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Tenofovir at the Crossroad of the Therapy and Prophylaxis of HIV and HBV Infections

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Abstract

For the treatment and/or prevention of HIV (human immunodeficiency virus) and HBV (hepatitis B virus) infections, 15 tenofovir-containing drug preparations have been commercialized: TDF (tenofovir disoproxil fumarate) and TAF (tenofovir alafenamide) for the therapy of HIV and HBV infections; TDF (or TAF) plus emtricitabine for the prophylaxis of HIV infections; TDF (or TAF) plus emtricitabine plus rilpivirine for the therapy of HIV infections; and several other tenofovir-containing drug combinations have been approved for the therapy of HIV infections: TDF (or TAF) plus emtricitabine plus elvitegravir plus cobicistat; TDF plus emtricitabine plus efavirenz; TAF plus emtricitabine plus bictegravir; TAF plus emtricitabine plus darunavir plus cobicistat; and TDF plus lamivudine with or without efavirenz or doravirine.

Keywords: HIV therapy; HIV prophylaxis; HBV therapy; Tenofovir disoproxil fumarate (TDF); Tenofovir alafenamide (TAF)

Introduction

Tenofovir, *alias (R)*-PMPA, was first divulged as an anti-HIV agent in 1993 [1]. That it would in 2012, become the first antiretroviral agent, approved by the US FDA (Food and Drug Administration) to prevent HIV infection, could have been predicted from the findings of Tsai et al. [2] showing the complete prevention of SIV (simian immunodeficiency virus) infection by *(R)*-PMPA in rhesus macaques. The limited oral bioavailability of *(R)*-PMPA prompted the design of an orally available prodrug, the bis (isopropyloxycarbonylmethyl) or disoproxil derivative [3,4], which would later be formulated as the fumarate salt, TDF (tenofovir disoproxil fumarate).

After TDF had been approved by the US FDA in 2001, it would become increasingly popular, for the treatment of HIV infections, not only in the US but also in the rest of the world. Combination of TDF with emtricitabine, efavirenz and rilpivirine heralded a new dimension to the anti-HIV drug era [5,6], but a big leap forward was set by the description of a new tenofovir prodrug, GS-7340 [tenofovir alafenamide (TAF)] which was preferentially taken up by the lymphatic tissue [7]. TAF was subsequently hailed as the successor of TDF in both the treatment and prophylaxis of HIV infections [8,9].

At present, there are fifteen anti-HIV drug preparations available in the market, which contain either TDF or TAF. They are listed in Table 1 and depicted in Figure 1. With the combination of TAF, emtricitabine and bictegravir (Bictarvy®) no drug resistance has been noted in HIV-1-infected women [10].

From TDF to TAF

As the patent protection for TDF expired in 2017, it was replaced by TAF in or before 2017 by the single drug administrations (Viread® → Vemlidy®) for the treatment of hepatitis B virus (HBV) infection, and, for the treatment of HIV infection, by the double drug combinations (Truvada® → Descovy®), the triple drug combinations (Complera®/Eviplera® → Odefsey®) and quadruple drug combinations (Stribild® → Genvoya®). A new quadruple drug combination (Symtuza®) was launched [11], and an old triple drug combination

TDF	:	Tenofovir disoproxil fumarate					:	Viread®
TDF	+	Emtricitabine (Emtriva®)					:	Truvada®
TDF	+	Emtricitabine	+	Efavirenz (Sustiva®, Stocrin®)			:	Atripla®
TDF	+	Emtricitabine	+	Rilpivirine (Edurant®)			:	Complera®, Eviplera®
TDF	+	Emtricitabine		Elvitegravir	+	Cobicistat	:	Stribild®
TAF	:	Tenofovir alafenamide					:	Vemlidy®
TAF	+	Emtricitabine					:	Descovy®
TAF	+	Emtricitabine	+	Rilpivirine			:	Odefsey®
TAF	+	Emtricitabine	+	Elvitegravir	+	Cobicistat	:	Genvoya®
TAF	+	Emtricitabine	+	Bictegravir			:	Biktarvy®
TAF	+	Emtricitabine	+	Darunavir	+	Cobicistat	:	Symtuza®
TDF	+	Lamivudine					:	Cimduo™
TDF	+	Lamivudine	+	Efavirenz (600 mg)			:	Symfi™
TDF	+	Lamivudine	+	Efavirenz (400 mg)			:	Symfi Lo™
TDF	+	Lamivudine	+	Doravirine			:	Delstrigo™

Table 1: Tenofovir in different commercial anti-HIV drug preparations.

Figure 1: Marketed formulations containing tenofovir (TDF or TAF).

(Atripla®) was not replaced. The advantage of TAF over TDF was that it could be given at a much lower dose (25 mg) as compared to 300 mg for TDF and that, concomitantly, TAF had a much lower risk for nephrotoxicity (tubular nephropathy) and bone toxicity (demineralization).

Dolutegravir combined with emtricitabine and TAF

For the treatment of HIV infection, either bictegravir or dolutegravir could be combined with TAF/emtricitabine [14-16], which means that efavirenz should be replaced by dolutegravir and TDF by TAF [16]. In fact, more weight gain was observed with dolutegravir than with efavirenz (400 mg) [17]. The combination of dolutegravir, emtricitabine and TDF gave similar efficacy and tolerability as the combination of elvitegravir, cobicistat, emtricitabine and TDF [18]. The benefits of tenofovir, lamivudine and dolutegravir in the treatment of HIV infections in sub-Saharan Africa substantially outweighed their risks [19].

