Liver Fibrosis Regression Measured by Transient Elastography in Human Immunodeficiency Virus (HIV)-Hepatitis B Virus (HBV)-Coinfected Individuals on Long-Term HBV-Active Combination Antiretroviral Therapy

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Background. Advanced fibrosis occurs more commonly in human immunodeficiency virus (HIV)-hepatitis B virus (HBV) coinfected individuals; therefore, fibrosis monitoring is important in this population. However, transient elastography (TE) data in HIV-HBV coinfection are lacking. We aimed to assess liver fibrosis using TE in a cross-sectional study of HIV-HBV coinfected individuals receiving combination HBV-active (lamivudine and/or tenofovir/tenofovir-emtricitabine) antiretroviral therapy, identify factors associated with advanced fibrosis, and examine change in fibrosis in those with >1 TE assessment.

Methods. We assessed liver fibrosis in 70 HIV-HBV coinfected individuals on HBV-active combination antiretroviral therapy (cART). Change in fibrosis over time was examined in a subset with more than 1 TE result (n = 49). Clinical and laboratory variables at the time of the first TE were collected, and associations with advanced fibrosis (≥F3, Metavir scoring system) and fibrosis regression (of least 1 stage) were examined.

Results. The majority of the cohort (64%) had mild to moderate fibrosis at the time of the first TE, and we identified alanine transaminase, platelets, and detectable HIV ribonucleic acid as associated with advanced liver fibrosis. Alanine transaminase and platelets remained independently advanced in multivariate modeling. More than 28% of those with >1 TE subsequently showed liver fibrosis regression, and higher baseline HBV deoxyribonucleic acid was associated with regression. Prevalence of advanced fibrosis (≥F3) decreased 12.3% (32.7%–20.4%) over a median of 31 months.

Conclusions. The observed fibrosis regression in this group supports the beneficial effects of cART on liver stiffness. It would be important to study a larger group of individuals with more advanced fibrosis to more definitively assess factors associated with liver fibrosis regression.

Keywords. antiretroviral therapy; fibrosis; HIV-HBV coinfection; transient elastography.
(TE) to liver biopsy in the setting of coinfection with HIV and hepatitis C [12–15]. Vibration-controlled transient elastography uses sound waves to measure the elasticity of the liver and thereby give an indirect measure of fibrosis. Vibration-controlled transient elastography has also been well validated in patients with HIV-HCV coinfection [13], HBV monoinfection [16], and more recently in HIV monoinfection [17]. Only one study to date has compared the accuracy of TE with liver biopsy in the setting of HIV-HBV coinfection, and this demonstrated good concordance between TE and liver biopsy with area under the receiver operating curves for significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4) of 0.85, 0.92, and 0.96, respectively [18].

In HBV monoinfection, HBV-active NRTIs have been associated with improvements in HBV-related disease outcomes [19] and in liver histology [20–23]. Improvement in fibrosis as measured by TE has also been observed in HBV-monoinfected patients receiving HBV-active NRTIs [24, 25]. Very little data have been published on changes in liver disease in HIV-HBV coinfected patients on HBV-active ART using TE. In the first published study that investigated TE changes in HIV-HBV coinfection, 17% of patients in the European cohort had an improvement in liver fibrosis staging as measured by TE, whereas 75% showed no improvement and 8% had an increase in liver fibrosis staging [26]. A reduction in liver fibrosis stiffness has also been observed after a median 7.8 months on TDF in a sub-Saharan HIV-HBV coinfection cohort study [27]. Data from another European cohort support this early reduction in liver stiffness as measured by TE, with the authors specifically noting that there remains a lack of long-term data regarding the duration and stability of these on-treatment liver stiffness decreases [28]. The impact of long-term HBV-active combination ART (cART) on liver disease progression in the setting of HIV-HBV coinfection therefore remains unclear and warrants further investigation.

