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Original Research Article

Starting Antiretroviral Therapy for Patients with HIV and Hepatitis B Virus: Lamivudine Plus Tenofovir Versus Lamivudine Plus Adefovir

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Abstract:

Background: In order to treat HIV/HBV coinfection, a combination of tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and efavirenz (EFV) is preferred. We hypothesised that TDF +3TC for the Indian population would not be as successful as an HBV active nucleoside reverse transcriptase (RT) inhibitor/nucleotide RT inhibitor backbone of adefovir dipivoxil (ADV) +3TC.

Objective: For these HIV/HBV coinfected patients; ADV + 3TC may be an alternate treatment option, keeping the dually active TDF + 3TC as a second line nucleoside backbone in the event that first line ART is unsuccessful.

Methods: At the ART Centre of SKMCH Muzaffarpur in Bihar, this randomised control study was conducted. The combination of lamivudine + tenofovir + EFV or lamivudine + adefovir + zidovudine + EFV was given to 78 treatment-naive HIV/HBV coinfected individuals (39 on each arm), and they were then monitored for 24 weeks (6 months).

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 antigen loss (9 vs. 5%), hepatitis B surface antigen seroclearance rate (6.06 vs. 18.75%) and death (3 vs. 3) at 24 weeks between TDF (n = 33) and ADV (n = 32), respectively.

Conclusions: In individuals who are HIV/HBV coinfected, adefovir with lamivudine is a successful substitute for tenofovir plus lamivudine in terms of long-term HBV treatment outcomes.

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

Introduction

High chronicity, high HBV DNA levels, and decreased rates of hepatitis B e antigen (HBeAg) loss and/or hepatitis B surface antigen (HBsAg) seroconversion are all associated with hepatitis B virus (HBV) coinfection in HIV-infected patients.[1-5] In order to reduce morbidity and mortality, the ultimate goal of HBV therapy is to stop the illness from progressing to cirrhosis, decompensated cirrhosis, and hepatocellular cancer.[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] To stop the establishment of a lamivudine mutation associated with HBV, two dually active nucleoside reverse transcriptase inhibitors (NRTIs) are used.[12-19]

Adefovir dipivoxil (ADV; 10 mg) inhibits both 3TC-resistant and HBV with the wild type.[20,21] When taken as prescribed (10 mg once daily), defovir is an HBV active drug without anti-HIV activity.[22] The tenofovir prodrug (TDF; 300 mg) is approved for the treatment of HIV-1 and HBV due to its demonstrated efficacy against both wild-type and 3TC-resistant HBV.[23-25]An essential therapeutic approach is to prevent the formation of drug-resistant HBV mutations while treating chronic HIV/HBV coinfection. In resource-constrained environments like India, the development of an appropriate therapy regimen that prevents the evolution of resistance for such coinfected individuals is critical.

To determine whether ADV/3TC could be used as a first-line HBV treatment option that is safe, effective, and able to prevent the emergence of HBV mutation so that tenofovir can be retained as the second-line treatment option for coinfected patients, we conducted a randomised control trial comparing AZT/3TC/ADV/EFV to TDF/3TC/EFV.

Materials and Methods

After receiving written, informed consent at the ART Centre of Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar, which was approved by the Institutional Ethics Committee of SKMCH, Muzaffarpur, Bihar, seventy eight (39 on each arm) treatment-nave HIV/HBV coinfected patients were enrolled in the open-label, randomised control trial.

This research is preliminary. Following a 24-week course of dual anti-retroviral therapy, there were no follow-up studies conducted in India with HIV/HBV coinfected patients.

Over the course of 24 weeks, patients were divided into two groups that received the treatment regimens Tenofovir (TDF) + Lamivudine (3TC) + EFV and Adefovir (ADV) + Lamivudine (3TC) + Zidovudine (AZT) + EFV. 65 patients in total were included with >2000 IU/ml HBV DNA. Ages 14 to 70, verified HBsAg serum positivity, creatinine <1.5 mg/dl, and treatment naive for antiretroviral medication were included in the study.

