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Original Article

Evolution of estimated glomerular filtration rate in HIV/HCV-coinfected patients who received direct-acting antivirals: A multicenter retrospective study

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Abstract *Background:* The short-term impact of sofosbuvir (SOF)-based direct-acting antivirals (DAAs) combined with antiretroviral therapy (ART) on renal function in patients with HIV/HCV-coinfection remains controversial.
Methods: This multicenter, retrospective study aimed to sequentially record the estimated glomerular filtration rate (eGFR) at baseline, end of therapy (EOT), 12 weeks off-treatment (SVR12), and at time points after SVR12 (post-SVR12) and to identify the factors associated with an eGFR decline to <60 ml/min/1.73 m^2 in HIV/HCV-coinfected patients receiving DAAs. The evolution of mean eGFRs between different ART and DAAs combinations among patients of different HIV transmission routes were compared using a generalized linear mixed effects model. The periods between baseline and EOT, between EOT and post-SVR12, and between baseline and post-SVR12 were defined as the on-treatment, post-treatment, and all-course periods, respectively. Acute kidney disease (AKD) was defined as a decline of eGFR to <60 ml/min/1.73 m^2.
Result: A total of 445 patients with baseline eGFRs >60 ml/min/1.73 m^2 were included. We found that eGFRs declined during the on-treatment period in the tenofovir-containing ART and SOF-based DAA groups. There were no differences in the slope coefficient during the on-treatment and post-treatment periods among all risk groups except for people who inject drug. Increasing age and plasma HIV RNA >20 copies/ml before DAA treatment were factors independently associated with AKD during the on-treatment period while increasing age was independently associated with AKD during the all-course period.
Conclusion: Only increasing age was an independent factor associated with AKD among HIV/HCV-coinfected patients during and after DAA treatments.

Introduction

Globally, an estimated 58 million people have chronic hepatitis C virus (HCV) infection, with approximately 1.5 million new infections occurring per year.[1] The overall HCV seroprevalence is estimated 4.0% among HIV-positive heterosexuals and pregnant women, 6.4%among men who have sex with men (MSM), and 82.4% among people who inject drug (PWID) worldwide.[2] The HCV seroprevalence rates are significantly higher among PWID than among bisexual MSM.[2] The interaction of the human immunodeficiency virus (HIV) and HCV epidemics has significant clinical and public health implications and raises many challenging issues for patients and their health care providers when it comes to HCV elimination in the current era of direct-acting antivirals (DAAs).[3]

While antiretroviral therapy (ART) has significantly improved the health outcomes among patients living with HIV (PLWH),[4] DAA regimens offer highly effective, well-tolerated treatment for patients with HCV infection.[5] Among these antiretroviral agents, tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) as a prodrug of tenofovir (TFV) have become the most frequently prescribed nucleos(t)ide reverse transcriptase inhibitors in the combination antiretroviral therapy (ART); both are converted intracellularly to the pharmacologically active moiety, tenofovir diphosphate.[6] However, TDF can lead to renal impairment, which is characterized by increases in serum creatinine, proteinuria, and proximal tubulopathy.[7] TAF is associated with less renal toxicity compared to TDF, as it achieves lower plasma TFV concentrations.[8] Among the different DAAs, sofosbuvir (SOF) is the only component of DAA regimens that is metabolized by the kidneys.[9] Notably, several studies have indicated that SOF may cause tubulointerstitial nephritis.[10,11] The HCV-TARGET study found that patients with a baseline estimated glomerular filtration rate (eGFR) ≤45 ml/min/1.73 m^2 were at a higher risk of worsening renal function than those with a baseline eGFR >45 ml/min/1.73 m^2 after receiving SOF-based DAAs.[12] However, the impact of SOF-based DAAs on worsening of renal function remains controversial among different populations studied.[13,14]

Comparing with HIV-negative patients, several studies have confirmed high rates of sustained virologic response 12 weeks (SVR12) with DAAs in PLWH coinfected with different HCV-serotypes.[15,16] In terms of eGFR changes during DAA treatment among PLWH, one study revealed eGFR declines in the period of SOF-based DAA treatment combined with TFV-containing ART.[17] Sun et al. reported the sequential median eGFR of the PLWH receiving SOF-based DAAs combined TDF or TAF-containing ARTs declined initially after the initiation of DAA but eGFR recovered later, while that of PLWH taking non—SOF—based DAAs combined TDF or TAF-containing ARTs increased or remained after DAA initiation and eGFR declined after DAA discontinuation.[15]

Liou et al. described the eGFR decline was more pronounced in those receiving TDF-containing ART, and eGFR recovered after discontinuation of sofosbuvir/ledipasvir.[16] Moreover, a prospective study found that HIV/HCV-coinfected patients receiving TFV-containing ART had less eGFR declines compared to those receiving ART not containing TFV during SOF-based DAA therapy.[18] However, studies from Liu et al. and Liou et al. discussed that eGFR changes in PLWH receiving TFV or non-TFV-containing ART during SOF-based DAAs treatment.[16,18] There were scanty information about the eGFR changes in patients receiving non−SOF−based DAAs combined TFV or non-TFV-containing ART. While Sun et al. reported the mean eGFR changes in different combinations of DAAs and ART,[15] this study only included HCV genotype 6.[15] Other studies had small case numbers in each group of different combinations of DAAs and ARTs.[17,18] In addition, changes of renal function after completion of DAA treatment is rarely assessed. We conducted the current multicenter retrospective study aiming to examine the evolution of eGFR during the treatment courses of different combinations of DAAs and ART among PLWH with HIV/HCV-coinfection regardless of HCV genotype. The factors associated with an eGFR decline to $<$60 ml/min/1.73 m^2 in the DAA treatment and post-DAA treatment periods were also investigated.

