Original Article

Lamivudine Plus Tenofovir versus Lamivudine Plus Adefovir for the Treatment of Hepatitis B Virus in HIV-Coinfected Patients, Starting Antiretroviral Therapy

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Abstract

Background: Combination of tenofovir disoproxil fumarate (TDF), lamivudine (3TC) and efavirenz (EFV) is preferred in the treatment of HIV/hepatitis B virus (HBV) coinfection. We postulated that a HBV active nucleoside reverse transcriptase (RT) inhibitor/nucleotide RT inhibitor backbone of adefovir dipivoxil (ADV) +3TC would be as effective as TDF +3TC for the Indian population. **Objective:** ADV + 3TC could be an alternative option for these HIV/HBV coinfected individuals, preserving the dually active TDF + 3TC as second-line nucleoside backbone following failure of the first-line ART. **Materials and Methods:** This randomised control trial (CTRI/2012/03/002471) was carried out at the ART Centre of Calcutta School of Tropical Medicine, India. Seventy-eight (39 on each arm) treatment-naïve HIV/HBV coinfected patients were randomised to receive either the combination of lamivudine + tenofovir + EFV or lamivudine + adefovir + zidovudine + EFV and followed up for 120 weeks. **Results:** Median age of the study participants was 36 years (21–62), majority were male (61/78; 78.2%) and heterosexually (39/78; 50%) infected. Baseline characteristics were identical in both arms. There was no statistically significant difference in median aspartate aminotransferase (37 vs. 29.5 U/L), alanine aminotransferase (ALT) (36 vs. 34.5 U/L), ALT normalisation rate (80 vs. 70%), AST to platelet ratio index (0.45 vs. 0.33), CD4 count (508 vs. 427 cells/mm^3), HBV DNA suppression (81.8 vs. 70%), hepatitis B e antigen loss (9 vs. 5%), hepatitis B surface antigen seroclearance rate (6.06 vs. 18.75%) and death (3 vs. 3) at 120 weeks between TDF (n = 33) and ADV (n = 32), respectively. **Conclusions:** Adefovir plus lamivudine is an effective alternative of tenofovir plus lamivudine in long-term HBV treatment outcome in HIV/HBV coinfected patients.

Keywords: Adefovir, anti-retroviral therapy, HIV/hepatitis B virus coinfection, lamivudine, tenofovir

Introduction

Hepatitis B virus (HBV) coinfection in HIV-infected patients is associated with high chronicity, high HBV DNA levels, and lower hepatitis B e antigen (HBeAg) and/or hepatitis B surface antigen (HBsAg) loss and anti-HBe or anti-HBs seroconversion rates.[1-5] The ultimate goal of HBV management is to prevent progression of the disease to cirrhosis, decompensated cirrhosis and hepatocellular carcinoma and thereby to decrease the morbidity and mortality.[6-10]

According to the guideline of the National AIDS Control Organisation (2012), Government of India, the first-line antiretroviral regimen for HIV/HBV coinfection is a combination of tenofovir disoproxil fumarate (TDF) + lamivudine (3TC) + efavirenz (EFV) and the second-line ART regimen is zidovudine (AZT) + tenofovir (TDF) + lamivudine (3TC) + ritonavir-boosted atazanavir (ATV/r).[11] The rationale for using two dually active nucleoside reverse transcriptase inhibitors (NRTIs) is to prevent the emergence of HBV-associated lamivudine mutation.[12-19]

Adefovir dipivoxil (ADV; 10 mg) is active against wild-type and 3TC-resistant HBV.[20,21] Adefovir is an HBV-active agent without anti-HIV activity in the dosage (10 mg once daily)

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used to treat HBV infection.[22] (TDF; 300 mg), prodrug of tenofovir, is licenced for the treatment of HIV-1 and HBV as it has been shown to have activity against both wild-type and 3TC-resistant HBV.[23-25]

Prevention of emergence of drug-resistant HBV mutants associated with treatment for chronic HIV/HBV coinfection is an important therapeutic strategy. Development of a suitable therapeutic regimen that limits emergence of resistance for such coinfected patients in resource-poor settings like India is very much needed. We have conducted a randomised control trial of AZT/3TC/ADV/EFV versus TDF/3TC/EFV combination among HIV/HBV coinfected patients to evaluate whether ADV/3TC could be used as a first-line HBV treatment option that will be safe and efficacious as well as be able to prevent emergence of HBV mutation so that tenofovir can be preserved as the second-line treatment option for coinfected patients.

