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Tenofovir-based Antiretroviral Therapy in Hepatitis B Virus/HIV Co-infection: Results from the TREAT Asia HIV Observational Database

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Abstract

Background—The World Health Organisation recommends Hepatitis B virus (HBV)/HIV co-infected individuals start antiretroviral therapy containing tenofovir. Here we describe first-line tenofovir use and treatment outcomes in co-infected patients in Asia.

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Methods—HBV surface antigen positive patients enrolled in the TREAT Asia HIV Observational Database who started first-line antiretroviral therapy were included. Logistic regression adjusted for period of treatment initiation was used to determine factors associated with tenofovir use. Generalised estimating equations were used to evaluate factors associated with alanine transaminase levels and CD4 cell count on treatment.

Results—There were 548 eligible patients, of whom 149 (27.2%) started tenofovir. Patients treated in high/high-middle income countries (odds ratio 4.4 vs. low/low-middle, 95%CI 2.6-7.4, $p<0.001$) and those with elevated baseline alanine transaminase (odds ratio 4.2 vs. normal, 95%CI 2.4-7.2, $p<0.001$) were more likely to receive tenofovir. Hepatitis C antibody positive patients (odds ratio 0.4 vs. negative, 95%CI 0.2-0.8, $p=0.008$) were less likely. In those starting antiretroviral therapy with elevated alanine transaminase, mean reduction after tenofovir initiation was 11.2 IU/L (95%CI 0.9-21.6, $p=0.034$) lower compared with those using a non-tenofovir-based regimen although this did not significantly increase the chance of alanine transaminase normalization. Tenofovir use was not associated with a superior CD4 response.

Conclusions—HBV/HIV co-infected patients in Asia are most likely to receive tenofovir if they are treated in a high/high-middle income country, have elevated alanine transaminase levels, and are hepatitis C antibody negative. Compared to other antiretroviral therapy, tenofovir-based regimens more effectively reduce liver inflammation in HBV/HIV co-infection but do not result in superior CD4 recovery.

BACKGROUND

Globally, HIV prevalence is estimated at 35 million and hepatitis B virus (HBV) prevalence at 400 million.[1, 2] Approximately 10% of HIV infected individuals are chronically infected with HBV, many of whom reside in Asia.

The World Health Organization (WHO) currently recommends initiation of antiretroviral therapy (ART) for all HBV/HIV co-infected patients requiring treatment for severe chronic liver disease, irrespective of HIV disease stage.[3] However, this recommendation is complicated by the absence of routine HBV screening in most resource-limited areas. Furthermore, previous WHO guidelines advised initiating ART among all HBV/HIV co-infected individuals who were considered to have chronic active hepatitis – a diagnosis that requires access to costly and often inaccessible methods for staging liver disease such as liver biopsy, transient elastography, and HBV DNA.[3]

The nucleoside reverse transcriptase inhibitors, lamivudine (3TC), emtricitabine (FTC) and tenofovir (TDF) are effective against both HIV and HBV. Although resistance develops quickly when 3TC is used as the only anti-HBV agent in an ART regimen,[4] TDF alone seems to lower HBV DNA as effectively as 3TC + TDF.[5] The WHO recommends HBV/HIV co-infected individuals start an ART regimen containing TDF,[3] however, there is currently a lack of observational data from Asia to support this advice.

The purpose of this analysis was to evaluate recent practice in first-line ART prescribing for HBV/HIV co-infected patients in a well characterized Asian HIV cohort and investigate whether TDF-based regimens protect against liver inflammation, produce superior CD4 cell recovery and improve survival when compared with non-TDF-based ART.

