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Treatment outcomes in a cohort of patients with chronic hepatitis B and human immunodeficiency virus co-infection in Mumbai, India

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ABSTRACT

Treatment experiences with patients co-infected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) in resource-limited settings remain poorly documented. This study aimed to evaluate the treatment outcomes in a cohort of HIV/HBV co-infected individuals receiving tenofovir/lamivudine (TDF/3TC)-based antiretroviral therapy (ART) in a programmatic setting in Mumbai, India. Additionally, a cross-sectional laboratory study was carried out measuring serologic and virologic parameters. A total of 57 patients who received TDF/3TC were included in the study. Of these, 52 (91%) were male and the mean age was 38.7 years. The median follow-up period was 16.8 months (IQR:7.9–37.9). Forty-three patients were included in the cross-sectional laboratory study, of whom 38 (67%) were $HBeAg^+$ positive. Four patients had serum HBsAg conversion to negative and had developed anti-HBs-antibodies. HBV-DNA became undetectable (<1.3 $\log_{10}$ copies/ml or <20 IU/ml) in 35.5% and 75% of the $HBeAg^+$ and $HBeAg^-$ patients, respectively. Overall, 46.5% of patients had undetectable HBV-DNA and 90.7% had adequately suppressed HBV-DNA (<3.3 $\log_{10}$ copies/ml or <2000 IU/ml). The median reduction in serum HBV-DNA was 6 $\log_{10}$ copies/ml. In 29 patients (63%) HIV viral load was undetectable. Outcomes included seven (12%) deaths, four (7%) lost to follow-up, one (2%) transferred out and 45 (79%) alive and on treatment. In conclusion, good treatment outcomes were achieved in a cohort of HIV/HBV co-infected patients in India. In regions with a high HIV/HBV burden, all HIV-infected individuals should be tested for chronic hepatitis B. A TDF/3TC-backbone could be considered as first-line standardized ART regimen in these settings.

1. Introduction

Of the estimated 36 million individuals worldwide living with the human immunodeficiency virus (HIV), nearly four million (about 10%) are chronically infected with hepatitis B virus (HBV).[1] The hepatitis B surface antigen (HBsAg) is over five times more prevalent among HIV-infected patients than in the general population.[2–4] In North America and Europe, more than half of HIV-infected men who have sex with men have evidence of past HBV infection, and 5–10% have chronic hepatitis B, which is defined as the persistence of HBsAg in serum for longer than 6 months.[5] C chronic hepatitis B is more likely to develop and persist after HBV in patients with HIV infection.[6,7] Patients with chronic hepatitis B and underlying HIV infection (HIV-HBV co-infection) are also

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at higher risk of cirrhosis and hepatocellular carcinoma when compared with HBV-mono-infected individuals.[8]

The ideal outcome of treatment for HBV would be to achieve HBsAg clearance with anti-HBs seroconversion, but this endpoint can be reached in only a few patients (fewer than 10% of HBV monoinfected patients have received interferon treatment, and probably even fewer HIV/HBV co-infected patients). A more realistic goal, therefore, is to efficiently and persistently suppress HBV replication and thus reduce the liver inflammation and scarring that can lead to liver cirrhosis and hepatocellular carcinoma.[9] Drugs used in industrialized countries for the treatment of HBV include standard interferon (IFN)-α-2a and 2b and pegylated (PEG)-IFN-α-2a, entecavir and adefovir. Two HIV medications, tenofovir disoproxil fumarate (TDF) and lamivudine/emtricitabine, are also active against HBV and are therefore being used worldwide. TDF anti-HBV efficacy in HIV-co-infected patients has been reported only in relatively small studies with relatively short durations of therapy.[10–16] Recommendations for the treatment of HBV in HIV co-infected patients are derived from what is known about the treatment of HBV monoinfected patients, and from the limited data available in HBV/HIV co-infected patients.[9] The most recent WHO recommendation regarding antiretroviral therapy (ART) for HBV/HIV co-infection is based on a limited and questionable body of evidence, and the panel that issued the guideline was able to identify only one randomized controlled trial on TDF effectiveness in HBV/HIV co-infection.[17,18]

Although the prevalence of HBV-HIV co-infection in India varies from 9% to as high as 30%, there is no published study describing experiences and treatment outcomes among such patients in India.[19–23]

The aim of the present study was to report on treatment and laboratory outcomes among HBV/HIV co-infected individuals who received TDF/lamivudine as a part of an antiretroviral regimen, in an urban, resource-limited setting in Mumbai, India.