Whether a three-drug regimen (dolutegravir + lamivudine + TDF) could be advantageously reduced to a two-drug regimen (dolutegravir + lamivudine) [20, 21], just in a drug-sparing attempt, is a debatable approach as it certainly violates the principles that the combination anti-HIV therapy was originally based upon: synergism, reduced risk of resistance development and lowering the drug dosages (and toxicities).

Cimduo, Symfi and Symfi Lo

The Medical Letter of 14 January 2019 reported that

the US FDA had approved three new once-daily fixed-dose antiretroviral drug combinations for the treatment of HIV-1 infection: Cimduo™ (Mylan), which contains lamivudine (300 mg) and TDF (300 mg), was approved for use in combination with other antiretroviral drugs. Symfi™ (Mylan) and Symfi Lo™ (Mylan) contain TDF (300 mg), lamivudine (300 mg) and efavirenz (600 mg in Symfi or 400 mg in Symfi Lo, respectively), were approved as complete antiretroviral drug regimens.

The ENCORE 1 study had indicated that a reduced dose of 400 mg efavirenz was non-inferior to the standard dose of 600 mg when combined with TDF (300 mg) and emtricitabine (200 mg) as the initial HIV therapy in antiretroviral-naive adults for a period of 48 weeks [22] and 96 weeks [23]. Whether the dosing of 400 mg for efavirenz could be globally advocated, i.e. during pregnancy and antituberculosis treatment, remains to be determined [24].

Delstrigo™

Delstrigo™ contains 100 mg doravirine (Pifeltro™), 300 mg lamivudine and 300 mg TDF. It has been approved in both the US and EU as a once-daily fixed-dose antiretroviral drug combination for the treatment of adults with HIV-1 infection. It represents a complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to doravirine, lamivudine or tenofovir [25].

In HIV-1 treatment-naive adults, Delstrigo™ demonstrated non-inferior efficacy to the combination of evafirenz (600 mg), emtricitabine (200 mg) and TDF (300 mg) at week 48 (DRIVE-AHEAD Trial) [26]. Switching to once-daily Delstrigo™ maintained HIV-1 virological suppression through 48 weeks in the DRIVE-SHIFT Trial [27].

Pre-Exposure Prophylaxis (PrEP) of HIV-1 Infection

A TDF-based PrEP has proven highly effective for the prevention of HIV infection [28-32]. The combination of emtricitabine with TDF (Truvada®) was approved on 16 July 2012 by the US FDA for the prophylaxis of HIV-1 infection. It was later approved worldwide for this indication. Its successor, Descovy® (combination of emtricitabine 200 mg with TAF 25 mg) has been approved by the US FDA for HIV pre-exposure prophylaxis in at-risk adults and adolescents weighing at least 35 kg who are HIV-negative, excluding individuals at risk from receptive vaginal sex (because effectiveness in this population has not been evaluated) [33]. PrEP with oral TDF or TDF/emtricitabine was associated with decreased risk of acquiring HIV infection compared with placebo or no PrEP [34], but, on the other hand, PrEP for HIV increased the incidence of other sexually transmitted infections (STIs) such as chlamydia, gonorrhea or syphilis [35]. The success of PrEP for HIV obviously depends on the uptake of PrEP following its roll-out [36].

In the context of topical PrEP, various drug formulations have been devised to ensure the vaginal delivery of tenofovir [37,38].

Long-lasting Anti-HIV Activity

As originally shown for cabotegravir, a strand-transfer integrase inhibitor, monthly (intramuscular) shots may replace daily anti-HIV pills [39,40]. Such long-acting injectable administration of cabotegravir may also be acceptable in the prevention of HIV infection [41]. As shown for 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA, MK-8591), subcutaneous implants may sustain efficacious plasma levels for 6 months or even longer [42-44].

For cabotegravir and rilpivirine, long-acting implants for the treatment and prevention of HIV have already proceeded to phase 2 clinical trials, and for TAF and MK-8591 they have been evaluated in animals [45]. Long-acting anti-HIV activity has been noted with rilpivirine, dapivirine, MK-8591 and cabotegravir formulations [46].

It is obvious that such long-lasting performance could be expected from tenofovir (or TAF)-containing implants as well. In fact, the long-acting PrEP potency of subcutaneously administered TAF and emtricitabine loaded nanoparticles in the prevention of HIV-1 vaginal transmission has been demonstrated in humanized mice [47].

Tenofovir (TDF, TAF) for Prevention or Therapy of HBV Infections

Both TDF (Viread®) and TAF (Vemlidy®) have been formally approved by the US FDA for the treatment of hepatitis B virus (HBV) infections [9]. In a real-world setting, TDF was found to prevent HBV transmission in mothers with high viral load [48]. Also, in a real-world study, long-term TDF monotherapy showed non-inferior antiviral efficacy compared with TDF-based combination therapy in patients with multidrug-resistant chronic HBV infection [49]. In HBeAg-positive chronic HBV patients, combination therapy of TDF with entecavir provided a higher virus inhibition than TDF monotherapy [50].

In a retrospective analysis of 29,350 patients with chronic HBV infection in China, treatment with TDF was associated with a lower risk of hepatocellular carcinoma (HCC) than treatment with entecavir over a median follow-up time of 3.6 years [51]. Switching from TDF to TAF therapy of HBV infection allowed the maintenance

of the antiviral activity and recovery of renal dysfunction [52].

Conflict of Interest

The author is co-inventor of tenofovir.

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