Exclusion criteria for the trial were co-infection with HCV, HAV, or HEV, a history of clinically significant renal failure within the last 12 months, any active mental health conditions, alcohol or drug use, pregnancy or breastfeeding, malignancy, and taking anti-HBV medications. The Microsoft Excel sheet calculated the median values and range of numerous parameters. Mann–Whitney Graph Pad Prism was used to compare continuous variables between groups using the U test and unpaired t test. The Fisher's exact test or the Chi square test, as appropriate, was used to evaluate

categorical variables. P <0.05 was deemed to be statistically significant for all 2 tailed P values.

Results

For all of the investigated measures, there were no statistically significant changes between the arms at the beginning [Table 1]. The majority of the patients (61/78; 78.2%) were male, exhibited heterosexual risk behaviour (39/78; 50%), and were between the ages of 21 and 62. The median age was 35 years. Twenty nine (29/78; 37.1%) individuals had illness development as indicated by WHO clinical Stages 3 and 4. HBeAg positives (51/78; 65.3%) had substantially higher median HBV DNA (6.05 [1.3-7.8] vs. 4.6 [1.3-6.9] log10 IU/ml and HIV RNA (5.1 [2.9-6.4] vs. 4.6 [3.5-6.0] log10 IU/ml; P = 0.03) levels than HBeAg negatives.

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 (log10 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

65 trial participants (33 on the TDF arm and 32 on the ADV arm) were able to complete the 120-week course of treatment and follow-up. Six patients (7.7%) died during the study's follow-up, three (3.8%) were moved to other ART clinics, and four (5.1%) patients were lost to follow-up.

The complete haemogram parameters (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 the ADV and TDF arm did not differ statistically significantly from one another. After 24 weeks, there was a statistically significant difference in the median serum AST levels in the ADV (41 vs. 37 U/L; P = 0.03) and TDF (47 vs. 29 U/L; P = 0.003) groups. In the ADV (80%) versus TDF (70%) arm, the ALT normalisation rate was not statistically significant [Table 2]. No patient was found to have impaired renal function or sustained increases of serum creatinine above the ULN.

Table 2: Changes of CD4 T cell count, serum alanine aminotransferase and aspartate transaminase for adefovir dipivoxiland tenofovir disoproxil fumarate arm after 6 weeks of treatment

Variable Median (range)	Tenofovir + lamivudine + efavirenz (TDF arm)			Adefovir + lamivudine + zidovudine/stavudine + efavirenz (ADV arm)		
	Baseline (0 month)	6 weeks	P	Baseline (0 month)	6 weeks	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.

There was no statistically significant difference between the ADV and TDF arm at the beginning of treatment and after 24 weeks [Tables 1 and 3]. After 24 weeks of treatment (Table 2), participants of an adefovir-based regimen saw a substantial decrease in their median APRI score (0.45 vs. 0.33; P = 0.003), but not among those receiving tenofovir.

Table: 3: Six weeks follow up characteristics of the human immunodeficiency virus/hepatitis B virus-coinfectedpatients

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.

Patients who were able to attain undetectable HBV DNA after 24 weeks compared favourably to those who were unable in terms of baseline characteristics such CD4 cell count, HIV RNA, and HBV DNA. HBeAg and subgenotype D, however, were more strongly linked to HBV DNA suppression [Table 4].

Table 4: Baseline characteristics of the 65 human immunodeficiency virus/hepatitis B virus-coinfected patients completing 24 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) CD4 cell count (cells/mm^3)	5.8 (3.58-6.43)	5.9 (2.93-5.90)	0.31
Baseline	212 (18-616)	192 (58-389)	0.98
6 weeks	488 (157-1096)	459 (239-670)	0.27
HIV RNA level (log 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 patients that were enrolled. D2 predominance was discovered through subgenotyping (32/72; 44.4%). The patients of these three genotypes did not show any statistically significant changes in any of the biochemical, serological, or virologic markers from baseline.