METHODS

The study population consisted of patients enrolled in the TREAT Asia HIV Observational Database (TAHOD). This cohort has been described previously.[6] Briefly, TAHOD enrolls patients with HIV from 21 adult treatment centers in 12 countries and territories in Asia, with the aim of assessing HIV disease natural history in treated and untreated patients in the region. Data are collected on a core set of demographic and clinical variables including sex, age, mode of HIV exposure, hepatitis B virus surface antigen (HBsAg) status, hepatitis C virus (HCV) antibody status, CD4 and CD8 cell counts, HIV viral load, routine laboratory results, ART history and adherence (based on the visual analogue scale [7]), AIDS illnesses, date and causes of death. Recruitment started in September 2003 and retrospective and prospective data continues to be collected. Currently, each TAHOD site has contributed data from approximately 100-500 patients. Data are transferred to the data management center at the Kirby Institute, Sydney, Australia twice annually in March and September. Ethics approvals are in accordance with the Helsinki Declaration and have been obtained from institutional review boards at each of the participating clinical sites where study patient enrolment takes place, as well as by separate review boards for the coordinating center (TREAT Asia, Bangkok, Thailand) and the data management center.

TAHOD patients from the September 2013 data transfer were included in this analysis if they had a positive HBsAg test at any stage of follow up and had initiated first-line ART during or after 2003. They were assumed co-infected from the date of enrollment. First-line ART was defined as the first regimen containing 3 antiretrovirals used for >14 days. TDF-based ART was defined as any regimen containing TDF. Non-TDF-based ART was defined as all other regimens.

Baseline was considered the first day of first-line ART. The window period for baseline alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin, HIV viral load, and creatinine was from first-line ART initiation to six months prior, and for baseline CD4 cell count it was from one month after ART initiation to six months prior. The measurement taken closest to ART initiation was used. Patients were considered HCV antibody positive if they had any record of a positive HCV antibody test in the database. Kidney dysfunction was defined as an estimated creatinine clearance <50mL/min based on the Cockcroft-Gault equation.[8] Country income status was defined according to The World Bank categorizations.[9] Tuberculosis treatment and ART adherence were evaluated as time-updated variables. Because concomitant medication use is not comprehensively recorded in TAHOD, patients were considered to be receiving tuberculosis treatment during any period of hepatotoxic prophylaxis (isoniazid, rifabutin, rifampicin, pyrazinamide) and for six months after a diagnosis of tuberculosis.[10] Data on HBV viral load, HBV e antigen, HBsAg serum levels, and platelet count was not available or insufficient for analysis.

First-line regimen modification was defined as a change of 1 antiretroviral that was continued for at least 14 days. Changes in ALT and CD4 cell count were measured as the difference from baseline in those with a documented baseline value. Patients were categorized by baseline ALT according to the upper limit of normal (ULN) defined by their clinic. Cause of death forms were checked for contributing causes of death.

Statistical analysis

Fisher's exact test and the Kruskal-Wallis test were used to assess differences between group proportions and group medians, respectively. Logistic regression was used to evaluate factors associated with TDF-based ART use. Generalised estimating equations adjusted for time on ART were used to assess factors associated with ALT and CD4 cell count change. Cox regression was used to determine predictors of mortality.

Follow up ALT and CD4 cell count values were only included in our analyses whilst patients were using first-line ART. Follow up time was divided into twelve, three-monthly intervals for ALT and six, six-monthly intervals for CD4 cell count. A window period of 1.5 months either side of each ALT time point, and three months either side of each CD4 time point was applied. If, for any given time interval, multiple values were recorded for a patient, the value nearest the mid-point of the interval was used. Intervals missing a record were kept as missing. Generalized estimating equations were restricted to those with a baseline (ALT or CD4) value and at least one subsequent measurement. Given the introduction of ART causes an early increase in ALT levels in HBV-positive (and HBV-negative) patients,[11] we restricted our models of ALT change to baseline and follow up measurements taken beyond six months of ART.

For the survival analysis, follow up time was left-censored. Right-censoring occurred at the last recorded clinic visit whilst still on first-line ART or at treatment modification without death.

