Mini-Review

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Renal safety of tenofovir alafenamide-based antiretroviral therapy in people with HIV: A mini-review

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SUMMARY Antiretroviral therapy (ART) has significantly enhanced the outlook for people with HIV(PWH), yet certain ART medications can adversely affect the renal function of these patients. Of particular concern is the nephrotoxicity associated with tenofovir disoproxil fumarate (TDF). Compared to TDF, tenofovir alafenamide (TAF), another prodrug of tenofovir (TFV), results in lower TFV plasma levels, thereby alleviating the TFV-associated mitochondrial toxicity on proximal renal tubular cells. Currently, numerous clinical trials and real-world studies have demonstrated the favorable renal safety profile of ART regimens incorporating TAF for PWH. This paper seeks to consolidate the available evidence regarding the renal safety of TAF-based regimens in PWH, encompassing both the general PWH and those with renal impairment or predisposing factors, in order to offer recommendations and insights for TAF clinical application.

Keywords people with HIV (PWH), tenofovir alafenamide (TAF), renal safety

1. Introduction

Kidney disease is a common complication of HIV infection and its treatment, affecting quality of life and life expectancy of patients (*1,2*). Across different countries and populations, the global prevalence of chronic kidney disease (CKD) among patients with HIV varies significantly, ranging from 1% to 49%. The highest prevalence is observed in Africa (*3-9*) (Figure 1).

Various definitions of kidney disease have been utilized in previous studies on renal disease in PWH. Despite the variations in definition, a significant percentage of PWH exhibit signs of renal impairment (*10*). For instance, a cross-sectional study defined kidney disease as meeting at least one of the following criteria: estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, hematuria, proteinuria, or microalbuminuria. According to this definition, 19.0% of HIV-infected individuals in the study were found to have kidney disease (*10*). Kidney disease in PWH is associated with multiple risk factors, in addition to factors related to the patients themselves, such as HIV infection, genetic susceptibility, comorbidities and co-infections. Renal toxicity of some antiretroviral drugs (ARVs) is also an important risk factor (*11*).

Nephrotoxicity is a prevalent adverse effect among some ARVs, particularly observed with TDF and certain protease inhibitors (such as Atazanavir and Lopinavir/ritonavir). TDF is still included in several first-line antiretroviral regimens due to its potent antiviral activity. However, extensive researches have consistently demonstrated that the risk of acute kidney injury (AKI), chronic kidney disease (CKD), nephrogenic diabetes insipidus, and proteinuria associated with TDF use are increased (*12*). Therefore, the nephrotoxicity of TDF has long been a matter of concern. TDF, a prodrug of tenofovir (TFV), exhibits limited plasma stability and an exceptionally short half-life of 0.4 minutes. In plasma, most TDF undergoes conversion to TFV (*13,14*), which is subsequently excreted *via* glomerular passive filtration and tubular active secretion (*11,15*). A prevailing hypothesis suggests that TFV accumulation inhibits mitochondrial DNA polymerase γ, resulting in reduced mitochondrial DNA content and oxidative respiratory chain dysfunction. This cascade ultimately leads to mitochondrial toxicity in proximal tubular cells, potentially explaining TDF-induced nephrotoxicity (*15-17*). Additionally, observations indicate that single nucleotide polymorphisms (SNPs) within the adenosine triphosphate-binding cassette transporters C2 (ABCC2) gene may be associated with tubular dysfunction induced by TDF. Although the precise underlying mechanism remains unclear, this link may be attributed to ABCC2's impact on the transport of various substances within

