Hepatitis B infection in HIV-1-infected patients receiving highly active antiretroviral therapy in Lomé, Togo: Prevalence and molecular consequences

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Background. No data are available on HIV/hepatitis B virus (HBV) or hepatitis C virus coinfection in Togo, and patients are not routinely tested for HBV infection.
Objectives. To determine the prevalence of HBV and the risk of HBV drug resistance during antiretroviral treatment in HIV-coinfected patients in Togo.
Method. This cross-sectional study was carried out in Lomé, Togo, from January 2010 to December 2011 among HIV-infected patients who had been on antiretroviral therapy (ART) for at least 6 months.
Results. In total, 1 212 patients (74.9% female) living with HIV/AIDS and treated with ART were included in the study. The seroprevalence of hepatitis B surface antigen (HBsAg) was 9.7% (117/1 212; 95% confidence interval (CI) 8.04 - 11.45). Of these 117 HBsAg-positive patients, 16 (13.7%) were hepatitis B e-antigen (HBeAg)-positive, and 115 (98.3%) were on lamivudine. The HBV DNA load was >10 IU/mL in 33/117 patients overall (38%), and in 87.5% of 16 HBeAg-positive patients ($p<0.0001$). In multivariate analysis, factors associated with HBV DNA load >10 IU/mL were HBeAg positivity (adjusted odds ratio (aOR) 6.4; $p=0.001$) and a higher level of education (aOR 6.5; $p=0.026$). The prevalence of HBV resistance to lamivudine was 13.0% (15/115; 95% CI 7.0 - 19.0). The detected resistance mutations were rtL180M (14/15 patients) and rtM204V/I (15/15).
Conclusion. The seroprevalence of HBV among ART-treated HIV-infected patients in Togo was 9.7%. The prevalence of HBV lamivudine resistance mutations after 2 years of ART was 13.0%. These results suggest that HBV screening before ART initiation can be based on HBsAg testing.

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Hepatitis B virus (HBV) is highly endemic in sub-Saharan Africa, with >60% of the population contracting HBV and 8 - 20% becoming chronic carriers and at risk of life-threatening liver disease.[1] HBV and HIV share several transmission routes and are major causes of morbidity and mortality in Africa. In sub-Saharan Africa, the main HIV transmission routes are sexual transmission, mother-to-child transmission and largely unexplained horizontal transmission between toddlers, with most infections occurring before the age of 5 years.[2] Sexual transmission is the main route of HBV transmission in adolescence and early adulthood. Healthcare workers are also at risk of parenteral and percutaneous transmission during occupational exposure.

Chronic HBV infection is therefore frequent among people living with HIV/AIDS in sub-Saharan countries, with reported HBV surface antigen (HBsAg) seroprevalence rates of 7 - 15% in West Africa[3,4] and East Africa.[5,6]

Before the introduction of antiretroviral therapy (ART), HBV/HIV-coinfected individuals were likely to die from the clinical consequences of HIV infection. However, since the introduction of ART, the proportion of deaths due to HBV-associated end-stage liver disease (ESLD) has increased[7] because progression of HBV infection towards cirrhosis, ESLD and hepatocellular carcinoma is more rapid in HIV-coinfected patients.[8]

In 2010, the World Health Organization (WHO) recommended HBV screening before ART initiation, and the use of ART regimens containing tenofovir plus either lamivudine or emtricitabine for HIV/HBV coinfection.[9] However, HBV screening may be unavailable in resource-limited settings, and lamivudine is often the only available drug active against HBV in sub-Saharan African countries. Use of lamivudine without tenofovir has been linked to gradual emergence of resistance mutations in the HBV polymerase gene.[10] The annual incidence of viral mutations in this setting has been estimated at about 22%, the main risk factor being high HBV viral load at ART initiation.[11] In contrast, no cases of HBV resistance have been described in tenofovir-treated patients.

In 2011, there were 103 HIV/AIDS care centres managing 80 000 patients in Togo, of whom 36 700 were receiving highly active ART. Expanded access to ART, combined with sustainable preventive interventions such as condom provision and health information, have reduced HIV-related morbidity and mortality in Togo.[12] In 2011,

national guidelines[13] recommended first-line therapy with stavudine, or zidovudine and lamivudine, plus either nevirapine or efavirenz. Tenofovir is available for second-line therapy in the case of treatment failure or severe anaemia caused by zidovudine.