Covariables were retained in the multivariate models if one or more categories exhibited a p-value < 0.05. Patients with missing data were included in all models but coefficients, odds ratios (ORs) and hazard ratios for missing categories are not reported.

Stata software version 13.1 was used for all statistical analysis.

RESULTS

A total of 548 patients were eligible for inclusion. Baseline data are presented in Table 1. First-line ART comprised of stavudine (d4T) + 3TC/FTC + a non-nucleoside reverse transcriptase inhibitor (NNRTI) for 193 (35.2%) patients, and zidovudine (AZT) + 3TC/FTC + a NNRTI for 144 (26.3%) patients. TDF-based ART was initiated by 149 (27.2%) patients. Of these, 113 (75.8%) were using a NNRTI, 32 (21.5%) were using a protease inhibitor or raltegravir, and 5 (3.4%) were using an all nucleoside reverse transcriptase inhibitor regimen. One (0.67%) patient was using TDF-based ART with a protease inhibitor and an NNRTI. ART adherence data was available for 62.8% of patients, of whom 10.1% had documentation of <100% adherence.

Tenofovir-based ART

A breakdown of ART use by country income status and period of ART initiation is provided in Figure 1. Use of TDF-based ART was associated with later period of ART start, treatment in a high/high-middle income country, high baseline ALT, and negative HCV antibody status (Table 2). Compared with patients starting ART in 2003 – 2006, those starting in 2007

– 2009 and 2010 – 2013 were 12.37 (95% confidence interval [95%CI] 5.56 to 27.52, $p<0.001$) and 21.00 (95%CI 9.20 to 47.95, $p<0.001$) times more likely to be using TDF-based ART, respectively. Treatment with a TDF-based regimen was 4.35 (95%CI 2.56 to 7.38, $p<0.001$) times more likely in a high/high-middle income country compared with treatment in a low/low-middle income country, and 4.19 (95%CI 2.44 to 7.20, $p<0.001$) times more likely in patients with a baseline ALT>ULN compared to patients with baseline ALT ≤ULN. Those with positive HCV antibody status were less likely to be started on TDF-based ART (OR 0.37 vs. HCV antibody negative, 95%CI 0.17 to 0.76, $p=0.008$).

Change in ALT with ART

In the first six months of ART, 53.6% of patients with a follow up measurement experienced an increase in ALT level from baseline (44.7% in the TDF group vs. 57.1% in the non-TDF group, $p=0.078$). After 36 months of non-TDF-based therapy, the mean change in ALT was –2.4 IU/L. After the same length of time, the mean change in ALT was –31.3 IU/L in patients using TDF-based ART.

TDF-based ART and elevated baseline ALT were both associated with a significantly lower follow up ALT. TDF-based ART was associated with a difference in ALT response of –7.8 IU/L (95%CI –15.1 to –0.5, $p=0.036$) compared with non-TDF-based ART. Compared with a normal baseline ALT, baseline ALT>ULN predicted an ALT change of –26.2 IU/L (95%CI –33.1 to –19.4, $p<0.001$). When baseline ALT and TDF use were included in the final model as an interaction term, the ALT lowering effect of TDF was specific to patients with elevated baseline ALT (–11.2 IU/L, 95%CI –21.6 to –0.86, $p=0.034$ for TDF-based ART vs. non-TDF-based ART). This difference remained significant when non-TDF-based ART was broken down into regimens containing d4T + NVP, two commonly hepatotoxic antiretrovirals, and other ART (–11.7 IU/L, 95%CI –23.0 to –0.4, $p=0.042$ for TDF-based ART vs. non-TDF-based ART with d4T + NVP regimens removed). Positive HCV antibody status was associated with a significantly higher ALT on ART compared with negative HCV antibody status (12.7 IU/L, 95%CI 3.6 to 21.8, $p=0.006$). Concomitant anti-tuberculosis drug exposure, ART adherence, and country income status were not associated with ALT change.