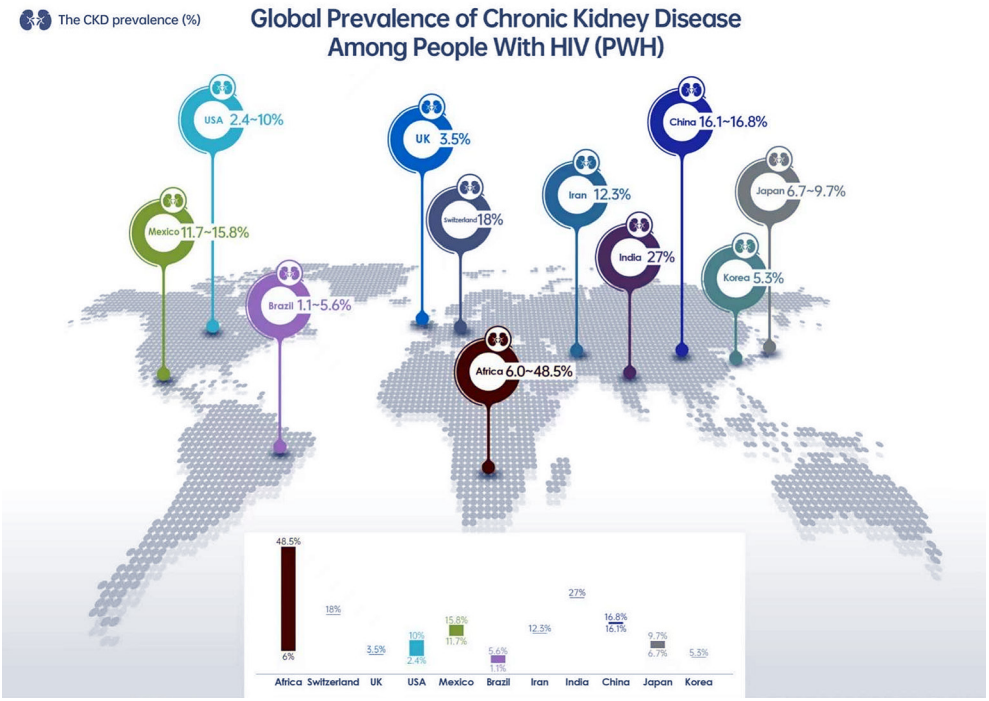

Figure1. Global prevalence of chronic kidney disease among people with HIV (PWH). The incidence of HIV-associated chronic kidney disease (CKD) varies significantly across different time periods, populations, and contexts. The highest prevalence is seen in Africa.

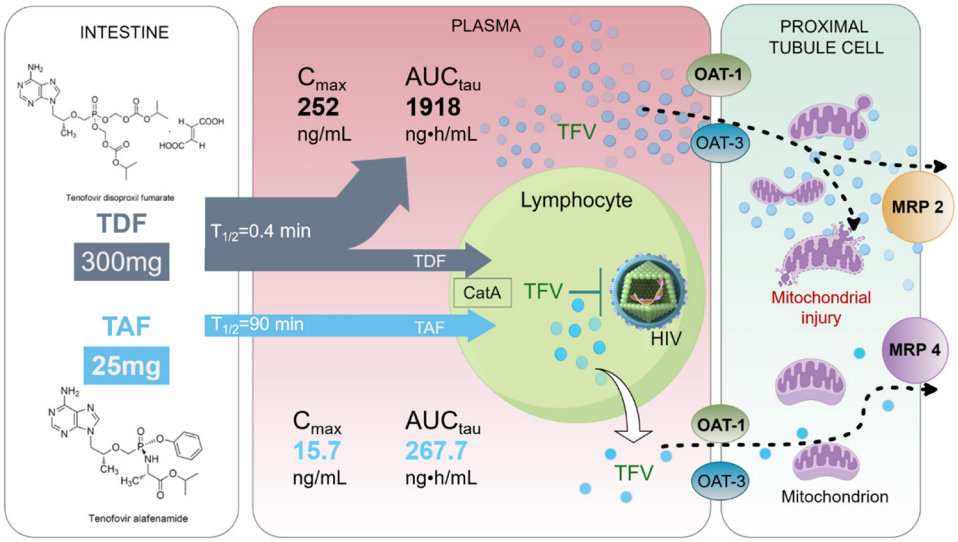

Figure 2. The differences in renal metabolism mechanisms between TAF and TDF. Compared to TDF, TAF exhibits better plasma stability (with a half-life of 90 minutes). After oral administration, TAF efficiently enters target cells and undergoes hydrolysis by the lysosomal carboxypeptidase cathepsin A (CatA) to form TFV. In contrast, TDF is readily hydrolyzed to TFV in the plasma. Large amounts of TFV enter proximal renal tubular cells vie organic anion transporter (OAT)-1 and OAT-3. Intracellular accumulation of tenofovir can cause mitochondrial toxicity and proximal tubular injury. TAF is not a substrate for OAT 1 and 3 and thus does not accumulate in proximal tubular cells, which may be the reason for the better renal safety of TAF (*78*).MRP: multidrug resistance-related protein.

tubular cells (*18,19*). Previous research underscores that tenofovir-related kidney injury is dose-dependent, with elevated TFV plasma concentrations correlating with an increased risk of renal damage (*15,20,21*).

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir (TFV), a nucleotide reverse transcriptase inhibitor. TAF has greater plasma stability and higher intracellular metabolism to TFV than its predecessor, tenofovir disoproxil fumarate (TDF). Therefore, 25 mg of TAF achieves higher concentrations of the active metabolite, tenofovir-diphosphate (TFV-DP), in target cells than 300 mg of TDF, while reducing the average systemic exposure to TFV in plasma by approximately 90% (*22,23*) (Figure 2). Pharmakinetic data from pivotal

Phase 3 studies show that HIV-infected individuals receiving elvitegravir/cobicistat/emtricitabine/TAF (E/c/F/TAF) have 91% (*24*) lower plasma TFV exposure than those receiving E/c/F/TDF. As a result, TAF improves renal safety and has been confirmed in numerous clinical trials (*25*). This review synthesizes existing evidence on the renal safety of TAF-containing regimens in HIV-infected patients, both in general and in those with concurrent kidney injury or related risk factors, aiming to provide guidance and reference for the clinical use of TAF-based regimens.