PARTICIPANTS AND METHODS

Study Participants
Individuals coinfected with HIV HBV who had undergone liver stiffness assessment by TE using Fibroscan at The Alfred Hospital and St Vincent’s Hospital Sydney from July 2008 to June 2014 were included in the study (n = 70). These participants had undergone TE as part of standard of care treatment for the assessment of fibrosis severity. Eligibility criteria included HIV antibody positivity, chronic HBV infection (defined as HBV surface antigen [HBsAg] and/or HBV-DNA positive on at least 2 occasions at least 6 months apart), and patients receiving HBV-active cART (LMV, FTC, or tenofovir, or combination). Hepatitis C virus (HCV) coinfection and/or hepatitis delta coinfection were not exclusion criteria. The study was conducted in accordance with the Declaration of Helsinki and approved by the relevant Human Research Ethics Committees in Sydney (St Vincent’s Hospital Sydney Human Research Ethics Committee) and Melbourne (Alfred Health Human Ethics Committee). Because this study was a low-risk project that analyzed standard-of-care deidentified data, the Human Research Ethics Committees approved a request for waiver of obtaining consent.

Analysis of fibrosis and associated factors were undertaken at the time of first TE (n = 70), and change in fibrosis and associated factors were assessed in those individuals with at least 2 TE results (n = 49). Individuals with <12 months between TE results were excluded from the analysis of change in fibrosis (n = 4).

Data Abstraction and Collection
Clinical and laboratory data were abstracted from medical records at study entry. Clinical data included demographics, any prior standard-of-care liver biopsy data and current anti-HIV and anti-HBV therapy (anti-HBV therapy was defined as any regimen that contained LMV and/or tenofovir/tenofovir-FTC). Laboratory measurements included the following: alanine transaminase (ALT), aspartate aminotransferase, platelets, hepatitis B e antigen (HBeAg), HBe antibody (anti-HBe), HB surface antibody (anti-HBs), hepatitis delta virus, HCV antibody, HCV ribonucleic acid (RNA), HIV RNA, TE result, CD4 count, and nadir CD4 count.

Transient Elastography
Liver stiffness was assessed by TE using Fibroscan (Echosens, Paris, France) as part of standard-of-care treatment for individuals coinfected with HIV HBV. Examinations were performed by trained clinicians who have regularly undertaken TE examinations for over 4 years. Vibration-controlled transient elastography examinations were performed with the individual lying supine and the right lobe of the liver identified by ultrasound. Ten valid readings were taken in the midaxillary line using the M probe. A valid reading was defined as having a ratio of interquartile range (IQR) to median of <0.3. Vibration-controlled transient elastography cutoffs used to stage fibrosis were as follows: F1 ≤ 5.8 kPa, F2 5.9–7.5 kPa, F3 7.6–9.3 kPa, and F4 > 9.4 kPa, using the Metavir scoring system [29] to grade fibrosis. These are the only liver biopsy-validated TE cutoffs in the setting of HIV-HBV coinfection that have been reported to date [18].

Statistical Analysis
Clinical and laboratory variables examined included gender, age, ethnicity, detectable HBV DNA, median HBV DNA (IU/mL), detectable HIV RNA (>50 copies/mL), median HIV RNA (copies/mL), HBsAg status, anti-HBs status, HBeAg status, anti-HBe status, HCV Ab status, duration known HIV positive, duration of cART, duration of HBV-active cART, current and nadir CD4 cell count, platelets, and ALT.

For cross-sectional analysis, individuals were classified as having mild to moderate (Stage 0–2) or advanced (Stage 3+) fibrosis based on the first TE result. Univariate association of advanced fibrosis with clinical and laboratory factors were
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determined by the Mann-Whitney U test for continuous variables and χ² (or Fisher’s exact test when cell numbers were small) for categorical variables. Binary logistic regression analysis was used to assess the effect of factors identified as significant at the univariate level. Goodness of fit for each multivariate model was assessed using the Pearson χ² test.

To assess change in fibrosis over time, individuals were classified according to change in fibrosis stage between first and last TE as either regression (increase by at least 1 fibrosis Stage) or no regression (no change); participants with fibrosis progression (n = 5) were excluded from this analysis. Clinical and laboratory factors associated with fibrosis regression were determined by the Mann–Whitney U test for continuous variables and χ² test (or Fisher’s Exact test when cell numbers were small) for categorical variables. Potential correlation between continuous variables was examined using Spearman’s rank correlation. Associations with change in median kPa (difference between first and last TE result) were also analyzed. Median difference in fibrosis stage and kPa between the first and last TE assessment was tested for significance using paired samples marginal homogeneity test and paired Wilcoxon signed-rank test, respectively. Statistical analyses were performed using SPSS 20 (Release 22.0; IBM, Armonk, NY), all tests were 2 tailed, and statistical significance was defined as P < .05.

