



# TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE/EFAVIRENZ (TDF/FTC/EFV600)

## GENERAL INFORMATION

- **Therapeutic class:** One nucleotide reverse transcriptase inhibitor (NtRTI), one nucleoside reverse transcriptase inhibitor (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) in a triple fixed-dose combination.
  - **2016 WHO Guidelines:** TDF/FTC/EFV is recommended for first-line treatment for adults, pregnant and breast-feeding women, adolescents and people co-infected with tuberculosis (TB) or hepatitis B virus (HBV). A lower dose of EFV (400mg versus 600 mg) is recommended as part of an alternative first-line regimen for adults and adolescents who are at least 12 years old (**see Spotlight on Access**).
- the 5th edition for children. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of FDCs and the development of appropriate new FDCs.
- Originator companies and product brand name: Gilead/Bristol-Myers Squibb (BMS)/Merck; Atripla.
  - First approved by US Food and Drug Administration (FDA): July 2006.
  - WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults. EFV is also included as a stand-alone product in
- World sales of the originator: 2015: US\$3.134 billion; 2014: \$3.470 billion; 2013: \$3.648 billion; 2012: \$3.6 billion; 2011: \$3.2 billion; 2010: \$2.9 billion; 2009: \$2.4 billion; 2008: \$1.6 billion; 2007: \$903 million; 2006: \$164 million.<sup>1</sup>

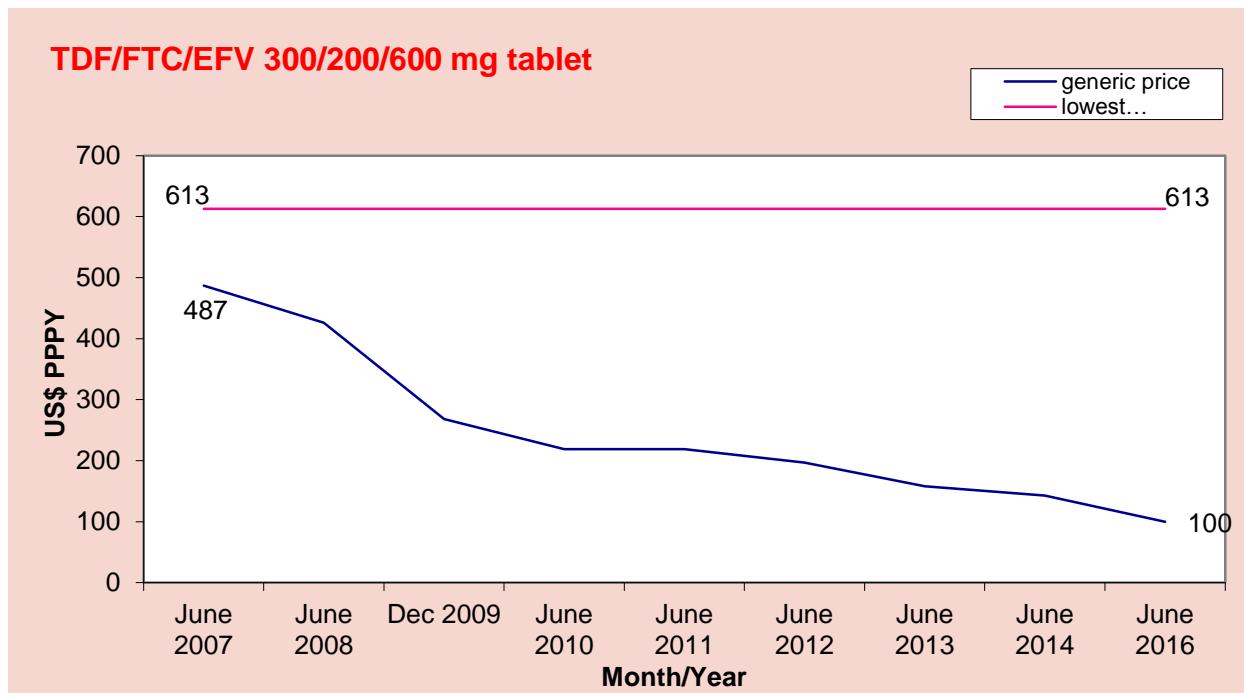
## PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products that are quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

There are currently six quality-approved generic sources of TDF/FTC/EFV<sub>600</sub>; the lowest price for this WHO-prequalified generic product is US\$100 per person, per year (pppy), which - for the first time - is less than the lowest reported price for TDF/3TC/EFV (at \$106 pppy).