2. Materials and methods

2.1. Study design

This was a prospective, observational cohort study using data routinely collected at each consultation and entered into FUCHIA monitoring software (Follow-Up and Care of HIV Infection and AIDS, Epicentre, Paris, France). In addition, a cross-sectional laboratory study was carried out to measure serological and virological parameters not routinely recorded at the clinic.

2.2. Setting and study population

Médecins Sans Frontières has been operating a clinic in the Khar area of Mumbai, India, since 2006. Khar is a generally affluent suburb that includes small and extensive slum areas. The clinic specializes in HIV care and provides free care and treatment to patients referred by accredited public and public-private ART centers in the greater Mumbai area and by a network of community non-governmental organizations (NGOs). At the time of the cross-sectional laboratory study, one public ART center (Sir J.J. Group of Hospitals, Center of Excellence in HIV Care, Mumbai, India) started providing diagnosis and treatment for HIV/HBV co-infected patients.

HIV-infected adult patients followed up exclusively in the MSF clinic with laboratory confirmed chronic hepatitis B ($HBsAg^+$ for at least 6 months) were offered a chance to participate in the study and signed an informed consent form. Patients were included in the study regardless of the time from their registration at the clinic or whether they were on TDF-based ART at the time the cross-sectional (laboratory) part of the study was carried out. Patients with HBV/HIV co-infection were treated with a standardized regimen consisting of tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV).

2.3. Data collection and laboratory testing

For all participants, the following data were recorded: demographic characteristics, ART history, alcohol use and ART adherence, absolute numbers of CD4 T lymphocytes at baseline and at 6-month intervals, alanine transaminase (ALT) serum level at baseline and at 6-month intervals, and plasma HIV RNA levels. Occasionally, patients referred to the MSF clinic had HBV DNA measured at private laboratories; these measurements were also recorded in the patients' files as 'baseline HBV DNA'.

All participants were asked to make an extra visit to the MSF clinic for blood sample collection. The clinic covered travel costs for the additional visit, during which the study objectives were explained to the patients and informed consent was obtained. Sera were collected to determine serum hepatitis B 's' and 'e' antigens (HBsAg and HBeAg), hepatitis B 's' and 'e' antibodies (HBsAb and HBeAb), HBV-DNA serum levels, HIV RNA levels, CD4 counts and ALT.

HBeAg and HBeAb were determined at baseline (first HBe Ag and Ab recorded) and during the cross-sectional laboratory study using enzyme-linked immunosorbent assay. All the samples were assayed at the same time by the same laboratory in Mumbai. Serum HBV-DNA and HIV RNA levels were determined at baseline (only when available: not performed systematically at the MSF clinic) and during the cross-sectional study via polymerase chain reaction (Cobas Amplicor HBV Monitor and Cobas TaqMan HIV-1 Assay, Roche). Absolute numbers of CD4 T lymphocytes were measured on whole blood by flow cytometry. The laboratory participated in a quality control scheme.

2.4. Statistical analysis

The study period was defined as the time for which patients had received TDF/lamivudine-based ART (February 2006 to July 2010). The main outcomes of interest were: HBsAg conversion to negative, adequately suppressed HBV DNA (defined as <3.3 $\log_{10}$ copies/ml or <2000 IU/ml), undetectable HBV DNA (defined as HBV-DNA <1.3 $\log_{10}$ copies/ml or <20 IU/ml) and undetectable HIV RNA (defined as <50 copies/ml). The Fisher exact test or χ^2 test was used to compare the proportion of patients with

an event. The Wilcoxon signed rank test or paired *t* test was used to assess changes from baseline in selected laboratory markers. Logistic regression models were fitted to assess factors associated with the outcomes of interest. The level of significance was set at p = 0.05. Analyses were performed using SPSS (version 16.0 for Windows; SPSS, Chicago, IL, USA).

