THE ROADMAP

SPECIAL EDITION REPORT

TENOFOVIR ALAFENAMIDE FUMARATE

April 2018

I·MAK

www.i-mak.org

Table of Contents

Abbreviations

General

API	Active pharmaceutical ingredient
CL	Compulsory license
FDC	Fixed-dose combination
HBV	Hepatitis B virus
LMICs	Low- and middle-income countries
PPPY	Per person per year
TB	Tuberculosis
WO	International Patent Publication Number

Organizations, Bodies and Companies

EMA	European Medicines Agency
EML	Essential Medicines List
EOI	Expression of interest
FDA	Food and Drug Administration (U.S.)
MPP	Medicines Patent Pool
PQm	World Health Organization Prequalification of Medicines
UNAID	The Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

HIV

ARV	Antiretroviral
HIV	Human Immunodeficiency Virus
NTRI	Nucleotide reverse transcriptase inhibitor
PBMC	Peripheral blood mononuclear cell
PLHIV	People living with HIV

ARVs

BIC	Bictegravir
COB	Cobisistat
DTG	Dolutegravir
EFV	Efavirenz
EFG	Elvitegravir
FTC	Emtricitabine
RIL	Rilpivirine
RTV	Ritonavir
TA	Tenofovir alafenamide
TAF	Tenofovir alafenamide fumarate
TAH	Tenofovir alafenamide hemifumarate
TD	Tenofovir disoproxil
TDF	Tenofovir disoproxil fumarate
XTC	Lamivudine

Executive Summary

Clinical Importance

- Tenofovir alafenamide fumarate (TAF) is a nucleotide reverse transcriptase inhibitor and an alternative prodrug form of tenofovir disoproxil fumarate (TDF). The advantage of TAF over TDF is its low dose of 25 mg/day (vs. 300 mg/day of TDF), which gives it the potential to be produced at a much lower cost in the absence of patent barriers.
- In clinical trials, laboratory safety markers for bone and renal toxicity favor TAF over boosted TDF. However, since boosted regimens are not WHO-recommended first-line treatment, this safety difference is not relevant in low- and middle-income countries. There are no significant differences in safety and efficacy of TAF than unboosted TDF.
- TAF is not included in the 20th Edition of the WHO Essential Medicines List or recommended in the 2016 WHO HIV treatment guidelines due to lack of data in pregnancy, during tuberculosis treatment, and in people with severe immunosuppression, all of which are relevant for low- and middle-income countries.

Cost & Access

- Originator company Gilead has signed licensing agreements that allow a total of 22 generic companies to produce generic TAF and TAF-based combination products, and provide them to 116 countries at a 5% royalty fee. These include a license to the Medicines Patent Pool that has been sublicensed to 13 generic suppliers, as well as bilateral voluntary license agreements with 9 additional generic suppliers.
- Thirty-six middle income countries including Argentina, Brazil, China, Colombia, Mexico, and Russia are excluded from these licenses and access to generic TAF. These 36 excluded middle income countries are home to approximately 3.7 million people living with HIV.
- At the time of publication of this report, only one generic TAF-based product (DTG/FTC/TAF from Mylan) has been approved by a stringent regulatory authority (U.S. FDA). TAF-based products are not yet eligible for review by WHO Prequalification of Medicines Programme because TAF is not included in the Essential Medicines List, nor is it recommended by WHO HIV treatment guidelines.
- Generic TAF at large-scale production has the potential to cost three- to four-times less than generic TDF, on a per-patient basis, given the lower dosage as compared to TDF. However, where generic access is not possible due to patent barriers these costs savings may not materialize.

Patents

- TAF currently has nine key published International Patents. If these patents enter the national phase of the designated countries and are granted, they would provide Gilead with a total market monopoly from 2001 to 2036, a duration of 35 years. The prodrug patent on TAF expires in 2021; eight additional secondary patents could be used to extend the patent life of TAF to 2036.
- We assess TAF's patents all to be weak in strength.

Strategies for Access

- Although TAF's lower dose could potentially result in cost-savings in low- and middle-income countries, there are knowledge gaps on its safety and efficacy during pregnancy and with tuberculosis treatment. These data will only become available in late 2020.

Executive Summary

- In countries where this prodrug patent has already been challenged, we recommend full pursuit of these on-going efforts as part of a strategy to set precedent for the examination of the remaining weak patents in the TAF patent portfolio.
- Where the prodrug patent has been granted, we do not recommend that advocates call for a compulsory license in excluded territories or a further expansion of the voluntary license. This is primarily because the prodrug patent term will expire at the same time as results from clinical trials that indicate whether TAF will be deemed appropriate for use in low- and middle-income countries. It is therefore advisable to wait for safety and efficacy data to become available before determining the appropriate strategy for increasing access.
- We recommend that governments continue to use TDF for HIV treatment in the near term until WHO determines whether to include TAF in treatment guidelines. In 2021, as explained in greater detail on page 28, multiple questions will need to be answered to determine the best route to universal, affordable access to the most clinically effective HIV treatment.

Patent Quality Summary

Patent Number	Patent Type	Applicant	Strength of Patent	Explanation
WO 2002/008241	Prodrug	Gilead Sciences, Inc.	Weak	Use of a known prodrug technique for nucleoside compounds including the same salt as used in TDF.
WO2004/064846	Combination	Gilead Sciences, Inc.	Weak	Combination of TDF and FTC already known and obvious to replace TDF with TAF. No enhancement of efficacy.
WO2013/052094	Method	Gilead Sciences, Inc.	Weak	Method for preparing compounds disclosed in earlier patents.
WO2015/108780	Solid Forms	Gilead Sciences, Inc.	Weak	Routine crystalline forms claimed and have no enhancement of efficacy.
WO2016/205141	Crystalline	Gilead Sciences, Inc.	Weak	Routine crystalline forms claimed and have no enhanced efficacy.
WO2017/004012	Combination	Gilead Sciences, Inc.	Weak	Combination of compounds already disclosed in the prior art and has no enhancement of efficacy
WO2013/025788	Salt	Gilead Sciences, Inc.	Weak	Hemifumarate salt of TD was already known and also disclosed in the earlier TA patent. No enhancement of efficacy.
WO2017/004244	Solid Dosage Form	Gilead Sciences, Inc.	Weak	Solid dosage forms of FTC and TA, including TAH, disclosed in prior art and has no enhancement of efficacy.
WO2017/083304	Combination	Gilead Sciences, Inc.	Weak	Combination of compounds already disclosed in the prior art and has no enhancement of efficacy

INTRODUCTION

Introduction

What is The Roadmap?

In August 2013, the Initiative for Medicines, Access & Knowledge (I-MAK) created ***The Roadmap: The HIV Drug Pipeline and its Patents***, summarizing key clinical, cost, and patent information on important HIV antiretroviral (ARV) medicines in the pipeline. In doing so, we aimed to help expand access to the next generation of life-saving ARVs in multiple ways, including:

- Helping people living with HIV (PLHIV) and treatment advocates prioritize efforts and make critical advocacy decisions for the coming years (e.g. filing patent challenges, advocating for compulsory licenses (CLs)).
- Supporting patent offices to strengthen examination of patents for ARVs.
- Assisting generic producers in making decisions about which ARVs to produce and/or which patents to challenge and/or which pipeline ARVs to invest in producing.
- Supporting procurement agencies in making decisions within the law regarding what products to purchase and where to source them.
- Providing policy-makers with an evidence base about trends in secondary patenting across this therapeutic class to inform law and policy reform.