No data are available on HIV/HBV or hepatitis C virus (HCV) coinfection in Togo, and patients are not routinely tested for HBV infection. National guidelines recommend HBV screening only when the alanine aminotransferase (ALT) level is more than three times higher than normal.[13]

Objectives

To determine the prevalence of HBV infection among HIV-infected patients in Togo, and the effect of lamivudine-containing ART on HBV replication and resistance.

Methods

Study design and setting

We conducted an analytical cross-sectional study in four HIV/AIDS care centres in Lomé, Togo, namely the Department of Pneumology and Infectious Diseases of Sylvanus Olympio teaching hospital and three centres run by non-governmental organisations: Aide Médicale et Charité (AMC), Association de Bien Etre Familial (ATEBF), and Espoir Vie Togo (EVT).

Study population

We studied HIV-infected patients aged ≥18 years who had been taking ART for at least 6 months and had not stopped taking their treatment for more than 3 months. The study flow chart is shown in Fig. 1.

Clinical investigations

Data were collected through a questionnaire-assisted interview and included socio-demographic information (sex, age, height, weight, nationality, partnership status, education, occupation) and medical information (history of blood transfusion and intramuscular (IM) and intravenous (IV) injections, alcohol consumption, pre-ART and current CD4 cell counts and HIV viral load if available, date of HIV diagnosis, date of first ART, current ART regimen, and treatment adherence). WHO criteria were used to determine the clinical stages of HIV infection.[9]

Laboratory investigations

Blood samples were taken from each participant for liver enzyme assay and a CD4 cell count. Serum (7 mL) and plasma (14 mL) samples were stored at –20°C until testing in the molecular biology and immunology laboratory (BIOLIM) of the Lomé Faculty of Medicine and Pharmacy.

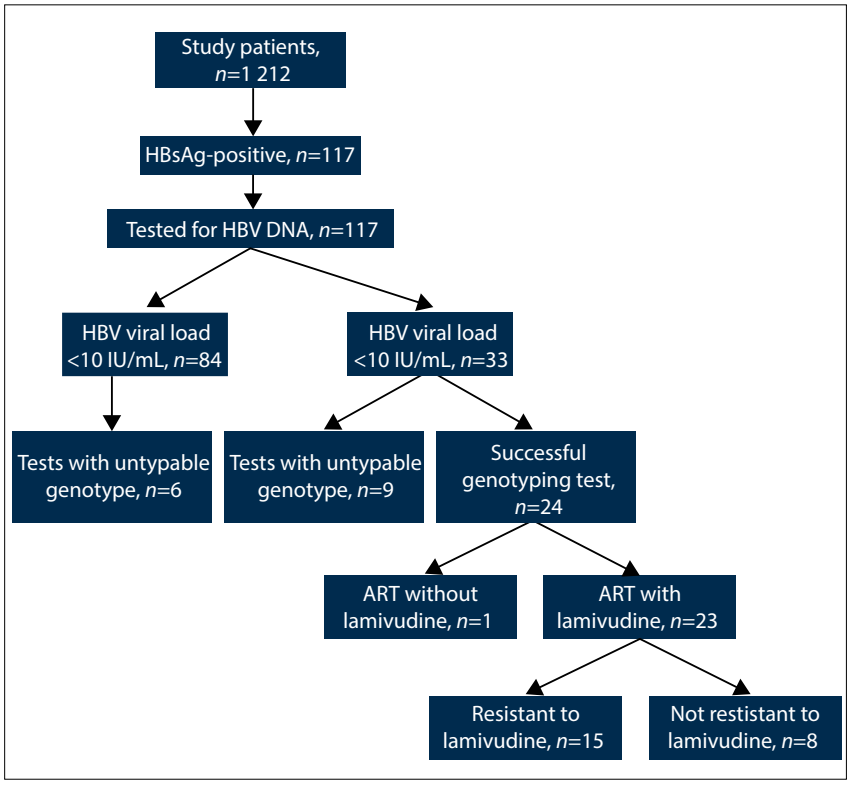

Fig. 1. Flow chart of patients included in the study.

