

# Human immunodeficiency virus and hepatitis B or C co-infection in KwaZulu-Natal: a retrospective analysis of a laboratory database

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Hepatitis B or C virus infection has an important influence on treatment and outcomes in human immunodeficiency virus (HIV)-infected individuals. HIV worsens the prognosis in hepatitis B- or C virus-infected patients, and patients on antiretroviral therapy are more likely to experience hepatotoxicity if they are co-infected with a hepatotropic virus. There is a paucity of data on the epidemiology of hepatotropic viruses in relation to each other and to HIV in KwaZulu-Natal. The aim of this study was to describe the seroprevalence of hepatitis B and C virus in HIV-positive and -negative individuals in KwaZulu-Natal from 2002-2010, using a large laboratory database of routine serological results. Patients who had an HIV or hepatitis B or C test performed at the National Health Laboratory Service Department of Virology in Durban from 2002-2010 were included in the study. The study revealed that the overall seropositivity of hepatitis B surface antigen (HBsAg) was 12.05%, and that of hepatitis C immunoglobulin G (IgG), 4.13%. Individuals who were seropositive for HIV had 3.19-fold increased odds of being positive for HBsAg, 2.06-fold increased odds of being hepatitis B virus e antigen-positive, and 2.91-fold increased odds of being hepatitis C virus IgG-positive. Of those individuals who were tested for HBsAg and hepatitis C virus IgG (irrespective of HIV status), 15.76% were seropositive for both markers. HIV-positive individuals are at increased odds of having markers for hepatitis B and C infection.

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## Introduction

Viral hepatitis and human immunodeficiency virus (HIV) are both major public health challenges. Worldwide, 350 million people are infected with the hepatitis B virus, and 170 million with the hepatitis C virus.<sup>1</sup> Of the 34 million people infected with HIV, 3 million are co-infected with hepatitis B, and 7 million with hepatitis C.<sup>2</sup> Sub-Saharan Africa has the highest prevalence of HIV in the world, and the second highest prevalence of hepatitis B and C, second only to Asia.<sup>1,3</sup> This significant burden of infection is characterised by several epidemiological and virological features that represent challenges with regard to prevention and control.

Co-infection of hepatitis B virus or hepatitis C virus and HIV occurs owing to shared routes of transmission. Understanding co-infections is increasingly important as HIV-infected individuals are able to live longer because of increasing availability and access to antiretroviral therapy (ART). Consequently, hepatitis B virus- and hepatitis C virus-related

conditions are becoming more apparent over time.<sup>1,3</sup> The natural history of hepatitis B virus and hepatitis C virus is altered by HIV, with higher rates of persistence, faster disease progression, and a greater risk of chronic liver disease, hepatocellular carcinoma and death.<sup>1-3</sup>

Furthermore, the potential for drug interactions and side-effects is increased in co-infected individuals, and the immune restoration associated with ART can lead to increased liver damage and disease progression.<sup>1,3</sup> Certain antiretroviral drugs (ARVs) also have a dual effect on HIV and hepatitis B virus.<sup>1,3</sup>

The prevalence of co-infections is determined by the transmission patterns of hepatitis B and C virus, which differ in high- and low-income countries. As such, prevalence data from Western countries cannot be extrapolated to an African setting. Studies on the prevalence of HIV and hepatitis B and C virus co-infection in sub-Saharan Africa show a wide geographical variation in the findings, ranging from

3.9-70% for hepatitis B virus, and 0.0-22.2% for hepatitis C virus.<sup>1-5</sup> Several studies have highlighted the need for epidemiological data on HIV and hepatitis co-infections in South Africa.<sup>3-6</sup>

The aim of this study was to describe HIV and hepatitis B or C virus co-infection in KwaZulu-Natal, the province with the highest HIV prevalence in South Africa. This retrospective study used a database that contained nearly 500 000 serological results of specimens received from government health facilities throughout the province over a nine-year period. The rationale for using a large database was to avoid the bias usually associated with studies that document co-infections in specific high-risk patient cohorts. The results of this study may guide public health decisions on the approach to the diagnosis, treatment and prevention of hepatitis B or C virus in HIV-infected individuals, particularly in high HIV-prevalence regions.

## Method

### *Ethics and consent*

Ethical approval to conduct this study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Reference Number BE 038/11). Informed consent was not required as the data were anonymised and unlinked to patient identifiers.