To date, stakeholders around the world report that The Roadmap has been used to inform decisions about whether patents should be granted on key ARVs, including use by select local patent offices to assist their examinations and raise awareness of the need for stronger examination of these patents.

Since ***The Roadmap*** was published, the need to provide safe, effective, tolerable, and **affordable** HIV treatment has grown more important than ever, given the World Health Organization's 2015 'treat-all' recommendation and the UNAIDS 90-90-90 treatment targets.[1,2] By 2025, 24.3 million people are predicted to be on first-line HIV treatment.[3] Since the ARV market is continually evolving, stakeholders need up-to-date information to fuel their efforts to increase ART access. Such information is particularly needed in middle-income countries, where up to 70 percent of all PLHIV will live by 2020.[4]

Why did we create the Special Edition Report?

I-MAK created ***The Roadmap Special Edition Report on Tenofovir Alafenamide Fumarate*** (TAF) to provide key information updates for this priority ARV. This report expands on the information provided in the original ***Roadmap*** to equip stakeholders with current clinical, cost, and patent information in order to inform decision-making about this product.

What information is included in this report?

- *Clinical Drug Information:* Overview, clinical relevance for resource-limited settings, side effects, knowledge gaps, and status in treatment guidelines.
- *Cost and Access Information:* Timeline of key events related to market access, potential production costs and savings, generic supplier landscape, generic accessible countries, price references, and future developments to watch for.
- *Patent Information:* Detailed patent information including international patent publication numbers and validity analyses focusing on legal requirements for inventive step and therapeutic efficacy.
- *Strategies for Access:* Recommended strategies to expand access to TAF.

CLINICAL DRUG INFORMATION

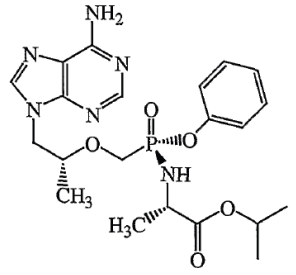
Clinical Drug Information

TAF is sold in fixed dose combinations (FDCs) for HIV treatment, as well as by itself as a treatment for infection with the hepatitis B virus (HBV).

Proprietor: • Gilead Sciences, Inc.

Drug class: • Nucleotide reverse transcriptase inhibitor (NRTI)

COMPOUND STRUCTURE



Producer	Brand Name (U.S.)	Components	U.S. FDA Approval	U.S. FDA Approved Indications (per package insert/label)	European Medicines Agency Marketing Authorization
Gilead Sciences	Genvoya®	EVG 150 mg/ COB 150 mg/ FTC 200 mg/ TAF 10 mg	November 2015	A complete HIV regimen for adults and children ≥25 kg who are ARV treatment-naïve, or to replace a current ARV regimen in people who are virologically suppressed* on a stable ARV regimen for ≥6 months, without past HIV treatment failure and without resistance to any of Genvoya®'s individual components.[5]	November 2015
Gilead Sciences	Odefesy®	RIL 25 mg/ FTC 200 mg/ TAF 25 mg	March 2016	A complete HIV regimen for adults and children ≥12 years who are ARV treatment-naïve and have HIV RNA of ≤100,000 copies/ mL, or to replace a current ARV regimen in people who are virologically suppressed* on a stable antiretroviral ARV regimen for ≥6 months, without past HIV treatment failure and without resistance to any of Odefsey's individual components.[6]	June 2016
Gilead Sciences	Descovy®	FTC 200 mg/ TAF 25 mg	April 2018	For use with other ARVs in adults and children who weigh at least 35kg, and for use with protease inhibitors that require a CYP3A inhibitor in children who weigh ≥25 kg, and <35 kg.[7]	April 2016

Producer	Brand Name (U.S.)	Components	U.S. FDA Approval	U.S. FDA Approved Indications (per package insert/label)	European Medicines Agency Marketing Authorization
Gilead Sciences	Biktarvy®	BIC 50 mg/ FTC 200mg/ TAF 25 mg	February 2018	A complete HIV regimen for adults who are ARV treatment-naïve, or to replace a current ARV regimen in people who are virologically suppressed* and have been on a stable antiretroviral regimen for 3 months, without past HIV treatment failure and without resistance to any of Biktarvy®'s individual components.[8]	
Mylan	None	DTG 50 mg /FTC 200 mg /TAF 25 mg	February 2018 (tentative approval under PEPFAR, for use in developing counties only)	The first TAF-based fixed-dose combination FDC that is targeted to HIV patients in low-income countries. However, this regimen is not yet WHO- recommended, due to lack of data on safety of TAF during pregnancy, and during TB tuberculosis treatment.[9]	

* HIV RNA <50 copies/ML

Vemlidy® was approved by the U.S. Food and Drug Administration (FDA) in November 2015 for treatment of chronic HBV infection in adults with compensated liver disease. European Medicines Agency (EMA) Marketing Authorization for Vemlidy® was granted in January 2017.[10]

HIGHLIGHTS

Safety

- Safety and efficacy of TAF and unboosted TDF are comparable.[11]
- TAF may be less likely to cause bone and kidney toxicity than boosted TDF, likely due to its reduced dose. A recent meta-analysis, however, showed no significant differences in safety and efficacy of TAF compared with unboosted TDF. At the present time, therefore, it has not been demonstrated that TAF is truly safer than unboosted TDF.[11]

Affordability

- The lower dose of TAF (25 mg/day un-boosted; 10 mg/day when taken with COB or, potentially, RTV) could generate significant cost savings over TDF (300mg/day), enabling countries to treat more people (See Estimated Production Costs).[12]
- TDF has become a mainstay of global HIV treatment but has likely reached its lowest sustainable price.[13]

Convenience for people living with HIV and treatment programs

- TAF's low dose and stability make it easy to co-formulate with other ARVs. Generics supplier Mylan has already co-formulated TAF into an FDC with FTC and DTG – a second-generation integrase strand transfer inhibitor recommended in 2015 by the World Health Organization (WHO) as an alternative first line ARV.[14] (See our ***Roadmap Special Edition Report on DTG***)
- Unboosted TAF has the potential to become a component of first-line therapy, given the cost advantages for treatment programs.
- Notably, Mylan received tentative approval from the U.S. FDA in February 2018 for TAF in combination with FTC and DTG. The total daily dose of this combination is only 275 mg.
- TAF may replace TDF in the coming years, but before this can happen, key knowledge gaps must be addressed. (See *Knowledge gaps and progress filling them*).[15,16]

THE DIFFERENCE BETWEEN TDF AND TAF

TAF and TDF are prodrugs of an active drug, tenofovir diphosphate (TD). TAF and TDF are converted into active drugs by enzymes in the human body, and both have proven equally effective in HIV and HBV clinical trials.[17-23]

The key difference between TDF and TAF is in how they are metabolized. After entering the bloodstream, TAF is absorbed from the bloodstream as tenofovir alafenamide (TA), and is taken up by peripheral blood mononuclear cells (PBMCs), where it is converted into TD by intracellular enzymes. TDF is converted into tenofovir before being absorbed from the bloodstream by PBMCs, where it is then converted into TD.[24,25]

The concentration of TD in PBMCs is five times higher with 25 mg doses of TAF than with 300 mg doses of TDF. The significance of this difference for long-term clinical and safety outcomes is not yet fully understood.