Materials and methods

Study design and participants

PLWH in Taiwan are provided with free-of-charge ART that is reimbursed by Taiwan Centers for Disease Control and the National Health Insurance (NHI). DAAs were conditionally included in the NHI coverage since January 2017. In January 2019, the HCV treatment program was expanded by providing free-of-charge testing and DAAs to include all patients with HCV viremia, including those with acute HCV infections. Hepatologists and HIV-treating physicians were permitted to screen and treat patients with HIV/HCV co-infection who meet the treatment criteria.[15,16]

This retrospective study was conducted at 11 major designated hospitals for HIV care around Taiwan. HIV/HCV-coinfected adult patients (age $\geq$20 years) who received ART and DAA treatments between January 1, 2018, and December 31, 2021, were included. ART and DAA regimens for each patient were chosen at the discretion of HIV-treating physicians or hepatologists. For further analysis of the factors associated with acute kidney disease (AKD), we included patients with a baseline eGFR $\geq$60 ml/min/1.73 m^2. We recorded eGFR data at four time points for each patient's study period, which included the initiation of treatment (baseline), end of therapy (EOT), sustained virologic response at 12 weeks off-treatment (SVR12), and any time point after SVR12 (post-SVR12). The periods between baseline and EOT, between EOT and SVR12, and between baseline and post-SVR12 were defined as the on-treatment, post-treatment, and all-course period, respectively.

The primary end point was the evolution of the mean eGFR among PLWH receiving different ART or DAA combinations. This retrospective study was approved by the Institutional Review Board or Research Ethics Committee of each participating hospital. The requirement for informed consent was waived.

Data collection and definitions

A standardized case report form was used to collect information on demographics, comorbidities, route of HIV transmission, ARTs, DAAs, and laboratory investigations. Tests for CD4 lymphocyte counts, plasma HIV RNA levels, HCV genotypes, serum creatinine levels, and eGFRs were performed according to the national HIV and HCV treatment guidelines.[19,20] ART were divided into groups of TFV-containing or non-TFV-containing, and TDF-containing or TAF-containing regimens. DAAs were divided into SOF-based regimens or glecaprevir-pibrentasvir. The risk groups of HIV transmission were classified as MSM, heterosexuals, or PWID. Undetectable plasma HCV and HIV levels were defined as 15 IU/ml and 20 copies/mL, respectively. eGFRs and urine protein/urine creatinine ratios (UPCR) were recorded at four time points: baseline, EOT, SVR12, and post-SVR12. Renal function was assessed based on eGFRs calculated using the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease (MDRD) equation. The IDMS-MDRD equation used was as follows: eGFR (ml/min/1.73 m^2) = 175 $\times$ (creatinine) $-$ 1.154 $\times$ (age) $-$ 0.203 $\times$ (0.742 if female) $\times$ (1.212 if the patient is black).[21] The urine protein/urine creatinine ratio (UPCR) was quantified using the colorimetric method, and the upper limit of normal for the quantification level was 150 mg/g. AKD was defined as a decline of eGFR to $<$60 ml/min/1.73 m^2.[22]

Laboratory investigations

Plasma HCV RNA was quantified using the COBAS AmpliPrep/COBAS TaqMan HCV Test (version 2.0, Roche Diagnostics GmbH, Mannheim, Germany; lower limit of quantification, 15 IU/ml). HBV surface antigen (HBsAg) levels were determined using chemiluminescent microparticle immunoassays (COBAS Elecsys HBsAg II, Roche). HCV genotypes were classified using reverse-transcription real-time PCR and sequencing (Abbott Real-Time HCV Genotype II). Serum creatinine levels were measured using Jaffe method in all participating hospitals. Urine protein levels were also quantified (Angene Biotechnology Co., Ltd., Taiwan). CD4 lymphocyte count (cells/mm^3) was quantified using flow cytometry.

Statistical analysis

Data were presented as the mean $\pm$ standard deviation (SD), proportion, or median (range). The baseline characteristics of the different study groups were shown as means and percentages, which were then compared using the independent two-sample *t*-test and chi-square test with Fisher's exact test, respectively. The evolution of eGFR among different risk groups for HIV transmission were compared using a generalized linear mixed effects model and it was presented from baseline to post-SVR12 using the slope coefficient. Using the generalized estimating equation (GEE), we showed differences in the crude slope coefficient with a 95% confidence interval (CI) for the

different groups. We examined the factors associated with development of AKD in the on-treatment period and all-course periods through univariate and multivariate analyses. Factors with a *p*-value <0.10 in the univariate analysis were included in the adjusted analysis to identify independent factors associated with AKD using multivariate logistic regression models. Hosmer-Lemeshow goodness-of-fit test was used to evaluate the predictive performance of the logistic regression model. A *p*-value of <0.05 was considered as statistically significant. The Statistical Program for Social Sciences software (SPSS Statistics version 22.0) was used for all statistical analyses.