RESULTS

Study Participants and Clinical Features at Study Entry

Characteristics of the cohort at study entry are displayed in Table 1. The majority of the cohort was male (95.7%), median age was 46.5 years, median duration known HIV positive was 16.7 years, and most of the cohort was white (85.7%). Approximately 30% of the cohort had tested HCV-Ab positive at the most recent test result, with a median duration known HCV positive of 13.1 (IQR, 7.4–18.9) years. Eighty percent of those who were HCV-Ab positive were also HCV-RNA positive (median HCV RNA log₁₀ 5.8 IU/mL; IQR, 3.4–6.3); however, the date of HCV-RNA test ranged from 8.2 years before to 1.9 years after the date of TE assessment. Twenty-five percent of the cohort was HIV-RNA positive (median HIV RNA log₁₀ 1.48 copies/mL; IQR, 1.30–1.70) and 25% was HBV-DNA positive (median HBV DNA log₁₀ 1.37 IU/mL; IQR, 1.3–2.55). Only 13.3% of the cohort was both HIV-RNA and HBV-DNA positive at the time of the first TE (median log₁₀ copies/mL HIV RNA 1.5 [IQR, 1.3–1.7] and median log₁₀ IU/mL HBV DNA 1.4 [IQR, 1.3–2.6]). Hepatitis delta results were available for approximately half the cohort (57%), and of these only 2 individuals were delta positive. Most individuals exhibited mild to moderate (≤F2) fibrosis (64.3%), with a median TE of 6.0 kPa (range, 2.8–35.8).

Factors Associated With Advanced Fibrosis at Study Entry

At the time of the first TE (n = 70), univariate analysis demonstrated a statistically significant association between advanced fibrosis (≥F3) at study entry and detectable (>50 copies/mL) HIV RNA (P = .045), higher ALT (P = <.001), and lower platelet count (P = .002) (Table 2). Hepatitis C virus Ab positivity (P = .05) almost reached the level of significance. In the multivariate analysis (MVA), only higher ALT and lower platelets remained significant (Table 3). Because HCV-Ab positive almost met statistical significance, a model including ALT, platelets, and HCV Ab was also analyzed. In this model (data not shown), only ALT and platelets remained statistically significant.

Liver Fibrosis Regression and Change in Kilopascal

Forty-nine individuals had at least 2 TE assessments, with a median 31.0 (IQR, 17.9–42.7) months between the first and last assessments. Fibrosis regression by at least 1 stage was observed in 28.5% of the cohort (Table 4). The majority (61.2%) had no change in fibrosis stage, and 10.2% (5 individuals) showed fibrosis progression by at least 1 stage between TE assessments. One

### Table 1. Cohort Demographics at Time of First TE Assessment

| Age, years | 46.5 (41.1–52.2) |
| Sex, n (%) |       |
| Male       | 67 (95.7) |
| Female     | 3 (4.3)  |
| Known duration HIV positive, years | 16.7 (8.4–22.8) |
| Ethnicity n (%) |       |
| Caucasian | 60 (85.7) |
| Asian     | 4 (5.7)  |
| African   | 4 (5.7)  |
| Hispanic | 2 (2.9)  |
| CD4 nadir, cells/µL | 284 (137–507) |
| Duration on cART, years | 10.7 (3.5–13.5) |
| Duration on HBV-active cART, years | 7.8 (3.3–11.7) |
| On HBV-active cART, % (n) | 91.4 (64) |
| HIV RNA positive (>50 copies/mL), % | 25.4 |
| HIV RNA, log₁₀ copies/mL | 1.5 (1.3–1.7) |
| HBV DNA positive, % | 25.4 |
| HBV DNA, log₁₀ IU/mL | 1.4 (1.3–2.6) |
| HBeAg positive, % | 29.2 |
| Most recent HCV Ab test positive, % | 28.6 |
| Most recent HCV RNA test positive, % | 22.9 |
| CD4 count, cells/µL | 381 (187–606) |
| CD4 count, % | 20.5 (14.0–31.3) |
| ALT, IU/mL | 34 (21–50) |
| Platelets, per mL | 185 (142–232) |
| 1st TE, kPa | 6.0 (4.8–10.3) |
| 1st TE fibrosis stage | 2 (1–4) |
| 1st TE fibrosis, stage % |       |
| F1       | 48.6 |
| F2       | 15.7 |
| F3       | 7.1  |
| F4       | 28.6 |
| Fibrosis classified as mild-moderate (≤F2), n (%) | 45 (64.3) |

