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

| Composition | Brand Names |
|-------------|-------------|
| TDF         | Viread®     |
| TDF + Emtricitabine (Emtriva®) | Truvada® |
| TDF + Emtricitabine + Efavirenz (Sustiva®, Stocrin®) | Atripla® |
| TDF + Emtricitabine + Rilpivirine (Edurant®) | Complera®, Evipla® |
| 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™ |
(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 efavirenz (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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