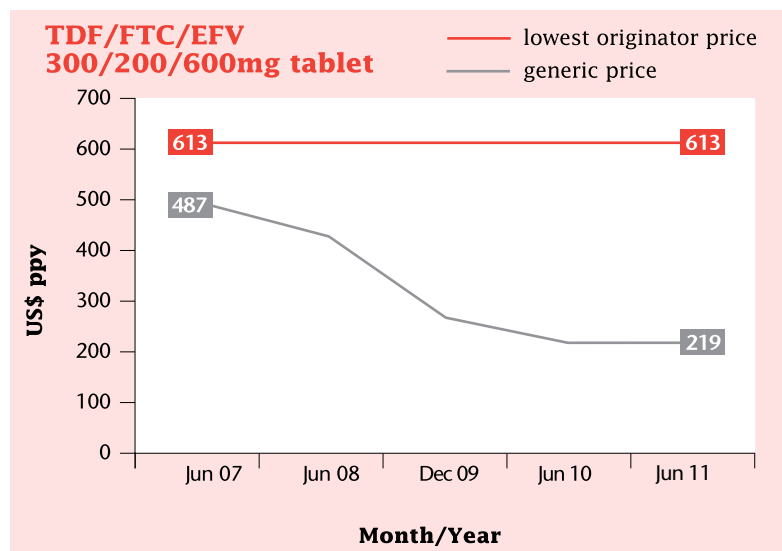
	Daily dose	BMS / Gilead / Merck		Cipla	Hetero	Matrix (CF)
		Category 1 countries	Category 2 countries			
Who can access this price?		See annex 2 & annex 10		See annex 2		
TDF/FTC/EFV 300/200/600mg tablet	1	613 (1.680)	1033 (2.830)	231 (0.633)	243 (0.667)	219 (0.600)

(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 2007:

As of May 2011, one generic source of TDF/FTC/EFV 300/200/600mg tablet was quality-assured by US FDA or WHO prequalification. Its price is shown here.

Since 2007, the originator price has remained stable, while generic prices have dropped by 55%.



Continued overleaf ❖

SPOTLIGHT ON ACCESS ISSUES

This is a one-pill-a-day fixed-dose combination, which makes it well-adapted to resource-poor settings, although TDF/3TC/EFV is more affordable.

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 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 are both 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

In addition, efavirenz (EFV) is the preferred NNRTI for use in patients starting ART while on tuberculosis treatment.

Patents

This combination is produced by Indian generic companies because none of the individual components is patented in India today. However, Gilead³⁰⁹ and BMS³¹⁰ have applied for patents related to TDF, including the one specifically related to this combination.³¹¹ If these patents are granted in India, generic competition for this product may be affected.

For further details on the patent status of TDF in India and Brazil, the voluntary licences agreements signed by Gilead and generic companies, and the Brazilian initiative for local production, please refer to the tenofovir drug profile.

Paediatrics

TDF is approved for adolescents from 12 years old, FTC is approved for use in children, and EFV is approved for use in children above three years old. All three medicines have the advantage of once-daily dosing.

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.

However, no paediatric fixed-dose combination has been developed with TDF, FTC and EFV.

There is an urgent need to have this combination developed for HIV and hepatitis B co-infected paediatric patients, for whom no treatment options currently exist, as well as for HIV/TB co-infected young children who cannot be given NVP because of interactions between NVP and TB drugs.

As there is still no established dosing of EFV for children less than three years of age, there is an urgent need to establish the dosing of EFV for this age group for children with HIV/TB co-infection.