TAF is also significantly more stable as a chemical than TDF. Because of this and the lower dose, formulating FDCs containing TAF is reportedly easier than with TDF.[26]

TAF IN TREATMENT GUIDELINES

TAF is not recommended by the 2016 WHO HIV treatment guidelines, nor is it included in the 2017 Essential Medicines List (EML). Results from ongoing trials generating this evidence are not expected until late 2020.

COMMON SIDE EFFECTS

Long-term side effects

Globally, TDF has been safely used by millions of people, as part of regimens to prevent and treat HIV infection, and to treat HBV infection.

Since TAF is metabolized within PBMCs, it leaves 90% less tenofovir circulating in plasma, where it can enter other tissues; this may improve its kidney and bone safety profile over boosted TDF.[24] HIV clinical trials comparing TAF-containing regimens to TDF-containing regimens have followed people for 48 to 144 weeks. In these studies, laboratory markers for bone and kidney safety favored TAF over boosted TDF (with the exception of lower lipid levels),[17,23] although safety and efficacy of TAF and unboosted TDF were comparable.[11] Long-term follow up is needed to see if the changes in bone and kidney laboratory parameters are clinically meaningful.[11,27-30]

Adverse events in clinical trials

In HIV clinical trials, rates of viral suppression, adverse events, severe adverse events, and treatment discontinuation were similar with TAF- and unboosted TDF-containing regimens. However, TAF-containing regimens were more effective, and there were fewer renal- and bone- related adverse events than boosted TDF-containing regimens.[11]

The most common adverse events for both drugs were diarrhea, nausea, headache, upper respiratory tract infections, fatigue, cough, vomiting, joint pain, rash, and fever.[31] The same pattern was reported from 48-week HBV clinical trials comparing TAF to TDF.[18,19]

KNOWLEDGE GAPS

Several key knowledge gaps relevant to LMICs led the WHO not to add TAF to the EML, in particular lack of data during pregnancy and whether it can be used during treatment of TB co-infection. Safety and efficacy data in children, adolescents, and people with severe immunosuppression are also needed to supplement information from clinical trials.[16]

Key ongoing and recently completed TAF trials include the following:

- The 1,100-person ADVANCE trial will identify the optimal regimen for LMICs by comparing DTG/FTC/TDF to DTG/FTC/TAF and the current first-line regimen (EFV/XTC/TDF), including ages 12-18. The week 48 results are expected in early 2019, and the study will continue to follow participants for 96 weeks.[32]
- The VESTED trial is comparing safety and efficacy of three ARV regimens, including DTG with TAF/ FTC during pregnancy and for 50 weeks afterwards. Results are expected by 2020.[33]
- TAF has been contraindicated for use with rifampicin, the backbone of TB treatment, because of a suspected drug-drug interaction, although this recommendation was made before the combination had been studied in people.[10] The RIFT (Rifampicin on Plasma PK of FTC, TAF and Intracellular TFV-DP & FTC-TP) trial evaluated the effects of rifampicin on TAF in HIV-negative volunteers.[34] Results suggest that it may not be necessary to adjust TAF dosing during rifampicin use; this needs to be confirmed by additional studies in HIV-positive people who have TB,[35,36] since drug levels sometimes differ in healthy study volunteers versus people living with HIV.[37]
- An ongoing trial is evaluating TAF-containing regimens in 100 adolescents, children and infants; results are expected in 2018.[38]
- The DISCOVER trial is comparing FTC with TAF or TDF as pre-exposure prophylaxis in 5,400 men and transgender women who have sex with men and are at risk of HIV-1 infection; results are expected in 2020.[39]

COST AND ACCESS INFORMATION

Cost and Access Information

TAF MARKET ACCESS TIMELINE

July 2014	The Medicines Patent Pool (MPP) expands licensing agreement with Gilead Sciences to include TAF, produced by generic suppliers in India and eligible to at least 112 countries.[40]
July 2015	The MPP agreement expands to allow manufacturers from China and South Africa to be sub-licensees and produce generic TAF.[41]
November 2015	U.S. FDA and EMA approves TAF FDC product Genvoya® (TAF/EVG/COB/FTC). Comparable to Gilead's Stribild® (TDF/EVG/COB/FTC).
March 2016	U.S. FDA approves TAF FDC product Odefsey® (TAF/FTC/RIL). EMA approves Odesfey® in June 2016. Comparable to Gilead's Complera® (TDF/FTC/RIL).
April 2016	U.S. FDA and EMA approves TAF fixed-dosed combination product Descovy® (TAF/FTC). Comparable to Gilead's Truvada® (TDF/FTC).
September 2017	The MPP extends the agreement with Gilead to include four additional generic-eligible countries – Belarus, Malaysia, Philippines, and Ukraine – thereby expanding access to TAF and any TAF-containing regimens to 116 countries.[42]
February 2018	Mylan's DTG/FTC/TAF (50/200/25mg) combination was approved by U.S. FDA, making it the first generic TAF-based FDC to be approved by a stringent regulatory authority.[43]
April 2018	To date not a single transaction for TAF or any TAF-based regimens have been recorded on the WHO's Global Price Reporting Mechanism database or The Global Fund's Price and Quality Reporting System.

LICENSING AGREEMENTS

The following license agreements dictate where generic TAF can be produced and sold.

Medicines Patent Pool

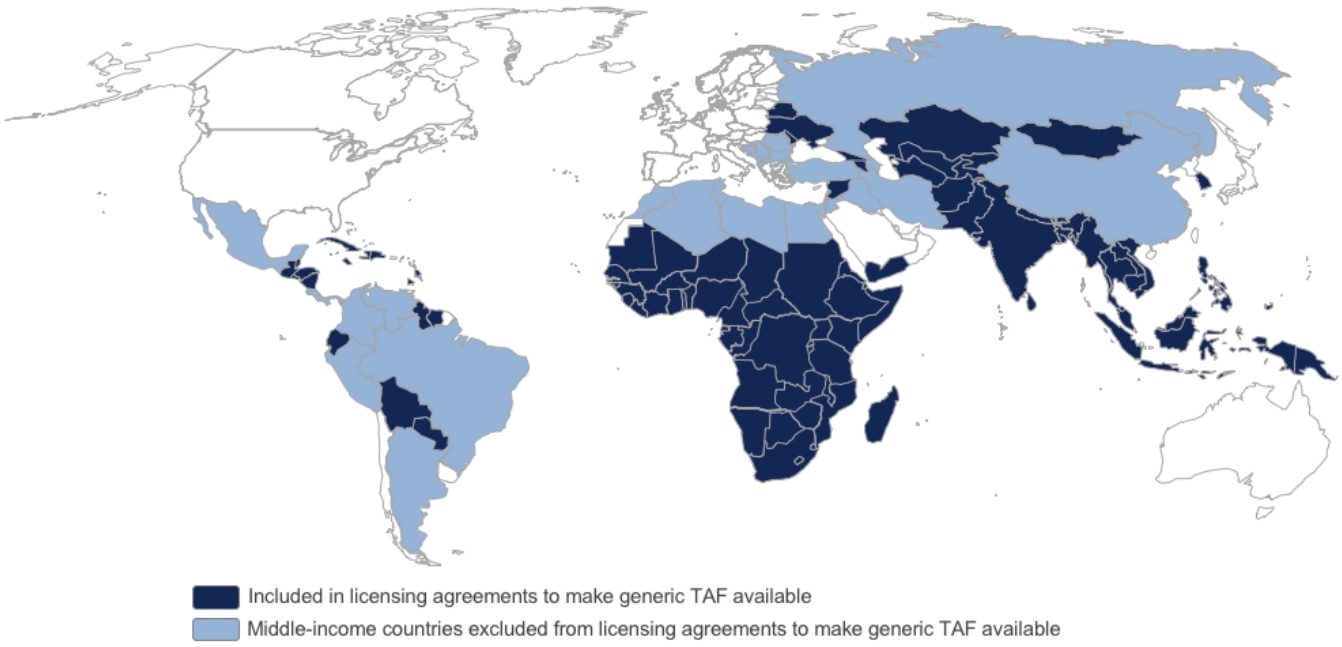
Gilead's agreement with the MPP in September 2017 allows for generic sublicensees to produce and distribute TAF to 116 countries. This was an expansion of the earlier agreement for TAF in July 2014. Thirty-six middle income countries are not eligible to procure generic TAF under the MPP license terms, meaning approximately 3.7 million PLHIV who are living in middle income countries are excluded from the license (See *Annex A*).