Daily Dose	Merck		Aspen	Aurobindo	Cipla	Hetero	Macleods	Strides	Sun Pharma
	Category 1 countries	Category 2 countries							
TDF/FTC/EFV 300/200/600mg tablet 1	<b>613 (1.680)</b>	<b>1033 (2.830)</b>	251 (0.689)	<b>112 (0.307)</b>	<b>122 (0.333)</b>	<b>110 (0.300)</b>	<b>120 (0.328)</b>	<b>103 (0.283)</b>	<b>100 (0.273)</b>



At the time of going to press, several generics companies are developing TDF/XTC/EFV<sub>400</sub>; none are as yet quality-assured. One price was provided for TDF/3TC/EFV<sub>400</sub> at \$97 pppy. Mylan Laboratories announced that it will file for US FDA tentative approval for an alternate first-line FDC containing tenofovir disoproxil fumarate, lamivudine, and a reduced dose of efavirenz (400mg vs 600mg) in Q1 2016, and make it available for \$99 pppy, subject to regulatory approval.<sup>2</sup>

## SPOTLIGHT ON ACCESS ISSUES

The originator version of TDF/FTC/EFV, marketed as Atripla, was the first triple-class antiretroviral FDC approved by the US FDA (in July 2006), and was the first collaboration between two US pharmaceutical companies combining patented HIV medicines into one product (Gilead's TDF and FTC with Bristol-Myers Squibb's EFV).<sup>3</sup> Atripla is jointly marketed in North America and Europe by Gilead and BMS; marketing and distribution in much of the developing world is handled by Merck.<sup>4</sup>

TDF/FTC/EFV<sub>600</sub> is an easy-to-use, one-pill-a-day fixed-dose combination (FDC) that continues to be recommended as the preferred first-line treatment option for adolescents and adults, pregnant and breast-feeding women, and during treatment for TB co-infection.

As an alternative option for first-line treatment, the same combination - with a lower dose of EFV (400mg) (TDF/FTC/EFV<sub>400</sub>) – can be used in adults and adolescents from 12 years of age. It has been shown to be as effective as TDF/FTC/EFV<sub>600</sub>, with a better adverse event profile.<sup>5</sup>

WHO requires further data before EFV<sub>400</sub> can be recommended during pregnancy, breast-feeding and rifampicin-based TB treatment, and in children under 12 years of age.<sup>6</sup>

FTC is an equivalent alternative to 3TC since it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV), and has the same resistance profile;<sup>7</sup> therefore these formulations are interchangeable with TDF/3TC/EFV.

**Paediatrics:** TDF/FTC/EFV is an alternative first-line treatment option for children ages 3 to 10, but there is no fixed-dose option for paediatrics; children have to take each drug separately. EFV 200mg tablets continue to be on the IATT optimal formulary list.<sup>8</sup>

The US FDA approved TDF for use in children over two years of age in January 2012. Approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets, but the paediatric formulations are only available from Gilead; there are still no quality-assured generics available.

### PATENTS (on TDF/FTC/EFV)

(Note: Patent information may be updated in 2016 to fully reflect the evolving landscape of patents, other forms of intellectual property, licensing and use of flexibilities for the particular drug)

Most patents related to TDF, FTC, TDF/FTC or EFV also affect this combination. Gilead and BMS jointly applied for patents specifically related to this combination in 2006,<sup>9</sup> which will last until 2026.