2. Renal safety data for the use of TAF-containing regimens in general PWH

Numerous studies have shown that TAF-containing regimens are safer for the kidneys than TDF-containing regimens in in general PWL. Several Phase 3 clinical trials have demonstrated that TAF-containing regimens improved renal function more than TDF-containing regimens in HIV-infected patients with a median baseline eGFR of 99.4 to 117 mL/min (*24,26-29*). No HIV-infected patients receiving TAF-containing regimens developed proximal renal tubulopathy or Fanconi syndrome. Substantial evidence supports the renal safety advantage of TAF-containing regimens over TDF-containing regimens. A meta-analysis of 26 clinical trials involving 9,322 HIV-infected patients with a median (IQR) baseline creatinine clearance (CrCl) of 108.6 (91.1, 129.3) mL/min showed that the TAF-containing regimen group had significantly fewer cases of proximal renal tubulopathy (0 case *vs*. 10 cases, $p < 0.0001$) and treatment discontinuation due to renal adverse events (3 cases *vs*. 14 cases, $p < 0.001$) than the TDF-containing regimen group; the TAF-containing regimen group also had a higher proportion of improvement in renal biomarkers during the 96-week treatment period (*30*). Furthermore, several Phase 3 clinical trials (*31-33*) have shown that TAF-containing regimens have similar renal safety as abacavir (ABC) and lamivudine (3TC)-based regimens in HIV-infected patients with a median baseline CrCl or eGFR > 100 mL/min; HIV-infected patients who switched from these regimens to TAF-containing regimens maintained stable CrCl, retinol binding protein to creatinine ratio (RBP/Cr), urine β2-microglobulin to creatinine ratio (β2-MG/Cr), urine protein to creatinine ratio (UPCR), and urine albumin to creatinine ratio (UACR), without developing proximal renal tubulopathy or Fanconi syndrome.

In addition to these clinical trials, long-term follow-up data and real-world studies confirm the favorable renal safety of TAF. Long-term follow-up results from two large Phase 3 clinical trials found that treatment-naïve HIV-infected patients receiving bictegravir (BIC)/emtricitabine (FTC)/TAF (B/F/TAF) therapy (with a median [IQR] baseline eGFR of 122 [104-143] mL/min) did not discontinue treatment due to renal-related adverse events or develop proximal renal tubulopathy during 5 years of treatment (*34*). The eGFR in HIV-infected patients declined slightly in the first four weeks and then stabilized, this decline is consistent with the inhibitory effect of BIC on the renal tubular secretion of creatinine *via* organic cation transporter-2 (*34,35*) . Moreover, a retrospective real-world study conducted in HIV-infected patients with normal baseline renal function (eGFR ≥ 90 mL/min/1.73 m^2) showed that the median annual eGFR change improved significantly from -2.79 mL/min/1.73 m^2/year to -0.28 mL/min/1.73 m^2/year ($p < 0.01$) when HIV-infected patients switched from TDF-containing regimens to TAF-containing regimens (*36*).

3. Renal safety data of TAF-containing regimens in PWH with renal impairment (Table 1)

3.1 PWH with mild renal impairment (60 ≤ eGFR < 90 mL/min/1.73 m^2)

Clinical trials and real-world studies have shown that switching from TDF-containing regimens to TAF-containing regimens improved renal function in HIV-infected patients with mild renal impairment. A prospective cohort study of 38 HIV-infected patients with a median (IQR) baseline eGFR of 77.0 (67.9, 83.3) mL/min/1.73 m^2 switched from TDF-containing regimens to TAF-containing regimens. After 12 months, the median (IQR) eGFR increased significantly to 84.3 (74.07, 95.0) mL/min/1.73 m^2 ($p = 0.001$) (*37*). A pooled analysis of a prospective randomized study and a retrospective cohort study involved 250 HIV-infected patients who had virological suppression on TDF-containing regimens and switched to TAF ($n = 130$) or ABC ($n = 120$) regimens due to significant eGFR decline. Significant eGFR decline was defined as an eGFR decline rate > 3 mL/min/year for > 5 years, an eGFR decline > 25%, or an eGFR > 90 mL/min at baseline and < 70 mL/min at the end of TDF-containing regimen treatment. At baseline, the mean eGFR for the TAF and ABC regimen groups was 73 and 68 mL/min, respectively, and 80% and 72% of patients, respectively, had an eGFR ≥ 60 mL/min. The results showed that at 48 weeks of treatment, both groups had a significant median eGFR increase from baseline, with 5.0 and 6.0 mL/min, respectively ($p > 0.1$ between the two groups); 23% and 26% of patients, respectively, had an eGFR increase >50% ($p > 0.1$ between the two groups). At 96 weeks of treatment, both groups had a similar median eGFR increase from baseline, with 6.0 and 8.5 mL/min, respectively ($p > 0.1$ between the two groups); 18% and 27% of patients, respectively, had an eGFR increase > 50% ($p > 0.1$ between the two groups) (*38*). Another cohort study of 309 HIV-infected patients who switched from TDF-containing regimens to TAF-containing regimens had a median (IQR) baseline eGFR of 78.6 (63.3, 96.4) mL/min/1.73 m^2. During TDF-containing regimen treatment, 40.8% and 22.7% of