Results

Patient characteristics

Of the 846 HIV/HCV-coinfected patients who received ART and DAAs were identified at the participating hospitals during the 4-year study period. Patients who did not receive a complete DAA treatment course (n = 3), had baseline eGFRs <60 ml/min/1.73 m^2 (n = 36), and those received DAAs rather than SOF-based regimens or glecaprevir-pibrentasvir (n = 9) were excluded. After excluding PLWH who had missing eGFR data at the four time points to be examined (n = 353), a total of 445 patients were included in the study (Fig. 1). Among these included patients, the average age was 43.31 ± 9.92 years, and 94.6% were male. The proportions of MSM and PWID were 43.8% and 48.3%, respectively. The proportion of PLWH testing positive for hepatitis B surface antigen (HBsAg) was 11.7%. The comparisons of clinical characteristics between PLWH included in this study and those were not included are shown in supplementary Table. Those non-included were more likely to be younger and MSM, fail to have achieved plasma HIV RNA <20 copies/ml, and have a higher mean eGFR before initiation of DAAs and EOT (supplementary Table).

Of all included patients, 61.4% and 38.6% were on TFV-containing and non-TFV- containing ART, respectively. SOF-based DAAs (66.3%) were the most commonly prescribed DAAs. Most PLWH (87.1%) had plasma HIV RNA <20 copies/ml before DAA treatment was initiated. At baseline, the average HCV RNA viral load was 6.24 ± 7.91 (x10,[6] IU/ml). HCV genotypes 1a, 1 b, 2, and 6 were the main genotypes in HIV/HCV-coinfected patients, accounting for 18.8%, 19.5%, 24.7%, and 25.1%, respectively.

The included patients were categorized into TFV-containing (n = 273) and non-TFV containing (n = 172) ART groups. Comparisons of the clinical characteristics between the two groups are summarized in Table 1. A higher proportion of SOF-based DAAs were initiated in the TFV-containing ART group (72.2% *vs*. 57.0%, *p* = 0.001). A higher HBsAg positivity rate was found in the TFV-containing ART group (16.8% *vs*. 3.5%, *p* < 0.001). HCV genotype 2 (21.1% *vs*. 30.2%, *p* = 0.03) and hypertension (11.1% *vs*. 19.8%, *p* = 0.01) were more prevalent in the non-TFV- containing ART group (Table 1). Comparisons of serum creatinine, eGFR and UPCR between the two groups at the time points of baseline, EOT, SVR12 and post-SVR12 are summarized in Table 2. The average serum creatinine, eGFR and UPCR at baseline before DAAs were initiated were 0.95 ± 0.17 (n = 445), 93.47 ± 21.81 (n = 445) and 86.2 (63.5–131.5) (n = 135), respectively. The average serum creatinine, eGFR and UPCR at EOT were 1.0 ± 0.2 (n = 445), 88.2 ± 20.4 (n = 445) and 83.0 (58.0–120.0) (n = 91), respectively. The average serum creatinine, eGFR and UPCR at SVR12 were 1.0 ± 0.21 (n = 445), 89.02 ± 30.48 (n = 445) and 75.0 (58.0–111.0) (n = 66), respectively. The average serum creatinine, eGFR and UPCR at post-SVR12 were 1.0 ± 0.19 (n = 445), 88.67 ± 21.98 (n = 445) and 73.5 (58.8–109.0) (n = 167), respectively. There were no statistically significant differences in comparisons of the serum creatinine, eGFR and UPCR between these two groups at the time points of baseline, EOT, SVR12 and post-SVR12 (Table 2).

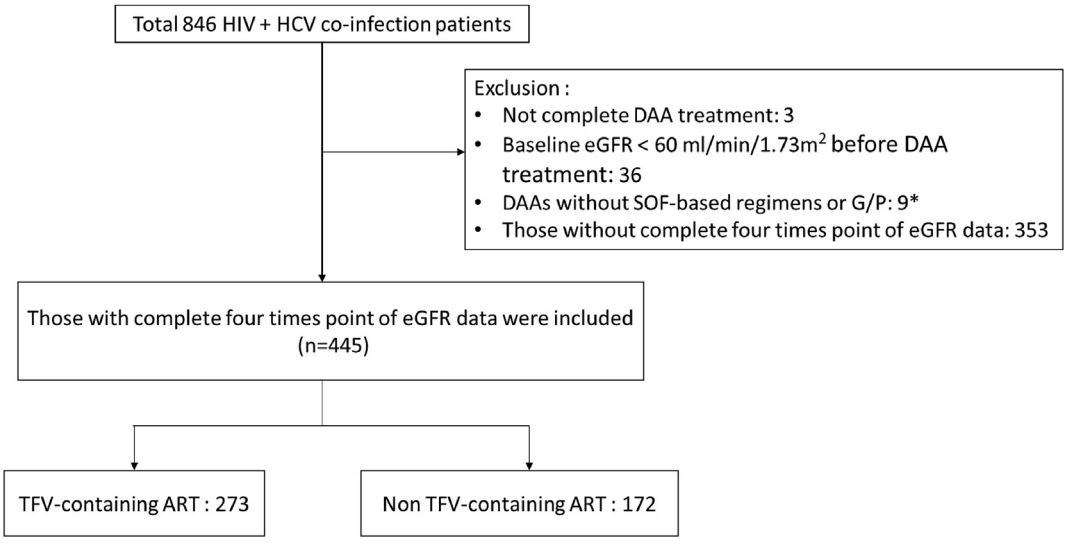

Figure 1. Flow chart of patients with HIV/HCV-coinfection. *DAA regimen in these nine patients was elbasvir/grazoprevir. Abbreviations: ART, antiretroviral therapy; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; G/P, glecaprevir-pibrentasvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SOF, sofosbuvir; TFV, tenofovir.