Materials and Methods

Study design

Study population

Seventy-eight (39 on each arm) treatment-naïve HIV/HBV coinfected patients were enrolled in the open-labelled, randomised control trial (Randomisation was done using Graph Pad Software, Quick Calcs, San Diego, CA, USA) after obtaining written, informed consent in their native language at School of Tropical Medicine, Kolkata, from July 2011 to January 2013 (Indian Council of Medical Research study; IRIS ID No. 2009-05630). This research work (CTRI/2012/03/002471) was approved by the Institutional Ethics Committee of School of Tropical Medicine, Kolkata.

This is a pilot study. There were no follow-up studies in India with HIV/HBV coinfected individuals taking dually active anti-retroviral therapy for 120 weeks of treatment duration. Patients were enrolled in two groups containing regimen of Tenofovir (TDF) + Lamivudine (3TC) + EFV [TDF arm] and Adefovir (ADV) + Lamivudine (3TC) + Zidovudine (AZT) + EFV [ADV arm]; over a period of 120 weeks. A total number of 65 patients were included with >2000 IU/ml of HBV DNA.

Inclusion criteria

Treatment naïve for antiretroviral therapy, age 14–70 years, documented positive serum HBsAg serum, creatinine <1.5 mg/dl were included in the study.

Exclusion criteria

Presence of coinfection with HCV, HAV or HEV, history of clinically significant renal dysfunction within the past 12 months, any active psychiatric illness or alcohol or drug use, pregnancy or breastfeeding, malignancy and receipt of anti-HBV drugs.

Laboratory methods

All the HIV/HBV coinfected patients enrolled in the study were subjected to clinical examination and adherence assessment by 'pill count' and 'self-report' once in a month when they used to come for drug pick-up. HBV genotyping and HIV-1 RNA quantification were done at baseline for all participants. HBsAg, HBeAg, anti-HBe antibody, quantitative HBV DNA estimation, CD4 count, liver function tests (serum bilirubin [conjugated and unconjugated], alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, total protein, albumin, globulin) and complete haemogram including platelet count and were performed at baseline and every 6 months thereafter. AST to platelet ratio index (APRI) was also calculated for all the patients[26,27] every 6 months.

HBV specific enzyme-linked immunosorbent assay kits were used for the detection of HBsAg, HBeAg and Anti-HBe (Diasorin, SPA, Saluggia, Italy). All the serological assays were performed according to the manufacturer's instruction. DNA was extracted from HBsAg positive samples using QIAamp DNA Blood Kit (Qiagen, Hilden, Germany) according to manufacturer's protocol. HBV DNA detection and quantification was done by a method described earlier,[28] stringent precautions were taken to avoid cross-contamination.[29] HBV genotype was determined by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, as previously described.[30] The results of PCR-RFLP were further confirmed by means of direct sequencing with Prism Big Dye kit and ABI 3130xl Genetic Analyser (Applied Biosystems, Foster City, USA). To detect the HBV drug-resistant mutations, partial HBV reverse transcriptase region was amplified by means of nested PCR followed by direct sequencing. The complete protocol and the thermal profile were described in the previous study.[31] Quantification of HIV RNA was measured by COBAS TaqMan HIV-1 test in COBAS Taqman 48 analyser using human plasma with the lower detection limit of 47 copies/ml.

Statistical analysis

Calculation of median values and range of different parameters were done by the Microsoft Excel sheet. Mann–Whitney U-test and unpaired *t*-test were performed for comparisons of continuous variables between the groups using the GraphPad Prism (version 4.0.3; San Diego, CA, USA). Categorical variables were analysed using the Chi-square test or Fisher's exact test, as appropriate. All *P* values were 2-tailed and $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

At baseline, there were no statistically significant differences between the arms for all the tested parameters [Table 1]. Majority of the patients were male (61/78; 78.2%), had heterosexual risk behaviour (39/78; 50%) with median age of 35 years (range 21–62 years). Twenty-nine (29/78; 37.1%) patients were in the WHO clinical Stages 3 and 4 signifying disease progression. Median HBV DNA

(6.05 [1.3–7.8] vs. 4.6 [1.3–6.9] $\log_{10}$ IU/ml; $P < 0.001$) and HIV RNA (5.1 [2.9–6.4] vs. 4.6 [3.5–6.0] $\log_{10}$ IU/ml; $P = 0.03$) were significantly higher among HBeAg positives (51/78; 65.3%) than HBeAg negative individuals (not shown in table).

