



## Is Tenofovir Alafenamide Safer than Tenofovir Disoproxil Fumarate for the Kidneys?

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## **Tenofovir: is TAF safer than TDF for the kidneys?**

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## **Abstract**

Tenofovir disoproxil fumarate (TDF) is currently the cornerstone of HIV treatment. Although it shows an overall good safety profile, numerous cases of nephrotoxicity have been reported. Tenofovir alafenamide (TAF) is a novel tenofovir prodrug which has been developed to improve renal safety. Pharmacokinetic studies suggest a better renal tolerance of TAF than TDF, probably because tenofovir plasma concentrations are lower after TAF administration. Consistently in clinical trials, renal tolerance seems to be improved in patients treated with TAF. However, some questions remain. First, whether tenofovir can accumulate and lead to nephrotoxicity under specific circumstances after TAF administration is unknown. Second, only "real-world practice" will inform us on long-term TAF renal safety. Last, TAF renal safety in patients with chronic kidney disease has not been studied in any randomized clinical trial. In conclusion, TAF appears as a very promising drug and long term safety will be an important determinant of its expansion.

**Keywords:** Drug nephrotoxicity, HIV, HBV, antiretroviral, chronic kidney diseases

**Key point:** Tenofovir alafenamide, a novel prodrug of tenofovir, has shown a better renal safety profile in clinical trials and pharmacological studies than tenofovir disoproxil fumarate. However questions remain about a potential residual nephrotoxicity as the endproduct after metabolism is still tenofovir.

## Introduction

Tenofovir Disoproxil Fumarate (TDF), the oral prodrug of TFV, is included in most recommended first-line anti-HIV regimens according to the international guidelines, and is the preferred drug to treat HIV/ Hepatitis B virus (HBV) coinfecting patients<sup>1,2</sup>. TDF is a highly effective drug with an overall good safety profile, but numerous cohort studies and case reports have highlighted the significant risk for renal toxicity since its market approval in 2001<sup>3</sup>. In most cases, TDF-associated nephrotoxicity consisted in a specific form of proximal tubulopathy called Fanconi syndrome<sup>4</sup>. The hallmarks of this syndrome include hypophosphatemia due to hyperphosphaturia, glycosuria without hyperglycaemia, metabolic acidosis with normal anion gap and hypokalemia. Other abnormalities may also include aminoaciduria, and hypouricemia, all reflecting tubular reabsorption deficiency. In some cases, the proximal tubulopathy can be associated with nephrogenic diabetes insipidus manifesting as a polyuria-polydipsia syndrome<sup>4</sup>. Finally, the tubular damage can also be associated with mineral bone disease, such as bone pain and fractures, presumably due to urinary loss of phosphorus<sup>5</sup>. TDF-induced nephrotoxicity is classically diagnosed between a couple of weeks and a couple of years after treatment initiation<sup>6</sup>, but very late occurrences have been reported<sup>7</sup>, which stresses the importance of unidentified triggering cofactors<sup>8</sup>. While the tubular outcome is consistently favorable 4 to 8 weeks after TDF discontinuation, acute kidney failure, when associated, is not always fully reversible<sup>9,10</sup>. Chronic nephrotoxicity has also been reported<sup>11,12</sup>.

As HIV infection require life-long treatments, safety of antiretrovirals is a major concern. Consequently, a new prodrug of TFV, tenofovir alafenamide (TAF), has been developed to optimize renal safety. In this article, we review the pharmacological and clinical data that have been published on TAF, and use it as a ground to discuss its renal safety.

## Pharmacological data

### Pharmacokinetics data: TAF is more stable than TDF in plasma

TFV harbors two negative charges which limit its cellular penetration and preclude oral administration<sup>13</sup>. TDF and TAF are both prodrugs of TFV which contain lipophilic groups that mask the charged phosphonate moiety, and improve oral bioavailability. To be activated, TAF and TDF need to be hydrolyzed to TFV<sup>13,14</sup>. Once in a target cell, TFV is sequentially phosphorylated by cellular AMP and ADP kinases. The resulting tenofovir diphosphate (TFV-DP) is the active drug (Figure 1).

TDF is rapidly metabolized to TFV in plasma<sup>14</sup>. In contrast, TAF shows a much stronger plasma stability, and penetrates target cells where it is rapidly converted into TFV<sup>15</sup>. As a consequence, plasma levels of TFV are high after oral administration of TDF and low after oral administration of TAF. Intracellular TAF is hydrolyzed to TFV by Cathepsin A, which is predominantly expressed in lymphoid cells, and also expressed in a broad range of tissues, including the kidneys, liver, macrophages, platelets, and testis<sup>15</sup>. TAF hydrolysis can also be performed by carboxylesterase 1 (CES1), which is mostly expressed in hepatocytes<sup>16</sup>.

