

# Prevalence of Hepatitis B and C among HIV Infected Patients in Nepal over 1990-2020

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## Citation

Shrestha DB, Budhathoki P, Sedhai YR, Shrestha LB, Awal S, Upadhaya Regmi B, et al. Prevalence of Hepatitis B and C among HIV Infected Patients in Nepal over 1990-2020. *Kathmandu Univ Med J.* 2021;73(1):132-9.

## ABSTRACT

### Background

Hepatitis B and C (HBV and HCV) are viral infections caused by corresponding viruses. Here in this study we planned to conduct this meta-analysis to pool data on the prevalence and risk factors of HBV and/or HCV among HIV patients in Nepal.

### Method

We used MOOSE guideline for the systemic review of available literature. We searched online databases using appropriate keywords. We used CMA-3 for data synthesis. Odds ratio, and proportion were used to estimate the outcome with a 95% confidence interval where appropriate. We assessed the heterogeneity using the I-squared ( $I^2$ ) test.

### Result

We included nine studies for our synthesis. Pooling of data showed HBV in 4.6% (CI: 3.7-5.6), HCV in 19.7% (CI: 10.8-33.0), both HBV and HCV in 1.3% (CI: 0.5-3.7) in HIV affected individuals. Among HBV co-infected HIV positive patients, 59.5% (CI: 25.5-86.3) were male; 76.1% (CI: 30.1-96.0) were married and 43.6% (CI: 3.8-93.8) had a history of intravenous drug use (IVDU). Among HCV co-infected HIV positive individuals 88.3% (CI: 73.6-95.4) were male; 63.6% (CI: 55.4-71.1) were married; 91.5% (CI: 68.6-98.1) were literate; 59.2% (CI: 49.9-67.9) were on ART; and 92.2% (95%CI: 84.9-96.1) had a history of IVDU.

### Conclusion

The pooled prevalence of co-infection with HBV, HCV, and combined HBV and HCV were 4.6%, 19.7% and 1.3% respectively among HIV positive patients. Thus, it is necessary to appropriately screen for HBV and HCV in individuals diagnosed with HIV and high-risk populations. IVDU remains the most common risk factor found in co-infected individuals.

## KEY WORDS

*Coinfection, Hepatitis B, Hepatitis C, HIV Infection, Intravenous, Substance abuse*

## INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is transmitted by contact with or transfer of blood, pre-ejaculate, semen, and vaginal fluids during sexual intercourse. Similarly, Hepatitis B and C are other blood borne diseases caused by Hepatitis B virus and Hepatitis C virus (HBV and HCV), respectively. There were 38 million people across the world infected with HIV/AIDS in 2019.<sup>1</sup> In Nepal, the prevalence of HIV is estimated to be around 0.13 in 2020 and 0.03 in young people aged 15-24 years.<sup>2</sup> According to WHO estimates in 2015, 257 million people were living with chronic hepatitis B infection (defined as hepatitis B surface antigen positive) which resulted in approximately 887,000 deaths, mostly from cirrhosis and hepatocellular carcinoma.<sup>3</sup> In Nepal, the prevalence of Hepatitis B was 0.9% in 1990.<sup>4</sup> However, there have been no studies done on a national level in recent times to estimate its prevalence. Hepatitis C is a liver disease caused by the Hepatitis C virus (HCV) and it can cause both acute and chronic hepatitis, varying in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Globally, an estimated 71 million people have chronic hepatitis C virus infection.<sup>5</sup> The global estimate of burden of HIV-HCV co-infection is 2.75 million of whom 1.3 million are people who inject drugs (PWID). Similarly, the global burden of HBV-HCV coinfection is 2.6 million.<sup>5</sup> The sero-prevalence of HCV in Nepal is estimated to be 0.6%.<sup>6</sup>

Because of similar routes of transmission, HIV-positive individuals are likely to become co-infected with HBV or HCV. These subset of co-infected individuals have worse prognosis as HIV tends to accelerate the course of hepatitis, with subsequent increased risk in liver-related morbidity and mortality.<sup>7</sup> As HIV/AIDS is being managed with antiretroviral therapy (ART), liver disease is becoming one of the most important causes of non-AIDS related death in this patient population.<sup>8</sup> Compounding this fact, treatment of HIV/AIDS with ARV is difficult in patients with HBV and HCV because of the possibility of hepatotoxicity of different ARTs.<sup>9</sup>

Although there are multiple studies focusing on the prevalence of HBV, HCV and HIV including their co-infections, these studies are usually limited to include population at risk or at a local geographic level. There is a lack of comprehensive data on the prevalence of HBV and/or HCV co-infection among HIV patients at a national level in low-to-middle-income countries (LMIC) like Nepal. So, we conducted our review on the title "Prevalence of Hepatitis B and C among HIV-infected patients in Nepal over 1990-2020: A Systematic Review and Meta-analysis". Using the available literature, we determined the prevalence and distribution of HBV and/or HCV among HIV patients.