### *Study design and setting*

This was an observational, retrospective study design which utilised the laboratory database at the Department of Virology of the National Health Laboratory Service (NHLS) in Durban.<sup>7</sup> This serves as the reference virology laboratory for the public sector in the province of KwaZulu-Natal. This laboratory receives the majority of specimens for viral assays in the region. There are 72 hospitals, 18 community health centres and 428 clinics in the KwaZulu-Natal public health sector.<sup>8</sup> Only 10-11% of the population has medical aid coverage and the rest rely primarily on state healthcare services. Therefore, approximately 90% of the population is served by the NHLS virology laboratory services.<sup>9</sup>

### *Data collection and definitions*

The Department of Virology laboratory database contains information on approximately 1.6 million routine clinical specimens, and approximately 5 million results that have been processed since 2002. Individuals who had received an HIV or a hepatitis B or C blood result on the database between January 2002 and December 2010 were included in this study (n = 507 834). The proportion of the study population that had a known HIV, hepatitis B and hepatitis C virus status was 52%, 51% and 15%, respectively.

The following procedure was used to ensure that only one result for a particular test was analysed for each individual.

Where individuals had more than one result for the same test, only one result was analysed, namely the first positive result where the individual tested positive at least once, and the first negative result, where the individual never tested positive.

The serological tests that had been performed during routine analysis included tests for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis C immunoglobulin G (IgG) and HIV. The attending healthcare provider chose the markers that were to be tested. Markers were selected based on clinical indications. HBsAb is usually tested after administration of the hepatitis B vaccination. HBeAg is tested only if the HBsAg is positive.

The serological assays were performed and interpreted as per the manufacturers' instructions, using commercial, fully automated kits and available instruments at the time. A specimen was regarded as positive for hepatitis B or C virus if the HBsAg or hepatitis C antibody were positive, respectively. A specimen was regarded as seropositive for HIV if two sequential, independent HIV enzyme-linked immunoassays performed on the same specimen were both positive, as per World Health Organization recommendations.<sup>10</sup>

### *Statistical analysis*

The hepatitis B and C virus results for each group (HIV-positive and HIV-negative) were totalled, and entered into a 2 × 2 table. The odds ratio (OR) and the 95% confidence intervals for the OR were then calculated. Differences in proportions were determined by the c-square test. Confidence intervals were calculated based on binomial distribution. Data capture, retrieval and analysis (totals of individual markers and serological profiles) were performed using Microsoft® Access® 2000 (Microsoft® Office®). SAS® 9.3 (SAS Institute, Cary, USA) was utilised for statistical analysis. A p-value of < 0.05 was regarded as significant.

## Results

The overall seropositivity of HBsAg was 12.05%, and that of hepatitis C virus IgG 4.13% (Table I). Males were more likely to be seropositive than females for both these markers [15.84% vs. 10.07% for HBsAg, and 4.54% vs. 3.92% for hepatitis C virus IgG]. The odds of having markers for hepatitis infection were increased in HIV-positive individuals (Table II). The odds of HIV-infected patients being positive for HBsAg, and being positive for the hepatitis C virus e antigen, were approximately three and two times more, respectively, than those without HIV (Table II). However, those with HIV were less likely to be positive for HBsAb (OR 0.36) (Table II). Those with HIV infection had 2.9 times the odds of being hepatitis C virus IgG-positive, than those without HIV (Table II). Of those individuals who were tested for HBsAg and hepatitis C virus IgG, 15.76% were seropositive for both markers (see Table III).

**Table I: The seropositivity of hepatitis B and C markers**

| Virus                 | Number of individuals (n) | Seropositivity | 95% CI      |
|-----------------------|---------------------------|----------------|-------------|
| HBsAg                 | 266 306                   | 12.05          | 11.92-12.17 |
| Hepatitis C virus IgG | 79 216                    | 4.13           | 3.99-4.27   |

CI: confidence interval, HBsAg: hepatitis B surface antigen, IgG: immunoglobulin G

**Table II: A comparison of hepatitis markers between human immunodeficiency virus-negative and human immunodeficiency virus-positive individuals**

| Hepatitis marker      | n      | Seropositivity in HIV-negative individuals* n (%) | Seropositivity in HIV-positive individuals* n (%) | OR (95% CI)      | p-value |
|-----------------------|--------|---|---|------------------|---------|
| HBsAg                 | 54 097 | 1 341 (3.40)                                      | 1 484 (10.10)                                     | 3.19 (2.95-3.44) | 0.0001  |
| HBsAb                 | 7 148  | 4 662 (72.96)                                     | 375 (49.47)                                       | 0.36 (0.31-0.42) | 0.0001  |
| HBeAg                 | 3 055  | 397 (25.16)                                       | 604 (40.89)                                       | 2.06 (1.76-2.40) | 0.0001  |
| Hepatitis C virus IgG | 17 838 | 266 (1.81)  | 174 (5.08)  | 2.91 (2.40-3.53) | 0.0001  |

CI: confidence interval, HBeAg: hepatitis B e antigen, HBsAb: hepatitis B surface antibody, HBsAg: hepatitis B surface antigen, HIV: human immunodeficiency virus, IgG: immunoglobulin G, OR: odds ratio

