Tenofovir: What We Have Learnt After 7.5 Million Person-Years of Use

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Abstract

Tenofovir was licensed for use in patients with HIV in 2001 and since then has become a firmly established anti-retroviral in both guidelines and routine practice. Data have been presented from many pivotal studies—informing on its efficacy, use, and adverse features—and there are also over 7.5 million patient-years of experience to date. We explore the data on this nucleotide reverse transcriptase inhibitor in HIV presented since 2008—focusing on efficacy, side effects, and utility.

Antiretroviral Therapy Strategies in HIV-1 Infection

Introduction

Tenofovir has become a fundamental component of many human immunodeficiency virus (HIV) anti-retroviral regimens since its introduction in 2001. Its use and supporting data were reviewed by Pozniak [1] in 2008, and since then significantly more data on efficacy, tolerability, and toxicities have been acquired. Tenofovir disoproxil fumarate (TDF) is soon to become generic in many countries, and in forthcoming years may be partially superseded by tenofovir alafenamide (TAF), a pro-drug of tenofovir in the late stages of development. It therefore seems timely to review the further knowledge gained since 2008 on this nucleotide reverse transcriptase inhibitor in HIV. This review is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Global Experience and Position in Guidelines

As of the end of 2014, it is estimated that over 7.5 million person-years of tenofovir have been prescribed globally (personal communication, Gilead Sciences, data on file). There is therefore very extensive patient and physician experience of this medication. It has also become a recommended drug in all international guidelines—as TDF tablets or as part of fixed-dose combinations (FDCs): Truvada® (TDF/emtricitabine; Gilead Sciences, Inc.), Atripla® (TDF/emtricitabine/efavirenz; Bristol-Myers Squibb & Gilead Sciences, Inc.); Eviplera®/Complera® (TDF/emtricitabine/rilpivirine; Gilead Sciences, Inc.); and Stribild® (TDF/emtricitabine/elvitegravir/cobicistat; Gilead Sciences, Inc.). Many of the pivotal anti-retroviral therapy (ART) studies undertaken in the last few years have assessed regimens that included TDF, and as a result much is understood of the combination of this drug with other currently available anti-retrovirals. Some guidelines concurrently have become more discriminating—not just listing preferred and alternative drugs in each class but directly drawing on the data available to recommend specific drug combinations. The International Antiviral Society (IAS)-USA guideline is one such example [2].

Efficacy

Over the years, TDF has been successfully used in combination with the newer non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INSTIs), showing high rates of undetectable serum HIV-RNA in clinical trials. Though cohorts can provide some supportive data on efficacy, their main use has been in delineating toxicities and adverse events and they will therefore be discussed predominately in later sections. Much of the informative data has been from studies in patients naïve to ART, though there have also been some important switch studies published.

Naïve Studies

The main naïve studies of note have either utilized TDF as part of the nucleoside/nucleotide backbone for studies of third agents; investigated the single-tablet regimens (STRs) that have been developed which contain TDF; or have specifically examined TDF compared to other nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)—principally abacavir.

Studies Comparing NRTIs

In the latter area—TDF compared to other NRTIs—the pivotal study since the last review has been the ACTG 5202 trial (ClinicalTrials.gov number, NCT00118898) [3, 4]. This placebo-controlled, randomized study of 1857 patients examined the time to virologic failure in patients treated with Truvada compared to Kivexa® (abacavir/lamivudine; known as Epzicom® in North America; GlaxoSmithKline Ltd.) in combination with either efavirenz or ritonavir-boosted atazanavir. This study was partially halted and unblinded (on the instruction of the Data Safety Monitoring Committee) as more virologic failures were seen in those with a high baseline viral load (>100,000 copies/ml) receiving Kivexa versus those receiving Truvada [hazard ratio of 2.33 (95% CI 1.46–3.72)]. Data on HLA-B5701 typing and baseline genotypic resistance analyses were not available in some subjects and this may theoretically have partially contributed to these results; however, a similar signal (favoring Truvada at high viral loads) was also seen in the randomized, open-label ASSERT study (ClinicalTrials.gov number, NCT00549198)—comparing Truvada and Kivexa, each in combination with efavirenz [5, 6].