During the follow-up, three patients on each arm passed away. Liver illness was not the cause of any of the deaths.

Discussion

HBV infection is more common and severe in people with HIV and co-infection with HBV than in people with HBV alone. Today, a variety of antivirals are accessible. The prevalence of antiviral treatment resistance, which varies depending on adherence, genetic barriers, and antiviral drug effectiveness, is the primary obstacle to long-term management of chronic HBV infection. Given how challenging it is to treat medication resistant HBV, further liver disease progression may follow. There are no long-term studies that specifically address this problem in HIV/HBV coinfection.

Thus, to determine whether there is any significant difference in outcome after prolonged treatment, we conducted a randomised trial of AZT/3TC/ADV/EFV combination versus TDF/3TC/EFV combination to determine whether ADV/3TC combination could be used as a first line treatment option that prevents the development of drug resistant mutant as well as be a safe and effective therapy for HIV/HBV/coinfection; consequently, tenofovir can be saved for the second line treatment.

The aim of the study was to compare ADV + 3 TC and TDF + 3 TC for their ability to decrease HBV DNA, normalise ALT, induce antigen seroconversion, and prevent the establishment of drug-resistant HBV mutations. The following measures after 24 weeks did not show any statistically significant differences: 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). greater CD4 rise (TDF 508, ADV 427; P = 0.52) and greater HBV DNA suppression rate (TDF 81.8%, ADV 70%; P = 0.26) linked with TDF administration were likewise unremarkable.

None of the study patients on each arm showed any drug resistant HBV mutations in HBV pol gene.

TDF outperformed ADV in chronic HBV monoinfected patients from Europe, North America, Australia, New Zealand, and China, according to studies by Marcellin et al. [27] and Hou et al. [28]. In individuals who were HIV/HBV coinfected, Lacombe et al. found that through week 48, tenofovir had better antiviral activity and a similar safety profile to adefovir.[29] Peters et al., who made a similar observation to ours, noted that 48 weeks of treatment with either ADV or TDF resulted in a clinically significant decrease of serum HBV DNA. They also believed both medications to be safe and effective for coinfected individuals.

Most of the patients (65.3%) in our cohort were HBeAg positive at baseline, which is comparable (61%–83%) to earlier published research on HIV/HBV coinfection in this area.[26,31]

When compared to HBeAg negative patients, the quantitative levels of HBV DNA and HIV RNA were greater in HBeAg positive persons, and the difference was statistically significant. As in earlier studies from this region, HBV/D was the most common genotype, followed by HBV/A, in the included patients.[26,32] According to different HBV genotypes, there were no appreciable differences in the clinical, biochemical, serological, or virologic results of this investigation (data not shown).

Martn Carbonero et al. found 2.6% HBsAg seroconversion yearly among the coinfected population.[33] In this study cohort, the overall HBsAg seroconversion rate was 3.6% (3/65).

Two investigations showed that coinfected individuals still experienced a sluggish decline in HBsAg levels even after HBV DNA suppression.[34,35]

When compared to people with HBV monoinfection, the rate of HBsAg drop was lower in coinfected people.[36] Similar to the findings of Jaroszewicz et al., the HBsAg drop rate in the current study was higher in HBeAg positive patients than HBsAg negative individuals.[37]

The HBsAg level was not closely correlated with the HIV RNA or CD4 count (did not show in the table). HBsAg drop and HIV RNA and CD4 count were found to be correlated by Maylin et al., although Thibault et al. did not discover this relationship.[34]

Conclusion

Patients who are co-infected with HIV and chronic hepatitis B still have few therapeutic choices. According to this tiny, pilot trial, adefovir may be a useful substitute for tenofovir in treatment-naive HIV/HBV coinfected individuals in order to keep tenofovir as the primary NRTI in second-line ART.

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