To assess the clinical significance of the ALT reduction induced by TDF, we investigated predictors of normal follow up ALT in those patients with a baseline ALT>ULN. Patients with a positive HCV antibody status (OR 0.31 vs. negative, 95%CI 0.14 to 0.73, $p=0.007$) had significantly reduced odds of achieving follow up ALT ≤ULN, however, ART regimen was not associated with an increased chance of ALT normalisation (OR 0.96 for TDF-based vs. non-TDF-based, 95%CI 0.46 to 1.99, $p=0.903$).

Change in CD4 cell count with ART

After 36 months of non-TDF-based therapy, the mean increase in CD4 cell count was 223 cells/mm³. After equivalent follow up time, CD4 cell count increased 242 cells/mm³ in patients using TDF. In our final model, positive HCV antibody status was associated with a difference in CD4 count change of –36 cells/mm³ (95%CI –61 to –11, $p=0.005$) compared to HCV antibody negative patients. TDF-based ART was associated with a non-significantly

higher CD4 count compared to non-TDF-based ART (6 cells/mm³, 95%CI -13 to 25, p=0.540). When the non-TDF-based ART group was broken down into AZT-containing and non-AZT-containing, neither group exhibited a significantly different CD4 response compared to TDF-based ART (-3 cells/mm³, 95%CI -26 to 20, p=0.792 for AZT-containing and -8 cells/mm³, 95%CI -29 to 13, p=0.462 for non-AZT-containing). Baseline CD4 cell count, ART adherence, and country income status were not associated with CD4 response.

Mortality on ART

Overall, the median time on initial ART was 2.18 years (IQR 1.10 to 3.89). Thirteen deaths occurred at a rate of 1.32 deaths per 100 patient/years (95%CI 0.76 to 2.27). Only two cause of death forms mentioned decompensated liver disease or hepatocellular carcinoma as a contributing cause. In patients receiving TDF- and non-TDF-based ART the mortality rates were 0.86 (95%CI 0.28 to 2.67) and 1.57 (95%CI 0.84 to 2.91) deaths per 100 patient/years, respectively. There was an insufficient number of outcomes to construct a multivariate model, however, patients with baseline ALT>ULN not using TDF had a 6.50 (95%CI 2.16 to 19.56, p=0.001) times greater risk of death compared to those with normal baseline ALT or high baseline ALT and using TDF. To further evaluate this finding, we compared HCV antibody status, CD4 cell count and AST:ALT ratio amongst these groups. The elevated ALT/non-TDF-based ART group had a significantly higher proportion of HCV antibody positive patients (30.1% vs. 14.0%, p<0.001) and lower median CD4 count at baseline (57 cells/mm³ vs. 120 cells/mm³, p<0.001) compared to the normal baseline ALT and/or TDF-based ART group. Since all patients with normal ALT were represented in one group they were excluded from the AST:ALT comparison. Amongst patients with elevated ALT, the proportion with an AST:ALT>1 was higher in those not using TDF compared to those on TDF-based ART (42.4% vs. 32.1%, p=0.288).

CONCLUSIONS

TDF entered the antiretroviral market in 2002 and has become increasingly recognized by prescribers and guideline providers as a safe, efficacious, and cost-effective alternative to AZT and d4T. Shortly after the introduction of TDF, it became apparent that it was active against HBV and an important component of HBV suppressive ART. Our findings show that TDF-based ART use has become more common over time amongst HBV/HIV co-infected patients in Asia, however, there was a greater likelihood of receiving TDF in wealthier countries of the region. Interestingly, TDF use amongst co-infected patients did not increase substantially in high/high-middle income countries after 2007 – 2009 indicating there is a need to continue expanding access in resource-rich and resource-limited areas of Asia. The finding that elevated baseline ALT was associated with the use of TDF-based ART probably represents selective use of TDF in those with signs of active HBV infection, while the relationship between negative HCV antibody status and TDF use was probably due to the ability of HCV to lower HBV viral load and HBsAg levels.[12, 13]

