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Longitudinal Evaluation of Liver and Renal Functions in Patients Undergoing Tenofovir Disoproxil Fumarate–Based Antiretroviral Therapy in Southern Vietnam

Thanh Nguyen Ai Tran[1,2] | Phuong Thi Be Nguyen[3] | Yen Thi Hoai Phan[4,5] | Hau Phuc Le[6] | Hong Anh Tran[2] | Chieu Nhu Ngoc Nguy[2] | Tung Ba Nguyen[7] | Vu Hoang Anh Nguyen[5]

[1]Board of Directors, Thu Duc City Hospital, Ho Chi Minh City, Vietnam | [2]Department of Internal Medicine, Thu Duc City Hospital, Ho Chi Minh City, Vietnam | [3]Quality Control Center for Medical Laboratory, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam | [4]Faculty of Public Health, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam | [5]Department of Psychosomatic Medicine, Thu Duc City Hospital, Ho Chi Minh City, Vietnam | [6]Outpatient Clinic for HIV/AIDS Patients, Chau Thanh District Medical Center, Vinh Long, Vietnam | [7]Department of Respiratory Medicine, University Medical Center, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam

Correspondence: Vu Hoang Anh Nguyen (hoanganhvu.psy@gmail.com)

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ABSTRACT

Introduction: Tenofovir disoproxil fumarate (TDF)–based antiretroviral therapy (ART) is widely used to manage HIV due to its efficacy and affordability. However, its potential adverse effects on liver and renal functions remain significant concerns, particularly in resource-limited settings such as Vietnam.

Methods: Prospective cohort study included 552 HIV-infected patients with normal baseline liver and renal functions, who received TDF-based ART at Thu Duc City Hospital. Clinical and laboratory data, including AST, ALT, and serum creatinine levels, were collected and analyzed over a 20-month follow-up period. Cox proportional hazards regression and Kaplan–Meier analyses were used to identify risk factors and time-to-onset of liver damage and renal impairment.

Results: The overall incidence of liver damage was 10.7%, while renal impairment was higher at 19.4%. Male sex and pretreatment AST levels emerged as independent predictors of renal impairment during TDF-based ART. In multivariate Cox models, male sex showed a strong association with both liver damage (HR = 2.19, 95% CI: 1.10–4.34) and renal impairment (HR = 14.06, 95% CI: 5.39–36.65). Elevated baseline AST was independently associated with renal impairment (HR: 1.05, 95% CI 1.01–1.10, $p = 0.029$).

Conclusion: TDF-based ART is associated with notable risks of liver and renal dysfunctions, particularly among male patients. Strengthened routine monitoring and individualized clinical management may help reduce these toxicities.

1 | Introduction

Despite remarkable advancements in antiretroviral therapy (ART), HIV continues to remain a global health challenge, causing an estimated 42.3 million deaths and affecting 39.9 million individuals by 2023 [1]. In Vietnam, approximately 250,000 people are living with HIV, with over 62,000 new cases and 4100 deaths reported in 2023 [2]. ART has significantly improved HIV management by suppressing viral replication, delaying disease progression, and enhancing life expectancy [3]. However, the long-term safety of ART remains a pressing concern.

Tenofovir disoproxil fumarate (TDF), a cornerstone nucleotide reverse transcriptase inhibitor (NRTI) in ART regimens, is widely used in Vietnam due to its cost-effectiveness and inclusion in the national health insurance program. While TDF offers potent antiviral efficacy, it is also associated with nephrotoxicity and hepatotoxicity, presenting a significant clinical dilemma. TDF-induced renal impairment primarily stems from its accumulation in proximal renal tubules, leading to impaired renal function and conditions such as the Fanconi syndrome [4–7]. Additionally, TDF and other ART agents contribute to liver dysfunction through mechanisms such as oxidative stress, mitochondrial damage, and lipid accumulation, raising the risk of drug-induced liver injury [8, 9]. In Vietnam, TDF-based ART regimens remain the cornerstone of HIV treatment due to their affordability and inclusion in the national health insurance program [10]. However, the long-term use of TDF is associated with significant risks of renal and hepatic complications, necessitating vigilant monitoring and evaluation. Regular assessment of liver biomarkers, such as ALT, AST, and bilirubin, alongside renal function parameters like glomerular filtration rate (GFR), is critical for the early detection of complications such as hepatotoxicity and renal impairment.

Timely identifying these issues allows for personalized adjustments to ART regimens, mitigating organ damage, improving long-term prognosis, and reducing mortality rates [11]. Continuous monitoring not only ensures an effective therapeutic response but also safeguards the overall health of HIV patients. This study aims to comprehensively evaluate the effects of ART on liver and renal functions among HIV-infected individuals in southern Vietnam. By uncovering the underlying risk factors for hepatic and renal dysfunctions, the research seeks to enhance early detection and intervention protocols. The findings are expected to inform the optimization of ART regimens, improving long-term outcomes and ensuring a higher quality of care for HIV patients. Ultimately, this work contributes to building a more robust and patient-centered healthcare system for managing HIV in Vietnam.

2 | Methods

2.1 | Study Design and Setting

This study was a prospective cohort study conducted at Thu Duc City Hospital, a multidisciplinary healthcare facility located at the intersection of three industrial hubs in southern Vietnam. Thu Duc City Hospital serves a diverse population, including a significant proportion of migrant workers and low-income individuals employed in nearby industrial zones. As a referral center for HIV/AIDS management, the hospital provides comprehensive care to patients, including ART, diagnostic services, and treatment for opportunistic infections. The hospital's strategic location and high patient volume make it a critical site for studying the impact of ART on liver and renal functions in a resource-limited setting.