Abbreviations: Ab, antibody; Ag, antigen; ALT, alanine transaminase; cART, combination antiretroviral therapy; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; RNA, ribonucleic acid; TE, vibration-controlled transient elastography.

*All data presented as median (IQR) unless otherwise stated. First TE assessments performed during the period 2008–2011.*
participant progressed from F2 to F4, whereas the other 4 progressed from F1 to F2 fibrosis. There was no significant difference in median time between TE assessments for those with fibrosis regression, those with no change in fibrosis stage, and those with fibrosis progression (31.9, 32.1, and 32.9 months, respectively). There was a significant difference in median fibrosis stage between the first and last TE by related sample analysis ($P = .0027$). The median kPa change between assessments was −0.60 kPa (IQR, −2.85 to +.55), with 65.2% of the longitudinal cohort showing an overall decrease in kPa. The median annual rate of change (overall change in kPa/years between TE) was −0.24 kPa (IQR, −1.02 to +.19). The difference in median kPa between the first and last TE was statistically significant ($P = .014$) by paired sample analysis. The presence of advanced fibrosis ($\geq$F3) decreased from 32.7% to 20.4% of the cohort.

**Predictors of Liver Fibrosis Regression**

At the univariate level, only higher HBV DNA ($P = .049$) at the time of the first TE was significantly associated with subsequent liver fibrosis regression of at least 1 stage (Table 5). There was no correlation between level of HBV DNA and duration of HBV-active cART ($P = .81$). Length of time between TE assessments was not significantly associated with fibrosis regression ($P = .79$).

**DISCUSSION**

Liver fibrosis in a cohort of HIV-HBV coinfected individuals on HBV-active cART was assessed using TE, with a subset having a follow-up TE performed after >12 months. Only one third of the individuals in this study exhibited advanced ($\geq$F3) fibrosis at the time of the first TE. This may be due to the impact of long-term ART, because the cohort had been receiving ART for a median of more than 10 years and HBV active ART for a median of over 7 years.

We identified higher ALT, lower platelets, and detectable HIV RNA as factors associated with advanced fibrosis at the

**Table 2. Factors Associated With Advanced Fibrosis ($\geq$F3) at Time of First TE Assessment (Univariate Level)**

| Continuous variables | Mild-moderate Fibrosis ($\leq$F2) (n = 45) | Advanced Fibrosis ($\geq$F3) (n = 25) | P Value |
|----------------------|------------------------------------------|--------------------------------------|---------|
| Duration of cART (years) | 12.0 (3.6–13.5) | 9.9 (2.3–13.2) | .298 |
| Duration of HBV-active cART (years) | 11.8 (3.6–13.5) | 9.9 (2.3–12.8) | .328 |
| Duration of ART (years) | 12.0 (9.1–21.2) | 11.7 (5.4–18.1) | .686 |
| HIV RNA (log10) | 1.30 (1.3–2.1) | 1.70 (1.3–2.3) | .092 |
| HBV DNA (log10) | 1.30 (1.3–2.6) | 2.55 (1.3–2.6) | .446 |
| ALT | 39.3 (50.0–30.5) | 50.0 (86.5–147.0) | <.001 |
| Platelets | 207.0 (165.5–268.0) | 147.0 (199.5–228.0) | .002 |

**Table 3. Multivariate Associations With Advanced Fibrosis ($\geq$F3) at Time of First TE Assessment**

| Outcome | Variable | OR | CI | P Value |
|---------|----------|----|----|---------|
| Significant fibrosis | ALT | 1.038 | 1.011–1.067 | .006 |
| | Platelets | 0.986 | 0.976–0.996 | .005 |
| | HIV RNA positive | 4.442 | 0.877–22.488 | .072 |