\*: Only in individuals who were tested for the respective hepatitis markers

**Table III: Hepatitis B and C co-infection, irrespective of human immunodeficiency virus status**

| Virus                      | HBsAg seropositivity n (%) | p-value                | OR (95% CI)      |
|----------------------------|----------------------------|------------------------|------------------|
| Hepatitis C virus-negative | 7 772 (11.91)              | 0.0001<br>(n = 68 308) | 1.38 (1.25-1.53) |
| Hepatitis C virus-positive | 484 (15.76)                |                        |                  |

CI: confidence interval, HBsAg: hepatitis B surface antigen, OR: odds ratio

## Discussion

This study has demonstrated the increased prevalence of hepatitis B and C virus co-infection in HIV-infected individuals. The prevalence of HBsAg and hepatitis C virus in HIV-infected individuals, was 10.10% and 5.08%, respectively. Individuals with HIV have considerably increased odds of being HBsAg-positive (OR 3.19) and hepatitis C virus-positive (OR 2.91). HIV-infected individuals are twice as likely to have evidence of active replication of hepatitis B virus, i.e. of being HBeAg-positive.

This study utilised approximately 500 000 results from across the KwaZulu-Natal province over a nine-year period. The prevalence described here is similar to the results from a systemic review by Barth, Huijgen, Taljaard and Hoepelman<sup>1</sup> of 60 studies conducted in sub-Saharan Africa, which reported a median prevalence of HBsAg [12.1% (3.9-70.3%)] and hepatitis C virus [4.8% (0.0-22.2%)], respectively, in HIV-infected individuals. The risk ratio (RR) for having a positive HBsAg in those with HIV, compared to those who were HIV-negative, was 1.40 (95% CI: 1.16-1.69). Similarly, the RR for hepatitis C virus was 1.60 (95% CI: 1.05-2.45).<sup>1</sup> In contrast to the findings described in this study, studies

of co-infection in smaller cohorts, and in urban or rural settings in particular, have shown differing prevalences. Lower hepatitis B virus prevalences of 6% and 4.8% were described by Lodenyo et al,<sup>11</sup> and Di Bisceglie,<sup>5</sup> respectively. These differences could be attributed to the small cohort of HIV-infected patients enrolled in an urban hospital setting, i.e. 100 and 502 patients, respectively.<sup>5,11</sup> Higher hepatitis B virus prevalence was reported in a retrospective, laboratory-

based, case control study by Mphahlele et al,<sup>12</sup> who found that 16.2% of HIV-positive patients were co-infected with hepatitis B virus. An even higher prevalence of 20% was shown in a retrospective cohort of male patients from the mining sector.<sup>13</sup> There is a large geographical variation in the findings of different settings. A rural Eastern Cape cohort estimated a hepatitis B virus prevalence of 7.1% in HIV-infected patients,<sup>14</sup> while Barth et al<sup>15</sup> described hepatitis B virus prevalence of 0.4%, and hepatitis C virus prevalence of 0.8%, in a rural cohort in Limpopo. There is also considerable variation among studies with regard to hepatitis C virus and HIV co-infection, i.e. 1% as described by Lodenyo,<sup>11</sup> 1.9% in a large multinational, randomised controlled trial<sup>13</sup> and 13.4% in a retrospective chart review of HIV-hepatitis C virus co-infected patients by Parboosing, Paruk and Lalloo.<sup>16</sup>

## Limitations

The serological assays were performed on specimens received from individuals who had clinical indications for these tests, and cannot be easily extrapolated to the general population. However, these specimens were received from a wide geographical distribution across the province, from all levels of public health facilities, and over a nine-year period. For this reason, generalisability of this study is probably greater than that of studies that used small cohorts in particular settings.

Because of the retrospective nature of this study, individuals were not followed-up to confirm that they were chronically infected with hepatitis B or C. Furthermore, this study represented an analysis of serological markers only, and the results of molecular tests, such as PCR, were not analysed for the purposes of confirming hepatitis C virus infection. The prevalence of hepatitis C virus may be inflated because of false positive serology.<sup>17</sup>

Despite these limitations, the results of this study are relevant to the management of HIV-infected individuals, who are at increased risk of hepatitis B and C infection. The findings of this study suggest that a significant number of HIV-infected individuals are likely to be co-infected with hepatitis B virus. The potential for drug interactions and side-effects is increased in co-infected individuals, while immune restoration associated with ART can lead to increased liver damage and disease progression, and some ARVs have a dual effect on HIV and hepatitis B virus. This study reinforces the need to screen for hepatitis B infection in those with HIV, as well as the need to vaccinate HIV-positive individuals who screen negative for hepatitis B, as recommended by the Southern African HIV Clinicians Society.<sup>18</sup>

## Conclusion

This retrospective laboratory database study of approximately 500 000 results, over a nine-year period, demonstrated that HIV-positive individuals were at increased odds of having markers for hepatitis B and C infection.

## Conflict of interest

The authors declare that they have no conflict of interest.

## Declarations

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