A decline in liver enzyme levels following initiation of anti-HBV ART in patients with elevated ALT was reported by Kosi *et al* (2013).[14] In their analysis of 96 HBV/HIV co-

infected patients receiving 3TC, TDF or 3TC + TDF, mean ALT levels dropped from 89 IU/L at baseline to 47 IU/L after one year of treatment ($p < 0.001$). This is in line with our results and the strong body of evidence showing that patients with a high baseline ALT have superior rates of HBsAg and HBV e antigen seroclearance on anti-HBV treatment.[15-17] Importantly, however, we found that increased ALT reduction in TDF-based ART users with elevated baseline ALT was insufficient to increase their probability of ALT normalization over 36 months of follow up. Patients with a positive HCV antibody status exhibited higher ALT levels after ART initiation and lower odds of ALT normalization when compared with HCV antibody negative patients. Despite reduced HBV activity in most patients with HBV/HCV co-infection, HCV accelerates liver disease progression and increases the risk of hepatocellular cancer.[18] European guidelines recommend HCV treatment in HBV/HCV co-infection,[19] however, such therapies are currently lacking in Asia [20].

Previous studies have shown that the immune response to ART is reduced or delayed in HBV/HIV co-infected patients [11, 21, 22] but this remains controversial [23, 24] and may rely upon the ART used. In contrast to our findings, a three-armed randomized trial of 3TC + TDF vs. 3TC + AZT vs. TDF + AZT found that the 3TC + TDF arm experienced a significantly greater increase in CD4 cell count after 48 weeks of treatment (195 cells/mm³ vs. 141 cells/mm³ in the 3TC group and 118 cells/mm³ in the TDF group, $p = 0.048$).[5] These trial results may have been influenced by the myelosuppressive effects of AZT,[25] although, we did not find a difference in CD4 response between AZT-containing ART and non-AZT-containing ART in our study population. This area of research requires further investigation using greater patient numbers as it appears any difference in immune response between HBV/HIV co-infected and HIV mono-infected patients, or between TDF-containing and non-TDF-containing ART in HBV/HIV infected patients, is small. Interestingly, our final model for CD4 response did not include ART adherence. This was due to the low rate of poor adherence documented during follow up.

Puoti *et al* (2006) reported that the use of 3TC as part of ART was associated with a reduced risk of liver-related mortality.[26] The relative risk of liver-related death per extra year of 3TC use in their cohort of 2,041 HBV/HIV co-infected patients was 0.73 (95% CI 0.59-0.90, $p = 0.004$). Our findings indicate TDF-based ART could also protect against mortality in HBV/HIV co-infection. However, since we were unable to adjust for HCV antibody status, CD4 cell count, and other important predictors of death, this should be interpreted very cautiously, particularly given the elevated ALT/non-TDF-based ART group had a low median CD4 cell count and high proportions of patients with positive HCV antibody status and AST:ALT > 1 (a crude indicator of cirrhosis in HBV infection [27, 28]).

This analysis had several important limitations. Unfortunately, data on HIV viral load, HBV DNA, HBV drug resistance, platelet count, and HBsAg and HBV e antigen seroconversion were insufficient or not available for our statistical analyses. These are also common impediments to HBV/HIV care across much of Asia. Although we used HCV antibody status to give an indication of outcomes in patients with HCV co-infection it should be noted that clearance rates of HCV are highly variable and therefore patients with a positive HCV antibody test may not have had chronic HCV infection. We did not have complete data on

concomitant drug use although it is very unlikely patients would have been using other forms of anti-HBV therapy.

The use of TDF-based first-line ART in HBV/HIV co-infected patients has increased substantially overtime in Asia. However, regimens without TDF remain common, particularly in low/low-middle income countries. Compared with other ART, TDF-based therapy produces superior yet clinically unsubstantial ALT reduction in HBV/HIV co-infected patients and does not produce a superior CD4 response.