None of the individual components are currently patented in India, so this combination is produced by several Indian generics companies. Gilead filed a patent application related to the combination of TDF/FTC/EFV,<sup>10</sup> which was challenged by generics producers through pre-grant oppositions<sup>11</sup> and rejected by the Indian patent office.<sup>12</sup>

In December 2013, people living with HIV in Argentina filed oppositions against patent applications covering TDF/FTC/EFV.<sup>11,13</sup> Since Argentina adopted new guidelines for the examination of pharmaceutical patents in May 2012, several low-quality patent applications have been rejected due

to a lack of novelty and inventive step. In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including on TDF/FTC/EFV. This licence will last until the patent expires in November 2024.<sup>14</sup>

Gilead has signed a number of voluntary licence deals with Indian manufacturers on TDF and TDF-based combinations, and entered into the licence agreement with the Medicines Patent Pool (MPP) in 2011, on TDF and other related ARVs.

The basic patent on EFV was filed by Merck in 1993 and expired in most countries in August 2013.<sup>15</sup> Gilead and BMS jointly filed patent applications on the combination of EFV with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), which will not expire before 2026 in countries where the patent applications have been granted.<sup>16</sup>

#### *Compulsory licences and anti-competition complaints*

In November 2006, Thailand issued a compulsory licence to import generic versions of EFV from India. As a result, the Thai government started purchasing EFV at \$106 per person, per year (pppy) – considerably lower than the previous price of \$511 pppy at that time.<sup>17</sup>

In May 2007, Brazil – after numerous unsuccessful negotiations with Merck – issued a compulsory licence to import more affordable generic versions from India.<sup>18,19</sup> At the time, the price of EFV in Brazil was \$580 pppy and had not changed since 2003. After the compulsory licence, Brazil began to import a WHO-prequalified generic version for \$190 pppy. In February 2009, the public manufacturer Farmanguinhos (Fiocruz) launched a locally-produced generic version for use in the Brazilian health system.<sup>20</sup>

In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including EFV. This licence lasted until the patent expired in August 2013.<sup>14</sup>

In South Africa, Merck's refusal to allow sufficient generic competition contributed significantly to the high price of the drug. This led the AIDS Law Project - acting on behalf of the Treatment Action Campaign - to file a complaint before the Competition Commission in November 2007. As a result, Merck agreed to licence its product to other producers, opening the opportunity for generic competition in South Africa, where six suppliers now market EFV or EFV-containing combination products.<sup>21</sup>

#### *Generic supplies*

In view of the main patent expiry in August 2013, several generics companies attempted to launch their versions of EFV. Multiple patent infringement cases were filed in the United States and elsewhere to block early generic competition. Some of these cases were decided in Merck's favour, which has delayed the launch of generic versions of EFV in the United States.<sup>22</sup>

To foster future competition and ensure supply security, the Kirby Institute and the Clinton Health Access Initiative (CHAI) have agreed to make the study data available to companies seeking to develop other generic versions, including a FDC containing TDF/3TC/EFV<sup>400</sup> (named TLE400).<sup>23</sup>

## PATENTS (on FTC)

The basic patents on FTC and lamivudine (3TC) expired between 2010 and 2011 in most countries.<sup>16</sup> Gilead filed combination patents containing FTC in several countries expiring in 2024 and 2026,<sup>16</sup> which might hinder access to FDCs containing FTC and 3TC.

Gilead has signed bilateral voluntary licences with generic producers, and signed voluntary licences with the Medicines Patent Pool on production and supply of several ARVs, including FTC. For more details of the evolution of, and issues with, the licences, see **PATENTS (on TDF), below**.