For countries that are "included" in the license deals, it is important to remember that these countries are only eligible to receive or procure generic products. Inclusion in the territory does not mean these countries are currently procuring generic TAF, nor does it mean they have in the past.

Bilateral Voluntary Licensing Agreements

In addition to the MPP, access to TAF is also available through direct bilateral agreements that Gilead has with a number of generic suppliers. Broadly the terms of these voluntary licenses are known to be similar to the terms granted through the MPP.[44] For TAF that includes a 5% royalty on net sales and the ability for the generic licensee to sell to the same set of 116 countries.

Figure 1: Countries Included and Excluded from Gilead Licenses



Internal analysis of TAF generic-eligible countries from MPP[41], Gilead bilateral agreements,[44] and 2017 World Bank middle income countries[45]

GENERIC SUPPLIER LANDSCAPE

Figure 2 summarizes the current landscape of generic suppliers of TAF when this report was published, including the thirteen generic suppliers from China and India that are sub-licensees of the MPP and the nine additional generic suppliers that have executed voluntary licenses directly with Gilead.

On the supply side, it is important to note that although all of these suppliers are eligible to produce generic TAF, very few of them are actually producing the product as of early 2018. This is in line with historical trends of how generic supply actually plays out after licenses are signed. To illustrate, in 2006 Gilead signed bilateral voluntary licenses with 11 manufacturers, but only a subset of the companies actually produced commercial quantities of TDF after signing.

Figure 2: Generic Supplier Landscape

License	Company	Country
Suppliers with rights to produce TAF as sublicensees of the Medicines Patent Pool[42]	1. Anhui Biochem Pharmaceutical Co. Ltd.	China
	2. Aurobindo Pharma Limited	India
	3. Cipla Ltd	India
	4. Desano Pharmaceuticals	China
	5. Dr. Reddy's Laboratories Ltd.	India
	6. Emcure Pharmaceuticals Limited	India
	7. Hetero Labs Ltd	India
	8. Huahai Pharmaceutical Co Ltd.	China
	9. Laurus Labs Ltd	India
	10. Lupin Limited	India
	11. Macleods Pharmaceutical Limited	India
	12. Micro Labs	India
	13. Natco Pharma Limited	India
Suppliers with bilateral agreements with Gilead (not included in the Medicines Patent Pool license)[44]	1. Alkem Laboratories Ltd	India
	2. Aspen Pharmacare	South Africa
	3. Cadila Healthcare Ltd	India
	4. Mcneil & Argus Pharmaceuticals	India
	5. Mylan Laboratories Limited	India
	6. SeQuent Scientific Limited	India
	7. Strides Shasun Ltd	India
	8. Sun Pharmaceuticals	India
	9. Unimark Remedies Ltd	India

As is standard for most generic market dynamics, the suppliers will produce a product in small scale for regulatory review and in larger commercial quantities in response to known or committed demand volumes. With TAF there is just a single generic company, Mylan Laboratories, which has secured U.S. FDA approval for their TAF-based FDC product.

WHO Prequalification of Medicines Programme (PQm) has not yet included TAF in its most recent expression of interest statement calling for supplier submissions of specific products. Therefore, TAF is not even eligible to be reviewed by WHO PQm for approval. As such, only suppliers that gain regulatory approval from other stringent regulatory authorities (e.g. Mylan's submission and approval through the U.S. FDA), will have products eligible to be procured by the Global Fund and other major treatment funders.

In summary, while there are a high number of generic suppliers that are eligible and could potentially produce TAF, the landscape of suppliers actually producing TAF will remain very limited until the drug is recommended and adopted more widely into national treatment guidelines and has validated ongoing demand. **The supply of TAF will follow demand, not vice versa.**

MARKET PRICE REFERENCES

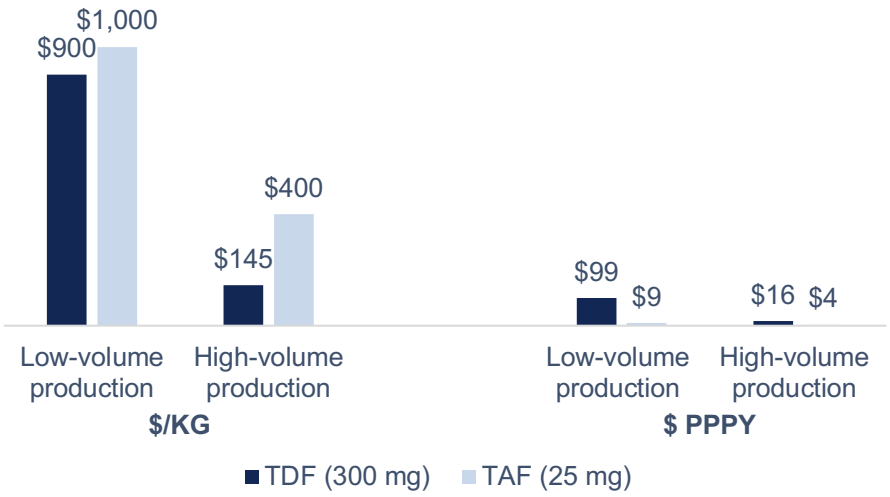
As expected with generic TAF at this time – and consistent for products that are not incorporated into national treatment guidelines and/or have few generic approvals from stringent regulatory authorities – there is very little public market purchasing activity and therefore benchmark pricing. At the time of publication of this report, there have not yet been any transactions for generic TAF or TAF-based regimens reported through either the Global Fund's Price and Quality Reporting database or WHO's Global Price Reporting Mechanism.