2.2 | Participants

This prospective cohort study was conducted at Thu Duc City Hospital from January 2023 to August 2024, with follow-up assessments over 20 months. A total of 552 HIV-infected patients receiving ART for at least 1 month were enrolled. The study focused on patients undergoing TDF-based ART regimens and aimed to evaluate liver damage and renal impairment over time, identifying trends and associated risk factors.

2.2.1 | Inclusion Criteria

- Adult patients aged 18 years or older.
- Diagnosed with HIV and initiating ART with baseline normal liver and renal functions.
- Availability of complete clinical and laboratory records, including liver function tests (AST, ALT, bilirubin) and renal function parameters (serum creatinine).

2.2.2 | Exclusion Criteria

- Pre-existing liver diseases, such as autoimmune hepatitis or alcohol-induced liver damage.
- Coinfection with HBV or HCV, or established cirrhosis.
- Concurrent use of hepatotoxic medications.
- Incomplete baseline or follow-up data for liver or renal function.

2.3 | Data Collection

Demographic characteristics, clinical features, ART regimens, and laboratory data were retrieved from patient records and entered into a coded database for analysis.

Liver and renal dysfunctions were assessed at multiple follow-up points. Based on guidelines from the World Health Organization and the US Department of Health and Human Services, liver and renal function tests were recommended every 3 months during the first year of ART initiation, with the intervals extended for patients without significant abnormalities thereafter [12, 13].

2.4 | Definitions

2.4.1 | Criteria for Liver Function Assessment

Patients were classified as having elevated liver enzymes if their AST or ALT levels were greater than two times the upper limit of normal values, defined as > 66 U/L for males and > 50 U/L for females, based on the American College of Gastroenterology (ACG) guidelines [14].

2.4.2 | Criteria for Renal Function Assessment

Renal function was evaluated using serum creatinine levels. Normal reference ranges were 0.6–1.2 mg/dL for males and 0.5–1.1 mg/dL for females. Renal impairment was defined as creatinine levels outside these ranges [15, 16].

Independent variables included patient demographic and clinical characteristics, including age and gender, baseline laboratory parameters (serum creatinine, AST, and ALT). In addition, treatment-related and comorbidity variables, including the type of ART regimen, history of diabetes mellitus, and cardiovascular disease, were collected as potential confounding factors.

2.5 | Statistical Analysis

The dataset was encoded and analyzed using R software (version 4.4.1), package "survival," and "survminer."

Multivariate logistic regression was employed to identify differences between groups with and without liver or renal dysfunction. Additionally, Cox proportional hazards regression was used to evaluate risk factors associated with liver damage and renal impairment over the duration of ART. Variables with $p < 0.20$ in univariate analysis, together with clinically relevant covariates, were included in the multivariate models to adjust for potential confounding. Multicollinearity was assessed using variance inflation factors (VIFs < 3).

The Kaplan–Meier curve estimates the probability of remaining free from liver damage and renal impairment in HIV patients undergoing TDF-based ART over time. It also allows for comparisons between patient groups based on risk factors such as age, gender, and the extent of pretreatment damage.

Statistical significance was set at $p < 0.05$.

2.6 | Ethical Considerations

This study was conducted according to the ethical principles outlined in the Declaration of Helsinki. Prior to the initiation of the study, approval was obtained from the Institutional Review Board of Thu Duc City Hospital.

All participants provided written informed consent before enrollment. The consent process was conducted individually in a private counseling room to ensure privacy and reduce potential stigma. Trained study staff explained the study objectives, procedures, potential risks and benefits, and the voluntary nature of participation using both verbal and written formats. Participants were given adequate time to ask questions before signing the consent form and were informed of their right to withdraw from the study at any point without affecting their clinical care. To protect confidentiality, all data were anonymized at the time of collection and stored in a secure, password-protected database accessible only to authorized research personnel. No identifiable information was used in any analyses or publications, and additional attention was given to safeguarding the privacy of individuals considered part of vulnerable populations.

Participants who exhibited abnormal liver or renal function during follow-up were referred for appropriate medical intervention, aligning with the study's commitment to ensuring the well-being of all enrolled patients.

3 | Result

A total of 552 HIV-infected patients undergoing TDF-based ART at Thu Duc City Hospital were included in the analysis. Our findings are structured into three sections: (1) baseline demographic, clinical, and liver and renal function characteristics; (2) longitudinal incidence patterns of liver damage and renal impairment; and (3) identification of key risk factors using Cox regression models.

3.1 | Participant Characteristics: Baseline Liver and Renal Functions and Follow-Up Assessment

The flowchart of participant screening and eligibility is presented in Figure 1. The final cohort comprised 552 patients who met all inclusion criteria. Baseline demographic and clinical characteristics are summarized in Table 1.

Baseline liver function was assessed using ALT and AST levels, with a median ALT of 23 U/L (IQR: 17–32) and a median AST of 24 U/L (IQR: 20–28). Renal function, evaluated using serum creatinine levels, remained within normal reference ranges for the majority of participants (0.6–1.2 mg/dL for males and 0.5–1.1 mg/dL for females).