Follow-up after 120 weeks of treatment

Out of total 78 study participants, 65 (33 on TDF and 32 on ADV arm) could complete 120 weeks of treatment and follow-up. Four (5.1%) patients were lost to follow-up, 3 (3.8%) got transferred out to other ART centres and 6 (7.7%) died during the study follow-up.

Biochemical response

There was no statistically significant differences for parameters of complete haemogram (Hb%, total lymphocyte count, differential count and platelet count), blood sugar (F), serum creatinine, serum electrolytes (potassium, chloride) and LFT (bilirubin [T], conjugated bilirubin, unconjugated bilirubin, total protein and globulin) between ADV and TDF arm (not shown in table). The decrease of median serum AST from baseline was statistically significant for both ADV (41 vs. 37 U/L; $P = 0.03$) and TDF (47 vs. 29 U/L; $P = 0.003$) arms after 120 weeks. The ALT normalisation rate was not statistically significant in ADV (80%) than TDF (70%) arm [Table 2 and Figure 1]. Impairment in renal function or sustained elevations in serum creatinine above the ULN was not observed in any patient during the study.

Aspartate aminotransferase to platelet ratio index

At baseline, significant fibrosis (1.0–2.0; >F2) was observed among six patients on TDF and eight patients on ADV arm. Following 120 weeks of follow-up, the APRI score got reduced significantly in most of these patients (<0.5 in 7 of ADV arm and 3 in TDF arm). In the rest four patients, the APRI came down between 0.5 and 1.0. APRI >2.0 was noted in five patients at baseline (ADV - 3 and TDF - 2). Of note, the APRI score significantly got diminished in four (<1.0) while one died due to cryptococcal meningitis. Among patients having baseline APRI <1.0 (ADV - 29 and TDF - 27), the APRI score rose to >1.0–<2.0 in 3 on ADV arm but none in TDF following 120 weeks of treatment.

At baseline and following 120 weeks of treatment, there was no statistically significant difference between ADV and TDF arm [Tables 1 and 3]. While the median APRI score was reduced significantly among recipients of adefovir-based regimen (0.45 vs. 0.33; $P = 0.003$) after 120 weeks of treatment [Table 2], the change in APRI among tenofovir recipients was non-significant.

Serological response

Hepatitis B e antigen loss and anti-hepatitis B e seroconversion

Proportionately, more patients in ADV arm (50%) could

Table 1: Baseline characteristics of study patients

Variables Median (range)	All study subjects ($n=78$)	ADV arm ($n=39$)	TDF arm ($n=39$)	P*
Age (years)	35 (21-62)	35 (21-55)	35 (23-62)	0.17
Male, *n* (%)	61 (78.2)	32 (82)	29 (74.3)	0.39
Clinical staging, III and IV (%)	29 (37.1)	14 (35.8)	15 (38.4)	0.81
AST (IU/ml)	41 (19-339)	47 (21-122)	41 (19-339)	0.75
ALT (IU/ml)	42 (12-406)	41 (17-129)	38 (12-406)	0.91
Alkaline phosphatase (U/L)	215 (106-775)	238.5 (135-775)	206 (106-758)	0.18
APRI	0.62 (0.2-5.8)	0.62 (0.2-2.2)	0.62 (0.3-5.8)	0.69
CD4 T-cell count (cells/mm^3)	202 (6-616)	206 (6-616)	198 (18-454)	0.83
HBeAg positivity (%)	51 (65.3)	24 (61.5)	27 (69.2)	0.45
HBV DNA ($\log_{10}$ IU/ml)	5.8 (1.3-7.8)	5.5 (1.3-7.8)	5.9 (1.3-7.5)	0.51
HIV RNA ($\log_{10}$ copies/mL)	5 (2.93-6.43)	5 (2.93-6.43)	4.88 (3.54-5.49)	0.97