After oral administration of 25 mg of TAF (or 10 mg when administered with cobicistat which act as an enhancer), plasma TFV exposure is 90% lower than after oral administration of 300 mg of TDF. In contrast, in peripheral blood mononuclear cells, TFV-DP exposure is 4 to 6 fold higher<sup>17–20</sup>. TAF is a substrate of the intestinal efflux transporter P-glycoprotein (P-gp)<sup>21</sup>. As a consequence, when TAF is co-administrated with cobicistat, which is an inhibitor of P-gp, TAF exposure is increased approximately 2-fold, and TAF doses can be reduced<sup>18–22</sup>. In summary, TAF generates lower plasma TFV exposure, and higher intracellular concentrations of TFV than TDF. Reducing TFV plasma exposure is expected to improve global drug safety, while enhanced intracellular exposure is expected to ensure efficacy.

### Pharmacodynamics data: TDF or TAF, the end-product is still TFV

Clinical reports suggest that an elevated TDF trough level is a risk factor for renal toxicity<sup>23,24</sup>. High plasma TDF exposures correlates with the development of proximal renal tubulopathy in animal models<sup>25</sup>.

TFV is excreted in urine by tubular secretion and by glomerular filtration<sup>14,26</sup>. TFV enters the proximal tubular epithelial cells (PTECs) at their basolateral pole through the human organic anion transporters (hOAT) 1 and 3 (Figure 3). It is secreted in urine by the multidrug resistance-associated protein (MRP) 4, located at the apical pole of PTECs<sup>27</sup>. Evidence from animal model<sup>28,29</sup> and clinical studies<sup>30,31</sup> suggest that TFV nephrotoxicity is due to a dose-dependent accumulation in the cytoplasm of PTECs, which results in mitochondrial DNA polymerase  $\gamma$  dysfunction. Mitochondrial morphological changes and dysfunction ensue<sup>32</sup>. Recently, Bam *et al.* showed that unlike TFV, TAF was not a substrate for renal hOAT 1 and 3<sup>26</sup>. As a consequence, it is unlikely that TAF will accumulate in PTECs in a hOAT-dependent manner (Figure 3). Importantly, this cannot be used as an indicator of a better renal tolerance of TAF. Indeed, as TDF is not an organic anion, it is probably not a substrate of hOAT either; only TFV is. Whether the administered prodrug is TAF or TDF, the end product is TFV. Furthermore, the fact that TAF is not a substrate for hOAT1 and 3 does not mean that it cannot enter PTECs. TAF is lipophilic and diffuses easily into cells. In non-hOAT expressing cells, TAF cytotoxicity was greater than that of TFV because of a higher cellular permeability to TAF than to TFV<sup>26</sup>. As a consequence, the expected better renal tolerance of TAF is related to its higher plasma stability and lower administered dose, both generating less plasma TFV than when TDF is used, with no correlation with hOAT1 or hOAT3 uptake.

After oral administration of a single dose of radiolabeled [<sup>14</sup>C]-TAF, two plasma peaks of radioactivity are observed. The first occurs approximately 2 hours after ingestion and mainly consists of TAF (73%). The second occurs approximately 1-2 days after ingestion and exclusively consists of uric acid (98%). Eight days after oral administration, 36% and 47% of the total radioactivity have been recovered in urine and the feces, respectively. Radioactive components found in urine are: TFV

(87%), uric acid (7.5%) and TAF (5.5%). In the feces, radioactivity exclusively consists of TFV (99%)<sup>33</sup>. Therefore, it can be estimated that approximately one third of orally administered TAF is eliminated through the kidneys as TFV. As a comparison, TDF oral bioavailability is about 40%<sup>14</sup>. Considering that it is rapidly hydrolyzed to TFV in plasma and that 80-100% of plasma TFV is eliminated in the urine<sup>14</sup>, we can estimate that elimination of TDF after oral administration is very similar (in proportions) to that of TAF, only that a 10 times higher dose of TDF is required to achieve clinical efficacy (Figure 2).

## **Clinical data**

### **TAF vs TDF in HIV-1 infected patients with normal kidney function**

In phase 1 studies in HIV infected patients, TAF demonstrated more potent antiviral activity against HIV-1 than TDF and a good overall safety profile in the short term<sup>17,34</sup>.

Phase 2 and 3 studies have compared the efficacy and safety profile of TAF and TDF in HIV-1 infected patients with normal (or minimally impaired) renal function, treated for 48 weeks<sup>18–20</sup>. Table 1 summarizes the main characteristics of these trials.

All studies were randomized, double-blinded, and controlled. About 150 patients (each phase 2 study) and 1744 patients (phase 3 study) were randomized to receive TAF or TDF. All subjects were treatment-naïve and were not infected with HBV or hepatitis C virus (HCV). The phase 2 studies excluded patients with a creatinine clearance estimated by Cockcroft and Gault formula ( $CrCl_{CG}$ ) below 70 ml/min as recommended for TDF treatment<sup>35</sup>. The phase 3 study excluded patients with a  $CrCl_{CG}$  below 50 ml/min. Associated antiretrovirals (ARV) consisted of elvitegravir, cobicistat and emtricitabine, (E/C/F) or darunavir, cobicistat and emtricitabine (D/C/F).