## METHODS

We used Meta-analysis of Observational Studies in

Epidemiology (MOOSE) guidelines for the systemic review of available literature.<sup>10</sup> Protocol for present meta-analysis was registered in PROSPERO (ID: CRD42020215764).

We included all papers (cross-sectional studies, case series reporting more than 50 patients, cohort studies) mentioning prevalence of HBV and/or HCV among HIV patients and/or details of HBV and/or HCV among HIV patients such as ART status, IVDU etc. Editorials, commentary, viewpoint articles and studies with no proper data of HBV and/or HCV among HIV patients and lacking adequate data about risk factors were excluded.

The study included all the patients diagnosed with HIV in the study population.

We tried to measure prevalence and risk factors of HBV and/or HCV among HIV patients in Nepal over 1990-2020. We also tried to determine subgroup analysis of HBV and/or HCV among HIV patients based on risk factors.

Studies were independently screened by two reviewers using Covidence. The conflicts were resolved by taking the opinion of the third reviewer. Assessment of biases and cross checking of selected studies were done by another reviewer.

We have included the electronic search strategy in Supplementary file 1.

We searched databases like PubMed, PMC (MEDLINE), Scopus, Google Scholar and Embase using appropriate keywords and Boolean operators with no language restriction. We extracted the data onto a standardized form designed in Excel including the outcomes of our interest.

We evaluated the quality of studies and included the outcome in the quantitative synthesis.

We used Joanna Briggs Institute (JBI) critical appraisal tool to analyze the risk of bias in table 1.<sup>11</sup>

We assessed the heterogeneity using the I-squared ( $I^2$ ) test. We used the Cochrane Handbook for Systematic Reviews of Interventions for interpretation of  $I^2$  test done as follows based on "0-40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity."<sup>21</sup> The importance of the observed value of  $I^2$  depends on magnitude and direction of effects and strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for  $I^2$ ).

We used CMA-3 for data synthesis. Odds ratio, and proportion were used to estimate the outcome with a 95% confidence interval where appropriate.

## RESULTS

We screened a total of 1427 records after database searching. After removal of 178 duplicates, we screened

**Table 1. JBI Bias assessment**

JBI CHECKLIST(ROW) /Study (COLUMN)	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if NOT, was the low response rate managed appropriately?	Overall Appraisal
Barnawal et al. <sup>12</sup>	YES	UNCLEAR	YES	YES	YES	YES	YES	YES	YES	INCLUDE
Bhattarai et al. <sup>13</sup>	YES	YES	YES	YES	YES	YES	YES	YES	YES	INCLUDE
Ionita et al. <sup>14</sup>	YES	UNCLEAR	UNCLEAR	YES	YES	YES	YES	YES	YES	INCLUDE
Kakchapati et al. <sup>15</sup>	YES	YES	UNCLEAR	YES	YES	YES	YES	YES	YES	INCLUDE
Kinkel et al. <sup>16</sup>	YES	YES	YES	YES	YES	YES	YES	YES	YES	INCLUDE
Ojha et al. <sup>17</sup>	YES	UNCLEAR	UNCLEAR	YES	YES	YES	YES	YES	YES	INCLUDE
Poudel et al. <sup>18</sup>	YES	UNCLEAR	UNCLEAR	YES	YES	YES	YES	YES	YES	INCLUDE
Silverman et al. <sup>19</sup>	YES	YES	UNCLEAR	YES	YES	YES	YES	YES	YES	INCLUDE
Supram et al. <sup>20</sup>	YES	YES	YES	YES	YES	YES	YES	YES	YES	INCLUDE

**Table 2. Qualitative synthesis**

Study	Location	Study period	Study Design	Sample size	HBV + HIV	HCV + HIV	HBV and HCV Positive
Barnawal et al. <sup>12</sup>	Dharan and Kathmandu	April 2010-March 2011	Descriptive cross-sectional study	313	18/313	130/313	10/313
Bhattarai et al. <sup>13</sup>	National Public Health Laboratory, Kathmandu	January-December 2015	Retrospective study	579	21/579	17/579	-
Ionita et al. <sup>14</sup>	35 districts of Nepal	2010-2011	Cross-sectional study	677	30/677	132/677	7/677
Kakchapati et al. <sup>15</sup>	Kathmandu, Pokhara and Eastern Terai districts	2015	Cross-sectional survey	1045	-	42/65	-
Kinkel et al. <sup>16</sup>	Midwestern, eastern and central region of Nepal	2013-2014	Cross-sectional study	397	-	72/397	2/397
Ojha et al. <sup>17</sup>	Tekku, Kathmandu	November 2011 – May 2012	Cross-sectional study	105	-	14/105	-
Poudel et al. <sup>18</sup>	Kathmandu, Nepal	February – March 2010	Cross-sectional survey	319	-	138/319	-
Silverman et al. <sup>19</sup>	Maiti Nepal, Nepal		Cross-sectional study	66	6/66	-	-
Supram et al. <sup>20</sup>	Manipal Teaching Hospital, Pokhara	2008-2013	Retrospective study	218	7/218	9/218	-

the title and abstract of 1249 studies. A total of 1196 studies were excluded, and we assessed the full text eligibility of 53 studies (fig. 1). We included nine studies for our qualitative analysis after exclusion of 44 studies with definite reasons explained in Table 2. We included nine studies in our quantitative analysis.