Table 1 Comparisons of clinical characteristics of HIV/HCV-coinfected patients who received TFV-containing antiretroviral regimens and those who received non-TFV-containing regimens.

Characteristics	Total[a]	TFV-containing[b]	Non-TFV-containing	*p*
N	445	273	172	
Age, mean (±SD), years	43.31 ± 9.92	43.34 ± 9.84	43.25 ± 10.08	0.93
Sex, n (%)				
Woman	24 (5.4)	12 (4.4)	12 (7.0)	
Man	421 (94.6)	261 (95.6)	160 (93.0)	0.28
HIV risk group, n (%)				
MSM	195 (43.8)	118 (43.2)	77 (44.8)	0.77
Heterosexuals	17 (3.8)	9 (3.3)	8 (4.7)	0.46
PWID	215 (48.3)	136 (49.8)	79 (45.9)	0.44
Unknown	18 (4.0)	10 (3.7)	8 (4.7)	0.63
The latest CD4 count before DAA, mean (±SD), cells/mm^3	556.46 ± 260.39 (N = 443)	547.42 ± 257.56 (N = 272)	570.85 ± 264.95 (N = 171)	0.36
The latest HIV plasma HIV RNA before DAA				
Not detected, n/N (%)	386/443 (87.1)	234/271 (86.3)	152/172 (88.4)	0.56
>20 copies/ml, n/N (%)	57/443 (12.9)	37/271 (13.7)	20/172 (11.6)	
DAAs, n (%)				
SOF-based[c]	295 (66.3)	197 (72.2)	98 (57.0)	<0.01
Glecaprevir-pibrentasvir	150 (33.7)	76 (27.8)	74 (43.0)	
HBsAg-positive, n (%)	52 (11.7)	46 (16.8)	6 (3.5)	<0.01
HCV baseline viral load (HCV RNA x 10^6 IU/ml), mean (±SD)	6.24 ± 7.91	6.47 ± 7.95	5.88 ± 7.85	0.45
HCV genotype, n/N (%)				
1a	83/442 (18.8)	54/270 (20.0)	29/172 (16.9)	0.46
1b	86/442 (19.5)	60/270 (22.2)	26/172 (15.1)	0.08
2	109/422 (24.7)	57/270 (21.1)	52/172 (30.2)	0.03
3	35/422 (7.9)	16/270 (5.9)	19/172 (11.1)	0.07
4	0	0	0	
5	0	0	0	
6	111/442 (25.1)	70/270 (26.0)	41/172 (23.8)	0.65
Mix	18/442 (4.1)	13/270 (4.8)	5/172 (2.9)	0.46
Cirrhosis by sonography, n/N (%)	42/280 (15.0)	24/157 (15.3)	18/123 (14.6)	>0.99
Hypertension, n/N (%)	64/443 (14.4)	30/271 (11.1)	34/172 (19.8)	0.01
Diabetes mellitus, n/N (%)	30/443 (6.8)	15/271 (5.5)	15/172 (8.7)	0.24
Hepatocellular carcinoma, n/N (%)	5/345 (1.4)	4/195 (2.1)	1/150 (0.7)	0.39

[a] Types of ART during DAA use, n (%): efavirenz/emtricitabine/tenofovir disoproxil fumarate, 15 (3.4); rilpivirine/emtricitabine/tenofovir disoproxil fumarate, 64 (14.4); dolutegravir/lamivudine/abacavir, 157 (35.3); elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, 118 (26.5); bictegravir/emtricitabine/tenofovir alafenamide, 47 (10.6); rilpivirine/emtricitabine/tenofovir alafenamide, 17 (3.8); Others, 27 (6.1).

[b] TFV- containing ART, n (%): TDF-containing, 92 (20.7); TAF-containing, 181 (40.7).

[c] SOF-based DAAs, n (%): sofosbuvir/ledipasvir, 209 (70.8); sofosbuvir/velpatasvir, 84 (28.5); others (SOF-based plus ribavirin), 2 (0.7).

Abbreviations: ART, antiretroviral therapy; DAAs, direct-acting antivirals; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MSM, men who have sex with men; PWID, people who inject drugs; SD, standard deviation; SOF, sofosbuvir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

n, number of data being positive, N, number of data being available.