Looking at relative market pricing for TAF vs. TDF in the U.S. market also provides limited insights. When Gilead launched the various TAF-containing FDCs, they priced each the same as the corresponding TDF-based products, essentially heralding the TAF versions as clinically improved products but not lower cost. This marketing-based approach to pricing is common amongst originators in the absence of generic competition. However, in generic-accessible countries, prices for generic drugs are more closely tied to actual costs of production given that generic suppliers compete on price. As such, given that the dosage of TAF is one-twelfth that of TDF, the far lower active pharmaceutical ingredient (API) requirement creates a cost advantage. The cost reduction may not be proportional to the dosing, though, as we expect API suppliers to require higher margins per unit to balance the reduction in volume.

ESTIMATED PRODUCTION COSTS

Both TAF and TDF are near-identical prodrug derivates of a common precursor compound (tenofovir). While both API syntheses share multiple production steps in common, TAF has certain unique chemical synthesis challenges that result in it being significantly more expensive to produce than TDF. Experts in chemical drug synthesis have estimated that it is possible to reduce the cost of TAF API from its current 'low-volume' level of US$1000/kg to approximately US$400/kg at high-volume production.[46] By comparison, the production cost of TDF, having been on the market for over ten years and produced at large-scale by dozens of generic suppliers on a regular basis (over 1,500 metric tons/year), is now approximately $145/kg – a six-fold decrease from the initial small-scale production costs of $900/kg.[47]

Despite per kilogram API costs that are nearly three-fold higher for TAF than TDF (even at high-volume production), there is still a four-fold potential cost savings with TAF on a per-patient basis given the lower amount of drug required, as seen in *Figure 3*.



WHAT TO WATCH FOR

1. WHO Prequalification to name TAF as eligible for regulatory approval. If results from clinical trials confirm safety and efficacy of TAF during pregnancy and TB treatment, suppliers will be able to submit TAF-based products to the WHO PQm for approval once TAF is listed in their annual Expression of Interest (EOI) statement to suppliers. For TAF to be included in an EOI it requires that TAF (or a specific TAF-based regimen) be listed in the EML and/or be recommended by a current WHO treatment guideline. TAF was submitted for consideration in the 2017 EML meeting but was not recommended by the expert committee. Given the clinical reasons cited earlier we do not expect TAF to be included in an EOI before 2020.

2. Additional TAF-based regimens to be approved outside of the WHO Prequalification. Until WHO PQm begins accepting TAF-based ARVs for review, suppliers seeking to gain regulatory approval for their TAF-based products will need to submit to the U.S. FDA, EMA, or other stringent regulatory authorities to gain approval for their products.

3. The first generic-accessible countries to incorporate TAF-based regimens into their preferred treatment guidelines. If LMICs with sizeable markets include TAF products in their national treatment guidelines, it will catalyze significant demand and suppliers will have the incentive to begin regular production.

PATENT INFORMATION

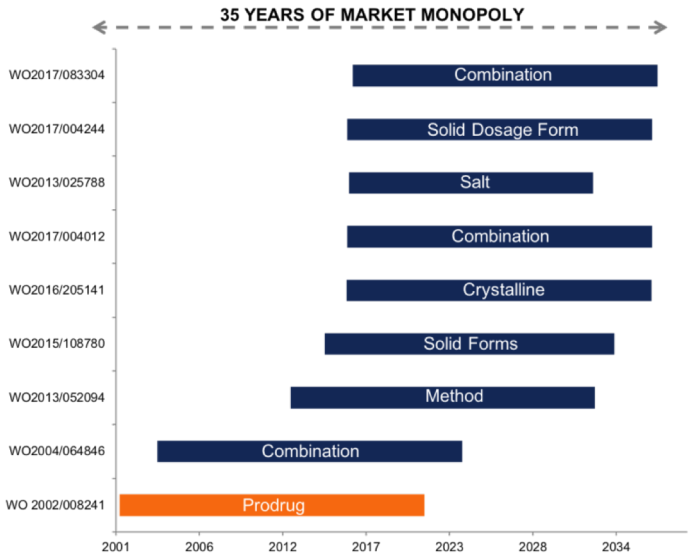
Patent Information

TAF PATENT LIFECYCLE

TAF currently has nine key published International Patents. If these patents enter the national phase of the designated countries and are granted, they would provide Gilead with a market monopoly from 2001 to 2036, **a duration of 35 years**. The prodrug patent on TAF expires in 2021, and eight additional secondary patents could be used to extend the patent life of TAF to 2036.

Chemical name for TAF
L-alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2E)-2-butenedioate (2:1).

Figure 4: TAF Patent Lifecycle



METHODOLOGY FOR ASSESSING PATENT STRENGTH

The strength of a drug's patents can help inform the strategies that are pursued to provide access. For example, CLs may be the better strategy for drugs with strong underlying patents in countries that are typically excluded from voluntary licenses. Patent oppositions may be more appropriate for drugs with weak and medium strength patents.

The strength of a patent is based on whether the drug product meets legal requirements for inventiveness and/or therapeutic efficacy:

- **Inventiveness:** In determining whether a drug is inventive by legal standards, we have adopted the standard approach of whether the invention claimed in a patent application would have been obvious to a person skilled in the field given the prior art available. Included in this assessment are practices that would be considered common general knowledge to a person in the art.
- **Efficacy:** Here we employ the legal standard of the Indian Supreme Court, as set out in its April 2013 decision in *Novartis AG vs. Union of India & Others*. We also focus on India because it is the home to the leading generic ARV producers.

In order to assess patent strength, our team of lawyers and scientists analyzed each of the patents from the patent landscape for TAF and the available prior art. We determined through this process that patents on TAF fall into one of three basic categories:

- **Weak:** Considerable prior art, common knowledge, and/or data to challenge the patent for lack of inventive step and/or on the grounds of lacking efficacy.
- **Medium/Questionable:** Prior art and data raise questions on inventiveness and/or efficacy, but further analysis of comparative data is required.
- **Strong:** Little or no prior art suggesting the patent falls into the above categories.

PATENT QUALITY ASSESSMENT SUMMARY

TA, formerly known as GS-7340, is not a new compound. It is another prodrug of tenofovir, but using a different ester as compared to the earlier known form TD. Given the existing prior knowledge for formulating antiviral compounds as prodrugs to allow intracellular absorption, substituting the disoproxil ester of tenofovir with an aryl phosphoramidate ester would have been obvious. **Therefore, we assess all TAF patents to be of weak strength.**

Gilead also claims the fumarate (the same salt as used in TDF) and hemifumarate salt of the ester prodrug. The use of the fumarate salt for formulation purposes would have been obvious in light of TDF, as would be the hemifumarate in light of the prior art. From an efficacy standpoint, as TAF is a prodrug and also claims the fumarate salt of tenofovir, it will be metabolized in the body to its active monophosphate form. As a result, the active species will be exactly the same as that generated from TDF and does not meet the efficacy standard.

We identified a number of other secondary patents that were also assessed to be weak.

Main Patent: WO02/008241 **PATENT QUALITY:** WEAK

Is it inventive?