**Table 4. Longitudinal TE Assessment (n = 49)**

| Variable | 1st TE | Last TE |
|----------|--------|---------|
| Fibrosis Stage, % | | |
| F1 | 53.1 | 59.2 |
| F2 | 14.3 | 20.4 |
| F3 | 6.1 | 4.1 |
| F4 | 26.5 | 16.3 |
| TE fibrosis stage (median) | 1 (1–4) | 1 (1–2) |
| TE kPa, median (IQR) | 5.7 (4.7–9.4) | 5.4 (4.4–7.0) |
| Change in kPa | −0.6 (−2.9 ± 0.6) | |
| Mild-moderate/advanced fibrosis, % | 67.3/32.7 | 79.6/20.4 |
| Decrease in kPa, % | – | 63.3 |
| Fibrosis regression by at least 1 stage, n (%) | – | 14 (28.6) |
| Change in F stage, n (%) | | |
| Regression 2 stages | – | 6 (12.2) |
| Regression 1 stage | – | 8 (16.3) |
| No change | – | 30 (61.2) |
| Progression 1 stage | – | 4 (8.2) |
| Progression 2 stages | – | 1 (2.0) |
| Time between 1st and last scan (months) | – | 31.0 (17.9–42.7) |

**Table 5. Factors Associated With Advanced Fibrosis ($\geq$F3) at Time of First TE Assessment**

| Categorical variables | Mild-moderate Fibrosis ($\leq$F2) (n = 45) | Advanced Fibrosis ($\geq$F3) (n = 25) | P Value |
|----------------------|------------------------------------------|--------------------------------------|---------|
| HIV RNA positive | 16.7 | 40.0 | .045 |
| HBV DNA positive | 24.4 | 27.3 | 1.000 |
| HCV Ab positive | 20.5 | 45.8 | .050 |

**Table 6. Longitudinal TE Assessment (n = 49)**

| Variable | 1st TE | Last TE |
|----------|--------|---------|
| Fibrosis Stage, % | | |
| F1 | 53.1 | 59.2 |
| F2 | 14.3 | 20.4 |
| F3 | 6.1 | 4.1 |
| F4 | 26.5 | 16.3 |
| TE fibrosis stage (median) | 1 (1–4) | 1 (1–2) |
| TE kPa, median (IQR) | 5.7 (4.7–9.4) | 5.4 (4.4–7.0) |
| Change in kPa | −0.6 (−2.9 ± 0.6) | |
| Mild-moderate/advanced fibrosis, % | 67.3/32.7 | 79.6/20.4 |
| Decrease in kPa, % | – | 63.3 |
| Fibrosis regression by at least 1 stage, n (%) | – | 14 (28.6) |
| Change in F stage, n (%) | | |
| Regression 2 stages | – | 6 (12.2) |
| Regression 1 stage | – | 8 (16.3) |
| No change | – | 30 (61.2) |
| Progression 1 stage | – | 4 (8.2) |
| Progression 2 stages | – | 1 (2.0) |
| Time between 1st and last scan (months) | – | 31.0 (17.9–42.7) |

**Abbreviations:** ALT, alanine transaminase; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; RNA, ribonucleic acid; TE, vibration-controlled transient elastography.
univariate level. Only ALT and platelets remained independently significant in MVA. Approximately 30% of the total cohort was HCV-Ab positive at the test closest to the date of the first TE, and detectable HCV Ab almost reached statistical significance with more advanced fibrosis at the univariate level. It was not statistically significant in a multivariate model with ALT and platelets. Hepatitis C virus RNA was detectable in 80% of those who were HCV-Ab positive; however, time between test result dates and TE date varied greatly, so this may be an overestimate of HCV replication. An association between ALT and fibrosis has been observed in previous TE studies in the setting of HBV monoinfection, HIV-HCV coinfection, and HIV-HBV coinfection [30–32]. Although increased necroinflammatory activity is known to be associated with increased fibrosis progression, high ALT is a known confounder of TE because acute transient liver inflammation affects the elasticity of liver tissue [33]. In chronic HBV monoinfection, it has been observed that acute liver flares (ALT > 10 times the upper limit of normal [ULN]) increased liver stiffness; however, this resolved by 6 months to near-normal ALT levels [34].