Comparisons of eGFRs among PLWH receiving different ART and DAA combinations during different periods

The crude slope coefficients of eGFR for PLWH receiving TFV-containing ART vs non-TFV-containing ART (Supplementary Fig. A), those receiving SOF-based DAAs vs. glecaprevir-pibrentasvir (Supplementary Fig. B), or those receiving different combinations of TFV-containing ART or non-TFV-containing ART with SOF-based DAAs or glecaprevir-pibrentasvir (Supplementary Fig. C, D, E, F), and those receiving TDF vs. TAF-containing ART (Supplementary Fig. G) were not significantly different during the on-treatment, post-treatment, and all-course periods, respectively (Table 3). During the on-treatment period, the crude slope coefficients of eGFR in PWID group had significantly greater eGFR decline rates than those in MSM group (PWID *vs*. MSM group, −9.36 (95% CI, −13.06, −5.66), $p < 0.01$) (Table 3, Supplementary Fig. H). During the all-course period, the crude slope coefficients of eGFR in PWID group also had significantly greater decline rates than those in MSM group (PWID *vs*. MSM group, −7.89 (95% CI, −12.25, −3.53), $p < 0.01$) (Table 3, Supplementary Fig. H).

Table 2 Laboratory parameters of HIV/HCV-coinfected patients who received TFV-containing antiretroviral regimens and those who received non-TFV-containing regimens at the point of baseline, EOT, SVR12, and post SVR12.

Characteristics	Total	TFV-containing	Non TFV-containing	*p*
N	445	273	172	
Latest serum creatinine before DAA, mean (±SD), mg/dl	0.95 ± 0.17	0.95 ± 1.17	0.95 ± 0.17	0.97
Latest eGFR before DAA, mean (±SD), ml/min/1.73m^2	93.47 ± 21.81	93.76 ± 22.41	93.03 ± 20.9	0.73
Latest urine UPCR, median (IQR), mg/g	86.2 (63.5–131.5) (N = 135)	87.3 (63.3–140.0) (N = 101)	80.9 (62.8–117.0) (N = 34)	0.31
Serum creatinine at EOT, mean (±SD), mg/dl	1.0 ± 0.20	0.99 ± 0.20	0.99 ± 0.18	0.43
eGFR at EOT, mean (±SD), ml/min/1.73m^2	88.2 ± 20.4	88.13 ± 21.42	88.1 ± 21.34	0.93
Urine UPCR at EOT, median (IQR), mg/g	83.0 (58.0–120.0) (N = 91)	82.5 (57.3–120.8) (N = 72)	91.0 (62.1–117.0) (N = 19)	0.72
Serum creatinine at SVR12 time-point, mean (±SD), mg/dl	1.0 ± 0.21	0.99 ± 0.19	1.0 ± 0.20	0.76
eGFR at SVR12 time-point, mean (±SD), ml/min/1.73m^2	89.02 ± 30.48	89.02 ± 22.4	88.1 ± 21.34	0.67
Urine UPCR at SVR12 time-point, median (IQR), mg/g	75.0 (58.0–111.0) (N = 66)	75.9 (57.5–111.0) (N = 49)	73.0 (58.5–101.5) (N = 17)	0.75
Serum creatinine post SVR12, mean (±SD), mg/dl	1.0 ± 0.19	1.0 ± 0.21	1.0 ± 0.20	0.79
eGFR post SVR12, mean (±SD), ml/min/1.73m^2	88.67 ± 21.98	90.1 ± 35.04	87.31 ± 21.3	0.35
Urine UPCR post SVR12, median (IQR), mg/g	73.5 (58.8–109.0) (N = 167)	72.0 (58.9–109.3) (N = 113)	74.5 (57.3–109.1) (N = 54)	0.60

Abbreviations: DAAs, direct-acting antivirals; eGFR, estimated glomerular filtration rate; EOT, end of therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; SVR12, sustained virologic response 12 weeks off-treatment; TFV, tenofovir; UPCR, urine protein/urine creatinine ratio.
n: number of data being positive, N: number of data being available.

Table 3 Slope coefficient differences of eGFR during the different periods of DAAs for PLWH who continued to receive ART.

Variables	On-treatment period		Post-treatment period		All-course period	
	Crude slope difference (95% CI), ml/min/1.73m^2	*p*	Crude slope difference (95% CI), ml/min/1.73m^2	*p*	Crude slope difference (95% CI), ml/min/1.73m^2	*p*
TFV-containing ART	0.27 (−3.38, 3.93)	0.88	2.97 (-0.88, 6.81)	0.13	1.76 (−2.41, 5.92)	0.41
SOF-based DAAs	−0.97 (−4.82, 2.89)	0.62	2.71 (-1.01, 6.42)	0.15	0.39 (−3.91, 4.68)	0.86
TFV-containing ART plus SOF-based DAAs vs. TFV-containing ART plus G/P	0.24 (−5.17, 5.65)	0.93	3.78 (−1.51, 9.08)	0.16	2.14 (−3.79, 8.06)	0.48
Non-TFV-containing ART plus SOF-based DAAs vs. Non-TFV-containing ART plus G/P	−2.43 (−8.03, 3.17)	0.39	−2.61 (−8.26, 3.04)	0.37	−2.21 (−8.18, 3.76)	0.47
TFV-containing ART plus SOF-based DAAs vs. Non-TFV-containing ART plus SOF-based DAAs	1.38 (−3.15, 5.92)	0.55	3.82 (−1.35, 9.0)	0.15	3.29 (−1.93, 8.52)	0.22
TFV-containing ART plus G/P vs. Non-TFV-containing ART plus G/P	−0.97 (−7.34, 5.41)	0.77	−0.84 (−7.39, 5.72)	0.8	−0.59 (−7.22, 6.04)	0.86
TDF-containing ART vs. TAF-containing ART	−1.54 (−6.54, 3.45)	0.54	7.38 (−1.37, 16.13)	0.10	6.02 (−4.05, 16.1)	0.24
PWID	−9.36 (−13.06, −5.66)	<0.01	2.93 (−1.39, 7.25)	0.18	−7.89 (−12.25, −3.53)	<0.01