The two studies that compared E/C/F/TAF to E/C/F/TDF showed that TAF achieved a higher or comparable rate of virological suppression<sup>18,19</sup>. The intention-to-treat rate of virological suppression was lower with D/C/F/TAF than with D/C/F/TDF. This was probably due to a higher rate of loss to

follow-up in the TAF group <sup>20</sup>. Rates of discontinuation for significant adverse events were similar in both arms.

In the 3 studies, the diminution of CrCl<sub>CG</sub> was more pronounced in the TDF arm than in the TAF arm. CrCl<sub>CG</sub> decreased in the first 2-4 weeks of treatment and then stabilized. It is important to note that all regimens included cobicistat which inhibits tubular secretion of creatinine (Figure 3)<sup>36</sup>. Consequently, creatinine clearance is expected to decrease at the initiation of the treatment without any change in actual GFR. However, the smaller decrease in CrCl<sub>CG</sub> in the E/C/F/TAF group than in the E/C/F/TDF group could be an indication of a better renal tolerance of TAF compared with TDF.

Proteinuria (estimated by the urinary protein/creatinine and albumin/creatinine ratios) was mostly comparable in the three studies. This is consistent with the absence of glomerular toxicity of TFV. More interestingly, in the 3 studies, urinary excretion of retinol binding protein (RBP) and of  $\beta$ 2 microglobulin (markers of proximal tubular dysfunction) decreased or increased less, respectively, in the TAF arm.

Recently, a study was published in which 959 patients were switched from various TDF-based regimens (including E/C/F/TDF) to E/C/F/TAF, while 477 patients continued their TDF-based regimen<sup>37</sup>. Efficacy was similar or higher in the TAF arm (depending on the regimen before the switch), after 48 weeks of treatment. Two renal adverse events in the TAF arm lead to discontinuation, but were unrelated to TAF. In the TDF continuation arm, 5 renal events leading to discontinuation were reported, including chronic renal disease, elevated serum creatinine, Fanconi syndrome, and nephrolithiasis. Significant improvements in tubular markers were found in patients who were switched from a TDF containing treatment to E/C/F/TAF, irrespective of previous treatment regimen. In contrast, tubular function worsened after 48 weeks of follow-up in patients who continued their initial TDF-containing regimen. A statistically significant decrease in serum creatinine was noted in patients who were switched from a ritonavir or a cobicistat-boosted regimen to E/C/F/TAF. Changes occurred in the first 2 weeks and persisted until week 48. As both cobicistat and ritonavir inhibit tubular secretion of creatinine <sup>38</sup>, this decrease could be an indicator of a better



renal tolerance of TAF than TDF. In contrast, serum creatinine increased in the group of patients who were switched from a regimen which contained neither cobicistat nor ritonavir (efavirenz, emtricitabine and TDF) to E/C/T/TAF, probably due to the inhibition of creatinine tubular secretion by cobicistat.

#### **TAF in HIV-1 infected patients with renal failure**

A study was presented at the 2013 Conference on Retroviruses and Opportunistic Infections (CROI) that included patients with severe renal impairment, characterized by a  $\text{CrCl}_{\text{CG}}$  between 15 and 29 ml/min<sup>39</sup>. TAF plasma exposure was minimally increased in case of severe renal impairment, as TAF area under the curve (AUC) was multiplied by less than 2 folds. In contrast, plasma TFV exposure was markedly increased (5.7 folds compared to patients with normal kidney function). However, plasma TFV AUC after oral administration of 25 mg of TAF in patients with severe renal impairment remained inferior to plasma TFV AUC after oral administration of 300 mg of TDF in patients with normal kidney function. This is probably due to the much greater stability of TAF than TDF in blood.

A multicenter open label study has assessed safety of TAF in HIV-1 infected patients with mild to moderate chronic renal impairment<sup>40</sup>. Eighty subjects with a  $\text{CrCl}_{\text{CG}}$  between 30 and 49 ml/min and 162 subjects with a  $\text{CrCl}_{\text{CG}}$  between 50 and 69 ml/min were switched from TDF- or non TDF-containing regimens to E/C/F/TAF without dose adjustment. Actual GFR, measured by iothexol clearance, was assessed in 32 patients. After 48 weeks of TAF treatment, actual GFR remained stable, regardless of whether the participants received TDF or not at time of the switch. Tubular proteinuria improved significantly only in patients receiving TDF at time of the switch. Frequency and grade of adverse events were similar in the two renal function groups. Pharmacokinetic measurements in a subgroup of 30 patients confirmed that TAF did not accumulate in case of moderate kidney impairment. In contrast, TFV exposure was greatly increased compared to an historical cohort of patients with a normal kidney function treated with TAF, but remained lower than TFV exposure of patients treated with TDF.