Meta-analyses have been performed assessing the question of the differential efficacy of Truvada and Kivexa at high viral loads and have produced variable results. Hill and Sawyer [7] and Lee et al. [8] determined that Truvada achieved greater virology success, while Cruciani et al. [9] found no significant differences.

Tenofovir as an NRTI Backbone in Studies of Other Anti-Retrovirals

Truvada has been the NRTI backbone most commonly utilized in naïve studies examining the efficacy and utility of the newer anti-retrovirals. Examples of such recent studies are shown in Table 1 and many of the newer agents still under development continue to be studied primarily in combination with tenofovir/emtricitabine.

Table 1 Main naïve anti-retroviral therapy studies informing guidelines and practice since 2008

The majority of these studies utilized TDF in both arms and therefore give little insight into the efficacy and utility of tenofovir as compared to other NRTIs, but they do give a wealth of encouraging data on the suitability of pairing these third agents with this nucleotide reverse transcriptase inhibitor—which can then be used to inform clinical practice on which combinations of anti-retroviral agents to use in individual patients.

Tenofovir as Part of New Fixed-Dose Combinations

Tenofovir has become an integral component of many of the FDCs and STRs developed in recent years. Atripla was licensed (in 2006 in the US and 2007 in Europe) on the basis of switch studies from efavirenz and Truvada, and pharmacokinetic modeling and bioequivalence assays.

Eviplera/Complera was licensed in 2011 on the basis of the ECHO/THRIVE (ClinicalTrials.gov numbers, NCT00540449 and NCT00543725) data comparing rilpivirine plus NRTIs and efavirenz plus NRTIs (100% of patients in ECHO, and 60% of participants in THRIVE received TDF/emtricitabine as their backbone) [10]. Its utility as an STR was assessed

further in naïve patients in the randomized unblinded STAR study (Eviplera/Complera vs. Atripla; ClinicalTrials.gov, number NCT01309243) [11].

Stribild was licensed in 2012 in the US and 2013 in Europe, on the basis of blinded comparisons to Atripla and to Truvada and atazanavir/ritonavir (GS-102 [ClinicalTrials.gov, number NCT01095796] and GS-103 [ClinicalTrials.gov, number NCT01106586] studies, respectively) [12, 13].

As with the studies listed in the preceding section, these trials reveal little on the efficacy or utility of TDF itself compared to other NRTIs, but do provide good data to support its use as part of these STRs.

Switch Studies

There have been switch studies designed to demonstrate data on the comparative efficacy and utility of tenofovir. BICOMBO was an open-label comparison of 333 patients stable on abacavir/lamivudine-based therapy, randomized to either remain on their present regimen or switch to a TDF/emtricitabine-based combination [14]. Treatment failure (and adverse events leading to discontinuation) was higher in those that remained on abacavir/lamivudine compared to those switched to TDF/emtricitabine. The SWIFT study (ClinicaTrials.gov number, NCT00724711) assessed a similar randomized open-label switch for 311 patients on stable abacavir/lamivudine and boosted PI regimen, with non-inferiority shown between the two arms (remaining on abacavir/lamivudine or switching to TDF/emtricitabine) [15]. Similar non-inferior results were seen in the 360 patients enrolled in the STEAL study (ClinicaTrials.gov number, NCT00192634), which examined switching stable patients' NRTIs to either abacavir/lamivudine or TDF/emtricitabine [16].

It must however be acknowledged that all switch studies have inherent biases that may influence results.

Other Knowledge Gained from Studies

We have also acquired data on the forgiveness of TDF/emtricitabine/efavirenz (Atripla) in terms of viral breakthrough and resistance development in the FOTO study

(ClinicalTrials.gov number, NCT00414635) [17]. It had been argued that the similar (intracellular) half-lives of the active agents in this combination would allow forgiveness of missed doses and avoid significant 'effective monotherapy' of agents with longer half-lives as a result of poor adherence. Cohen et al. [17] assessed the viral control in stable patients (with CD4 >200 cells/ml) who had been well controlled on daily TDF/emtricitabine/efavirenz and who switched to taking the Atripla Monday–Friday but missing dosing on Saturdays and Sundays (FOTO is an acronym for Five On Two Off). Similar viral control (with no excess in rebound or resistance) was seen compared to those who continued daily Atripla dosing. Though this dosing regimen is not specifically advocated, it significantly helps to inform discussion with patients on the potential impact of missed or late doses.