Comparisons across groups showed no significant differences in age, occupation, residence, BMI, CD4+ T-cell count, diabetes, or cardiovascular disease between participants with normal versus abnormal liver or renal function (all $p > 0.05$). However, male sex was significantly associated with both liver damage and renal impairment ($p = 0.01$ and $p < 0.001$, respectively). Baseline ALT levels were higher in participants who later developed liver damage ($p = 0.019$), and baseline AST levels were higher in those who developed renal impairment ($p = 0.049$).

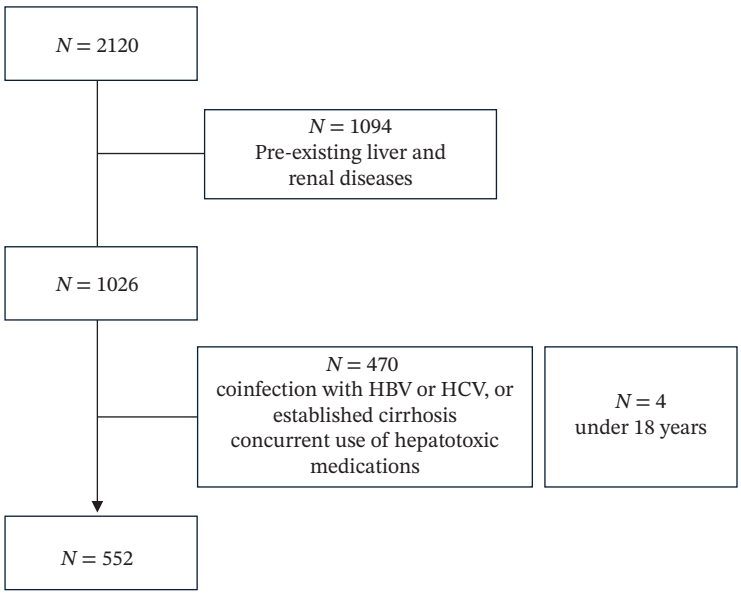


FIGURE 1 | Flowchart of the study participant selection process.

TABLE 1 | Demographic and clinical characteristics of patients at baseline.

	Total	Liver function group		*p*	Renal function group		*p*
		Normal	Abnormal		Normal	Abnormal	
	n = 552	*n* = 493	*n* = 59		*n* = 445	*n* = 107	
Gender				0.010			< 0.001
Male	355 (64.3)	307 (62.3)	48 (81.4)		252 (56.6)	103 (96.3)	
Female	197 (35.7)	186 (37.7)	11 (18.6)		193 (43.4)	4 (3.7)	
Age	34 (27–42)	34 (27–42)	32 (27–42)	0.793	35 (27–42)	31 (25–40)	0.705
Area				0.786			0.589
Ho Chi Minh City	145 (26.3)	132 (26.8)	13 (22)		118 (26.5)	27 (25.2)	
Other provinces	407 (73.7)	361 (73.2)	46 (78)		327 (73.5)	80 (74.8)	
Occupation				0.099			0.392
Unstable job	145 (26.3)	122 (24.8)	23 (39)		118 (26.5)	27 (25.2)	
Stable occupation	238 (43.1)	218 (44.2)	20 (33.9)		191 (42.9)	47 (43.9)	
Other occupations and no income	169 (30.6)	153 (31)	16 (27.1)		136 (30.6)	33 (30.8)	
BMI	20.83 (20.76–21.3)	20.83 (20.76–21.3)	20.81 (19.6–22.77)	0.550	20.83 (20.76–21.3)	20.83 (20.76–21.3)	0.751
CD4+ cell count (cells/μL)				0.192			0.969
< 500	227 (41.1)	206 (41.8)	21 (35.6)		182 (40.9)	45 (42.1)	
≥ 500	325 (58.9)	287 (58.2)	38 (64.4)		263 (59.1)	62 (57.9)	
AST pre (U/L)	24 (20–28)	23 (20–28)	26 (22–30)	0.717	23 (20–28)	25 (21–29)	0.049
ALT pre (U/L)	23 (17–32)	23 (17–31)	29 (21–39)	0.019	23 (17–31)	28 (19–34)	0.595
Diabetes				0.528			0.433
No	508 (92)	455 (92.3)	53 (89.8)		411 (92.4)	97 (90.7)	
Yes	44 (8)	38 (7.7)	6 (10.2)		34 (7.6)	10 (9.3)	
Cardiovascular				0.619			0.527
No	513 (92.9)	460 (93.3)	53 (89.8)		417 (93.7)	96 (89.7)	
Yes	39 (7.1)	33 (6.7)	6 (10.2)		28 (6.3)	11 (10.3)	

Note: Age, BMI, AST pre and ALT pre were defined as non-normally distributed variables based on the results of the Kolmogorov–Smirnov test, and results are expressed as the median and interquartile range (IQR). Categorical variables were compared using the chi-squared or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann–Whitney *U* test.