### **TAF vs TDF in hepatitis B**

Preliminary studies indicated that TAF is efficiently delivered to dog and human hepatocytes where it is converted into TFV by carboxylesterase<sup>16</sup>. Consequently, a phase I study was conducted to assess short term efficacy and safety of TAF for the treatment of chronic hepatitis B infection<sup>41</sup>. Fifty-one subjects with chronic hepatitis B were randomized to receive TDF (300 mg) or TAF (8, 25, 40 or 120 mg) once daily. After 28 days of treatment, TAF was safe and well tolerated. Similar mean changes in serum HBV DNA were found with all the TAF dosage regimens and with TDF. Kinetics of viral decline was also similar in all the groups. No subject experienced any serious or severe adverse event. Serum creatinine increase was smaller in the TAF group than in patients treated with TDF. Proximal tubular functions were not evaluated in this study.

### **TAF vs TDF in HIV and HBV coinfecting patients.**

The preliminary results of a switch study from TDF-based regimens to E/C/F/TAF in 67 HIV-1/HBV coinfecting patients have been presented at the 2015 IAS conference<sup>42</sup>. After 48 weeks of treatment, patients switched to E/C/F/TAF maintained HIV suppression and maintained or achieved HBV suppression. No serious renal adverse event was declared. CrCl<sub>CG</sub> was not significantly different at week 24, but improved at week 48, from 95 to 99.4 ml/min. No significant change in proteinuria was observed. A diminution of tubular proteinuria (urinary RBP and  $\beta$ 2 microglobulin) was found at week 24 but was not confirmed at week 48.

## Discussion

### Can TFV accumulate after TAF administration?

Pharmacological data support an improved renal safety profile of TAF compared with TDF. TAF stability in plasma leads to a lower plasma TFV exposure and potentially to a lower nephrotoxicity. In contrast, high TFV intracellular concentrations probably ensure a high and sustained viral efficacy. Nevertheless, even though TFV plasma exposure is 90% lower, it is not null after administration of TAF. TFV formed in cells after TAF hydrolysis still needs to be eliminated, mainly by tubular excretion. This fraction of circulating TFV can probably accumulate under specific circumstances such as acute kidney injury (AKI)HBV, which is a frequent event in people living with HIV <sup>43</sup>. Indeed, TFV accumulation after TAF oral administration is considerable when the GFR drops below 30 ml/min<sup>39</sup>.

Considering that TAF is lipophilic, it can probably diffuse easily in any cell. TAF is able to enter PTECs <sup>26</sup>, where it is probably converted into TFV by cathepsin A<sup>15</sup> and ubiquitous esterases.

It is therefore not excluded that acute nephrotoxicity will occur after TAF treatment in case of incident AKI. TAF could be responsible for a vicious circle (similarly to what is sometimes observed with TDF) in which AKI causes TFV accumulation, which in turn leads to proximal tubular damage, further deteriorating kidney function.

Finally, the fact that TAF is a substrate for P-gp can be a concern in HIV infected patients who often suffer from diarrhea. Diarrhea is associated with intestinal epithelial cell destruction and overall decrease in P-gp activity, resulting in an accumulation of specific P-gp substrates <sup>44</sup>. In people living with HIV, diarrhea could lead to TFV accumulation both because of pre-renal acute kidney failure and of diminished clearance through P-gp. This is the reason why a lower dose of TAF is to be prescribed in case of co-administration with cobicistat, which is an inhibitor of P-gp.

### **Renal tolerance of TAF needs to be confirmed in “real-world practice”**

Clinical data partially confirm a good renal safety profile of TAF as compared to TDF. However, caution is warranted as follow-up in this pre-marketing studies is relatively short (48 weeks). TDF-related acute nephrotoxicity can occur several years after the beginning of the treatment, and necessitate large cohort studies to be evidenced. Studies with a longer follow-up are needed to assess more precisely TAF renal safety. In addition, even if the number of patients receiving TAF was relatively high in the phase 3 trial, it might not be sufficient to highlight TFV induced nephrotoxicity.

In these studies, as it is commonly the case for clinical trials, subjects were highly selected in order to form homogenous cohorts. Patients with possible risk factors of TFV-induced nephrotoxicity such as ARV-exposed patients, subjects with HBV or HCV coinfections, a low body weight, an age higher than 65 years, or treated with didanosine or a ritonavir-boosted protease inhibitor or concomitant nephrotoxic treatments, were excluded <sup>45</sup>. Yet, these patients represent a substantial proportion of the people living with HIV. Consistently, clinical trials involving TDF showed an overall good renal safety profile, while only post-marketing independent cohort studies reported TDF nephrotoxicity<sup>46</sup>. Furthermore, women and patients with advanced HIV disease, who are prone to developing kidney diseases <sup>47</sup>, were underrepresented in these studies. Ongoing studies will provide us with crucial information about TAF safety in these special populations (NCT01705574 is a clinical trial that include women exclusively). As didanosine and boosted protease inhibitors (PI) were commonly associated in reported cases of TDF nephrotoxicity and might play a role in intracellular TFV accumulation in PTECs, TAF regimens including these drugs should be prescribed with a dedicated renal monitoring if necessary.