Tenofovir and the combination of TDF/emtricitabine have been heavily investigated in pre-exposure prophylaxis (PrEP)—therapy to at-risk HIV-negative individuals to prevent acquisition of HIV. Though a full review of this strategy is outside the scope of this paper, significant protection was demonstrated for TDF or TDF/emtricitabine in many settings [18–21]. Topical (mainly vaginal) tenofovir has also demonstrated efficacy [20, 22].

Tolerability and Toxicity

In 2008, 7 years after its licensing as an anti-retroviral, Pozniak [1] reported on the safety of TDF and concluded that a considerable amount of clinical data and experience supported the favorable tolerability of TDF. With a further 7 years of clinical experience, it is timely to re-review its safety profile.

General

Tenofovir disoproxil fumarate, and the FDCs that contain this NRTI, are generally well tolerated by HIV-infected patients with the most reported adverse events being some dizziness and gastro-intestinal discomfort (i.e., low-grade diarrhea and nausea), rarely significant enough to cause discontinuation [23, 24]. Furthermore, 7-year follow-up data of TDF monotherapy in chronic hepatitis B (HBV)-infected patients have demonstrated a very low drug-related discontinuation rate of 0.5% [25].

Renal

The key potential toxicity of TDF remains renal tubular dysfunction. This can vary from low-grade plasma creatinine increases (with a consequent drop in the estimated glomerular filtration rate [eGFR]) to significant renal tubular dysfunction and Fanconi's syndrome. Such renal adverse effects were already well recognized by the time of Pozniak's review in 2008 [1], but further data and understanding have since been acquired.

The commencement of TDF may be associated with an initial decline in eGFR and actual glomerular filtration rate within the first few months. However, long-term follow-up studies (e.g., the extended phase-3 studies GS903E [10 years] and GS934 [5 years]—comparing TDF to either zidovudine or stavudine [26–29]) have demonstrated that the mean eGFR subsequently stabilizes. In the combined 3-year renal analysis of the GS934 and GS903E studies, no patients discontinued because of adverse renal events and there was no apparent increased risk of clinically significant renal dysfunction associated with TDF [28]. Subsequently, large meta-analyses have demonstrated a significantly greater loss of renal function in those on TDF (as compared to non-TDF-containing regimens), but only rare severe renal dysfunction [30]. However, in those who develop significant tenofovir-associated renal impairment there is frequent, but not universal, reversibility on TDF discontinuation [31].

There are many other potential causes and confounders for renal impairment in patients commencing anti-retrovirals (e.g., age, concomitant illnesses and medications) and therefore the impact on renal physiology of TDF in healthy HIV-negative subjects in PrEP studies has been examined. Small declines in eGFR after TDF initiation were again seen [32, 33]. A drawback is the limited duration of TDF use in these PreP studies to date, in conjunction with a short follow-up time.

Fanconi's syndrome remains a rare side effect of TDF therapy. After initial case reports [34–37], case series and cohorts have provided more solid proof for this association. For example, the US Food and Drug Administration examined 164 adverse event reports fulfilling the definition of Fanconi's syndrome [38]. It became apparent that the majority of patients were receiving a PI (83%, with 74% also on ritonavir boosting) in conjunction with TDF. Some further studies also suggested an association between TDF-related renal tubular dysfunction

and boosted PI use [37, 39, 40]. The randomized ACTG 5202 study (ClinicalTrials.gov number, NCT00118898) demonstrated an increase in the calculated creatinine clearance at week 96 in those receiving TDF with efavirenz, with a drop only being seen in those receiving TDF with boosted atazanavir [41].

Though the potential mechanisms behind such an association are still unclear, there are plausible pathophysiologic interactions. Tenofovir is eliminated via the kidney by a combination of glomerular filtration and active tubular secretion facilitated by multidrug-resistant protein type 4 [42–45]. This latter protein does not seem to be affected by the PIs, however, they may increase net intestinal absorption of tenofovir, and this may (in theory) lead to higher renal tubular cell tenofovir levels and thereby potentially contribute to nephrotoxicity [46–48].

TDF Renal Toxicity in HBV

However, concomitant medications do not appear to be a prerequisite for Fanconi's syndrome development with TDF. In HBV mono-infection, Fanconi's syndrome cases have been reported, though potentially at lower rates than in HIV-infected patients [49–52]. Whether this may be partially related to improved renal monitoring in these patients (following lessons learnt from the HIV-infected patients) is unclear.