Tenofovir alafenamide

- This application discloses TA as structure 6 (page 6). The application also claims the racemic forms of TA and their separate stereoisomers. TA is specifically claimed in claim 23 (page 57).
- A review of the prior art shows that the claims relating to TA lack inventive step.
- Tenofovir prodrugs such as TD (US5,922,695/ WO99/05150) already existed in the art at the priority date.
- The use of a phosphoramidate group to increase antiviral activity of nucleoside compounds such as stavudine (d4t)[48] and zidovudine (AZT)[49] was already known at the priority date. These compounds present potent anti-HIV activity and a phosphoramidate moiety with a strong structural resemblance to that of TA.
- The ester in the chain of the phosphoramidate moiety of TA is an isopropyl ester whereas it is a methyl ester in the prior art.[48,49] No evidence is provided by WO02/008241 of a technical effect associated to the isopropyl ester compared to other structurally close ester substituents previously disclosed,[48,49] such as a methyl ester. Accordingly, the selection of an isopropyl ester, already known from TD, results from an arbitrary choice and does not involve an inventive step.
- Regarding the claims for the various stereoisomers of the racemic mixture of TA, it is generally recognized that such practice does not involve an inventive step.
- Therefore, it would have been obvious to apply the phosphoramidate approach, which has been successfully applied to nucleoside analogues, to tenofovir or its prodrug, such as TD, with the expectation that this would improve the cell permeability and anti-HIV activity.

Tenofovir alafenamide

- This application discloses TAF as structure 7 (pages 6-7). TAF is specifically claimed in claim 24 (page 57).
- Fumaric acid was already used with TD, also known as TDF (US5922695 and WO99/05150).
- In view of the advantages given by the phosphoramidate moiety, it would have been obvious to apply the phosphoramidate approach to TDF with the expectation that this would improve the cell permeability and anti-

Is there efficacy?

Given that TA (and its fumarate salt) is a prodrug of tenofovir and will be metabolized in the body to its active monophosphate form, the active species will be exactly the same as that generated from TDF. As such, TAF does not be considered to meet the efficacy requirement.

No experimental data showing a potential anti-viral effect of TAF are provided in WO02/008241. Example 10 describes plasma and PBMC exposures following oral administration of TA to beagle dogs. However, these data cannot be considered to sufficiently demonstrate the effective anti-viral treatment by TAF in humans.

Combination Patent: WO WO2004/064846 **PATENT QUALITY:** WEAK

Is it inventive?

- This application is directed to a combination comprising TA (or a physiologically functional derivative) and FTC for the treatment of the symptoms or effects of an HIV infection in an animal. This application also covers a pharmaceutical composition, a patient pack, a chemically stable combination, and a chemically stable oral pharmaceutical dosage form comprising this combination.
- A review of prior art shows that the combination of TA (or a functional derivative) with FTC would be an obvious result.
- Combinations of TDF with FTC were already known.[50] Gilead had previously announced its development of a co-formulation of TDF and FTC as a potential FDC treatment for patients with HIV.[51]
- Combination therapy comprising at least three antiviral agents was the established practice in the treatment of HIV at the priority date of this international application. Combination treatments are now commonly used for maximizing the suppression of virus replication and minimizing the development of resistance whilst avoiding drug toxicity and compliance issues.[52-54] Therefore, it would have been obvious to replace TD/TDF with TA (fumarate), which was already disclosed in WO02/008241, in combination with FTC, and additionally a third antiviral agent.
- The oral administration of a once daily pill of the combination of TAF, or a functional derivative, with FTC would be obvious in light of the prior art. The choice and the determination of the amount of pharmaceutically acceptable carriers, excipients, and glidants result from routine experimentations in the field of pharmaceutical compositions, and would also be obvious.

Is there efficacy?

According to WO04/064846 the combination of TAF and FTC is both chemically stable, and either synergistic and/or reduces the side effect of one or both of the active ingredients.

However, there is no data in the application showing the synergistic effect of the composition of TAF and FTC. In addition, there is no data in the application showing that the combination of TAF and FTC reduces the side effects of one or both of the active ingredients. Furthermore, the application does not provide technical data showing that the claimed combinations have an effect in the treatment of the symptoms of effects of an HIV infection.

Under the current legal standards in India, this application does not meet the efficacy requirement.

Note: WO04/064845 covers the therapeutic combination of TDF and FTC, and their pharmaceutical composition as a once daily pill. Claim 21 of this application combines TDF, FTC, and TAF. The corresponding European application was opposed by Teva Pharmaceuticals and Generics U.K Ltd. All claims were subsequently revoked.

Hemifumarate Salt Patent: WO 2013/025788 **PATENT QUALITY:** WEAK

Glaxosmithkline LLC

Is it inventive?

- This application is directed to tenofovir alafenamide hemifumarate (TAH), pharmaceutical compositions comprising TAH, the use of TAH in medical therapy, and in the prophylactic or therapeutic treatment of HIV or HBV infection. TAF is specifically claimed on claim 1.
- WO13/025788 discloses that the monofumarate form of TA is not thermodynamically stable in acetonitrile and partially converts in to the hemifumarate form. The application further states that the preparation of TAF with acetonitrile as the solvent followed by washing with acetonitrile inevitably yields TAH.
- Example 4 of WO02/08241 discloses the preparation of TAF, which involves the reaction of TA with fumaric acid and acetonitrile. The product is then isolated by filtration, rinsed with acetonitrile, and dried. Based on the disclosure in WO13/025788 and the process described in WO02/0824, it can be argued that it would have been obvious to yield TAH through preparation of TAF with acetonitrile as the solvent followed by washing with acetonitrile.
- It can be further argued that TAH is not inventive in light of US2009/0176983, US2009/0286981, and WO2008/143500, which disclose the co-crystal of TD and fumaric acid where two units of TD with one unit of fumaric acid are co-crystalized leading to tenofovir disoproxil hemifumarate.
- WO02/08241 already discloses the difference between TA and TD lies in the presence of a phosphoramidate moiety in TA, instead of two carbonate groups in TD. It would have been obvious to replace the carbonate groups in tenofovir disoproxil hemifumarate by the phosphoramidate of TA, thereby arriving to TAH, with the expectation that this would improve the activity and stability of the compound.
- With respect to the claimed pharmaceutical compositions and therapeutic uses using TAH, WO02/08241 also discloses such uses for TAF. Accordingly, it would have been obvious to expect the use of TAH in the form of a pharmaceutical composition for treating HIV or HBV. Also, adding an additional antiviral agent to the pharmaceutical composition is an established practice in the treatment of HIV and HBV and therefore lacks any inventive step.
- The preparation of TAH using seedings is a common practice to prepare crystal products. As such, these claims should be considered obvious.

Is there efficacy?

The application does not provide technical data showing an antiviral effect of TAH in itself or in combination with another agent. The only data provided in the application relates to chemical stability, which is not sufficient for meeting the efficacy requirement.

Sold Forms Patent: WO 2015/108780 **PATENT QUALITY:** WEAK

Is it inventive?

- This application relates to crystalline forms of tenofovir, compositions comprising crystalline forms of tenofovir, uses of the crystalline forms of tenofovir for the manufacture of TD and TA, and their uses in the treatment or prevention of a viral infections, such as HIV and HBV.
- Example 1 of US5977089 discloses tenofovir and the crystalline form I of tenofovir monohydrate. In addition, this process can also lead to alternative crystalline forms of tenofovir.