Table 1. Renal safety data for the use of TAF-containing regimens in HIV-infected people with normal renal function and in those with concurrent kidney injury

Author Reference	Study design	Regimen	Sample (*n*)	Study period	Outcomes of eGFR	Outcomes of renal biomarkers
HIV-infected people with normal renal function (eGFR > 90 mL/min/1.73 m²)						
Gupta *et al.* Aids.2019 (*30*)	Pooled analysis	TAF-based regimen *vs*.TDF-based regimen	9,322	96 weeks	Naive patients: Median CrCl had declined less in the TAF group compared with the TDF group (difference in LSM 6.0 mL/min, $P < 0.001$ forweek 96); Switch patients: Median CrCl increased in the TAF group while no change was seen in the TDF group (difference in LSM 5.2 mL/min, $P < 0.001$ for week 96).	Naive patients: Median UACR decreased by 5.2% with TAF *vs*. an increase of 4.9% with TDF ($P < 0.001$). Median RBP:Cr increased by 13.8% with TAF compared with an increase of 74.2% on TDF($P < 0.001$). Median β2M:Cr declined by32.1% with TAF compared with an increase of 33.5% on TDF ($p < 0.001$); Switch patients: Median UACR decreased by 5.4% on TAF and increased by 27.0% on TDF ($p < 0.001$). Median RBP:Cr decreased by 2.3% on TAF and increased 61.2% on TDF ($p < 0.001$). Median b2M:Cr decreased by 25.8% with TAF and increased by 53.0% on TDF ($p < 0.001$).
Orkin *et al.* Lancet HIV.2020 (*32*)	Phase III RCT	BIC/TAF/FTC *vs*. DTG/ ABC/3TC	631	144 weeks	Median eGFR: -9.6 mL/min in the BIC/TAF/FTC group *vs*. -11.7 mL/min in the DTG/ABC/3TC group ($p = 0.34$).	Median UACR:2.6 mg/g in the BIC/TAF/FTC group *vs*. -1.6 mg/g in the DTG/ABC/3TC group ($p = 0.94$) ; Median β2M:Cr:-26.4 μg/g in the BIC/TAF/FTC group *vs*. -34.2μg/g in the DTG/ABC/3TC group ($p = 0.41$); Median RBP:Cr:19.6 μg/g in the BIC/TAF/FTC group *vs*. 15.4μg/g in the DTG/ABC/3TC group ($p = 0.83$).
Sax *et al*. eClinicalMedicine. 2023 (*34*)	Phase III RCT	B/F/TAF	634	5 years	The median change at Week 240 in $eGFR_{CG}$ was -8.4 mL/min, consistent with BIC inhibition of organic cation transporter-2 and tubular creatinine secretion.	
HIV-infected people with mild renal impairment (60 ≤ eGFR < 90 mL/min/1.73 m²)						
Rieke *et al.* HIV Glasgow.2018 (*37*)	Observational clinical cohort	FTC/TAF-based regimens *vs*. FTC/TDF-based regimens	38	48 weeks	Median eGFR increased significantly from time of switch to month 12 (from 77.0 to 84.3 mL/ min/1.73m², $p = 0.001$).	
HIV-infected people with rapid or sharp decline in eGFR. *Sharp eGFR defined as: eGFR decline of > 3 mL/min/yr during ≥ 5yrs of TDF use or > 25% eGFR decline or eGFR < 70 mL/min with eGFR > 90mL/min at TDF initiation*						
Verwij*set al.* CROI.2020 (*38*)	Observational clinical cohort	TAF based regimen *vs*. ABC-based regimen	250	96 weeks	50% eGFR recovery observed in 18% with TAF and 26% with ABC ($p > 0.1$); Median eGFR increase in TAF group is 6.0 mL/min, in ABC group is 8.5 mL/min, ($P > 0.1$).	