Lesser degrees of renal dysfunction have also been seen in HBV mono-infected individuals treated with TDF. Buti et al. [25] summarized 7-year efficacy and safety data from the original TDF-HBV registration trials incorporating 437 patients and reported only 1.7% where renal function had been noticed to significantly alter. However, only serum creatinine, serum phosphate, and eGFR were utilized as measures of TDF toxicity. Contrary, Tien et al. [53] assessed the $TmPO_4$ (maximal rate of tubular reabsorption of phosphate)/GFR ratio in HBV-infected patients treated for >18 months with TDF and reported an increased risk of proximal tubular dysfunction.

Renal Monitoring in Those on TDF

The above discrepant data illustrate the potential importance of the methodology of renal monitoring. There is no universally accepted method of monitoring renal physiology or detecting renal tubular dysfunction in this clinical setting. It is clear that eGFR measurement

alone is not adequate to exclude more subtle, but potentially severe, changes in kidney physiology.

Increased phosphaturia, normoglycemic glucosuria, and aminoaciduria are markers of proximal tubular dysfunction, and periodic evaluation for these may aid in the diagnosis of incipient tubular injury. Maggi et al. [54] evaluated TDF-induced tubular dysfunction in patients randomly assigned to either a TDF- or abacavir-containing regimen through analysis of urinary excretion of phosphate and uric acid. Although there was no significant variation in eGFR, there was a significant increase in urinary excretion of phosphate in patients on TDF compared to those on abacavir after 6 and 12 months. To date, no long-term follow-up studies have yet reported on the development of early tubular dysfunction markers over time while on TDF.

Pregnancy and Breast Milk

There are only a very limited number of studies evaluating the pharmacokinetic profile of TDF during pregnancy. TDF has been shown to cross the placenta resulting in significant fetal concentrations (as measured by paired maternal plasma and umbilical cord samples) [55]. However, there appears to be no increased rate of fetal abnormalities in studies nor in the Anti-Retroviral Pregnancy Registry in those receiving this NRTI [56]. Of 1800 reported pregnancies where the mother had taken TDF, no increased rates of congenital abnormalities above controls have been seen. The number of exposed women was expected to have been sufficient to detect at least a 1.5-fold increase in risk of overall birth defects and a twofold increase in risk of birth defects in the more common classes—cardiovascular and genitourinary systems. A similar observation was noted in the DART trial (controlled-trials.com number, ISRCTN13968779) with no increase in congenital, renal, or growth abnormalities with in utero tenofovir exposure [57].

To date, the main study evaluating TDF concentrations in breast milk was performed in Côte d'Ivoire in a small group of 5 women with 16 breast milk samples [58]. TDF is excreted in breast milk although in very small concentrations (0.03% of the proposed oral infant dose).

Bone

Compared to the general population, HIV-infected patients are at increased risk of developing osteoporosis and fractures [59, 60]. A meta-analysis of cross-sectional studies using dual-energy X-ray absorptiometry to measure bone mineral density (BMD) demonstrated reduced BMD and increased rates of osteoporosis in HIV-infected versus non-HIV-infected patients (pooled odds ratios of 6.4 and 3.7, respectively) [59].

The etiology of osteoporosis in HIV-infected patients is multifactorial with traditional risk factors, such as hypogonadism, low vitamin D, smoking, age, and low body weight being at least partially responsible [61]. Low nadir CD4 cell counts have been associated with larger declines in BMD [62]. It is probable that HIV-related immune activation may also be a causative factor, with cytokines such as OPG and RANKL (associated with osteoclast activation and bone resorption) being present at higher concentrations in untreated HIV-infected patients compared to those with treated HIV or non-HIV-infected controls [63].

However, anti-retroviral agents have also been implicated in causing osteoporosis [64–66] —with several studies specifically focusing on the potential association with TDF [27, 67, 68]. In the randomized ASSERT study, patients on TDF had a significantly greater decline in hip BMD compared to those in the abacavir arm (-3.5% versus -2.2% at week 96) [5]. Furthermore, bone turnover markers like P1NP, osteocalcin, and alkaline phosphatase were increased in those receiving TDF compared to those on abacavir at both week 48 and week 96 [5, 69]. Similarly, individuals using TDF for PrEP demonstrated small but statistically significant declines in BMD at the total hip (0.8–1.1% at months 24–30) and femoral neck (1.51% at month 30) compared to placebo [70, 71]. Long-term exposure to TDF has also been shown to be associated with an increased risk of osteoporotic fracture [72].