### **Lack of safety data in patients with renal impairment treated with TAF**

Chronic kidney disease is common among people living with HIV and/or HBV <sup>48,49</sup>. When GFR drops below 60 ml/min/1.73 m<sup>2</sup>, it is recommended to avoid TDF when possible, because of an increased risk of tubular dysfunction and chronic kidney disease progression<sup>48</sup>. When no other

satisfying therapeutic option exists, a dose adjustment to renal function must be observed, because of a reduced TFV clearance<sup>14</sup>. TAF has shown efficacy and safety in HIV infected patient with GFR between 30 and 59 ml/min, without dose adjustment after 48 weeks of follow-up<sup>40</sup>. However, detailed pharmacokinetics data are lacking to assess TAF and TFV systemic exposure after TAF administration in patients with various degrees of renal impairment. The studies by Ramanathan *et al.* and by Pozniak *et al.* show a significant increase in TFV exposure in patients with eGFR lower than 60 ml/min<sup>39,40</sup>, and dose adjustment might be necessary, at least in patients with severe renal impairment. Data concerning renal and general safety of TAF compared to TDF in a randomized trial (as opposed to a switch study) in patients with chronic kidney disease are lacking. In the phase 3 trial by Sax *et al.*, theoretically, patients with a CrCl<sub>CG</sub> as low as 50 ml/min could be included. However, median CrCl<sub>CG</sub> at inclusion was approximately 115 ml/min and inter-quartile range was 100-135 ml/min in both arms, indicating that a vast majority of patients with normal kidney function were included<sup>19</sup>. Similarly, in the study in HIV-HBV coinfecting patients and in the switched study, patients with a CrCl<sub>CG</sub> >50 ml/min were included but median CrCl<sub>CG</sub> at inclusion was respectively 95 ml/min (Q1Q3 interquartile range: 77-117 ml/min) and 105.7 ml/min (89.4–126.0)<sup>37,42</sup>.

## Conclusion

Because of its pharmacokinetic properties and improved renal safety in patients with normal kidney function in clinical trials, TAF appears as a very interesting alternative to TDF. As HIV infection require a long life treatment, all patients currently treated with TDF could benefit from an improved tolerance. Furthermore, the small active dose of TAF compared to TDF will allow the development of the first PI-containing single tablet regimen (STR). The development of STRs is expected to increase adherence as well as viral suppression<sup>50</sup>.

However, the encouraging initial results with TAF need to be confirmed in post-market studies with less selected patients and a longer follow-up. Convincing TAF renal safety data in patients with

chronic kidney diseases is as of yet lacking. Thus, caution will be required in case of prescription of TAF to patients who experienced a TDF-induced renal adverse event.

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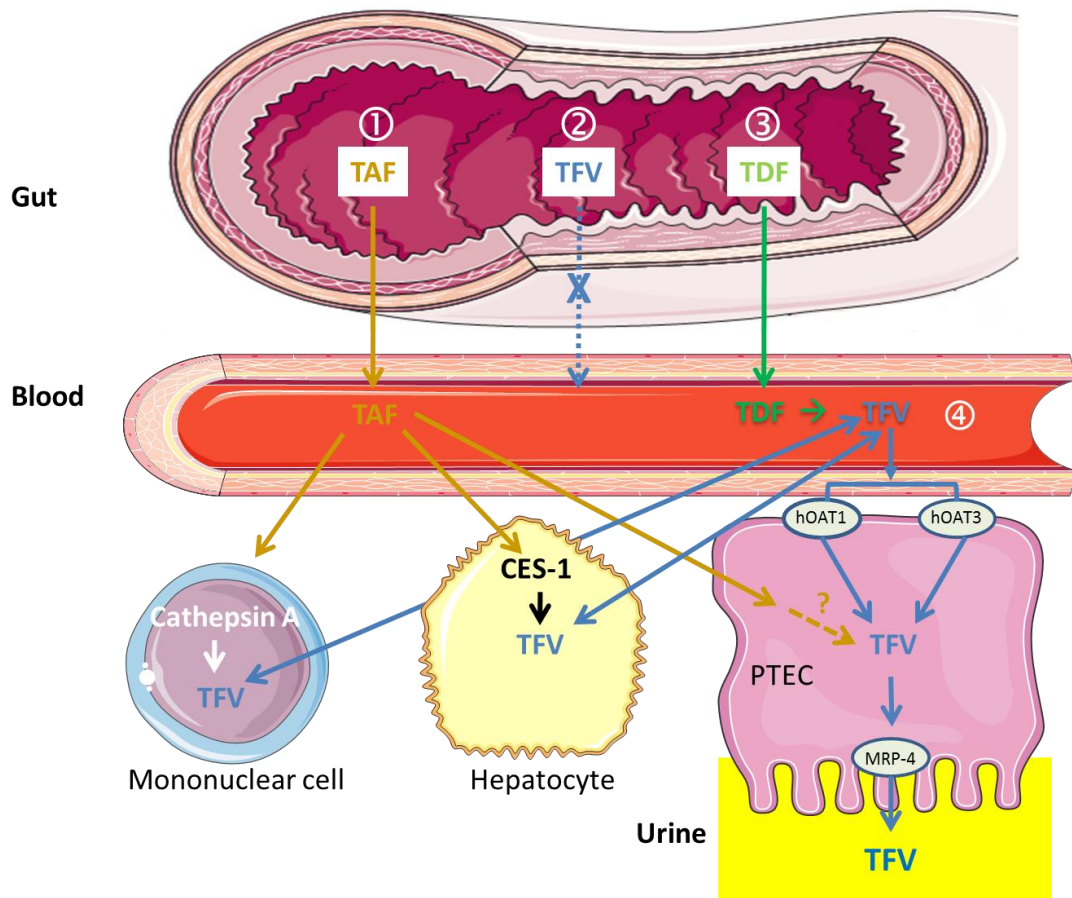
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**Table 1: Phase 2 and 3 studies comparing TAF and TDF in HIV-1 infected, treatment-naïve patients.**