A similar effect has been noted even with mild to moderate ALT elevations (2–10 times ULN) in chronic HBV, where a decline in ALT to normal levels was observed in more than three quarters of the cohort after 6 months of treatment with nucleoside or nucleotide analogs [35]. Decreased platelets are surrogate markers of more advanced liver disease, so this association with more advanced liver fibrosis was not unexpected.

The association of detectable HIV RNA at the first TE with more advanced liver fibrosis was significant in univariate analysis but did not remain significant in the multivariate model with higher ALT and lower platelets. We and others have previously reported that HIV RNA was associated with advanced liver fibrosis and fibrosis progression, in HIV-HCV and HIV-HBV coinfection [36–38]. However, 2 other studies have not found HIV RNA associated with fibrosis progression in HIV-HCV coinfection [39, 40]. Detectable HIV RNA may also indicate that adherence to ART was less than optimal, although not all those HIV-RNA positive also had detectable HBV DNA.

In approximately 30% of longitudinal participants, there was a reduction in liver fibrosis by at least 1 stage over a median 31.0 months and fibrosis progression was uncommon. These results are higher than those reported in an earlier study, in which regression was observed in 17% of the cohort over a median 40 months of follow up [26]. The cohort in the earlier study had received cART for a shorter duration than our cohort, a smaller proportion were on an HBV-active regimen, and more than 20% were hepatitis delta antibody positive. In addition, the earlier study used a set of fibrosis grade cutoffs that was validated in HBV-monoinfected cohorts, whereas we used cutoffs that have been validated in HIV-HBV coinfection. In spite of the differences, the general pattern of response was similar in both studies, with no change observed in fibrosis stage for majority of patients and a larger percentage with regression than progression. Higher HBV DNA was significantly associated at the univariate level with subsequent fibrosis regression, which would be expected because fibrosis is a known outcome of HBV-associated liver disease [41].

This study had a number of limitations. The cohort was retrospective, and demonstration of regression in individuals with minimal fibrosis at the time of the first TE was not possible. Despite this we were still able to demonstrate regression. There may have been also some survival bias in our study, as often
occurs in cross-sectional studies given that individuals with advanced fibrosis may have had reduced survival. Most of the cohort was Caucasian and male, thus limiting the extrapolation of these results to other populations. In addition, different clinicians performed the TE measurements, although all were highly experienced, so we do not believe this was a significant confounder. Data on body mass index (BMI), renal function, and class of ART were not collected, and data on alcohol consumption were not available. These factors could also have affected liver stiffness. Elevated BMI is associated with higher rates of invalid TE measurements, particularly when BMI > 30 kg/m² [42], although we did exclude participants with invalid TE readings. High alcohol intake is known to result in higher rates of both necroinflammation and fibrosis [43, 44], and decreased TE measurements have been observed with alcohol abstinence in the setting of alcoholic liver disease [45]. Finally, no liver biopsies were performed at the time of TE so we cannot validate these results against biopsy.

**CONCLUSIONS**

In summary, the majority of individuals with HIV-HBV co-infection on HBV-active ART in this cohort had mild to moderate fibrosis at the time of the first TE. Elevated ALT, reduced platelets, and higher HIV RNA were associated with advanced liver fibrosis, and the prevalence of advanced fibrosis (≥F3) decreased 12.3% (from 32.7% to 20.4%) over a median follow up of 31 months. Approximately 30% of those with >1 TE subsequently showed liver fibrosis regression, and higher baseline HBV DNA was associated with this regression. Although advanced fibrosis is not common in HIV-HBV coinfected patients on HBV-active cART, there is evidence of fibrosis regression in these individuals supporting the beneficial effects of long-term cART on liver stiffness.

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**Author contributions.** S. R. L., J. S., G. V. M., and J. A. participated in the development of the study protocol. C. R. performed data acquisition in Sydney. G. V. M. supervised data acquisition in Sydney. J. A. and C. R. performed the statistical analyses. S. A. performed data acquisition in Melbourne. J. A. and C. R. performed the original drafting of the manuscript. S. R. L. and J. S. supervised the analysis and drafting of the paper. All authors provided comment on the manuscript and approved the final manuscript.

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