HIV and HBV viral loads for patients with HBsAg were measured at the BIOLIM laboratory in Lomé and the virology laboratory at Cochin Hospital, Paris, France. ALT, aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) were assayed using standard methods. The upper normal limits of ALT and AST levels were both 40 IU/L. CD4 cells were counted by flow cytometry on a Becton Dickinson FACSCalibur device (Becton Dickinson, USA). Screening for HBV infection was based on HBsAg detection; positive samples were tested for hepatitis B e-antigen (HBeAg) and anti-HBe antibodies. Samples negative for HBsAg were screened for antibodies to HBsAg and hepatitis B core antigen (HBcAg). Serological tests were performed with enzyme-linked immunosorbent assay methods using reagents from DIASource (Belgium).

Participants who tested negative for all HBV markers were classified as HBV-susceptible, those who were positive for both anti-HBc and anti-HBs were classified as having been exposed to HBV, and those who were anti-HBc-negative and anti-HBs-positive were classified as probably vaccinated.

Samples positive for HBsAg were tested for HIV and HBV viral load. HIV viral load was determined with a polymerase chain reaction (PCR) method targeting the polymerase gene (Abbott Real Time HIV, Abbott Diagnostics, France). HBV viral load was determined with a PCR method (Abbott Real Time HBV, Abbott Laboratories, USA). Results were expressed in IU/mL and log10 copies/mL. HBV DNA loads <10 IU/mL were classified as undetectable.

Samples positive for both HBsAg and HBV DNA were HBV genotyped by phylogenetic methods, and the HBV polymerase gene was sequenced to detect mutations known to be associated with lamivudine resistance (rtV173L, rtV180M, rtA181T/V, rtT184G and rtM204V/I) using Bioedit software (http//:www.mbio.ncsu.edu/bioedit).

Ethical issues

The study was designed and implemented in accordance with the Declaration of Helsinki and approved by the Comité Bioéthique pour la Recherche en Santé (CBRS) (Ref. No. 006/2009/CBRS, 12 November 2009) before implementation. The patients gave their written informed consent, recorded in a form, for their data to be used for the study. The HBsAg, CD4 cell count and HIV viral load results were given to each patient by a doctor in a private room in the clinic.

Statistical analysis

Baseline values of continuous variables were expressed as means or medians and ranges

and categorical variables as frequencies and percentages.

The χ^2 test or Fisher's exact test were used as appropriate for bivariate analysis of categorical variables, and the Mann-Whitney test was used for continuous variables. The main endpoint was the prevalence of HIV/HBV coinfection, HBV infection being defined by the presence of HBsAg. Multivariate backwards stepwise logistic regression was used to identify factors independently associated with active HBV replication (HBV DNA >10 IU/mL). All variables significant in bivariate analysis ($p<0.05$) and variables with p-values <0.1 were included in the model. We then removed variables that were not significant at a p-value of <0.05, in stepwise fashion. We also assessed the significance of the likelihood ratio of the test. No interaction was found among variables included in the model.

Results

Study population

From April to December 2011, we enrolled 1 212 HIV-infected patients (mean age 41 years, range 21 - 79). Table 1 shows the sociodemographic, immunovirological and hepatic characteristics of the study population. Females represented 74.9% of the patients (n=908). Five hundred and eighty-two patients (48.0%) were living with a partner, 598 (49.3%) had attended secondary school, 1 043 (86.1%) had received at least one IM or IV injection, 209 (17.2%) had received a blood transfusion, and 25 (2.1%) reported HBV vaccination.

AST and ALT levels ranged from 35 to 364 IU/L and from 30 to 264 IU/l, respectively. The median CD4 cell count was 143/μL (interquartile range (IQR) 63 - 205).

One thousand and eighty patients (89.1%) were on a first-line ART regimen comprising two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor, and 123 patients (10.1%) were on second-line ART. Most patients were on at least one antiretroviral drug active against HBV: lamivudine in 1 092 cases (90.1%) and tenofovir in 110 (9.1%).

Prevalence of HBV markers

Serological tests showed that 48.3% of the patients (585/1 212) had been exposed to HBV; of the 1 212 patients, 117 (9.7%) were HBsAg-positive, 243 (20.0%) were anti-HBs- and anti-HBc-positive, and 498 (41.1%) were only anti-HBc-positive. Sixteen patients (1.3%) were only anti-HBs-positive and were considered as vaccinated against HBV, while 337 patients (27.8%) were negative for all the serological markers of HBV infection and were categorised as HBV-susceptible.