2.5. Ethics

The study was approved by the Institutional Ethics Committee of Grant Medical College and Sir J.J. Group of Hospitals, Mumbai, India and by the Ethics Review Board of Médecins Sans Frontières.

3. Results

3.1. Characteristics of the study population

From February 2006 to July 2010, 57 patients over 15 years of age were diagnosed with chronic hepatitis B and referred to the MSF clinic, mostly by public ART centers in greater Mumbai, particularly the JJ Hospital ART center. Diagnosis and treatment for HIV/HBV co-infected patients in the public sector became available after January 2009. The main baseline characteristics of the patients are shown in Table 1. The patients were predominately males in their late 30s. Four patients had a history of injectable drug use, one of the four was using injectable drugs at the time of the study. Thirty eight patients (67%) were $HBeAg^+$, but the HBeAg status for five patients was not known (all five patients were lost to follow-up). While most patients had elevated ALT (>41 IU/litre), the elevation was rather mild (49 IU/litre). Baseline HBV-DNA was available for only 15 $HBeAg^+$ and eight $HBeAg^-$ negative patients; these patients had their laboratory tests done at private laboratories before their referral to the MSF clinic. There were no statistically significant differences between $HBeAg^+$ and $HBeAg^-$ patients with regard to demographic characteristics or baseline biologic markers. Median time on follow-up was 27.5 months (IQR: 11.5–46.1) and median time on TDF/lamivudine-based antiretroviral treatment was 16.8 months (IQR: 7.9–37.9). Half of the patients were ART naive when they started TDF/lamivudine-based treatment. Four patients were lost to follow-up and two patients died before starting ART.

Table 1
Baseline characteristics of a cohort of 57 HIV/HBV co-infected patients studied in Mumbai, India

Characteristic	Total (n = 57)	$HBeAg^+$ (n = 38)	$HBeAg^-$ (n = 14)
Age (years, mean ± SD)	38.7 ± 7.6	39.5 ± 6.2	39.2 ± 10.6
Sex			
Male	52 (91)	35 (92)	13 (93)
Female	5 (9)	3 (8)	1 (7)
Marital status			
Married	36 (63.2)	31 (81.6)	5 (35.7)
Single	16 (28.1)	6 (15.8)	6 (42.8)
Widowed/divorced	4 (7.0)	1 (2.6)	2 (14.3)
Profession			
Manual laborer	28 (49.1)	20 (52.6)	6 (42.9)
Office worker	10 (17.5)	6 (15.8)	4 (28.6)
Sex worker	3 (5.3)	0 (0)	0 (0)
Unemployed	8 (14.0)	7 (18.4)	1 (7.1)
Unknown	8 (14.0)	5 (13.2)	3 (21.4)
Hepatitis B			
Serum ALT (IU/litre)	49.0 (41.2–71.0)	49.5 (41.0–65.7)	49.0 (41.0–74.0)
Patients with elevated serum ALT (>41 IU/litre)	44 (77.2)	32 (84.2)	10 (71.4)
HBV-DNA $\log_{10}$ copies/ml (n = 15 $HBeAg^+$ and n = 8 $HbeAg^-$)	7.04 (4.8–7.4)	7.11 (4.0–7.9)	6.30 (5.0–7.3)
HIV infection and antiretroviral treatment			
Baseline CD4 count (cells/μl)	132 (64–181)	121.5 (56–171)	152 (56–174)
Treatment naive when enrolled	28 (49.1)	18 (47.4)	8 (57.1)
ART regimen			
TDF/3TC/EFV	45 (78.9)	34 (89.5)	10 (71.4)
TDF/3TC/PI (2^{nd} line)	6 (10.5)	3 (7.9)	3 (21.4)
Never started ART	6 (10.5)	1 (2.6)	1 (7.1)
Time on follow-up (months)	27.5 (11.5–46.1)	20.2 (9.2–44.8)	24.0 (11.4–44.4)
Time to ART initiation (months)	2.4 (2.1–4.2)	2.4 (2.0–3.3)	2.4 (2.1–9.2)
Duration of ART (months)	16.8 (7.9–37.9)	16.8 (6.9–37.9)	15.9 (8.9–34.4)
Alcohol			
Alcohol use during the past year	11 (23.4)	7 (21.2)	4 (30.8)
Alcohol use previously	15 (31.9)	11 (33.3)	4 (30.8)
Treatment adherence			
Good (<5% pills missed)	25 (53.1)	17 (51.5)	7 (53.8)
Average (5–15% pills missed)	18 (38.2)	12 (36.3)	6 (46.2)
Poor (>15% pills missed)	4 (8.5)	4 (12.1)	0