Table 1. Renal safety data for the use of TAF-containing regimens in HIV-infected people with normal renal function and in those with concurrent kidney injury (continued)

Author Reference	Study design	Regimen	Sample (*n*)	Study period	Outcomes of eGFR	Outcomes of renal biomarkers
HIV patients with moderate renal impairment (30 ≤ eGFR < 60 mL/min/1.73 m^2)						
Podzamczer *et al.* IAS.2017 (*41*)	Phase III single-arm study	E/C/F/TAF	242	144 weeks	Median changes from baseline at Week 144 with prestwich TDF use: $eGFR_{CKD\text{-}EPI}$, sCr: 3.6 mL/min/1.73 m^2 $eGFR_{CKD\text{-}EPI}$, cysC: 3.7 mL/min/1.73 m^2	Of those participants with clinically significant albuminuria (UACR ≥ 30 mg/g) at baseline, 47% had resolution by Week 144; The median UACR decreased from 41 mg/g at baseline to 10 mg/g at the 144 weeks.
HIV patients with severe renal impairment (15 ≤ eGFR <30 mL/min/1.73 m^2)						
Custodio *et al.* Antimicrobial agents and chemotherapy.2016 (*43*)	Phase I single-dose study	TAF	14	14 days	No clinically relevant changes in the median serum creatinine level, eGFR, or phosphate level were observed in any subject in either group.	

patients had an eGFR decline rate > 3 and 5 mL/min/1.73 m^2/year, respectively. These patients had a significant eGFR improvement after switching to TAF-containing regimens, with mean annual increases of 2.72 and 2.78 mL/min/1.73 m^2, respectively (both $p < 0.001$) (*39*).

3.2 PWH with moderate renal impairment (30 ≤ eGFR < 60 mL/min/1.73 m^2).

TAF-containing regimens are safe for the kidneys in HIV-infected patients with moderate renal impairment (30 ≤ eGFR < 60 mL/min/1.73 m^2), according to clinical trials and real-world studies. A Phase 3 clinical trial switched 242 HIV-infected patients with viral suppression and baseline eGFR of 30-69 mL/min to TAF-containing regimens, and 42% and 49% of them had significant proteinuria and albuminuria at baseline (*40*) . In this study, 158 patients (65%) who had used TDF-containing regimens at baseline improved their median eGFR significantly at 144 weeks after switching to TAF-containing regimens; while 84 patients (35%) who had used non-TDF regimens at baseline did not change their median eGFR significantly at 144 weeks after switching to TAF-containing regimens. The urine RBP/Cr ratio and β2-MG/Cr ratio improved significantly at 1 week and remained stable for 144 weeks in patients who switched from TDF-containing regimens to TAF-containing regimens(*40-42*). The median UACR decreased from 41 mg/g at baseline to 10 mg/g at week 144. Patients did not develop proximal tubular dysfunction or Fanconi syndrome (*41*). Another prospective cohort study showed that the proportion of patients with moderate renal impairment decreased from 9.1% at baseline to 3.0% after 12 months of switching from TDF-containing regimens to TAF-containing regimens (*37*) .

3.3 PWH with severe renal impairment (eGFR < 30 mL/min/1.73 m^2)

Few studies have explored the application of TAF-containing regimens in HIV-infected patients with severe renal impairment, but they suggest that these patients can use TAF-containing regimens based on their clinical needs. A Phase 1 clinical trial tested the safety of TAF in non-HIV-infected patients with severe renal impairment who did not receive hemodialysis. The study involved 14 non-HIV-infected patients with severe renal impairment (mean eGFR of 24.0 mL/min) and 13 non-HIV-infected patients with eGFR ≥ 90 mL/min as a control group. They received a single dose of TAF 25 mg and had a 14-day follow-up. The results showed that the patients with severe renal impairment had higher TAF exposure than the control group, but the difference was not clinically significant. The patients with severe renal impairment also had higher TFV exposure than the control group, but lower than the levels in previously studied subjects without renal impairment who received a single dose

of TDF 300 mg. The adverse event rates were similar between the two groups (6 events in the severe renal impairment group and 7 events in the control group), and no clinically significant changes occurred in serum creatinine or eGFR (*43*) . Although this study showed preliminary safety of TAF in non-HIV-infected patients with severe renal impairment who did not receive hemodialysis, Phase 3 clinical trial data are lacking on the use of TAF-containing regimens in HIV-infected patients with severe renal impairment who did not receive hemodialysis. Therefore, TAF-containing regimens are not approved for use in HIV-infected patients with estimated creatinine clearance (CrCl) of 15-30 mL/min or with end-stage renal disease (ESRD, CrCl < 15 mL/min) who did not receive long-term hemodialysis (*44-46*). The safety of TAF-containing regimens in this subgroup of HIV-infected patients requires further validation.