Of the 117 patients who were HBsAg-positive, 16 (13.7%) were also HBeAg-positive, 86 (73.5%) were also anti-HBe-positive, and 15 (12.8%) had neither HBe marker.

Table 1. Sociodemographic, biological and immunovirological characteristics of the study population

Descriptive variables	Overall (*N*=1 212)	HBsAg+ (*N*=117)	HBsAg– (*N*=1 095)
Sociodemographic characteristics			
Age (years), median (IQR)	40.8 (34.1 - 47.8.)	37.9 (32.4 - 44.9)	40.8 (34.7 - 47.9)
Males, *n* (%)	304 (25.1)	31 (26.5)	273 (24.9)
Partnership status, *n* (%)			
One of a couple	582 (48.0)	50 (42.7)	532 (48.6)
Alone	630 (52.0)	67 (57.3)	563 (51.4)
Education level, *n* (%)			
No school or primary	614 (50.7)	54 (46.2)	560 (51.1)
Secondary or higher	598 (49.3)	63 (53.8)	535 (48.9)
Income-generating activity, *n* (%)	998 (82.3)	97 (82.9)	901 (82.3)
Body weight (kg), median (IQR)	63 (55 - 72)	61 (55 - 68)	63 (55 - 72)
Alcohol consumption, *n* (%)	350 (28.9)	36 (30.8)	314 (28.7)
Transfusion of blood products, *n* (%)	209 (17.2)	26 (22.2)	183 (16.7)
IV or IM injection, *n* (%)	1 043 (86.1)	104 (88.9)	939 (85.7)
Immunovirological characteristics			
CD4 cell nadir (/μL), median (IQR)	142 (63 - 205)	139 (54 - 193)	142 (65 - 207)
Last CD4 count (/μL), median (range)	338 (216 - 474)	313 (183 - 427)	340 (219 - 479)
Last CD4 cell count (/μL), *n* (%)			
<200	362 (29.9)	44 (37.6)	318 (29.1)
200 - 350	336 (27.7)	31 (26.4)	305 (27.9)
>350	514 (42.4)	42 (35.9)	472 (43.1)
HIV RNA (copies/mL), median (IQR)	40 (0 - 975)	40 (0 - 5 915)	40 (0 - 185)
HIV RNA values (copies/mL, *n* =117), *n* (%)			
<40	-	43 (36.7)	-
>40	-	74 (63.3)	-
WHO stage of HIV, *n* (%)			
1 or 2	831 (68.6)	80 (68.4)	751 (68.6)
3 or 4	381 (31.4)	37 (31.6)	344 (31.4)
Ongoing antiretroviral treatment, *n* (%)	1 212 (100.0)	117 (100.0)	1 003 (91.6)
Type of antiretroviral treatment, *n* (%)			
1st-line therapy	1 080 (89.1)	108 (92.3)	972 (88.8)
2nd-line therapy	123 (10.1)	9 (7.7)	114 (10.4)
Containing lamivudine or emtricitabine	1 102 (90.9)	115 (98.3)	987 (90.1)
Containing tenofovir	110 (9.1)	9 (7.7)	101 (9.2)
Duration of antiretroviral treatment (months), mean (range)	31.0 (18.2 - 57.6)	30.2 (19.1 - 38.9)	32.6 (18.2 - 57.1)
Hepatic status			
ALT (IU/mL), median (range)	30 (5 - 264)	28 (8 - 174)	29 (6 - 232)
Hepatic decompensation, *n* (%)	16 (1.3)	1 (0.8)	15 (1.4)
Vaccinated against HBV, *n* (%)	25 (2.1)	7 (6.1)	18 (1.6)

Active HBV replication

Among the 117 HIV/HBV-coinfected patients, 115 (98.3) were on lamivudine. HBV DNA loads were >10 IU/mL in 33/117 (28.2%) of these patients and 84/117 (71.8%) had HBV DNA loads <10 IU/mL. Of the 16 HBeAg-positive patients, 14 (87.5%) had HBV DNA loads >10 IU/mL(p<0.0001), while 12 (75%) had HBV DNA loads >1 500 IU/mL.