*P value for comparison between ADV and TDF arm. ADV: Adefovir dipivoxil, TDF: Tenofovir disoproxil fumarate, ALT: Alanine aminotransferase, AST: Aspartate transaminase, APRI: AST to Platelet Ratio Index, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus, HIV: Human immunodeficiency virus

Table 2: Changes of CD4 T cell count, serum alanine aminotransferase and aspartate transaminase for adefovir dipivoxil and tenofovir disoproxil fumarate arm after 30 months of treatment

Variable Median (range)	Tenofovir + lamivudine + efavirenz (TDF arm)			Adefovir + lamivudine + zidovudine/stavudine + efavirenz (ADV arm)		
	Baseline (0 month)	30 months	P	Baseline (0 month)	30 months	P
CD4 T-cell count (cells/mm^3)	194 (19−339)	508 (200−848)	<0.001	219 (6−616)	417 (157−870)	<0.001
ALT (U/L)	38 (12−406)	36 (23−161)	0.11	41 (17−129)	34.5 (17−124)	0.07
AST (U/L)	41 (19−339)	37 (22−111)	0.03	47 (21−122)	29 (18−98)	0.003
APRI	0.62 (0.3−5.8)	0.62 (0.2−2.2)	0.09	0.45 (0.15−0.91)	0.33 (0.18−1.57)	0.003

ADV: Adefovir dipivoxil, TDF: Tenofovir disoproxil fumarate, ALT: Alanine aminotransferase, AST: Aspartate transaminase, APRI: AST to Platelet Ratio Index

Table: 3 Thirty months follow-up characteristics of the human immunodeficiency virus/hepatitis B virus-coinfected patients

Variables Median (range)	Tenofovir + lamivudine + efavirenz (*n*=33)	Adefovir + lamivudine + zidovudine/stavudine + efavirenz (*n*=32)	*P*
CD4 count (cells/mm$^{3)}$	508 (200-848)	427 (157-870)	0.52
AST (U/L)	37 (22-111)	29.5 (18-98)	0.31
ALT (U/L)	36 (23-161)	34.5 (17-124)	0.44
Alkaline phosphatase (U/L)	239 (121-369)	182 (123-533)	0.004
ALT normalisation rate, %	21/30 (70)	25/32 (80)	0.77
Percentage of patients with negative or undetectable HBV DNA at 30 months	27/33 (81.8)	21/30 (70)	0.26
HBsAg negativity (%)	2/33 (6.06)	6/32 (18.75)	0.11
HBeAg negativity (%)	10/22 (40.9)	9/20 (45)	0.78

ALT: Alanine aminotransferase, AST: Aspartate transaminase, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen

achieve HBeAg negativity after 120 weeks of treatment as compared to TDF (41%) arm although the difference was not statistically significant. However, anti-HBe seroconversion rate was low among the treatment recipients (TDF– 3/33; 9%, ADV– 2/32; 5%) and non-significant changes were observed in the rate of seroconversion between both treatment arms.

Hepatitis B surface antigen decline, hepatitis B surface antigen loss and anti-hepatitis B e seroconversion

Four out of six patients experiencing 2.3 $\log_{10\ IU}$/ml reduction of HBsAg level after 6 months of treatment could clear HBsAg at 18 months. Only eight patients could achieve HBsAg loss (ADV-6/32 [18.75%] and TDF-2/33 [6.06%]) after 120 weeks of treatment [Figure 2]. Median HBV DNA (4.7 [1.9–6.2] vs. 5.75 [1.3–7.6] log10 IU/ml; $P = 0.01$) was significantly lower for the patients who could clear HBsAg as compared to those who failed to do so. Three patients in ADV arm developed anti-HBs titre of >10 IU/ml after 120 weeks of follow-up, but none in TDF arm.

Immunologic response

CD4 T cell count

There was significant rise of CD4 cell count at 120 weeks from the baseline level in both TDF and ADV arms. However, the difference in median CD4 count was not statistically significant between ADV (427 cells/mm^3) and TDF (508 cells/mm^3) arms [Table 2].