Phase 3 clinical trials and real-world studies show that switching to TAF-containing regimens is safe and tolerable for HIV-infected patients with ESRD who receive hemodialysis, and maintains high virologic suppression rates (*47-51*). A multicenter Phase 3b study switched 55 HIV-infected patients with virologic suppression and ESRD undergoing hemodialysis to E/c/F/TAF, and during a 2-year period, only 4 patients (7.3%) discontinued the treatment due to adverse events, with 2 cases related to the study drug. The patients had virologic suppression rates of 81.8% at 1 year and 55% at 2 years (*47,48*). In this study, 10 patients who completed 2 years of E/c/F/TAF treatment entered an open-label extension phase and switched to B/F/TAF treatment. At 1 year of treatment, no patients discontinued the treatment due to adverse events, and all patients had virologic suppression (*49*). Another retrospective study of 17 HIV-infected patients with ESRD undergoing hemodialysis who switched ART regimens, with 15 patients switching to TAF-containing regimens (12 of them to B/F/TAF), showed that only 1 patient discontinued the treatment due to adverse events, and the overall virologic suppression rate was 82% at 1 year (*50*). Case reports also showed that 6 HIV-infected patients with ESRD undergoing hemodialysis who switched to B/F/TAF had no adverse events, and the virologic suppression rate was 100% at 1 year (*51*). Based on these data, HIV-infected patients with ESRD who undergo long-term hemodialysis can use TAF-containing regimens; E/c/F/TAF, B/F/TAF, and dolutegravir/rilpivirine (DTG/RPV) are the only approved complete single-tablet regimens for HIV-infected patients with ESRD who receive hemodialysis (*44,46,52*).

4. Renal Safety Data of TAF-Containing Regimens in PWH at Risk of Kidney Injury (Table 2)

4.1. Elderly PWH

Kidney disease is more likely in HIV-infected individuals with advanced age(*53,54*), so renal safety of antiretroviral drugs is crucial for elderly HIV-infected patients on antiretroviral therapy. Subgroup analyses of two large multicenter Phase 3 clinical trials showed good renal safety of TAF-containing regimens in elderly HIV-infected patients with normal renal function. The studies involved 196 HIV-infected patients aged ≥50 years who received B/F/TAF (n = 96), DTG+FTC/TAF (n = 59), or DTG/ABC/3TC (n = 41). The baseline median (IQR) eGFR values were 99.0 (83.7–114.0), 104.0 (84.2–121.8), and 101.9 (83.2–130.5) mL/min, respectively. The 144-week treatment results showed that no patients in the B/F/TAF or DTG+FTC/TAF group discontinued the treatment or developed proximal renal tubulopathy due to renal adverse events, while one patient in the DTG/ABC/3TC group discontinued the treatment due to renal failure, which was not related to the study drugs. The median eGFR changes at week 144 from baseline were -9, -9, and -11 mL/min in the three HIV-infected groups, which matched the effect of BIC and DTG inhibiting creatinine secretion by inhibiting organic cation transporter 2 (*55*).

Clinical trials and real-world studies show good renal safety of TAF-containing regimens in elderly HIV-infected patients with mild renal impairment. A multicenter Phase 3 clinical trial switched 167 HIV-infected patients aged ≥ 60 years who had virologic suppression and received TDF-containing regimens to E/c/F/TAF (n = 111) or continued with TDF-containing regimens (n = 56). The baseline median (IQR) eGFR was 80 (68–91) mL/min. The 48-week treatment results showed that both groups maintained stable eGFR and serum creatinine levels. The E/c/F/TAF group improved significantly in UACR, UPCR, RBP/Cr, and β2-MG/Cr than the TDF-containing regimen group at week 48 (percentage change from baseline): UACR (-27.8% *vs*. -7.7%, p = 0.0042), UPCR (-49.8% *vs*. -3.8%, p = 0.00027), RBP/Cr (-41.5% *vs*. 15.2%, $p < 0.0001$), and β2-MG/Cr (-58.7% *vs*. 13.6%, $p < 0.0001$) (*56*). Another retrospective Italian cohort study of 93 HIV-infected patients aged ≥ 55 years who switched to B/F/TAF-containing regimens had a baseline median (IQR) eGFR of 83 (74–91) mL/min/1.73 m^2. After 48 weeks of switching, serum creatinine and eGFR levels did not change significantly, and the median change compared with baseline at 48 weeks was 0. (*P*-values were 0.073 and 0.737, respectively) (*57*).

TAF-containing regimens also keep renal function stable in elderly HIV-infected patients with moderate renal impairment. A Phase 3b clinical trial switched 86 HIV-infected patients aged ≥ 65 years who had virologic suppression and received E/c/F/TAF or TDF-containing regimens to B/F/TAF treatment. The baseline median (IQR) eGFR was 76.2 (39.6–130.2) mL/min (*58*). The 96-week treatment results showed that there were no renal adverse events, treatment discontinuations, proximal renal tubulopathy, or Fanconi syndrome (*58,59*).