- It is universally accepted that the systematic investigation of a compound to determine whether it is prone to polymorphism is common general knowledge in the art and routine practice in the pharmaceutical industry. It is also known that most substances when investigated reveal more than one crystal structure. Furthermore, the methods to screen for polymorphs are well known in the art.
- In the present case, no unexpected result is achieved by the crystalline forms claimed in the international application compared to crystalline forms disclosed in the prior art. Therefore, the choice of alternative crystalline forms IV, VI, and IX of tenofovir are a result of routine testing of crystallization conditions in pharmaceutical development.

Is there efficacy?

The advantages of the crystal forms claimed in this application are described as improvement of processing and manufacturing, specifically filtration rates.

Table 6 of the application shows the filtration time of two batches, one with a crystal form IV and one with a crystal form I. However, no comparison with other forms known from the prior art are provided. The international application also does not provide other experimental data showing particular effects achieved by the claimed invention.

Furthermore, none of the advantages of the crystal forms claimed in this application meet the enhancement of efficacy as defined by legal standards.

Solid Oral Dosage Form Patent: WO WO2017/004244 **PATENT QUALITY:** WEAK

This application is directed to a solid oral dosage form of TA or a pharmaceutically acceptable salt, such as the hemifumarate salt of TA, and FTC.

Is it inventive?

- A review of the prior art shows that the solid oral dosage form of TA and FTC lacks inventive step.
- WO13/116720 discloses a unit dosage for oral administration in the form of tablets comprising FTC and TA coated with a film, including polymers, for use in the treatment of HIV. A percentage of TAH of the weight of the unit dosage form is disclosed.
- WO04/064846 discloses an oral solid dosage formulation in the form of a tablet comprising TA and FTC in various proportions and optionally coated.
- WO15/022351 discloses solid oral dosage formulations comprising various amounts of FTC and TA.
- Therefore, the claimed invention of a solid dosage form of TA or a pharmaceutically acceptable salt, such as the hemifumarate salt of TA, and FTC would have been obvious.

Is there efficacy?

The application does not provide experimental data showing a particular anti-viral effect of the claimed dosage form.

The application does provide data relating to stability. However, under current standards, stability is not considered to meet the requirements of the efficacy test.

OTHER SECONDARY PATENTS RELATED TO TAF

The following patents were identified as important for making TA (fumarate/hemifumarate) but not key from a freedom to operate perspective.

Method for Preparing TAF: WO 2013/052094

PATENT QUALITY: WEAK

This application is directed to a method for the crystallization of TA (compound 16), comprising of subjecting a solution including a mixture of diastereomers at the phosphorus atom (compound 15) to a suitable solvent and a suitable base. This application also relates to methods for preparing the synthetic intermediates useful for the preparation of TA (i.e. compound 12, compound 13, and compound 15 of the international application).

A review of the prior art shows that the preparation of diastereomerically pure TA via crystallization using acetonitrile and seed crystals of TA was already known from US2005/0009043, US2008/0227754, and WO02/08241. Therefore, the claimed invention should be considered obvious.

The application does not provide any data that would meet the requirements of the efficacy standard.

Co-crystal and Solid Form: WO 2016/205141

PATENT QUALITY: WEAK

This application is directed to salts and crystalline forms of TA, including tenofovir alafenamide sesquifumarate, tenofovir alafenamide oxalate, tenofovir alafenamide malonate, tenofovir alafenamide L-malate, tenofovir alafenamide saccharin, tenofovir alafenamide mucate, tenofovir alafenamide maleate, tenofovir alafenamide hydrochloride, tenofovir alafenamide ethanesulfonate, tenofovir alafenamide benzenesulfonate, and tenofovir alafenamide sulfate, and their pharmaceutical compositions.

Most salts of TA were already disclosed in the prior art. The application WO15/040640 relates to the preparation of TA or acceptable salts, pharmaceutical composition, and method of using TA or acceptable salts to treat antiretroviral infections.

Accordingly, this patent application should be considered obvious.

Furthermore, no data is provided in the application that shows a particular antiviral effect for any of the claimed salts. Therefore, this application does not appear to meet the requirements of the efficacy standard.

TAF, RIL, and FTC: WO 2017/004012

PATENT QUALITY: WEAK

This application is directed to a solid oral dosage form comprising RIL, TA, and FTC for use in the treatment of HIV infections. The claims cover various amounts of active ingredients, coated tablet and multilayer tablet comprising RIL, TA, and emtricitabine, and a method of therapeutic treatment of HIV infection.

WO2012/068535 discloses a single multilayer formulation of RIL, FTC, and TDF. TA and its properties were already known from WO02/0824. Given the prior existing knowledge of the compounds in this claimed invention and that combination therapy is established practice, it would have been obvious to try and replace TDF with TA and combine it with RIL and FTC.

The application fails to provide any data relating to the efficacy of the solid oral dosage form comprising RIL, TA and FTC.

BIC, TAF, and FTC: WO 2017/083304 **PATENT QUALITY:** WEAK

This application relates to solid oral dosage forms comprising BIC, FTC, and TA for use in the treatment of viral infections such as HIV.

A review or prior art shows that BIC was already disclosed in WO14/100323 for the treatment of HIV infection, combination of compounds (such as compounds 42 and 45) with one or more additional therapeutic agents including FTC and TAF, and a tablet as a single dose.

In addition, TA and FTC were both known to be therapeutically effective in the treatment of HIV (WO02/008241). Similarly, compositions of TA and FTC were also already known to be useful for the treatment of viral infections in the form of a tablet (WO04/064846, WO13116720, WO15/022351).

Combination therapy comprising at least three antiviral agents was the established practice in the treatment of HIV at the priority date of this application.

Accordingly, it can be argued that the claimed solid oral dosage results from an arbitrary choice which would not involve an inventive step.

Furthermore, there is no data showing an enhancement of efficacy of the use of a solid oral dosage form comprising BIC, FTC, and TA, or a synergic effect of these compounds.

STRATEGIES FOR ACCESS

Strategies for Access

Although TAF is currently used in high-income countries, assessing whether and where TAF should be adopted in LMICs, and the steps to be taken to facilitate such adoption, requires balancing multiple factors. In particular, we identified four inter-related considerations:

- Patent status: The prodrug patent is weak and will expire in 2021. Additional secondary patents are weak but if granted could extend Gilead's monopoly until at least 2036.
- Safety and efficacy data: Additional safety and efficacy data, which will be available in late 2020 at the earliest, are needed for WHO inclusion of TAF as part of a preferred treatment regimen for LMICs. Furthermore, the actual benefit of TAF for patients in LMICs seems to be relatively limited on the basis of current data. Although safety data favor TAF over boosted TDF, boosted regimens are not used in first-line treatment in LMICs. Safety and efficacy of TAF and unboosted TDF are comparable.
- Lower production cost of TAF: TAF can be manufactured more cheaply than TDF. However, Gilead's patent strategy could result in a total of 35 years of exclusivity (until 2036). Cost savings achieved through lower manufacturing costs of TAF compared to TDF will not be relevant in countries where Gilead maintains and enforces a monopoly on TAF.
- Ensuring availability of low-cost, generic TDF: TDF is off-patent and open for generic supply in all countries. If TAF is increasingly adopted, it is important to consider whether generics will continue to supply TDF as the market shifts, particularly in countries excluded from the license where Gilead will maintain market control. This scenario warrants further strategic consideration since TDF is off-patent.