Definitions: treatment period, baseline to EOT; post-treatment period, EOT to post-SVR12; all-course period, baseline to post-SVR12.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; DAAs, direct-acting antivirals; eGFR, estimated glomerular filtration rate; EOT, end of therapy; G/P, glecaprevir-pibrentasvir; PWID, people who inject drugs; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks off-treatment; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Table 4 Independent factors associated with development of acute kidney disease during the on-treatment period.

	Univariable analysis		*P*	Multivariable analysis OR (95% CI)	*P*
	No (N = 422)	Yes (N = 23)			
Age, (mean ± SD), years	43 (35.0–49.0)	52 (44.0–55.0)	<0.01	1.09 (1.04, 1.13)	<0.01
MSM, n (%)	191 (45.3)	4 (17.4)	0.01		
PWID, n (%)	197 (46.7)	18 (78.3)	<0.01		
Rilpivirine/emtricitabine/tenofovir disoproxil fumarate, n (%)	64 (15.2)	0	0.06		
Bictegravir/emtricitabine/tenofovir alafenamide, n (%)	42 (10.0)	5 (21.7)	0.08		
Sofosbuvir/velpatasvir, n (%)	76 (18.0)	8 (34.8)	0.06		
Latest CD4 count before DAA, median (IQR), cells/mm^3	529.5 (382.7–713.9) (N = 420)	432.7 (323.0–549.8) (N = 23)	0.03		
Latest HIV PVL count before DAA (>20 copies/ml), n/N (%)	49/420 (11.7)	8/23 (34.8)	<0.01	3.47 (1.35, 8.97)	0.01
HCV genotype 6, n/N (%)	100/419 (23.9)	11/23 (47.8)	0.02		
Cirrhosis by sonography, n/N (%)	35/260 (13.5)	7/20 (35.0)	0.02		
Hypertension, n/N (%)	56/420 (13.3)	8/23 (34.8)	0.01		

Definition: on-treatment period, baseline to EOT.
Abbreviations: CI, confidence interval; DAA, direct-acting antiviral agent; EOT, end of therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; PWID, people who inject drugs; SD, standard deviation.
N: number of data being positive, N: number of data being available.
Hosmer-Lemeshow goodness-of-fit test $p = 0.25$.

Factors associated with acute kidney disease during the different periods

The factors associated with AKD with an eGFR decline to <60 ml/min/1.73 m^2 during the on-treatment period were increasing age, PWID, lower CD4 count before DAA treatment, plasma HIV RNA >20 copies/ml before DAA treatment, HCV genotype 6, cirrhosis of the liver, and hypertension in univariate analysis (Table 4). The independent factors associated with AKD during the on-treatment period in multivariate analysis were increasing age (1.09; 95% CI, 1.04, 1.13) and plasma HIV RNA >20 copies/ml before initiation of DAA treatment (3.47; 95% CI, 1.35, 8.97) (Table 4). The factors associated with AKD during the all-course period were increasing age, age >65 years, PWID, lower CD4 count before DAA treatment, HCV genotype 1a, and cirrhosis in univariate analysis (Table 5). The only independent factor associated with AKD during the

Table 5 Independent factors associated with development of acute kidney disease during the all-course period.

	Univariable analysis		*p*	Multivariable analysis (95% CI)	*P*
	No (N = 418)	Yes (N = 27)			
Age (mean ± SD), years	43 (35.0–50.0)	48 (44.0–59.0)	<0.01	22.68 (3.55, 144.98)	<0.01
MSM, n (%)	192 (45.9)	3 (11.1)	<0.01		
PWID, n (%)	193 (46.2)	22 (81.5)	<0.01		
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide, n (%)	116 (27.8)	2 (7.4)	0.02		
Bictegravir/emtricitabine/tenofovir alafenamide, n (%)	41 (9.8)	6 (22.2)	0.05		
Latest CD4 count before DAA, median (IQR), cells/mm^3	531.5 (385.9–716.5) (N = 416)	379.0 (264.0–549.8) (N = 27)	0.01		
HCV genotype 1a, n/N (%)	73/415 (17.6)	10/27 (37.0)	0.02		
HCV genotype 1 b, n/N (%)	85/415 (20.5)	1/27 (3.7)	0.04		
Cirrhosis by sonography, n/N (%)	35/260 (13.5)	7/20 (35.0)	0.02		

Definition: all-course period, baseline to post-SVR12.
Abbreviations: CI, confidence interval; DAA, direct-acting antiviral agent; HCV, hepatitis C virus; IQR, interquartile range; MSM, men who have sex with men, PWID, people who inject drugs; SD, standard deviation.
n: number of data being positive, N: number of data being available.
Hosmer–Lemeshow goodness-of-fit test $p = 0.63$.

all-course period in multivariate analysis was increasing age (22.68; 95% CI, 3.55, 144.98) (Table 5). There was no significant evidence of lack of fit in any of the final models, as the *p*-values were >0.05 in the Hosmer–Lemeshow goodness-of-fit tests.