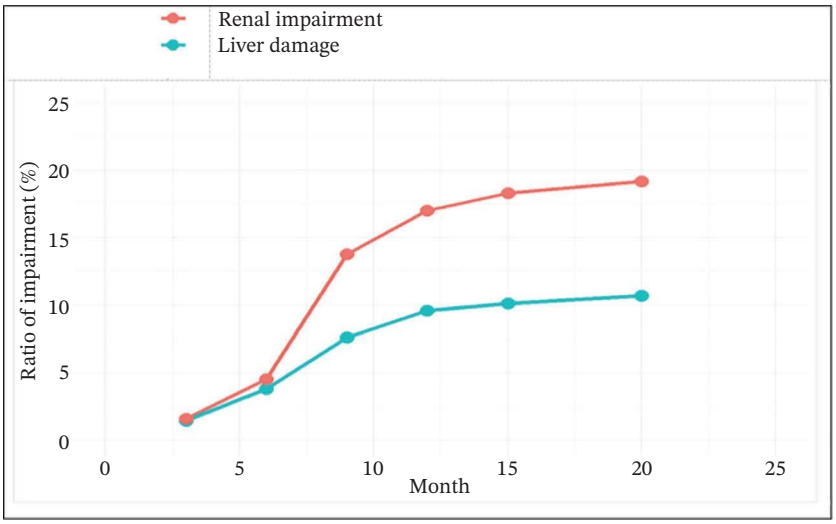


FIGURE 2 | Ratio of liver damage and renal impairment grades in patients undergoing TDF-based ART.

We assessed the rates of liver damage and renal impairment at each follow-up point (Figure 2). The overall incidence of liver damage was 10.7% (IQR: 8.2%–13.6%). From the third to the sixth month, the rate of liver damage increased by 3.8%. After the sixth month, the rate stabilized, remaining below 10.7% until the 20th month. Meanwhile, the overall rate of renal impairment was 19.4% (IQR: 16.2%–22.9%). The rate rose from 1.63% at the third month to 19.2% at the 20th month, outpacing the rise in liver damage rates. Renal impairment showed a rapid increase during the first 6 months, escalating from 1.63% to 4.53%, with a notable surge between the sixth and ninth months, reaching 13.77%. After the 15th month, the rate increased slightly until stabilizing at the 20th month.

The Kaplan–Meier curve illustrates the time to onset of liver damage and renal impairment in HIV patients undergoing TDF-based ART. At 9 months, the cumulative incidence of liver damage was 11.5%, while the cumulative incidence of renal impairment was significantly higher at 23.1% (Figure 3).

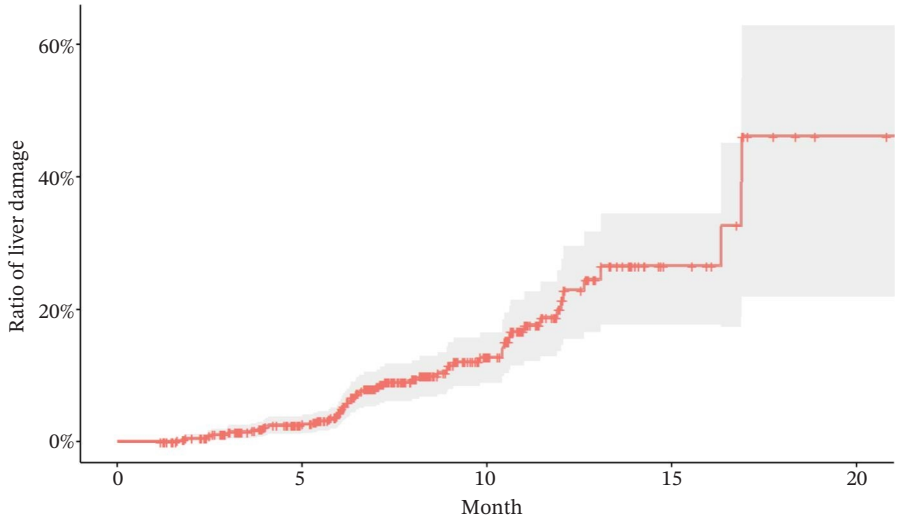
Liver damage increased rapidly from 3 to 9 months, with the 6–9 month period showing the highest increase (3.81%). After 9 months, the rate of increase slowed down, with only a slight rise during the 12–15 month period (0.54%). Meanwhile, renal impairment increased significantly during the 6–9 month period (9.24%), much higher than in other periods. Similar to liver damage, the rate of increase slowed down after 9 months, with only a minimal rise during the 12–15 month period (1.27%).

As shown in Table 2, the univariate Cox regression analysis identified gender as a significant risk factor for both liver damage and renal impairment in patients on TDF-based ART. Male patients had a significantly higher risk of liver damage (HR = 2.51, 95% CI: 1.31–4.83, $p = 0.006$) and an even greater risk of renal impairment (HR = 14.43, 95% CI: 5.39–38.58, $p < 0.001$). Elevated pretreatment ALT levels were significantly associated with an increased risk of liver damage (HR = 1.03, 95% CI: 1.01–1.06, $p = 0.005$), while pretreatment AST levels did not show a statistically significant association with liver damage ($p = 0.051$). For renal impairment, pretreatment AST levels were significantly associated with increased risk (HR = 1.03, 95% CI: 1.00–1.07, $p = 0.047$), but ALT levels showed no significant correlation ($p = 0.319$). Other factors such as residence, BMI, CD4+ T-cell count, ART regimen, diabetes, and cardiovascular disease showed no significant association with liver damage or renal impairment, except for age, which was associated with renal impairment ($p = 0.002$) and stable occupation, which reduced the risk of liver damage.