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DCB, SKe and ML designed the analysis. DCB performed the analysis. DCB, SKe, RD, RC, PCKL and ML drafted the manuscript. RD, RC, PCKL, TPM, TTTP, SKi, NK, SV, CKCL, NVK, SP, WWW, AK, FZ, EY, JYC, SO, OTN, PK, MM, WR contributed patient data. All authors have reviewed and approved the final manuscript.

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Figure 1. Initial antiretroviral therapy by period of initiation and country income status
 Values in parenthesis represent total number of patients starting treatment in period in specified country income level. TDF=tenofovir; 3TC/FTC=lamivudine/emtricitabine; d4T=stavudine; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; AZT=zidovudine; ART=antiretroviral therapy.

Table 1

Baseline data.

Baseline characteristic	Overall (n=548)	TDF (n=149)	Non-TDF (n=399)
Male	427 (77.9%)	121 (81.2%)	306 (76.7%)
Age, years			
<30	144 (26.3%)	40 (26.8%)	104 (26.1%)
30-40	242 (44.2%)	55 (36.9%)	187 (46.9%)
>40	162 (29.6%)	54 (36.2%)	108 (27.1%)
Median [IQR]	35.3 [29.8 to 41.8]	36.4 [29.9 to 44.3]	35.1 [29.6 to 41.1]
HIV exposure			
Heterosexual	307 (56.0%)	69 (46.3%)	238 (59.6%)
Homosexual	141 (25.7%)	62 (41.6%)	79 (19.8%)
Intravenous drug use	68 (12.4%)	11 (7.4%)	57 (14.3%)
Other	32 (5.8%)	7 (4.7%)	25 (6.3%)
HCV antibody status			
Negative	399 (72.8%)	111 (74.5%)	288 (72.2%)
Positive	82 (15.0%)	12 (8.1%)	70 (17.5%)
Unknown	67 (12.2%)	26 (17.4%)	41 (10.3%)
ALT			
ULN	239 (43.6%)	55 (36.9%)	184 (46.1%)
>ULN	161 (29.4%)	64 (43.0%)	97 (24.3%)
Unknown	148 (27.0%)	30 (20.1%)	118 (29.6%)
Median [IQR], IU/L	35.0 [23.0 to 61.0]	45.0 [28.0 to 85.0]	31.0 [22.0 to 51.0]
AST			
ULN	142 (25.9%)	46 (30.9%)	96 (24.1%)
>ULN	171 (31.2%)	55 (36.9%)	116 (29.1%)
Unknown	235 (42.8%)	48 (32.2%)	187 (46.9%)
Median [IQR], IU/L	39.0 [28.0 to 66.0]	42.3 [30.0 to 77.0]	39.0 [26.5 to 62.5]
AST:ALT ratio			
1	141 (25.7%)	54 (36.2%)	87 (21.8%)
>1	172 (31.4%)	47 (31.5%)	125 (31.3%)
Unknown	235 (42.9%)	48 (32.2%)	187 (46.9%)
Bilirubin			
ULN	165 (30.1%)	65 (43.6%)	100 (25.1%)
>ULN	23 (4.2%)	13 (8.7%)	10 (2.5%)
Unknown	360 (65.7%)	71 (47.7%)	289 (72.4%)
Kidney dysfunction			
No	261 (47.6%)	85 (57.0%)	176 (44.1%)
Yes	13 (2.4%)	4 (2.7%)	9 (2.3%)
Unknown	274 (50.0%)	60 (40.3%)	214 (53.6%)

