TENOFOVIR DISOPROXIL FUMARATE/LAMIVUDINE (TDF/3TC)

GENERAL INFORMATION

- **Therapeutic class:** One nucleotide reverse transcriptase inhibitor (NtRTI) and one nucleoside reverse transcriptase inhibitor (NRTI) in a fixed-dose combination (FDC).
- **2016 WHO Guidelines:** TDF/3TC is recommended as part of first-line treatment for adults, including pregnant and breast-feeding women, adolescents, and people co-infected with tuberculosis (TB) or hepatitis B virus (HBV). In adolescents above the age of 10, TDF/3TC is the preferred first-line NRTI backbone. In children 3 to 10 years old, TDF/3TC is an alternative first-line NRTI backbone.
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on both TDF and 3TC meant that generic companies were able to produce this therapeutically interesting fixed-dose combination.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults. 3TC is included as a stand-alone product in the 5th edition for children. 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.
- World sales of originator product: not applicable

PRICE INFORMATION

Developing country prices in US$, per person, per year (pppy), as quoted by companies

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

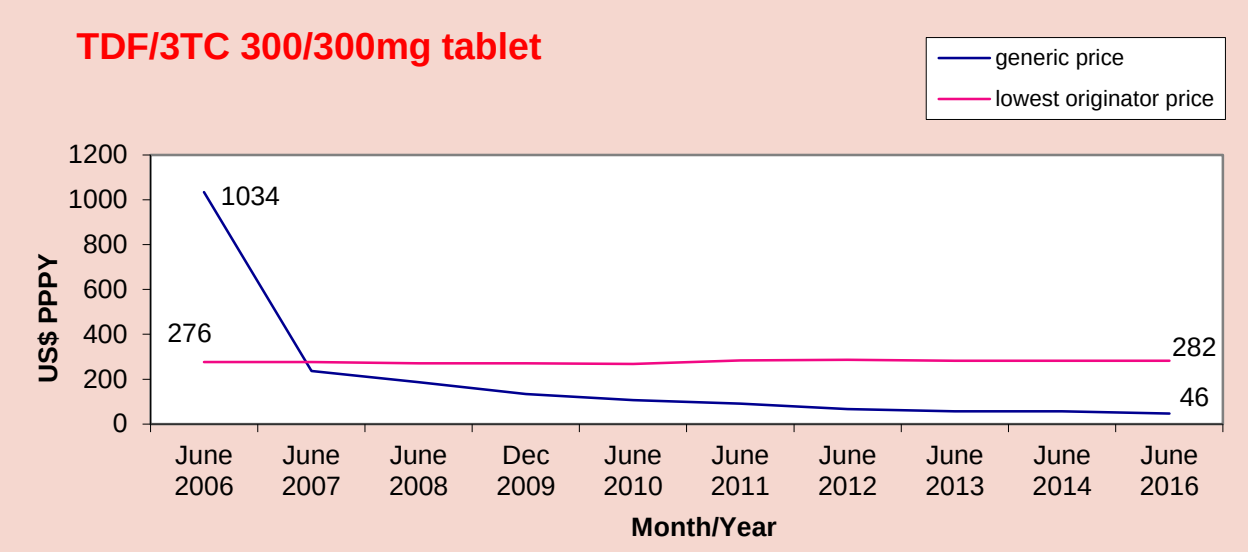
Evolution of the lowest quoted price for developing countries since 2006:

As of May 2016, there are eight generic sources of TDF/3TC 300/300mg tablet which are quality assured by US FDA or WHO prequalification, seven of which quoted a price this year. The lowest price is shown here.

	Daily Dose	Aurobindo	Cipla	Hetero	Macleods	Microlabs	Quality Chemicals	Sun Pharma
TDF/3TC 300/300mg tablet	**1**	**57 (0.155)**	**58 (0.158)**	**46 (0.125)**	**50 (0.138)**	**47 (0.130)**	**84 (0.230)**	**52 (0.143)**

As there is no originator fixed-dose combination, the price shown for the originator product is the sum of the two individual originator products.

Since 2006, the generic price has decreased by 95%.



SPOTLIGHT ON ACCESS ISSUES

3TC is an equivalent alternative to FTC, as it is structurally related, shares the same efficacy against HIV and HBV, and has the same resistance profile,[1] therefore this formulation is interchangeable with TDF/FTC. FTC-based FDCs continue to be priced higher than 3TC. There are multiple quality-assured generic formulations of TDF/3TC available; the lowest price is US$46 per person, per year (pppy), compared to $64 pppy for TDF/FTC.