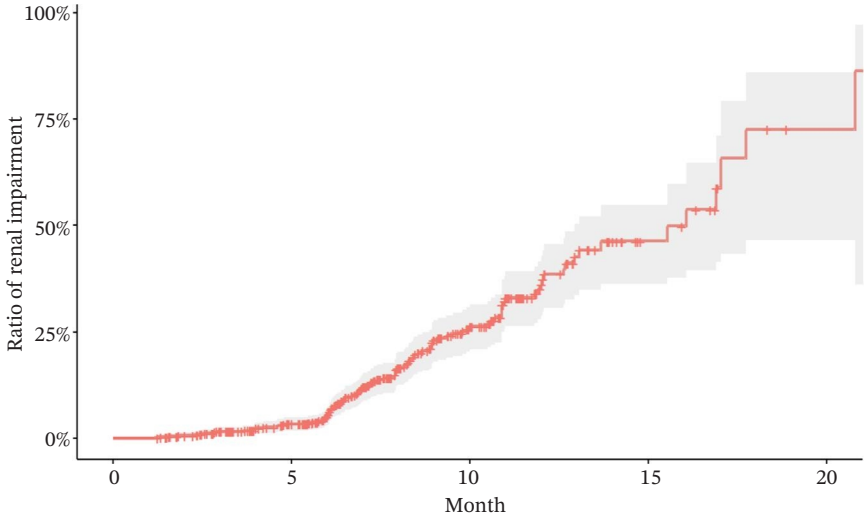
The multivariate Cox regression analysis (Table 3) reinforced the significance of gender as a key risk factor for both outcomes. Male patients had a higher risk of liver damage compared to females (HR = 2.19, 95% CI: 1.10–4.34, $p = 0.025$) and a substantially greater risk of renal impairment (HR = 14.06, 95% CI: 5.39–36.65, $p < 0.001$). Pretreatment AST levels were significantly associated with renal impairment (HR = 1.05, 95% CI: 1.01–1.10, $p = 0.029$) but not with liver damage ($p = 0.721$).

The findings underscore significant gender disparities in the risk of liver damage and renal impairment among HIV patients receiving TDF-based ART, with male patients facing substantially higher risks for both outcomes (Figure 4). This disparity is particularly pronounced for renal impairment, suggesting that biological or behavioral factors specific to males may play a role. Furthermore, the strong association between baseline liver enzyme levels and renal impairment highlights the importance of pretreatment biomarker evaluation for risk stratification. Notably, the lack of correlation between baseline liver enzyme levels and renal impairment indicates that different biomarkers may be more predictive of organ-specific adverse events. These results emphasize the critical need for personalized risk assessments and tailored monitoring strategies, particularly for male patients, to enable early identification and management of liver and renal dysfunction in this population.

For liver damage, male patients exhibited a substantially higher cumulative incidence compared to females. By the 20th month, the cumulative incidence among males reached approximately 57%, whereas the rate in females remained around 16% ($p = 0.0043$). The divergence between the two groups became more evident after the sixth month, underscoring the need for closer liver function monitoring in male patients. Regarding renal impairment, the gender difference was even more pronounced. At the 20th month, the cumulative incidence in males



(a)



(b)

FIGURE 3 | Kaplan–Meier curves for time to onset of liver damage and renal impairment in HIV patients undergoing TDF-based ART. (a) Cumulative incidence of liver damage in HIV patients undergoing TDF-based ART. (b) Cumulative incidence of renal impairment in HIV patients undergoing TDF-based ART.

exceeded 80%, while the rate in females remained below 40% ($p < 0.0001$) (Figure 4).

The Kaplan–Meier analysis stratified by baseline AST levels (> 25 vs. ≤ 25 U/L) reveals slight trends in the cumulative incidence of both liver damage and renal impairment, though the differences did not achieve statistical significance. For liver damage, patients with baseline AST > 25 U/L showed a marginally higher incidence compared to those with AST ≤ 25 U/L ($p = 0.061$). Similarly, for renal impairment, the cumulative incidence was higher in patients with elevated baseline AST levels, but the difference was not statistically significant ($p = 0.12$). These results suggest that while baseline AST levels may indicate trends in organ-specific risk, they are not strong predictors of adverse outcomes in this cohort.

In contrast, baseline ALT levels demonstrated a significant association with liver damage during TDF-based ART. Patients with baseline ALT > 25 U/L experienced a significantly higher cumulative incidence of liver damage compared to those with ALT ≤ 25 U/L ($p = 0.019$). For renal impairment, patients with elevated baseline ALT levels also showed a slightly higher cumulative incidence, but the association was not statistically significant ($p = 0.075$). These findings emphasize the predictive value of baseline ALT levels for liver damage risk and suggest that patients with elevated ALT may benefit from closer monitoring to prevent hepatic complications during treatment (Figure 5).

4 | Discussion

4.1 | Incidence and Patterns of Liver and Renal Dysfunctions During TDF-Based ART

Our study demonstrated distinct temporal patterns of hepatic and renal dysfunctions during TDF-based ART. Liver injury increased mainly within the first 3–6 months of treatment and

TABLE 2 | Univariate analysis of risk factors for liver damage and renal impairment in HIV patients on TDF-based ART.