Overall, however, it appears that the main impact of anti-retrovirals (including TDF) on BMD is within the first 48 weeks of commencement, with apparent stabilization subsequently [73]. It is unclear whether the impact is diminished in those already stabilized on anti-retrovirals before switching to TDF (as seen in the BICOMBO [14, 74] and STEAL studies [75]).

Switching away from NRTIs may help reverse some of the loss in BMD—as seen in the small GUSTA study (ClinicalTrials.gov number, NCT01367210) [76]. Of 27 patients (the majority

treated with TDF), 13 switched to the non-NRTI combination of maraviroc/darunavir/ritonavir and were noted to have improvements in their proximal femur BMD from baseline to week 48 (mean increase of 2.06%), whilst those that did not switch had a mean decrease (-2.77%).

Several mechanisms have been postulated as to how anti-retrovirals could be associated with loss of BMD—mitochondrial toxicity induced by NRTIs may be involved (as it is in other ART-related adverse events like lactic acidosis and lipodystrophy) [77]. Tenofovir may cause a greater degree of initial BMD loss secondary to urinary phosphate wasting and renal osteodystrophy [78]. However, more research is required to fully determine the prevalence, causes, and consequences of these changes in BMD.

Cardiac

There has not been a signal of increased ischemic cardiovascular events in those receiving TDF (as there is with some other anti-retrovirals, e.g., abacavir, didanosine, and certain PIs) in cohorts such as D:A:D [79]. Conversely, it has become apparent that TDF has a lipid-lowering effect [15, 80], and though this has beneficial effects on calculated cardiovascular risk we are presently lacking good data on actual influence on clinical cardiac events.

Tenofovir Alafenamide (TAF)

Following recognition of the nephrotoxic potential of TDF Gilead developed TAF, like TDF a pro-drug of tenofovir, which is currently being reviewed by regulatory agencies. TAF is primarily metabolized to active tenofovir within lymphoid cells and not plasma—thereby decreasing systemic exposure to tenofovir (as compared to TDF) while maintaining high lymphoid intracellular concentrations.

In HIV, TAF has been co-formulated into a single-tablet regimen with elvitegravir/cobicistat/emtricitabine (E/C/F/TAF; Gilead Sciences, Inc.) and compared against Stribild (elvitegravir/cobicistat/emtricitabine/TDF; ClinicalTrials.gov number, NCT01497899) [81]. Non-inferior virologic control at week 48 was demonstrated (88.4% and 87.9% of patients with HIV-RNA levels <50 copies/ml, respectively). Furthermore, these

trials have shown a similar general safety profile between the regimens and statistically significant differences with respect to renal and bone markers favoring TAF, though with a decrease in apparent beneficial effects upon lipid levels (potentially correlating with less systemic tenofovir exposure with TAF vs. TDF).

Further studies are required to more fully determine any beneficial influences of TAF versus TDF (on toxicity and efficacy); whether there are any detrimental impacts (such as potential decreases in TDF-related lipid-lowering activity); and the optimal renal monitoring (if any) required with this agent.

Overall, it is likely that TAF and TAF-containing FDCs will supersede TDF in coming years, although caution is required with respect to any potential toxicities as yet unrevealed by the development program.

Conclusions

With more than 7.5 million person-years of TDF experience and many pivotal clinical studies, tenofovir has proven to be a very effective and generally safe drug. There are potential issues related to renal dysfunction and BMD, however, this medication has been a pivotal component of successful anti-retroviral regimens for many patients globally.

In the next few years, TDF will become available as a generic drug in most parts of the world, tenofovir is likely to find a niche in PrEP, and the disoproxil formulation may be partly superseded by TAF in Western nations. TAF is also being made available to generic manufacturers to allow the production of affordable products in developing countries. Tenofovir is therefore likely to remain of great utility in HIV for many years to come.

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Compliance with ethics guidelines

This review is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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Electronic supplementary material

Below is the link to the electronic supplementary material.

Supplementary material 1 (PDF 197 kb) (download PDF ⭳)

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