Table 2. Renal safety data of TAF-containing regimens in PWH at risk of kidney injury

Author Reference	Study design	Regimen	Sample (*n*)	Study period	Outcomes of eGFR	Outcomes of renal biomarkers
HIV/HBV coinfection						
Surial *et al.* J Acquir Immune Defic Syndr.2020 (*62*)	Observational clinical cohort	Switched from TDF-based regimen to TAF-based regimen	106	14.1 months-14.6 months	60 mL/min/1.73 m^2 < baseline eGFR < 89 mL/min/1.73 m^2:eGFR increased by 3.2 mL/min/1.73 m^2 1 year (95% CI 1.2 to 5.2) after switching to TAF (*P*-value for slope difference 0.001). Baseline eGFR < 60 mL/min/1.73 m^2 :eGFR increased by 6.2 mL/min/1.73 m^2 1 year after the switch (95% CI 2.4 to 10.0, *P*-value for slope difference, 0.001).	Switching to TAF led to a change in urine protein-tocreatinine ratio of -6.3 mg/mmol 1 year after the switch (95% CI -10.0 to -2.7, *P*-value for slope difference 0.01).
HIV/HCV coinfection						
Huhn *et al.* PLoS One. 2020 (*63*)	Phase IIIb RCT	E/C/F/TAF or R/F/TAF	148	36 weeks	Median baseline $eGFR_{CG}$ was 99.8 mL/min, with the median change 2.2 mL/min at W8, 0.9 mL/min at Post-HCV W4, and 0.1 mL/min at Post-HCV W12.	Quantitative measures of urine protein (urine ratios of albumin, retinol binding protein, and beta-2-microglobulin to creatinine) were reduced after switch to an F/TAF-based regimen; these reductions were maintained after the addition of LDV/SOF and for the duration of the study.
Elderly PWH						
Mills *et al.* CROI. 2020 (*55*)	Pooled analysis	BIC/TAF/FTC *vs.* DTG/ABC/3TC *vs.* DTG+F/TAF	196	144 weeks	At the 144 weeks, the changes of median eGFR in the three groups (BIC/TAF/FTC, DTG/ABC/3TC, DTG+F/TAF) were -9, -9 and -11 mL/min, respectively.	Median UACR decreased by 23% with B/F/TAF *vs.* an increase of 34% with DTG/ABC/3TC. Median RBP:Cr increased by 1% with B/F/TAF compared with an increase of 11% with DTG/ABC/3TC. Median β2M:Cr declined by 54% with B/F/TAF compared with an decrease of 39% with DTG/ABC/3TC.
Maggiolo *et al.* The Lancet HIV. 2019 (*56*)	Phase III RCT	Regimen containing TDF *vs.* EVG/c/FTC/TAF	167	48 weeks	Change from baseline in eGFR: EVG/c/TAF/FTC group (median change -2·4 mL/min [IQR -7·2 to 6·6]) *vs.* TDF group (median change 0·6 mL/min [-5·7 to 5·4]), ($p = 0·44$).	Median UACR decreased by 27.8% with EVG/c/TAF/FTC *vs.* an decrease of 7.7% with TDF-based regimen ($p = 0·0042$) . Median urine protein to creatinine ratio(UPCR) decreased by 49.8% with EVG/c/TAF/FTC *vs.* an decrease of 3.8% with TDF-based regimen ($p = 0.00027$) . Median β2 microglobulin to creatinine ratio decreased by 58.7% with EVG/c/TAF/FTC *vs.* an increase of 13.6% with TDF-based regimen ($p < 0·0001$) Median retinol-binding protein to creatinine ratio decreased by 41.5% with EVG/c/TAF/FTC *vs.* an increase of 15.2% with TDF-based regimen ($p < 0·0001$).
HIV patients with diabetes						
Stein *et al.* ASM/ICAA. 2016 (*68*)	Phase III RCT	EVG/c/FTC/TAF	33	96 weeks	eGFR remained stable, and the change of median eGFR from baseline was 0.0 mL/min ($p = 0.86$).	The following markers of proteinuria and proximal tubular lesions improved (baseline *vs.* median at the 96 weeks): UPCR (269 *vs.* 135 mg/g), UACR (58 *vs.* 35 mg/g), RBP/Cr ratio (2,119 *vs.* 247 g/g) and β2-MG/Cr ratio (2,449 *vs.*328g/g) (except UACR, all other improvements were statistically significant).

A pooled analysis of four international clinical trials switched 140 virologically suppressed HIV-infected patients aged ≥ 65 years from other regimens to B/F/TAF treatment. The baseline median (range) eGFR was 74 (38–130) mL/min. The 48-week results showed a slight and stable median eGFR decline (a decrease of 2.7 mL/min from baseline at week 48), and no renal adverse events, treatment discontinuations, or proximal renal tubulopathy occurred in the patients (*60*).