	Liver damage			Renal impairment		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Gender						
Female	1.00			1.00		
Male	2.51	1.31–4.83	0.006	14.43	5.39–38.58	< 0.001
Age	0.99	0.96–1.02	0.426	0.97	0.95–0.99	0.002
Area						
Other provinces	1.00			1.00		
HCM City	1.16	0.62–2.20	0.628	0.96	0.61–1.51	0.869
Occupation						
Unstable job	1.00			1.00		
Stable occupation	0.47	0.26–0.86	0.013	0.92	0.57–1.48	0.731
Other occupations and no income	0.66	0.35–1.25	0.207	1.19	0.71–2.01	0.509
BMI	1.01	0.94–1.09	0.760	0.97	0.91–1.04	0.419
CD4+ cell count (cells/μL)						
< 500	1.00			1.00		
≥ 500	1.30	0.76–2.22	0.342	0.99	0.68–1.45	0.968
AST pre (U/L)	1.04	0.99–1.08	0.051	1.03	1.00–1.07	0.047
ALT pre (U/L)	1.03	1.01–1.06	0.005	1.01	0.99–1.03	0.319
Diabetes						
No	1.00			1.00		
Yes	1.27	0.52–3.10	0.596	1.06	0.55–2.03	0.859
Cardiovascular						
No	1.00			1.00		
Yes	1.48	0.65–3.41	0.353	1.52	0.83–2.79	0.172

subsequently plateaued, remaining below 10.7% throughout the 20-month follow-up. This pattern suggests that hepatotoxicity associated with TDF tends to occur early after treatment initiation and stabilizes thereafter.

In contrast, renal impairment showed a higher cumulative incidence, with a rapid rise during the first 6 months, peaking between the sixth and ninth months before stabilizing. These findings indicate that renal toxicity represents a more prominent adverse effect of TDF than liver injury in routine clinical practice.

Our results are consistent with previous studies from diverse settings. A retrospective cohort study conducted in Northwest Ethiopia found a renal dysfunction incidence rate of 28.31 per 100 person-years among TDF users, compared to 12.53 per 100 person-years in non-TDF users. Patients on TDF-based regimens had a 1.7-fold higher risk of renal dysfunction (adjusted HR = 1.70; 95% CI: 1.02–2.82) compared to those on non-TDF regimens [17]. Similarly, a African cohort study by Agbaji et al. reported that prolonged TDF exposure significantly increased the likelihood of renal impairment, with rates rising from 10% at 24 weeks to 45% at 144 weeks of treatment [18]. Our findings are also consistent with a study from Japan by Nishijima et al., which identified a strong correlation between cumulative TDF exposure and kidney tubular dysfunction [19].

At a broader level, a systematic review and meta-analysis involving over 88,000 individuals receiving TDF-based regimens reported a pooled chronic kidney disease prevalence of 7%, with substantial regional variation. The highest burden was observed in Sub-Saharan Africa (11.7%), whereas multiregional cohorts reported substantially lower rates (approximately 3%) [20].

TABLE 3 | Multivariate analysis of risk factors for liver damage and renal impairment in HIV patients on TDF-based ART.

	Liver damage			Renal impairment		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Gender	2.19	1.10–4.34	0.025	14.06	5.39–36.65	< 0.001
Age	1.00	0.97–1.03	0.828	0.99	0.97–1.01	0.352
Occupation	0.8	0.54–1.18	0.258	1.21	0.90–1.62	0.205
AST pre (U/L)	1.01	0.95–1.07	0.721	1.05	1.01–1.10	0.029
ALT pre (U/L)	1.03	0.99–1.06	0.116	0.98	0.96–1.01	0.155

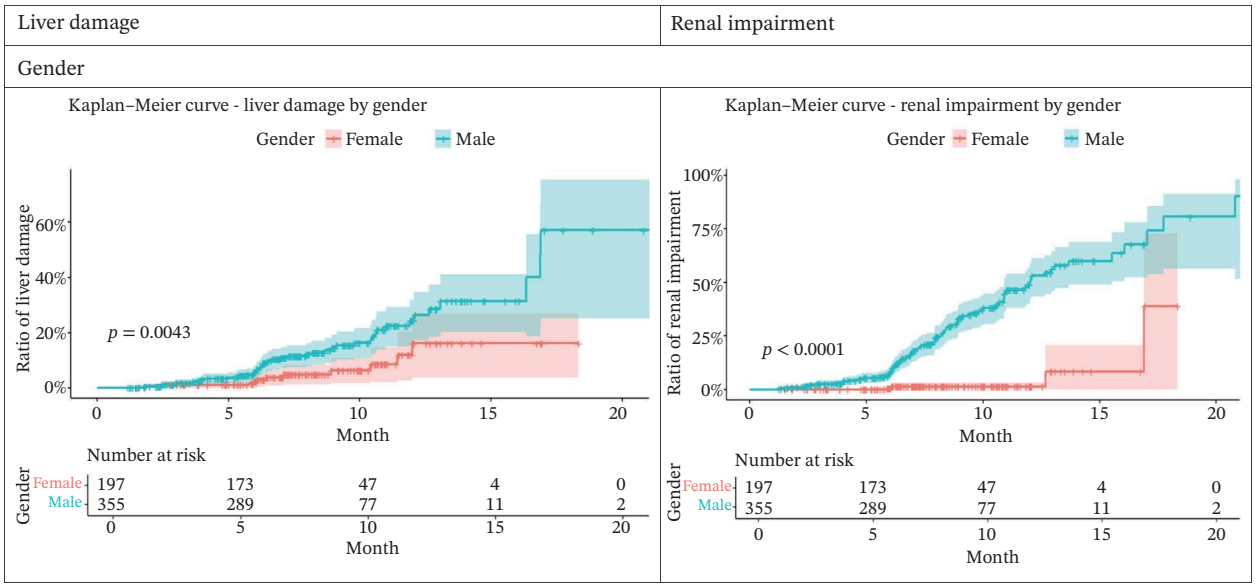


FIGURE 4 | Kaplan–Meier analysis of liver damage and renal impairment by gender in HIV patients receiving TDF-based ART. *Note.* Kaplan–Meier curves showing the cumulative incidence of liver damage and renal impairment stratified by gender among patients receiving TDF-based ART. Shaded areas represent 95% confidence intervals. The log-rank test was used to compare survival functions between males and females. Numbers at risk at each time point are displayed below each panel.