As noted above, significant knowledge gaps must be addressed before TAF could potentially replace TDF in LMICs, and due to this TAF would not be included in the WHO EML until 2021 at the earliest and is unlikely to be part of a WHO-recommended treatment regimen until then. Despite its exclusion from the WHO guidelines and EML, TAF has already been included in Thailand's national treatment guidelines.

Because of its potentially lower production cost, there have been efforts to expand access to TAF, even in the absence of any near-term demand. This includes efforts to expand the geographic scope of the voluntary license between Gilead and the MPP, and challenges to the prodrug patent applications in at least three countries (patent oppositions in Argentina and Brazil; a third-party observation in Thailand). While a revision to the MPP license with Gilead for TAF was recently expanded to include Belarus, Philippines, Malaysia, and Ukraine.

Until safety and efficacy data are available and assessed in late 2020, we recommend that governments and treatment providers continue to use TDF. In addition:

- Gilead has filed a range of secondary patents on TAF to block generic competition in LMICs and in high-income countries. We assessed these secondary patents as weak and recommend that patent offices reject these applications where they have been filed.
- Where patent challenges to Gilead's prodrug patent application have been filed, they should be seen to completion since these cases can set a precedent for examination of the remaining TAF patents.
- In territories not included in either the bilateral or MPP voluntary licenses and where Gilead's prodrug patent has been granted, we do not recommend pursuit of a CL on the prodrug patent or further expansion of the voluntary license. This is primarily because the prodrug patent is expected to expire at the same time as when the evidence will determine whether TAF will be appropriate for use in LMICs.

If TAF is included in WHO treatment guidelines in 2021, we believe four broad questions need to be answered at that time to determine how TAF should be used over the subsequent years, which can also inform what additional measures may need to be taken to ensure affordable access to HIV treatment.

1. Will additional data emerge that indicates TAF is preferred or inferior to unboosted TDF? Additional data may indicate that TAF provides better or worse clinical outcomes for patients compared to unboosted TDF.
2. What will be the patent status of TAF in LMICs? While all secondary patents that have been filed by Gilead are weak and should be rejected, the issuance of such patents, which could block generic competition in countries excluded from a voluntary license, would prevent access to low-cost versions of TAF
3. What will be the scope of Gilead's voluntary licenses for TAF? The current voluntary license includes 116 countries. It is not clear whether Gilead will choose to expand the voluntary license to include some or all of the 36 middle income countries that are currently excluded from the agreement.
4. What would be the impact of scaling up of production of TAF on the manufacture of TDF? If generic manufacturers that currently produce TDF at a large-scale start to produce TAF in response to increased demand, it is not clear whether these generic manufacturers will continue to manufacture TDF. It is also not clear whether other generics manufacturers would start producing TDF if the more established generics companies were to shift to TAF. The availability of generic TDF is especially relevant for middle-income countries where patent protection may prevent access to low-cost versions of TAF. Without continued availability of low-cost, generic TDF, such countries may have to pay higher prices for branded versions of TAF.

We hope that such questions are taken into consideration in 2021 to inform strategies taken forward to ensure that all patients, irrespective of where they live, will have affordable access to the most clinically effective HIV treatment.

ANNEX A

Annex A

Middle Income Countries Included and Excluded from Licensing Agreements

Excluded Countries

COUNTRY	PLHIV
Albania	1,700
Algeria	13,000
America Samoa	
Argentina	120,000
Azerbaijan	9,200
Bosnia and Herzegovina	
Brazil	830,000
Bulgaria	3,500
Cabo Verde	2,800
China	780,000
Colombia	120,000
Costa Rica	13,000
Egypt (Arab Republic of)	11,000
Iran (Islamic Republic of)	66,000
Iraq	
Jordan	500
Kosovo	
Lebanon	2,200
Libya	
Macedonia	
Marshall Islands	
Mexico	220,000
Micronesia	
Montenegro	500
Morocco	22,000
Panama	22,000
Paraguay	19,000
Peru	70,000
Romania	16,000
Russian Federation	1,300,000
Serbia	2,700
Tunisia	2,900
Turkey	
Venezuela (Bolivarian Republic of)	120,000
West Bank and Gaza	
TOTAL	**3,767,000**

UNAIDS 2016 data for all countries[55] except for China[56] and Russia[57]

Included Countries

COUNTRY	PLHIV
Afghanistan	7,500
Angola	280,000
Anguilla	
Antigua and Barbuda	
Armenia	3,300
Aruba	
Bahamas	8,200
Bangladesh	12,000
Barbabdos	2,600
Belarus	
Belize	4,300
Benin	67,000
Bhutan	
Bolivia (Plurinational State of)	19,000
Botswana	360,000
British Virgin Islands	
Burkina Faso	95,000
Burundi	84,000
Cabo Verde	2,800
Cambodia	71,000
Cameroon	560,000
Central African Republic	130,000
Chad	110,000
Comoros	<200
Congo	91,000
Democratic Republic of the Congo	370,000
Cote d'Ivoire	460,000
Cuba	25,000
Djibouti	8,600
Dominica	
Dominican Republic	67,000
Ecuador	33,000
El Salvador	24,000
Equatorial Guinea	35,000
Eritrea	15,000
Ethiopia	710,000
Fiji	<1,000
Gabon	48,000
Ghana	290,000
Grenada	
Guatemala	46,000
Guinea	120,000
Guinea-Bissau	36,000
Guyana	8,500
Haiti	150,000
Honduras	21,000
India	2,100,000
Indonesia	620,000
Jamaica	30,000
Kazakhstan	26,000
Kenya	1,600,000
Kiribati	
Kyrgyz Republic	8,500
Lao, People's Dem Rep	11,000
Lesotho	330,000
Liberia	43,000
Madagascar	31,000
Malawi	1,000,000
Malaysia	97,000
Maldives	
Mali	110,000
Mauritania	11,000
Mauritius	
Moldova, Rep of	
Mongolia	<500
Montserrat	
Mozambique	1,800,000
Myanmar	230,000
Namibia	230,000
Nauru	
Nepal	32,000
Nicaragua	8,900
Niger	48,000
Nigeria	3,200,000
Pakistan	130,000
Papua New Guinea	46,000
Philippines	56,000
Rwanda	220,000
Saint Kitts and Nevis	
Saint Lucia	
Saint Vincent & the Grenadines	
Samoa	
Sao Tome and Principe	
Senegal	41,000
Seychelles	
Sierra Leone	67,000
Solomon Islands	
Somalia	24,000
South Africa	7,100,000
South Sudan	200,000
Sri Lanka	4,000
Sudan	56,000
Suriname	4,900

UNAIDS 2016 data for all countries[55]

Included Countries, cont.

Swaziland	220,000
Syria Arab Republic	
Tajikistan	14,000
Tanzania, U Rep of	1,400,000
Thailand	450,000
Timor-Leste	
Togo	100,000
Tonga	
Trinidad and Tobago	11,000
Turkmenistan	
Turks & Caicos	
Tuvalu	
Uganda	1,400,000
Ukraine	240,000
Uzbekistan	
Vanuatu	
Viet Nam	250,000
Yemen	9,900
Zambia	1,200,000
Zimbabwe	1,300,000
TOTAL	**30,058,800**

UNAIDS 2016 data for all countries[55]

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