4.2. People with HIV and hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection

HBV and HCV co-infection is an independent risk factor for kidney disease in HIV-infected individuals (*61*) . Studies show that TAF-containing regimens are safe for the kidneys in two subgroups of patients. A prospective cohort study switched 106 HIV/HBV co-infected patients to TAF-containing regimens after receiving TDF treatment and achieving HIV virologic suppression. At baseline, 79.2% of the patients had eGFR levels of 60-89 mL/min/1.73 m², and 20.8% had eGFR < 60 mL/min/1.73m². After one year of TAF-containing regimens, the mean (95% CI) eGFR levels increased from baseline by 3.2 (1.2-5.2) mL/min/1.73m² and 6.2 (2.4-10.0) mL/min/1.73 m² in the two groups of patients, respectively. Additionally, the overall population had a mean decrease of 6.3 mg/mmol in UPCR compared to baseline. TAF-containing regimens reversed the worsening trend in eGFR and UPCR in the study patients during the year before baseline when they received TDF-containing regimens (all *P*-values< 0.05) (*62*). Another Phase 3b clinical trial included 148 HIV-infected patients with HCV co-infection and HIV virologic suppression who were randomly assigned to rilpivirine(R)/F/TAF (*n* = 74) or E/c/F/TAF (*n* = 74) treatment. After 8 weeks, they started a 12-week course of HCV antiviral therapy while continuing with TAF-containing regimens. The median (IQR) baseline eGFR in the two groups of patients was 100 (75-118) mL/min/1.73 m² and 99 (79-115) mL/min/1.73m², respectively. The results showed that the eGFR was stable during the study period, and the median eGFR change for the overall patients after 12 weeks of HCV antiviral therapy was 0.1 mL/min/1.73m². Furthermore, the R/F/TAF group showed improvement in renal function including UACR, RBP/Cr, and β2-MG/Cr, with median changes from baseline of -6.9%, -27.6%, and -70.0%, respectively. In the E/c/F/TAF group, the median changes were -1.2%, -18.2%, and -52.7% (*63*). In China, a multicenter study switched 243 HIV-infected patients with concurrent HCV infection and HIV virologic suppression to TAF-containing regimens and started a 12-week course of HCV treatment after 4 weeks. The results showed good safety and tolerability, and no patients discontinued treatment due to adverse events (*64*).

4.3. PWH with comorbidities

Comorbidities such as diabetes and hypertension, or a history of kidney disease, can increase the risk of kidney disease in HIV-infected individuals (*65,66*). Several studies suggest that TAF-containing regimens maintain stable kidney function in HIV-infected patients with these comorbidities(*40,42,59,67,68*). For example, in the Phase 3b clinical trial mentioned above, 86 HIV-infected patients aged ≥ 65 years with a baseline median (IQR) eGFR of 76.2 (39.6-130.2) mL/min (51.2% with a history of hypertension) received TAF-containing regimens for 96 weeks without renal adverse events, treatment discontinuation, proximal renal tubulopathy, or Fanconi syndrome (*58,59*) . In another Phase 3 study, 33 HIV-infected patients with moderate renal impairment (baseline eGFR of 30-69 mL/min) and diabetes received TAF-containing regimens for 96 weeks, resulting in stable eGFR and improvements in UPCR, UACR, RBP/Cr, and *β*2-MG/Cr (median values at baseline *vs*. week 96): UPCR (269 *vs*. 135 mg/g), UACR (58 *vs*. 35 mg/g), RBP/Cr ratio (2,119 *vs*. 247 μg/g), and β2-MG/Cr ratio (2,449 *vs*. 328 μg/g). Except for UACR, all improvements were statistically significant(*68*). In a multicenter, single-arm, open-label, Phase 4 clinical trial, 31 HIV-infected patients with a history of TDF-related proximal renal tubulopathy and eGFR >30 mL/min/1.73 m² received F/TAF-containing regimens. The baseline median eGFR (IQR) calculated using the serum creatinine formula and cystatin C formula was 75 (69-92) mL/min/1.73 m² and 60 (52-69) mL/min/1.73 m², respectively. The 96-week results showed no recurrence of glycosuria or proximal renal tubulopathy. The eGFR calculated using the creatinine formula declined slightly (-1.9 mL/min/1.73 m²/year, $p = 0.024$), but the eGFR calculated using the cystatin C formula did not decline significantly (-0.9 mL/min/1.73 m²/year, $p = 0.16$). Ten and five cases of rapid eGFR decline (> 5 mL/min/1.73 m²/year) occurred based on the creatinine and cystatin C formulas, respectively, but the relation to TAF was unclear. The patients did not change significantly in UACR, RBP/Cr, and phosphate excretion fraction (all *P*-values > 0.2) (*67*).

In summary, clinical trials and real-world studies show the renal safety of TAF-containing regimens for HIV-infected patients, including those with renal insufficiency or at risk of kidney injury. Individual case reports of renal safety events in HIV-infected patients treated with TAF-containing regimens exist, but most of these patients had risk factors for kidney disease (such as HCV co-infection, diabetes, hypertension, history of kidney disease, or long-term use of antiretroviral drugs with renal injury risk, such as TDF) (*69-74*). These reports do not prove that TAF causes renal safety issues. International guidelines recommend TAF-containing regimens for most HIV-infected patients (*75-77*). HIV-infected patients with renal impairment, including TDF-

related renal injury, can also consider TAF-containing regimens as a safe alternative.

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