Together, these findings suggest that although early renal decline during TDF therapy is consistently reported, its magnitude and timing vary across populations, underscoring the importance of contextualizing local findings.

The early increase in renal dysfunction observed in our cohort aligns with reports indicating that TDF-related tubular toxicity typically develops within the first 3–6 months of treatment [21]. Comparative studies have also shown that tenofovir alafenamide

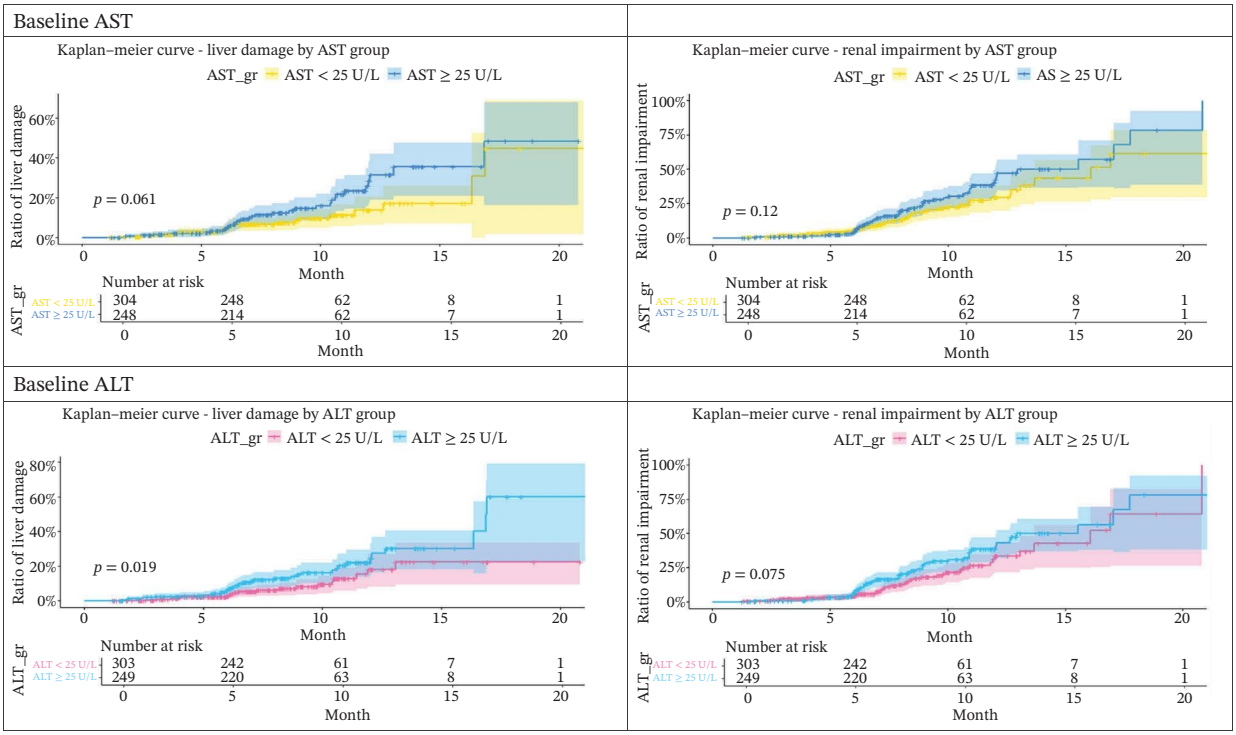


FIGURE 5 | Kaplan–Meier analysis of liver damage and renal impairment by baseline AST and ALT levels in HIV patients receiving TDF-based ART. *Note.* Kaplan–Meier curves depicting time to liver damage and renal impairment according to baseline AST and ALT categories (> 25 U/L vs. ≤ 25 U/L). Shaded regions denote 95% confidence intervals. Differences in cumulative incidence between groups were assessed using the log-rank test. Numbers at risk are shown below each plot to illustrate changes in cohort size over time.

(TAF) is associated with a substantially improved renal safety profile compared with TDF, owing to lower systemic tenofovir exposure. In a pooled analysis of 26 clinical trials, Gupta et al. demonstrated markedly lower rates of renal adverse events and treatment discontinuation among patients receiving TAF than among those receiving TDF [22].

4.2 | Factors in Predicting Liver Damage and Renal Impairment in HIV Patients

Our study observed a higher incidence of renal impairment among male patients; however, this association should be interpreted cautiously, as underlying mechanisms were not directly assessed. Proposed explanations in the literature, including greater muscle mass affecting creatinine-based GFR estimation and hormonal influences on renal hemodynamics [23, 24], could not be evaluated in our cohort due to the lack of relevant data. Further studies incorporating these variables are warranted to clarify sex-related differences in TDF-associated nephrotoxicity.