Values are no. (%) or median (IQR).
ALT: alanine transaminase, ART: antiretroviral therapy, HBV: hepatitis B virus, HbeAg: hepatitis B 'e' antigen, TDF/3TC/EFV: tenofovir/lamivudine/efavirenz.

Table 2
Clinical outcomes of treatment in a cohort of 57 HIV/HBV co-infected patients in Mumbai, India

Outcome	Total (n = 57) n (%)	HBeAg$^+$ (n = 38) n (%)	HBeAg$^-$ (n = 14) n (%)
Alive and in care	45 (78.9)	30 (78.9)	13 (92.9)
Dead	7 (12.3)	6 (15.8)	0 (0)
Lost to follow-up	4 (7.0)	2 (5.3)	1 (7.1)
Transferred out	1 (1.8)	0 (0)	0 (0)

3.2. Treatment outcomes and response to TDF-based therapy

Among the 57 patients, seven (12.3%) died, four (7%) were lost to follow-up, one (1.8%) transferred to another health facility and 45 (78.9%) were still on treatment (Table 2). There were no statistically significant differences between HBeAg$^+$ and HBeAg$^-$ patients regarding mortality and other overall outcomes.

Forty-three patients were included in the laboratory study (Table 3, Figure 1). All 43 patients were on a TDF/3TC-based regimen. Of these, four with laboratory outcomes verified (two HBeAg$^+$ and two HBe$^-$) had serum HBsAg conversion from positive to negative at the end of the study period and four patients had developed detectable anti-HBs antibodies. Overall, almost half of the patients had undetectable HBV-DNA (HBV-DNA <1.3 $\log_{10}$ copies/ml or <20 IU/ml) while 39 patients (90.7%) had adequately suppressed HBV-DNA (<3.3 $\log_{10}$ copies/ml or <2000 IU/ml). The median reduction of HBV-DNA was 6 $\log_{10}$ copies/ml (IQR = 3.7–6.3) and was statistically significant ($p<0.0001$). No hepatic flares were recorded in this cohort of patients.

3.3. HBeAg$^+$ patients

Serum HBeAg conversion from positive to negative was observed in four (12.9%) of the HBeAg$^+$ patients surveyed (n = 31) and was associated with acquisition of serum HBeAb in three patients (9.6%).

Twenty-seven (87.1%) HBeAg$^+$ patients had adequately suppressed HBV-DNA and eleven of them (35.5%) had undetectable HBV-DNA (Figure 1). All 15 HBeAg$^+$ patients who had a baseline HBV-DNA, allowing for comparison, had a decline in HBV-DNA serum level of at least 1 $\log_{10}$ copies/ml. The median reduction of serum HBV-DNA at the end of follow-up was 6.1 $\log_{10}$ copies/ml (IQR = 3.0–6.9) ($p<0.0001$). One out of four patients normalized serum ALT but in this cohort of patients baseline and post-treatment median ALT (49.5 IU/litre, IQR = 41.0–65.7 and 43 IU/litre, IQR = 39.0–56.0 respectively) were not particularly elevated.

Of the studied factors associated with achieving an adequately suppressed serum HBV-DNA (<3.3 $\log_{10}$ copies/ml) in HBeAg$^+$ patients, only current use of alcohol was found to be significant in the univariate analysis. When univariate analyses were performed to study factors associated with achieving an undetectable serum HBV-DNA (<1.3 $\log_{10}$ copies/ml), only treatment adherence was found to be significant. Other factors included in the models were age, sex, previous ART experience (treatment naive/non-naive) and CD4 counts at treatment initiation. However, in multivariate binary logistic regression models, no factors remained independently associated with serum HBV-DNA undetectability or adequate suppression of HBV-DNA.