	<b>Sax PE. JAIDS 2014</b>	<b>Mills A. JAIDS 2015</b>	<b>Sax PE. Lancet 2015</b>
Study design	Phase 2, randomized, double-blind, multicenter, active-controlled study.	Phase 2, randomized, double-blind, multicenter, active-controlled study	Phase 3, randomized, double-blind, multicenter, non-inferiority, active-controlled study
Number of patients and ARV exposure	170 treatment-naïve patients without HBV or HCV coinfection	153 treatment-naïve patients without HBV or HCV coinfection	1744 treatment-naïve patients without HBV or HCV coinfection
ARV regimens	E/C/F/TAF (n=112) E/C/F/TDF (n=58)	D/C/F/TAF (n=103) D/C/F/TDF (n=50)	E/C/F/TAF (n=866) E/C/F/TDF (n=867)
Follow-up	48 weeks	48 weeks	48 weeks
Virologic suppression (<50 copies/ml). TAF vs TDF	88.4% vs 87.9%. NS	ITT: 76.7% vs. 84.0% (95% CI: -19.9% to 7.4%)*. Rate of loss to follow up: 6.8% vs. 2%	92% vs 90%. NS
Minimum required CrCl <sub>CG</sub> at inclusion	70 mL/min	70 mL/min	50 mL/min
Observed CrCl <sub>CG</sub> (median (IQR)), mL/min	115 TAF arm 113 TDF arm	116 (97-138) TAF arm 110 (93-131) TDF arm	117 (100-136) TAF arm 114 (99-134) TDF arm
Serum creatinine variation (TAF vs. TDF)	Median change NS	Mean change: 0.06 mg/dL vs. 0.09 mg/dL; p=0.053	Mean change: 0.08 mg/dL vs. 0.12 mg/dL; p<0.001
ClCr <sub>CG</sub> median change (mL/min)	-5.5 vs. -10.1; p=0.041 (4th week, then stabilization)	-2.9 vs. -10.6; p=0.017 (2nd week, then stabilization)	-6.4 vs. -11.2; p< 0.001 (2nd week, then stabilization)
Urinary protein/creatinine ratio median change	NS	NS	-3 vs 20 mg/g; p<0.001
Urinary albumin/creatinine ratio median change	NS	NS	-5 vs 7 mg/g; p<0.001
Urinary RBP/creatinine ratio median change	-0.1 vs 20.7 µg/mL; p=0.001	9 vs. 54 %; p=0.003	9 vs 51 µg/g; p<0.001
Urinary β2-µgb/creatinine ratio median change	-33.6 vs 0.4 µg/mL; p=0.008	-42.0 vs. 2.3 %; p=0.002	-32 vs 24 µg/g; p<0.001
Renal adverse events	None declared	TDF arm: 1 discontinuation because of tubular proximal nephropathy	TDF arm: 4 treatment discontinuations: 3 because of GFR decrease, and 1 because of nephropathy
Metabolic parameters TAF vs TDF	Greater increase in total cholesterol, HDL cholesterol and LDL cholesterol in TAF arm. Total cholesterol/HDL ratio, fasting glucose and triglycerides unchanged in both arms	Greater increase in total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides in TAF arm. Total cholesterol/HDL ratio, and fasting glucose unchanged in both arms	Greater increase in total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides in TAF arm. Total cholesterol/HDL ratio unchanged in both arms
Pharmacokinetics data in a subset of patients TAF vs TDF	Plasma AUC of TFV 91% lower (n=26) and intracellular concentration of TFV 5.3 times higher (n=26)	Plasma AUC of TFV 90% lower (n=32) and intracellular concentration of TFV 6.5 times higher (n=22)	Plasma AUC of TFV 91% lower (n=65) and intracellular concentration of TFV 4.1 times higher (n=35)