In bivariate analysis, active HBV replication was associated with >24 months of ART (odds ratio (OR) 1.02; p=0.045) and HBeAg positivity (OR 22.7; p<0.0001) (Table 2).

In multivariate analysis, two factors were significantly associated with active HBV replication, namely HBeAg positivity (6.4-fold increase; adjusted OR (aOR) 6.4; p=0.001), and a higher level of education (aOR 6.5; p=0.026) (Table 3).

Table 2. Factors associated with active HBV replication (HBV DNA >10 IU/mL)

Variable	OR	95% CI	*p*-value
Age (years)	1.02	0.96 - 1.10	0.52
CD4 cell count before ART (/µL)	0.99	0.98 - 1.00	0.44
Last CD4 cell count	1.00	0.99 - 1.00	0.86
Duration of ART (months)	1.02	1.00 - 1.04	0.045
Type of antiretroviral treatment			0.98
1st-line therapy	1	1	
2nd-line therapy	0.01	0.01 - 99.99	
Sex			0.55
Male	1	1	
Female	0.70	0.22 - 2.25	
Education level			0.10
No school or primary	1	1	
Secondary or higher	2.75	0.82 - 9.22	
HBeAg status			<0.0001
Negative	1	1	
Positive	22.75	6.06 - 86.42	
HIV viral load			0.73
Detectable (>40 IU/mL)	1	1	
Undetectable	0.82	0.26 - 2.57	
CD4 cell count before ART (/µL)			0.51
<200	1	1	
≥200	0.48	0.05 - 4.30	
Last CD4 cell count(/µL)			0.59
<200	1	1	
200 - <350	2.17	0.49 - 9.64	
≥350	1.49	0.34 - 6.50	

Table 3. Factors independently associated with HBV replication (HBV DNA >10 IU/mL) among 117 HIV/HBV-coinfected patients

Variable	aOR	95%CI	*p*-value
Duration of ART	1.0	0.9 - 1.1	0.074
Education level			0.026
No school or primary	1	1	
Secondary or higher	6.5	1.2 - 34.1	
HBeAg status			0.001
Negative	1	1	
Positive	6.4	2.1 - 19.5	

HBV resistance mutations

The prevalence of HBV resistance to lamivudine was 13.0% (15/115; 95% CI 7.0 - 19.0). Genotyping was successful in 24 of the 33 patients with active HBV replication, all 24 having HBV DNA loads >2 000 IU/mL. Genotype E was found in all 24 patients. HBV resistance mutations to lamivudine were detected in 15/23 patients (65.2%; 95% CI 48.7 - 87.7), and consisted of rtL180M in 14 cases and rtM204V/I in 15.

Discussion

The prevalence of chronic HBV infection, based on the presence of HBsAg, was 9.7% among HIV-infected adults receiving ART in Lomé, Togo, while 48.3% of the study population had serological evidence of exposure to HBV. Among HIV/HBV-coinfected patients positive for HBsAg, 13.7% were also positive for HBeAg. Of the 117 HBV-coinfected patients, 98.3% were on an antiretroviral regimen in which lamivudine was the only drug active on HBV. Active HBV replication was detected in 33 (28.2%) of these 117 patients. The prevalence of HBV genotypic resistance to lamivudine was 65.2% (15/23 successfully tested patients). The only resistance mutations in the HBV polymerase gene were rtL180M (14/15) and rtM204V/I (15/15).

Prevalence of HBV infection and HBeAg

The prevalence of chronic HBV infection among HIV-coinfected patients in our study was similar to that observed in the general population of Burkina Faso.[14] The situation in Togo is therefore quite different from that reported in European countries, where chronic HBV infection is about ten times more prevalent among HIV-infected people than in the general population. In France, for example, the prevalence of chronic HBV infection is 7% among HIV-infected persons and only 0.7% in the general population.[15,16] The profile of infection in Togo suggests that HBV is usually acquired in childhood, before acquisition of HIV infection.