3.4. HBeAg$^-$ patients

Median serum HBV-DNA decline among the 12 HBeAg$^-$ patients was 5.8 (IQR = 5.8–6.3) $\log_{10}$ copies/ml after a median period of 15.9 months of ART. Nine of 12 (75%) HBeAg$^-$ patients became serum HBV-DNA undetectable but all 12 patients had adequately suppressed. HBV-DNA (Figure 1). More HBeAg$^-$ patients were found to have undetectable HBV-DNA and this difference was significant ($p = 0.03$), while no significant difference was observed between HBeAg$^+$ and HBeAg$^-$ patients regarding adequate suppression of HBV-DNA.

Table 3
Laboratory outcomes of treatment in the 43 patients surveyed out of the 57 HIV/HBV co-infected patients recruited to the study

Outcome	Total (n = 43)	HBeAg$^+$ (n = 31)	HBeAg$^-$ (n = 12)
Loss of HBsAg	4 (9.3)	2 (6.4)	2 (16.6)
Anti-HBs detected	4 (9.3)	2 (6.4)	2 (16.6)
Serum ALT (IU/litre)	43 (35.0–55.0)	43 (39.0–56.0)	39.4 (34.0–54.7)
Patients who normalized serum ALT (=<40 IU/litre)	17 (39.5)	10 (32.2)	7 (58.3)
Seroconversion among HbeAg$^+$ (n = 38)			
Loss of HBeAg		4 (12.9)	
Anti-HBe seroconversion		3 (9.6)	
HBV-DNA			
Patients with undetectable HBV-DNA (<1.3 $\log_{10}$ or <20 IU)	20 (46.5)	11 (35.5)	9 (75.0)
Patients with adequately suppressed HBV-DNA (<3.3 $\log_{10}$ or <2000 IU)	39 (90.7)	27 (87.1)	12 (100)
HBV-DNA $\log_{10}$ copies/ml (n = 15)	1.47 (0.0–2.6)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Drop in median HBV-DNA (n = 15 HBeAg$^+$ and n = 8 HbeAg$^-$)	6 (3.7–6.3)	6.1 (3.0–6.9)	5.8 (5.8–6.3)
HIV			
Patients with undetectable HIV RNA (<50 copies/ml)	29 (63.0)	21 (67.7)	8 (80.0)
CD4 count (cells/μl)	263 (200–385)	263 (200–419)	261 (163–361.5)

Values are no. (%) or median (IQR).
ALT: alanine transaminase, HbeAg: hepatitis B 'e' antigen, HBsAg: hepatitis B 's' antigen, HBV: hepatitis B virus.