Virologic response

Hepatitis B virus DNA suppression rate

The overall HBV DNA suppression rate was 76.9% (50/65), without any significant difference between ADV (22/32; 70%) and TDF (27/33; 81.8%) arms [Table 3]. Most of the patients could suppress the HBV DNA within 6 months of treatment (ADV-77.4%, TDF-82.7%) [Figure 3]. Baseline characters such as CD4 cell count, HIV RNA and HBV DNA were similar among patients who could achieve undetectable HBV DNA at 120 weeks as compared to those failing to do so. However, HBeAg and subgenotype D were more significantly associated with HBV DNA suppression [Table 4].

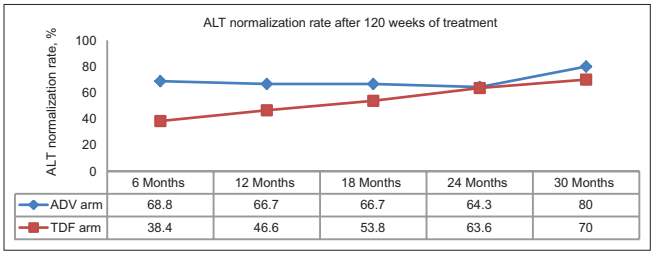

Figure 1: Alanine aminotransferase normalisation rate after 120 weeks of treatment

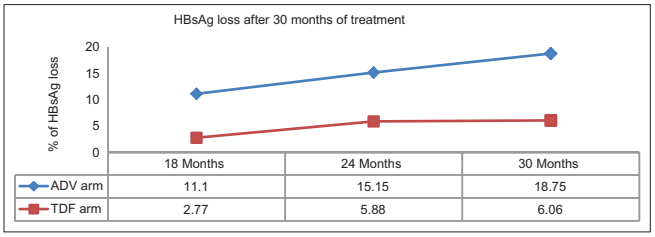

Figure 2: Hepatitis B surface antigen loss rate after 120 weeks of treatment

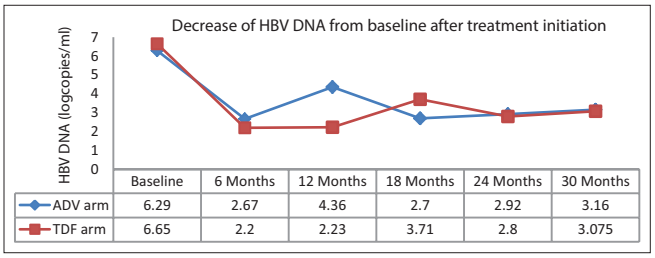

Figure 3: Hepatitis B virus DNA suppression with treatment progression

Hepatitis B virus mutation development

None of the patients in either arm developed HBV resistance mutation at pol gene of HBV. Two patients had double mutation at pol gene (rtL180M + M204V) at baseline, one from each arm, but HBV DNA became undetectable in both of them during treatment.

Clinical Response according hepatitis B virus genotype

Genotype HBV/D (52/72; 72.2%) was the predominant genotype followed by HBV/A (15/72; 20.8%) and

Table 4: Baseline characteristics of the 65 human immunodeficiency virus/hepatitis B virus-coinfected patients completing 120 weeks of follow-up by hepatitis B virus DNA suppression status

Characteristics Median (range)	HBV DNA suppressed, (n=50)	HBV DNA not suppressed, (n=15)	P
ALT level, (U/L)	38 (17-161)	34 (18-124)	0.83
APRI	0.40 (0.15-1.57)	0.41 (0.18-0.56)	0.70
Baseline HBV DNA level, (log_{10} IU/ml)	5.8 (3.58-6.43)	5.9 (2.93-5.90)	0.31
CD4 cell count (cells/mm^3)			
Baseline	212 (18-616)	192 (58-389)	0.98
30 months	488 (157-1096)	459 (239-670)	0.27
HIV RNA level (log_{10} copies/mL)	5.11 (3.58-6.43)	5 (2.93-f5.90)	0.36
Positive HBeAg status (%)	32 (78)	9 (22)	<0.0001

ALT: Alanine aminotransferase, AST: Aspartate transaminase, APRI: AST to Platelet Ratio Index, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus

HBV/C (5/72; 7%) among the enrolled patients. Subgenotyping revealed predominance of D2 (32/72; 44.4%). At baseline, there were no statistically significant changes for biochemical, serological and virologic parameters among the patients of these three genotypes.

Death

Three patients died on each arm during the follow-up. None of the death was due to liver disease.