HBeAg may be present or absent in patients with chronic hepatitis B.[17] The generally long duration of HBV infection in Togolese individuals explains why most of them are HBeAg-negative and have relatively low HBV DNA loads, and why some are healthy carriers with no ongoing HBV replication. This was also the case in a recent study conducted in Abidjan, Côte d'Ivoire, where 33% of HIV/HBV-coinfected patients were

healthy carriers of HBV, being HBsAg-positive but HBV DNA-negative.[18] Studies in other sub-Saharan African countries have also shown that most HBV-infected patients are HBeAg-negative.[17]

Prevalence of anti-HBc

Anti-HBc was the only serological marker of HBV exposure in 41.1% of our patients. Previous studies of HIV-coinfected patients have also shown a high prevalence of isolated anti-HBc positivity, ranging from 24.5% to 37.8%.[19-21] In a recent study conducted in Spain, isolated anti-HBc positivity was associated with younger age and anti-HCV antibodies,[22] but those two factors were not analysed in our study.

Active HBV replication in HBsAg-positive patients

After a median of 31 months on ART, 71.8% of patients with chronic HBV infection had HBV DNA suppression when their ART regimen contained lamivudine. Only 28.2% of the patients with chronic HBV infection had HBV DNA levels indicating active replication, and the main factor associated with HBV replication was the presence of HBeAg. It has been reported that 48 weeks of combined tenofovir-lamivudine therapy is often too short to achieve undetectable HBV DNA in HIV/HBV-coinfected patients, despite undetectable HIV viraemia. This was explained by associated factors such as positive HBeAg and high baseline HBV DNA.[23]

Our results are also consistent with the findings of a recent study performed in Thailand, where the rate of HBV DNA suppression in HIV/HBV-coinfected patients was 67% after 48 weeks of lamivudine-containing ART and in which HBV breakthrough was exclusively observed in HBeAg-positive patients.[24]

In contrast to other studies,[25] neither the duration of ART nor active HIV replication was associated with HBV replication in our study. The presence of HBeAg is a fairly reliable marker of HBV replication. In fact, at the initiation of ART, HBV and HIV/HBV coinfection markers were not determined in our study. Furthermore, 98.3% of patients in our study were receiving ART containing only lamivudine. It is known that the HBV viral load is related to the presence of HBeAg,[4] and lamivudine alone is less effective in reducing the HBV viral load.[26,27]

We also found that a higher level of education was associated with active HBV replication. This may be because patients with a lower level of education tend to acquire HBV infection earlier during childhood, through horizontal transmission among toddlers, and have therefore lost HBeAg, whereas patients with a higher level of education tend to acquire HBV later in life through sexual exposure. Low socioeconomic status and poor hygiene are commonly associated with a higher risk of HBV infection.[28]

Prevalence of HBV resistance to lamivudine

The prevalence of HBV resistance to lamivudine usually reaches 40 - 50% after 2 years of treatment in studies of Western cohorts of HIV/HBV-coinfected individuals taking lamivudine as the only drug active against HBV,[10,29] whereas prevalence rates <15% have been reported in similar populations in sub-Saharan Africa. This discrepancy could be related mainly to differences in the timing of HBV infection relative to HIV infection, or less probably to the fact that African studies usually involved shorter follow-up (24 months). A cross-sectional study in Cameroon found resistance mutations in 13% of 54 patients at 24 months.[30] A retrospective analysis in the Gambia found lamivudine resistance mutations in 14% of 21 patients followed up for between 6 and 56 months.[31] In two recent prospective cohort studies conducted in Nairobi, Kenya, lamivudine resistance occurred in only 9.5% of 27 coinfected patients after 18 months of therapy[32] and in only one of 159 women followed up for a median of 3.4 years.[33]

Conclusion

After a median of 31 months on ART, 28.2% of HIV-infected patients with chronic HBV coinfection had active HBV replication. HBeAg positivity was associated with HBV replication and with the occurrence of HBV resistance mutations. These findings suggest that a two-step approach may be suitable for HBV screening of HIV-infected patients prior to ART initiation in resource-limited settings, consisting of HBsAg screening in all patients and HBeAg screening of patients positive for HBsAg.

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Author contributions. AAP, DS-C, J-FM, SB and ACD conceived and designed the study and wrote the manuscript. DEL and BS were involved in data analysis and interpretation. They wrote and revised the manuscript. AK and MS were involved in laboratory investigations and manuscript writing. PP and DS-C were responsible for the overall scientific management of the study, analysis and interpretation, and the preparation of the final manuscript. All the authors read and approved the final manuscript submitted for publication.

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