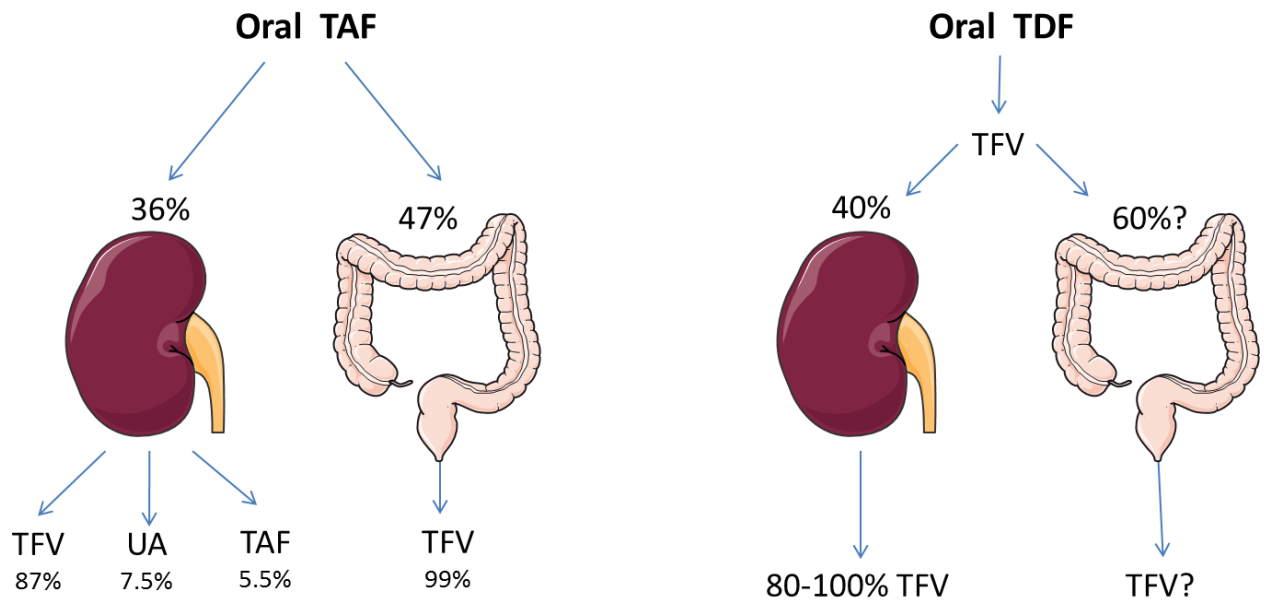
\* The difference is considered significant as the lower bound of the 2-sided 95% confidence interval of the weighted difference in response rate (TAF-TDF) was pre-specified at -12%. ARV: Antiretroviral. AUC: area under the curve. NA: Not applicable or not studied. NS: not statistically significant. CrCl<sub>CG</sub>: estimated creatinine clearance by Cockcroft and Gault formula. E/C/F: Elvitegravir/ Cobicistat/ Emtricitabine. D/C/F: Darunavir/ Cobicistat/ Emtricitabine. IQR: Interquartile range. ITT : Intention to treat.  $\beta$ 2- $\mu$ gb:  $\beta$ 2 microglobulin. RBP: Retinol Binding Protein. TAF: tenofovir Alafenamide. TDF: tenofovir disoproxil fumarate. TFV: tenofovir.