Discussion

In HIV/HBV coinfection, HBV infection is frequent and more severe than in HBV monoinfected patients. Several antivirals are available nowadays. The main challenge of long-term management in chronic HBV infection is the incidence of antiviral drug resistance that varies according to the adherence, genetic barrier and potency of antiviral drugs. Drug-resistant HBV could result in more liver disease progression since the drug-resistant virus is difficult to treat. In HIV/HBV coinfection, there are no long-term studies that directly address this issue. Hence, to ascertain whether there is any significant difference in outcome following prolonged treatment, we conducted a randomised trial of AZT/3TC/ADV/EFV combination versus TDF/3TC/EFV combination to evaluate whether ADV/3TC combination could be used as a first-line treatment option that combats development of drug-resistant mutant as well as be a safe and efficacious therapy for HIV/HBV/coinfection; therefore, tenofovir can be preserved for the second-line treatment option. The purpose of the study was to ascertain whether ADV + 3 TC was equally efficacious as TDF + 3TC in terms of suppression of HBV DNA, ALT normalisation, e-antigen seroconversion and emergence of drug-resistant HBV mutations. There were no statistical significant differences observed in regard with the mentioned parameters: HBeAg loss (45 vs. 40.9%; P = 0.78), ALT normalisation (80 vs. 70%; P = 0.77) and HBsAg loss (18.75 vs. 6.06%; P = 0.11) at 120 weeks. Similarly, higher HBV DNA suppression rate (TDF-81.8%, ADV-70%; P = 0.26) and CD4 rise (TDF-508, ADV-427; P = 0.52) associated with TDF use was also non-significant. None of the study patients on each arm showed any drug-resistant HBV mutations in HBV pol gene.

Marcellin *et al*.[32] and Hou *et al*.[33] showed superiority of TDF over ADV in chronic HBV monoinfected patients from Europe, North America, Australia and New Zealand and from China, respectively. In HIV/HBV coinfected patients, Lacombe *et al*. observed that tenofovir had superior antiviral efficacy with a similar safety profile as compared to adefovir through weeks 48.[34] However, Peters *et al*. observed that 48 weeks of treatment with either ADV or TDF resulted in clinically important suppression of serum HBV DNA and they considered both of the drugs to be safe and efficacious for coinfected population,[35] similar to our observation.

At baseline, majority of the patients (65.3%) of this cohort were HBeAg positive, which is similar (61%–83%) to other published studies in this region on HIV/HBV coinfection.[31,36] Among the HBeAg positive individuals, the quantitative HBV DNA and HIV RNA was higher as compared to HBeAg negative patients and the difference was statistically significant. HBV/D was the predominant genotype followed by HBV/A, circulating among the enrolled patients as observed in previous studies from this region.[31,37] In this study, there was no significant difference in clinical, biochemical, serological and virologic outcomes according to different HBV genotypes (data not shown).

Among coinfected population Martín-Carbonero *et al*. documented 2.6% HBsAg seroconversion annually.[38] Overall, HBsAg seroconversion rate was 4.6% (3/65) in this study cohort. Two studies documented slow rate of HBsAg level decrease even after HBV DNA suppression in coinfected subjects.[39,40] HBsAg decline rate was lower in coinfected as compared to HBV monoinfected individuals.[41] In the present study, the HBsAg decline rate was higher in HBeAg positive than HBsAg negative patients, similar to observations of Jaroszewicz *et al*.[42] The HIV RNA or CD4 count was not directly associated with HBsAg level (Did not shown in the table). Maylin *et al*. noted a correlation of HBsAg decline with HIV RNA and CD4 count,[40] but Thibault *et al*. did not find any such association.[39]

Conclusion

The treatment options for chronic hepatitis B and HIV coinfected patients are still limited. This small, pilot study indicates that adefovir can be an effective alternative to tenofovir in treatment-naïve HIV/HBV coinfected patients for preserving tenofovir as NRTI backbone of second-line ART.

Limitation of the study

While all the study participants had baseline HIV RNA estimated, the 6-monthly follow-up HIV-1 viral load was not

done; and thus, the HIV virologic response rate in each arm could not be ascertained. Liver stiffness measurement by transient elastography and liver biopsy were also not performed in HIV/HBV coinfected patients.

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Conflicts of interest

There are no conflicts of interest.

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