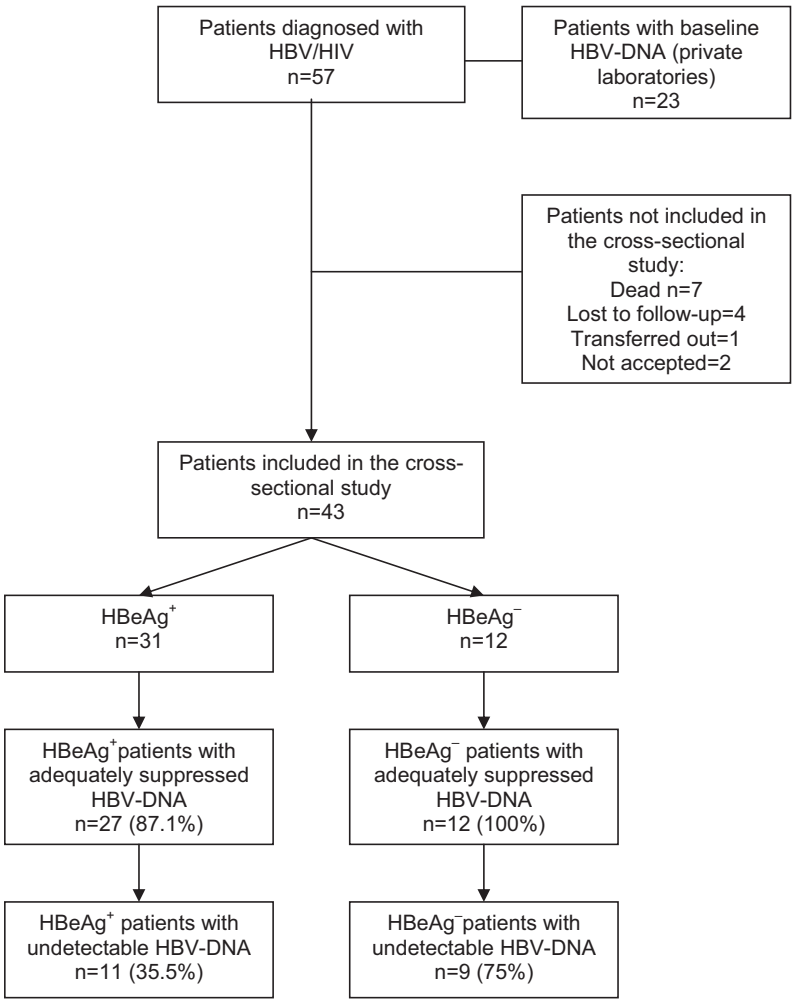

Figure 1. Flow of patients and HBV virological outcomes among HBV/HIV co-infected patients, Mumbai, India. HbeAg: hepatitis B 'e' antigen, HBV: hepatitis B virus.

3.5. HIV RNA and CD4 cell counts

Twenty-nine patients (63%) had undetectable viral load, after a median of 16.8 months on ART, achieving the treatment goal for antiretroviral therapy. More HBeAg$^-$ than HBeAg$^+$ patients had undetectable or suppressed HIV RNA, but differences were not statistically significant.

The median CD4 counts at the time of TDF/lamivudine-based treatment initiation and at the end of the study period were132 cells/μl (IQR: 64–181) and 263 cells/μl (IQR: 200–385) respectively. Median CD4 gain was +131 cells/μl (IQR: 61.5–237). Figure 2 shows the evolution of median CD4 counts over time in this cohort of HBV/HIV co-infected patients.

4. Discussion

This is one of the first studies describing treatment outcomes among HBV/HIV-co-infected patients in India to show a satisfactory clinical, immunologic and virologic response to therapy. Moreover, these results come from a program setting and therefore are likely to reflect the operational reality on the ground.

The median reduction in serum HBV-DNA after approximately 17 months of therapy was substantial, at

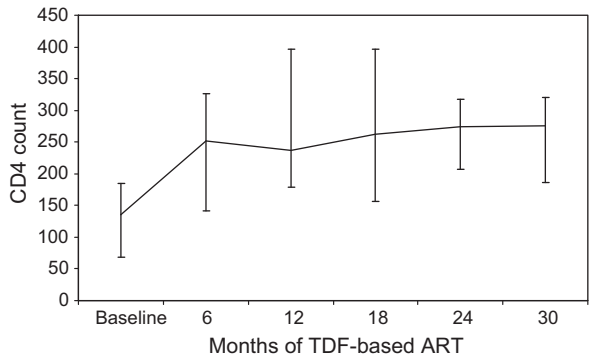

Figure 2. CD4 evolution over time in HBV/HIV co-infected patients, Mumbai, India. ART: antiretroviral therapy, HBV: hepatitis B virus, TDF: tenofovir.