Discussion

In the current study examining the eGFR changes in the periods of on-treatment, post-treatment and all-course among PLWH receiving different combinations of DAA and ART, we found a decline in eGFR in HIV/HCV-coinfected patients regardless of the combination of DAA and ART used during the on-treatment period (Table 3, Supplementary Fig. C, D, E, F). The eGFR improved during the post-treatment period, even in PLWH receiving TFV- containing ART in combination with SOF-based DAA (Supplementary Fig. C and E). SOF-based DAA or TFV- containing ART use was not an independent factor associated with development of AKD during the on-treatment or all-course periods (Tables 4 and 5). The findings of our study were in line with those of a recent study, which also revealed TDF combined with SOF-based DAA treatment was not related to AKI in patients coinfected with HIV/HCV.[17]

Concerning the changes of eGFR with SOF-based DAA use, our study was in agreement with a large cohort study[23] and another retrospective study,[24] in which HCV-mono-infected patients receiving SOF-based DAA exhibited a quadratic trend, with eGFR declines during the on-treatment period and eGFR increases during the post-treatment period.[23,24] Tsai et al. also reported that DAA treatment led to a significant decline in eGFR at EOT, the follow-up eGFRs increased slightly at SVR12.[25] However, the trends of eGFR decline in the patients receiving SOF-based DAAs did not increase at SVR12.[25] The discrepancy in the changes of eGFR observed between these studies may be due to the different populations included in the studies. Tsai et al. included liver transplant recipients who (89%) almost exclusively received SOF-based DAA,[25] as it is known that liver transplant recipients usually received immunosuppressive agents, which may also contribute to eGFR declines. Moreover, liver transplantation was an independent risk factor for renal function deterioration.[25] Our study and those by Liu et al.[23] and Huang et al.[24] did not include liver transplant recipients. Through systemic review and meta-analysis, Borgia et al. suggested that SOF-based regimens may be used safely and effectively in HCV-mono-infected patients with stage 4–5 CKD.[26] As a result, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend treatment for all patients with HCV infection who have access to DAA therapies, including those who have kidney function impairment and/or who are on dialysis.[19] Our findings that SOF-based DAA use was not an independent risk factor of AKD during on-treatment and all-course periods support the recommendation.

Patients receiving TFV-containing and those receiving non-TFV-containing ART with SOF-based DAAs or glecaprevir-pibrentasvir showed eGFR declines during the treatment period (Supplementary Fig. C, D, E, F). Patients in the TFV-containing ART group, as compared to those in the non-TFV-containing ART group, had improved eGFRs during the post-treatment period (Supplementary Fig. A and E). Furthermore, TFV- containing ART use was not an independent risk factor for AKD during the all-course period. Liu et al. conducted a prospective study of renal function changes in HIV/HCV-coinfected patients who received both DAAs and ART.[18] They found that HIV/HCV-coinfected patients receiving TFV-containing ARTs had smaller eGFR declines compared to those receiving TFV-free ART during SOF-based DAA therapy.[18] Our study revealed a similar trend in eGFR changes during the treatment period; however, there were no significant differences in the eGFR changes between patients receiving TFV-containing ART and those receiving non-TFV-containing ARTs in our study. The sample size (n = 172) of PLWH receiving non-TFV-containing ART group in our study was larger than that in the study (n = 51) conducted by Liu et al.[18] Clinicians might be prone to prescribing medications with less nephrotoxicity for PLWH with poor renal function. Therefore, the changes may be lower in PLWH receiving non-TFV-containing ART than in those receiving TFV-containing ARTs.

Exposure to TDF may increase the risk of renal adverse event.[27,28] A pooled analysis of 26 clinical trials revealed more favorable renal biomarker profile observed in patients receiving TAF than those receiving TDF in the 96-week follow-up.[28] Although TAF is expected to result in a lower risk of clinically relevant kidney toxicity compared with TDF-containing regimens, AKI has been reported with TAF use.[29] A recent meta-analysis included 11 randomized head-to-head trials of TDF versus TAF found that there were no differences in terms of efficacy between TAF and TDF and marginal differences in renal safety when ritonavir and cobicistat were not used,[30] which suggests that unboosted TDF could have a similar renal safety profile as TAF in the short-term observation.[30] In our study, PLWH received TDF and those receiving TAF-containing ART did not significantly differ in the changes of eGFR during the on-treatment, post-treatment, and all-course periods, respectively (Supplementary Fig. G). Because all included PLWH received unboosted ART in the TDF group and the duration of DAA was 8 or 12 weeks, the adverse impact of TDF on renal function was not observed in our study.