Evidence from other regions shows considerable heterogeneity. While an Ethiopian cohort identified male sex as an independent risk factor for chronic kidney disease [25], a Thai case–control study reported a higher risk of TDF-associated proximal tubulopathy among females [26]. These discrepancies suggest that sex-related susceptibility to TDF toxicity varies across populations, highlighting the importance of locally derived evidence such as that from our Vietnamese cohort.

In our study, male patients also demonstrated a higher risk of liver injury, with the Kaplan–Meier analysis indicating a more rapid accumulation of hepatic events. Although previous studies have reported no significant sex differences in liver enzyme elevations during TDF therapy [27], the observed association in our cohort should be interpreted cautiously, as potential behavioral or contextual factors, including alcohol use, were not assessed.

Baseline ALT was associated with liver injury only in univariate analysis, suggesting it reflects the underlying hepatic vulnerability rather than serving as an independent predictor. In contrast, baseline AST showed a modest but statistically significant independent association with renal impairment, possibly indicating early systemic or mitochondrial stress. Overall, male sex remained the most consistent predictor of both hepatic and renal injuries, whereas baseline transaminases contributed limited additional prognostic value.

4.3 | Clinical Implications and Applications

As observed in our clinical setting, the continued reliance on TDF-based regimens persists despite well-established international recommendations for baseline and periodic renal and hepatic screening. This pattern reflects structural constraints that remain common in many Southeast Asian HIV programs [28, 29], including limited access to TAF, insurance-driven formularies, and competing clinical demands that restrict routine laboratory monitoring. These contextual pressures align with regional evidence indicating that nephrotoxicity risk may be amplified where self-medication with NSAIDs is widespread, comorbidities are underdiagnosed, and sex-specific differences in renal vulnerability may be overlooked.

In Vietnam, a substantial proportion of people living with HIV belong to low-income groups and face persistent economic and social challenges. Previous studies have reported a moderate overall quality of life among HIV patients, with particularly low scores in mental health and social functioning, reflecting barriers to sustained healthcare access [30, 31]. Although the inclusion of ART in the national health insurance program has markedly reduced treatment costs and improved access to first-line therapy, the financial burden associated with advanced regimens and long-term care remains substantial. These constraints strongly influence regimen selection and limit the feasibility of widespread transitions to newer, less nephrotoxic agents.

TDF remains the backbone of first-line ART in Vietnam, as the recommended TDF/3TC/DTG regimen is fully covered by health insurance. In contrast, TAF, which offers improved renal safety, requires out-of-pocket payment and is therefore inaccessible to many low-income patients. Under these circumstances, universal switching to TAF is not currently feasible.

4.4 | Limitations

This study has some limitations to consider. First, the follow-up period of 20 months may not be sufficient to capture the long-term adverse effects of TDF-based ART on liver and renal functions. Chronic complications may manifest after prolonged treatment, necessitating further studies with extended follow-up durations. Second, the study was conducted at a single center, Thu Duc City Hospital, which may limit the generalizability of the findings to other populations in Vietnam or regions with different socioeconomic or healthcare contexts.

Additionally, the scope of biomarkers assessed in this study was limited to AST, ALT, and creatinine. While these are standard markers for liver and renal functions, they do not provide a complete picture. Biomarkers such as estimated glomerular filtration rate (eGFR), tubular proteinuria, or mitochondrial damage indicators could offer deeper insights into TDF-associated toxicity. Moreover, potential confounding variables, including alcohol consumption, dietary habits, and genetic predispositions, were not measured, which could influence the observed outcomes.

Renal impairment in this study was defined using serum creatinine values outside standard reference ranges. While this definition aligns with routine clinical monitoring practices in the study setting, it may not capture subtle or transient changes in renal function that could be identified using dynamic criteria, such as absolute or relative increases in creatinine- or eGFR-based definitions. Therefore, a certain degree of outcome misclassification cannot be fully excluded.

Despite these limitations, the study provides meaningful preliminary evidence on the early hepatic and renal effects of TDF-based ART within a real-world clinical context. The insights gained here help delineate the initial trajectory of organ toxicity and contribute to the growth of evidence relevant to routine HIV care. At the same time, these constraints highlight important directions for future research, including extended longitudinal follow-up, multicenter investigations to enhance generalizability, and the incorporation of more comprehensive biomarker panels to better clarify the mechanisms and determinants of TDF-associated toxicity.

5 | Conclusion

This study highlights the significant risks of liver damage and renal impairment associated with TDF-based ART in HIV-infected patients in southern Vietnam. Over 20 months, renal impairment (19.4%) occurred more frequently than liver damage (10.7%), with male patients at substantially higher risk for both outcomes. Elevated baseline ALT levels were significantly associated with liver damage, while elevated AST levels predicted renal impairment, underscoring the importance of pretreatment biomarker evaluation.

These findings emphasize the need for personalized care, including routine monitoring of liver and renal functions, particularly in high-risk groups such as male patients. While TDF remains a cost-effective and accessible option in Vietnam, efforts to expand access to safer alternatives, such as TAF, are critical to improving long-term outcomes and reducing treatment-related complications.

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Ethics Statement

The study protocol was reviewed and approved by the Institutional Review Board of Thu Duc City Hospital. All procedures adhered to the ethical standards of the institutional and national research committees and complied with the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analyzed during the current study contain confidential patient information and cannot be made publicly available due to institutional data protection policies. Deidentified data or analytic code may be provided by the corresponding author upon reasonable request and with approval from Thu Duc City Hospital.

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