Baseline characteristic	Overall (n=548)	TDF (n=149)	Non-TDF (n=399)
Median [IQR] creatinine clearance, ml/min	86.3 [70.6 to 104.5]	89.0 [72.3 to 109.6]	84.7 [70.1 to 104.0]
CD4 cell count, cells/mm³			
>200	140 (25.5%)	45 (30.2%)	95 (23.8%)
100 - 200	110 (20.1%)	31 (20.8%)	79 (19.8%)
<100	234 (42.7%)	51 (34.2%)	183 (45.9%)
Unknown	64 (11.7%)	22 (14.8%)	42 (10.5%)
Median [IQR]	110 [31 to 226]	134 [33 to 245]	95 [31 to 213]
HIV viral load, copies/ml			
Unknown	244 (44.5%)	25 (16.8%)	219 (54.9%)
Median [IQR]	78,166 [14,827 to 254,386]	61,425 [20,175 to 128,874]	89,350 [11,793 to 336,274]
NRTIs in first-line regimen			
Lamivudine/emtricitabine	536 (97.8%)	148 (99.3%)	388 (97.2%)
Zidovudine	171 (31.2%)	6 (4.0%)	165 (41.4%)
Stavudine	201 (36.7%)	0 (0.0%)	201 (50.4%)
Other	47 (8.6%)	6 (4.0%)	41 (10.3%)
NNRTI/PI/raltegravir in first-line regimen			
Efavirenz	270 (49.3%)	106 (71.1%)	164 (41.1%)
Nevirapine	205 (37.4%)	7 (4.7%)	198 (49.6%)
PI or raltegravir	67 (12.2%)	32 (21.5%)	35 (8.8%)
Country income status			
Low/low-middle	215 (39.2%)	32 (21.5%)	183 (45.9%)
High/high-middle	333 (60.8%)	117 (78.5%)	216 (54.1%)
Year of ART start			
2003 - 2006	173 (31.6%)	8 (5.4%)	165 (41.4%)
2007 - 2009	204 (37.2%)	74 (49.7%)	130 (32.6%)
2010 - 2013	171 (31.2%)	67 (45.0%)	104 (26.1%)

Values are n(%total) unless otherwise specified. IQR=interquartile range; HCV=hepatitis C virus; ALT=alanine transaminase; AST=aspartate aminotransferase; ULN=upper limit of normal; IU=international units; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; ART=antiretroviral therapy; TDF=tenofovir.

Table 2

Factors associated with first-line tenofovir-based antiretroviral therapy (n=548).

Covariables	Univariate OR (95%CI)	p	Multivariate ^b OR (95%CI)	p
Baseline ALT^a				
ULN	1.00		1.00	
>ULN	2.21 (1.43 to 3.41)	<0.001	4.19 (2.44 to 7.20)	<0.001
HCV antibody status^a				
Negative	1.00		1.00	
Positive	0.44 (0.23 to 0.85)	0.015	0.37 (0.17 to 0.76)	0.008
Year of ART start^a				
2003 – 2006	1.00		1.00	
2007 – 2009	11.74 (5.46 to 25.23)	<0.001	12.37 (5.56 to 27.52)	<0.001
2010 – 2013	13.29 (6.13 to 28.79)	<0.001	21.00 (9.20 to 47.95)	<0.001
Country income status^a				
Low/low-middle	1.00		1.00	
High/high-middle	3.10 (2.00 to 4.80)	<0.001	4.35 (2.56 to 7.38)	<0.001
Sex				
Male	1.00		1.00	
Female	0.76 (0.47 to 1.22)	0.258	0.78 (0.45 to 1.34)	0.365
Kidney dysfunction				
No	1.00		1.00	
Yes	0.92 (0.28 to 3.07)	0.893	0.63 (0.16 to 2.42)	0.500

Significant multivariate ORs are bolded.

ALT=alanine transaminase; ULN=upper limit of normal; HCV=hepatitis C virus; ART=antiretroviral therapy; OR=odds ratio; 95%CI=95% confidence interval.

^a Included in final model^b Adjusted for covariables included in the final model.