Paediatrics: TDF/3TC is an alternative first-line treatment option for children aged 3 to 10 years, but there is no fixed-dose option available for paediatrics, and children requiring it would have to take each drug separately.

The US FDA approved TDF for use in children over two years of age in January 2012. The 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 paediatric generic versions available.

There are four WHO-prequalified generic sources of 3TC oral solution – the lowest reported price is $23 pppy. The oral solution formulation of lamivudine may become more important, due to WHO recommendations for earlier neonatal treatment. The preferred treatment for infants 0-2 weeks old is zidovudine (AZT) + 3TC + nevirapine (NVP); for infants aged 2 weeks to 3 months old, the preferred treatment is abacavir (ABC) or AZT + 3TC + lopinavir/ritonavir (LPV/r) syrup. As such, 3TC oral solution was added back to the limited use category of the 2016 IATT paediatric formulary.[2]

PATENTS (on TDF/3TC)
(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)

Patents related to TDF or to 3TC also affect this combination. As neither of the individual components is currently patented in India, this combination is produced by several Indian generic companies.

In October 2012, the Brazilian government announced the introduction of two new fixed-dose combinations: TDF/3TC (300/300mg) and TDF/3TC/EFV (efavirenz) (300/300/600mg).[3]

Gilead has signed voluntary licences bilaterally, and also through the Medicines Patent Pool (MPP) on TDF and related antiretrovirals. More details of these licences and their impact on access can be found in the product profiles of TDF and 3TC, see below.

Patent barriers related to 3TC are minimal, as the basic patent held by IAF Biochem expired in most countries in 2010. There are several WHO prequalified or FDA-approved generic manufacturers already making this drug.

A new formulation patent has also been filed in many countries.[4,5] This patent was granted in Brazil, China, and in ARIPO and OAPI countries, and will not expire before 2018.[6] In addition, patent applications on specific combinations could create access barriers to 3TC-containing FDCs in countries where combination patents might be granted.[5] This, for instance, would involve FDCs of dolutegravir (DTG)/3TC/abacavir (ABC); more details are available from the DTG and ABC profiles.

In November 2012, Ecuador issued a compulsory licence on key patents related to ABC and 3TC to manufacture ABC/3TC. The licence was issued to Ecuadorean manufacturer Acroxmax, in a bid to reduce the price by 75%.[7]

In March 2016, GlaxoSmithKline (GSK) made a statement[8] on its future policy of patenting in developing countries, including the waiver of filing patent applications on its new drugs in Least-Developed Countries (LDCs), which already benefits from a waiver, until 2033, from implementing TRIPS obligations on pharmaceutical patents. It remains unclear whether GSK will withdraw granted patents on the 3TC formulation and combinations in LDCs, including those in OAPI and ARIPO jurisdictions.

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.[9] Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997, and patents related to the fumarate salt of tenofovir disoproxil in 1998.[10] 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.[6]

Patent oppositions and compulsory licences: expanding spaces for access

The price of TDF fell dramatically since 2005, due to generic production that started in India, and thanks to patent oppositions filed by civil society groups.[11] In a major victory for access to medicines, the Indian patent office rejected several patent applications in September 2009 relating to the pro-drug,[12] the fumarate form,[13] the intermediate,[14] the combination of TDF with FTC,[15] and the once-a-day pill TDF/FTC/EFV.[16] In Brazil, civil society groups filed an opposition contesting Gilead's patent application for TDF in December 2006.[17] After the Brazilian government declared TDF as a medicine of public interest and the Brazilian patent office rejected the patent in September 2008,[5] 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[18] and then rejected, in another victory for access to medicines, in May 2011.[19]

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.[20]

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.[21] Generic competition was not automatically triggered after 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 that remain valid. 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.[22] 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 rejected in India.

However, the patent invalidation set 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 improve patient outcomes in China, and people with hepatitis B would be able to access life-saving treatment at a more affordable price.

Voluntary licencing 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).[23] 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).[24] After receiving criticism from civil society about the limitations contained in its first agreement,[25,26] 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.[27]

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.[28] With these amendments, both Chinese and South African generic manufacturers are eligible to join as sub-licencees, provided that they hold the Good Manufacturing Practice (GMP) qualifications that the licence requires.[29] 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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