## PATENTS (on TDF)

The Academy of Sciences of the former Czechoslovakia applied for the basic patent on TDF in 1986; it has now expired in most countries.<sup>24</sup> Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997, and patents related to the fumarate salt of tenofovir disoproxil in 1998.<sup>25</sup> These are due to expire in 2017 and 2018, respectively. Gilead and BMS have also applied for some combination patents concerning TDF/FTC, TDF/FTC/efavirenz (EFV) and TDF/FTC/rilpivirine (RIL), which, where granted, will not expire before 2024 and 2026 respectively.<sup>16</sup>

### *Patent oppositions and compulsory licences: expanding spaces for access*

The price of TDF has fallen dramatically since 2005, due to generic production that started in India, and thanks to patent oppositions filed by civil society groups.<sup>26</sup> In a major victory for access to medicines, the Indian patent office rejected several patent applications in September 2009 relating to the pro-drug,<sup>27</sup> the fumarate form,<sup>28</sup> the intermediate,<sup>29</sup> the combination of TDF with FTC,<sup>30</sup> and the once-a-day pill TDF/FTC/EFV.<sup>31</sup>

In Brazil, civil society groups filed an opposition contesting Gilead's patent application for TDF in December 2006.<sup>32</sup> After the Brazilian government declared TDF as a medicine of public interest and the Brazilian patent office rejected the patent in September 2008,<sup>16</sup> Gilead launched a legal challenge against the patent office's decision in January 2010, which is still pending. Gilead also requested a divisional patent, which was opposed by civil society groups,<sup>33</sup> and then rejected, in another victory for access to medicines, in May 2011.<sup>34</sup>

In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including TDF and its combination with FTC and Efv. This licence will last until the end of the patent period in November 2024.<sup>14</sup>

In July 2013 the Patent Re-Examination Board of China's State Intellectual Property Office declared that one of the earlier granted patents on TDF, CN98807435.4, was invalid. This was a significant decision that occurred after China made changes in its patent law.<sup>35</sup> Generic competition was not automatically triggered after the invalidation of this patent, as other blocking patents related to TDF are still valid in China, especially two layers of divisional patents on CN98807435.4. The first layer has two divisional patents (1) 200410046290.X and (2) 200710196265. In addition, the divisional patent (1) has a sub-divisional patent (200510099916), which has also been granted.<sup>36</sup>

These divisional patents in China remain unchallenged to date. In addition, the pro-drug patent of TDF (CN97197460.8) remains valid and unchallenged while its equivalent patent has been opposed in India.

However, the patent invalidation was an important precedent in China, since it scrutinized pharmaceutical patents that had been wrongly granted. If all relevant patent barriers on TDF were removed, affordable generic once daily TDF- based FDCs would immediately improve patient outcomes in China, and people with hepatitis B would be able to access life-saving treatment at a more affordable price.

*Voluntary licensing and its impact on access*

Gilead signed problematic voluntary licensing (VL) agreements in 2006 with key generic manufacturers in India and South Africa, with control over the manufacture and distribution of the active pharmaceutical ingredient (API) and the finished product that excluded a number of countries (including middle-income countries with a substantial burden of HIV).<sup>37</sup> In July 2011, Gilead signed a licence agreement with the MPP concerning a range of products: TDF, FTC and cobicistat (COBI); elvitegravir (EVG), and the ‘Quad’ (TDF/FTC/COBI/EVG).<sup>38</sup> After receiving criticism from civil society about the limitations contained in its first agreement,<sup>39,40</sup> the MPP licence has been amended several times, with an expansion to include tenofovir alafenamide (TAF) in its July 2014 amendment, and a June 2015 amendment to make manufacturers from China and South Africa eligible to join as sub-licencees; these amendments have changed the situation from its first licence when only generic producers from India were previously eligible to join.<sup>41</sup>

The amendments have helped to expand the scope and improved some terms and conditions of the licence, such as inclusion of the hepatitis B indication for TDF, and inclusion of TAF, applying the same terms and conditions for generic production and supply.<sup>41</sup> With these amendments, both Chinese and South African generics manufacturers are eligible to join as sub-licencees, provided that they hold the Good Manufacturing Practice (GMP) qualifications that the licence requires.<sup>42</sup> However, some high burden and generic-producing countries remain excluded from its territory for generic supply, such as Brazil and China; Chinese companies can only join the licence and produce for other countries' markets, and not for their own home populations.

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