6 $\log_{10}$ copies/ml, suggesting good efficacy of a TDF/lamivudine-based antiretroviral regimen for the treatment of HBV infection under program conditions. HBV-DNA became undetectable in 35.5% and 75% of the $HBeAg^+$ and $HBeAg^-$ patients, respectively. Overall, the proportion of patients with undetectable HBV-DNA was similarly high at 46.5% and the overall proportion of patients with adequately suppressed HBV-DNA was very high, at 90.7%. The rate of serum HBeAg loss among the $HBeAg^+$ patients and of ALT normalization were also high. These results are similar to those reported in the literature from studies conducted in healthcare settings that were not resource-limited.[10–16]

The TDF/lamivudine-based treatment was adequately effective against HIV replication. Although a large proportion of patients had undetectable HIV RNA, especially $HBeA^-$ patients, one-third of the patients studied were not successfully treated. If we consider a less strict HIV RNA cut-off for treatment success of <1000 copies/ml, the response seems more satisfactory. Several studies have shown that chronic HBV infection significantly increased liver-related mortality in HIV-1-infected patients but did not have a direct impact on progression to AIDS or on viral and immunological responses to ART.[24–26] However, studies from Taiwan found that individuals with chronic hepatitis B were less likely to achieve HIV RNA suppression at 4 and 24 months after initiation of ART.[26,27] Overall, it is still debated whether HBV co-infection might negatively affect the efficacy of antiretroviral therapy.

Our study has several limitations, mainly as a result of its design, it not being a randomized controlled study, and of the limited access to resources. First, the cohort size was relatively small (to date, most published studies on HBV/HIV co-infection treatment outcomes report on small cohorts) and the cross-sectional design did not allow for assessment of the durability of treatment response. Even though we haven't found a statistically significant difference in the overall mortality between $HBsAg^+$ and $HBsAg^-$ patients (16% vs 0%), most probably because of the small sample size, this was a finding of importance. There has been no systematic screening for HBV among HIV patients in the ART centers in Mumbai and the rest of India to date. Access to HBV-DNA measurements and to hepatitis C and D serology is limited to private laboratories in large urban centers. Moreover, TDF was not available in the Indian public ART centers until very recently, and it is currently reserved for patients who fail first-line ART. Second, because of lack of resources we were unable to study lamivudine resistance patterns among ART naive and ART non-naive patients. However, half of our patients had received antiretroviral treatment and it is reasonable to hypothesize that these patients would have been exposed to lamivudine, and possibly developed some form of resistance. From this standpoint, our results are even more encouraging with regard to the efficacy of the TDF/lamivudine ART regimen. Similarly, limited resources meant that we were unable to perform liver biopsies and had no access to pathology data. However, several studies in HBV-infected patients have shown a strong correlation between HBV-DNA suppression and a decreased risk of liver damage, hepatocellular carcinoma, and related mortality.[28–30]

Overall, we acknowledge the fact that we mainly report on surrogate laboratory markers rather than long-term treatment outcomes. However, we recorded encouragingly low death rates and loss-to-follow-up rates in this cohort of co-infected patients. Long-term, prospective studies are needed to assess the durability of the response, to study HBeAg seroconversion, to describe the emergence and patterns of drug resistance, and to assess histological improvement among HIV/HBVco-infected patients.

Considering the relatively high burden of HBV, and the consequent high HBV/HIV co-infection burden in India and other similar settings, an efficacious and standardized first-line ART regimen such as TDF/lamivudine would be very useful for managing the co-infections in resource-limited settings.[19] Bender et al. have shown that incorporating TDF as part of first-line ART in India is cost-effective by international standards and will improve survival.[31] In settings with limited resources, affordable and reliable laboratory tests are also needed for the virological follow-up of the patients, as the existing tests are costly.

Good treatment outcomes were achieved in a cohort of HIV/HBV co-infected patients receiving TDF/3TC-based ART in a program setting in Mumbai, India. In regions with a high burden of HIV/HBV co-infection, all HIV-infected individuals should be tested for chronic hepatitis B to detect co-infection. A TDF/3TCnucleoside reverse transcriptase inhibitor (NRTI) backbone could be considered as a first-line standardized ART regimen in these settings.

Authors' contributions: PI and TADM conceived and designed the study. PI and RZ analyzed the data. HM, TADM, EDS, BV, JL, AD, LA and TR interpreted the data. PI drafted the manuscript. HM, RZ, TADM, EDS, BV, JL, AD, LA and TR critically revised the manuscript for intellectual content. All authors read and approved the final version. PI is guarantor of the paper.

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Competing interests: none declared.

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