Some studies found that chronic HCV infection without DAA treatments was a risk factor for renal deterioration.[31,32] Unlike previous studies that focused on DAAs and ART,[18,25] our study included more parameters in HIV/HCV-coinfected patients for analysis. The factors associated with AKD during DAA treatments were increasing age and plasma HIV RNA >20 copies/ml before initiation of DAAs. HIV infection can cause HIV-associated nephropathy (HIVAN). In PLWH, HIV viremia (plasma HIV RNA >20 copies/ml) may increase the risk of kidney disease.[33] Our finding was similar to that of a study in an HCV mono-infection cohort,[23] which reported that increasing age was independently associated with a decline in eGFR in HCV-infected patients receiving DAAs.[23] In addition, another HCV mono-infection cohort also found that age >65 years was an independent risk factor of renal function deterioration.[25] A retrospective study aiming to investigate the incidence, outcomes, and risk factors of renal function deterioration in a large Taiwanese adult cohort also found that increasing

age was one of the risk factors of renal function deterioration.[34] Renal function decline might be a natural occurrence associated with increased age, as in ours and other studies.[23,25]

Both PWID and MSM are common risk groups for acquiring HCV/HIV-coinfection. Some studies suggested that injection drug use was associated with progressive kidney disease and renal function that may progress to the stage that requires renal replacement therapy.[35,36] Rhabdomyolysis with acute renal function deterioration was found to be more severe in patients with heroin use than in those without heroin use.[36] However, the trends of eGFR decline during combined DAA and ART in these PWID has rarely been investigated. Our study revealed a significant eGFR decline in PWID compared to that in MSM during on-treatment and all-course periods, which might be attributed to the adverse effects of other intravenous substances. However, further studies are required to confirm these findings.

Our study has several limitations. First, a significant proportion of PLWH were not included because of missing data of serum creatinine and eGFR at the required time points in this retrospective study, although most of the clinical characteristics were not significantly different (Supplementary Table), except that PLWH included in the analysis were older and had lower eGFR values in the time points of baseline and EOT. Second, eGFRs were calculated using the MDRD formula, which was originally developed to identify patients with an eGFR $<$60 ml/min/1.73 m^2 and who were at risk of renal failure.[37] Thus, it may not be sensitive for the identification of patients with stage 1 or 2 CKD. In addition to eGFR data, urinary albumin/creatinine ratio (UACR), urinary protein/creatinine ratio (UPCR), cystatin C level, and β_2M level data are recommended for monitoring CKD.[38,39] However, our study was limited by the fact that the assessment of UPCR and urine β_2M levels were not routinely performed at the participating hospitals. Owing to the retrospective nature of the study, there were limited data records of all medications, including nephrotoxic agents used in this study.

Conclusions

Our study revealed that eGFR declines were noted in HIV/HCV-coinfected patients receiving TFV-containing ARTs and SOF-based DAAs during the on-treatment period. There were no statistically significant differences in the slope coefficients of eGFR changes during the on-treatment, post-treatment, and all-course periods among patients receiving different combinations of ART or DAAs. PWID had a significantly greater eGFR decline than MSM during the on-treatment and all-course periods. Increasing age and plasma HIV RNA $>$20 copies/ml before DAA were independent risk factors associated with AKD during the treatment period, while only increased age was an independent factor associated with AKD during the course of the study.

Data availability statement

The data sets used during the current study are available from the corresponding author on reasonable request.

Author's contributions

Tsai CY: Designed the study, performed the systematic literature search, review, data extraction, statistical data analysis and interpretation, and wrote the first draft of the manuscript.

Tsai CY, Lee CH and Hung CC: Verified data extraction, data analysis, and reviewed the manuscript.

Lee CH and Hung CC: Supervised the data acquisition, data analysis and interpretation, and wrote the final version of the manuscript.

Tsai CY, Chen GJ, Tsai CS, Liou BH, Yang CJ, Tsai HC, Lin CY, Huang SH, Lin KY, Wang NC and Chen TC: Performed the acquisition of data.

All authors read and approved the final manuscript.

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Ethical approval

The study was approved by the Research Ethics Committee or Institutional Review Board of the 11 participating hospitals, including Kaohsiung Chang Gung Memorial Hospital (202002017A3C), National Taiwan University Hospital (201003112 R), National Cheng Kung University Hospital (A-BR-110-039), Hsinchu Mackay Memorial Hospital (18MMHIS008e), Far Eastern Memorial Hospital (110156-F), Kaohsiung Veterans General Hospital (VGHKS19-CT4-02), National Taiwan University Hospital, Yunlin Branch (201003112 R), National Taiwan University Hospital, Hsinchu Branch (109015-E), National Taiwan University Hospital, Jinshan Branch (201003112 R), Tri-Service General Hospital (1-105-05-057), Kaohsiung Municipal Ta-Tung Hospital (KMUHIRB-20130016 and KMUHIRB-20130017).

Sequence information

Not applicable.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.03.009.

Update

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Corrigendum

Corrigendum to Evolution of estimated glomerular filtration rate in HIV/HCV-coinfected patients who received direct-acting antivirals: A multicenter retrospective study [J Microbiol Immunol Infect 56 (2023) 718–728]

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On page 726 in ethics approval, "The study was approved by the Research Ethics Committee or Institutional Review Board of the 11 participating hospitals, including Kaohsiung Chang Gung Memorial Hospital **(202002017A3C)**." should read "The study was approved by the Research Ethics Committee or Institutional Review Board of the 11 participating hospitals, including Kaohsiung Chang Gung Memorial Hospital **(202002017A3)**." I would like to apologise for any inconvenience caused.