## Figures



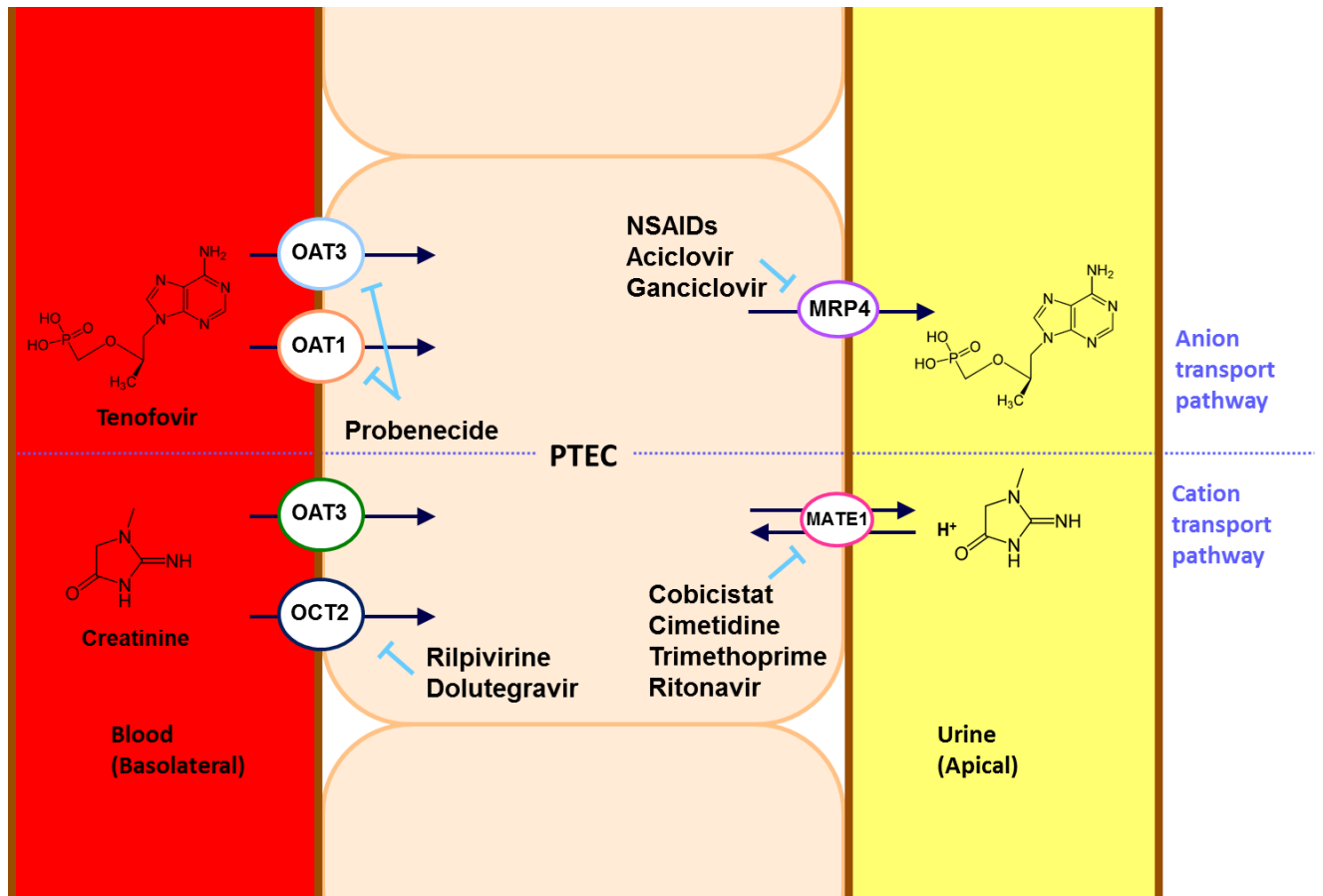
**Figure1: Schematic representation of the metabolism of tenofovir (TFV) and its two prodrugs, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF).**

1: After oral ingestion, intact TAF is absorbed through the gut and transits directly into target cells where it is activated in TFV by cathepsin A in lymphoid cells and by carboxylesterase 1 (CES1) in hepatocytes. 2: TFV is not absorbed in the gut because of its two negative charges. 3: TDF is rapidly converted into TFV in plasma by esterases. Plasma TFV is then taken up by cells. 4: Clearance of TFV is ensured by the proximal tubular epithelial cells (PTEC), and is controlled by membrane transport proteins human organic anion transporter (hOAT) 1 and hOAT3 at their basolateral pole, and MRP4 at their apical pole.



**Figure 2: Elimination of TAF and TDF after oral ingestion.**

After oral administration of radioactive tenofovir alafenamide (TAF), 36 % of the total radioactivity is eliminated by the kidneys mostly as tenofovir (TFV) with a minimal renal excretion of unchanged TAF and uric acid (UA). 47% of radioactivity is eliminated in the feces as TFV. After oral administration of tenofovir disoproxil fumarate (TDF), bioavailability is about 40%, which means that 60% of oral TDF is eliminated in the feces, probably as TFV because TDF is not stable. As TDF is totally hydrolyzed to TFV in plasma, and as plasma TFV is mainly eliminated unchanged in the urine, we can deduce that about 30% of oral TDF is eliminated in the urine as TFV. Thus, TAF and TDF, are both eliminated in urine and feces primarily as TFV.



**Figure 3: Tubular secretion of tenofovir and creatinine.**

Tenofovir is secreted through the proximal tubular epithelial cell (PTEC) by the anion transporter pathway, which include the organic anion transporters (OAT) 1 and 3 at the basal pole of the cell, and the multidrug resistance proteins (MRP) 4 at the apical pole of the cell. Some drugs frequently used to treated people living with HIV can inhibit these transporters and interfere with tenofovir elimination.

Creatinine is secreted through PTECs by the organic cation transporter (OCT) 2 and OAT3 at the basal pole of the cell and the multidrug and toxin extrusion (MATE) 1 transporter at the apical pole. Here again, specific drugs can inhibit these transporters and interfere with creatinine secretion. The result is an increased serum creatinine, and a decreased estimated glomerular filtration rate (when assessed with the Cockcroft and Gault, MDRD or CKD-EPI equations based on creatinine). The actual glomerular filtration rate is not modified.