#### Quantitative analysis

Total 9 studies were included in quantitative synthesis.

#### 4.1. Prevalence of Hepatitis B, Hepatitis C or Both Co-infection in HIV patients

##### A. HBV co-infection

We found 5 studies reporting HBsAg prevalence among 1853 HIV infected patients. Pooled data using fixed effect model showed HBV co-infection prevalence rate in HIV positive individuals to be 4.6% (95% CI: 3.7-5.6; I<sup>2</sup>:34.1) (fig. 2). Sensitivity analysis performed by excluding individual studies did not show significant differences (Supplementary file 2; fig. 1).

##### B. HCV co-infection

Pooling data using random effect model from 7 studies with 3653 patients reporting HCV co-infection in HIV positive individuals showed a prevalence rate of 19.7% (95% CI:

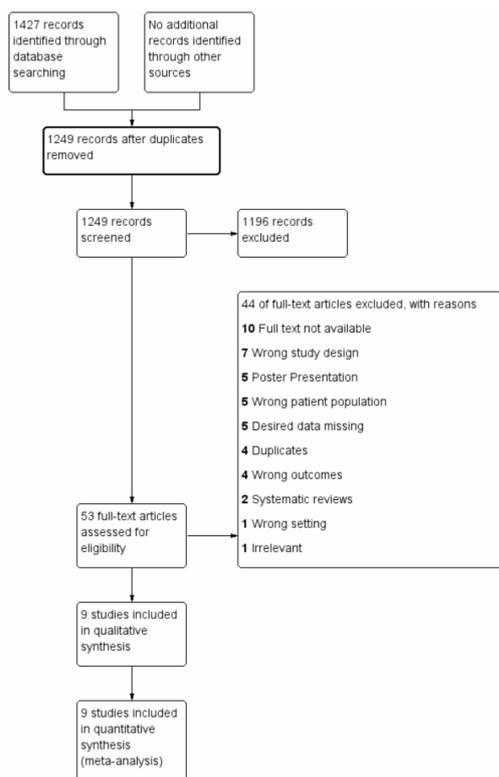


Figure 1. PRISMA Flow Diagram

10.8-33.0;  $I^2:97.6$ ) (fig. 3). Sensitivity analysis performed by excluding individual studies did not show significant differences (Supplementary file 2; fig. 2).

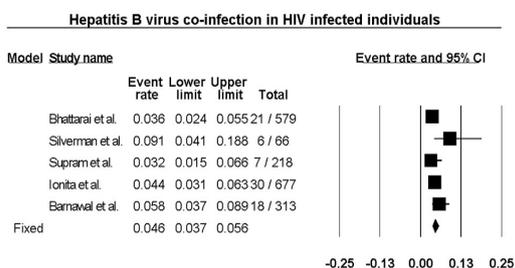


Figure 2. Prevalence of Hepatitis B co-infection among HIV positive individuals

C. Both HBV and HCV co-infection

Pooling data using random effect model from 3 studies reporting both HBV and HCV co-infection in HIV positive individuals showed a prevalence rate of 1.3% (95% CI: 0.5-3.7;  $I^2:77.2$ ) (fig. 4). Sensitivity analysis performed by excluding individual studies did not show significant differences (Supplementary file 2; fig. 3).

4.2. Distribution of HBV co-infection among HIV positive individuals

A. Gender distribution

Analysis on gender distribution of HBV co-infection among HIV positive individuals showed 40.5% (95% CI: 13.7-74.5;  $I^2: 77.6$ ) were female and 59.5% (95% CI: 25.5-86.3;  $I^2: 77.6$ ) were male (fig. 5).

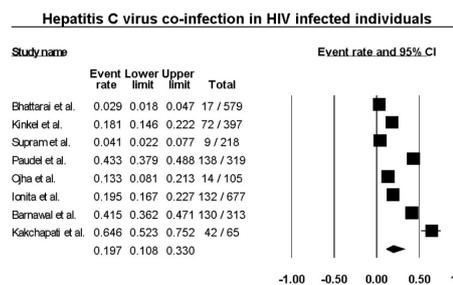


Figure 3. Prevalence of Hepatitis C co-infection among HIV positive individuals

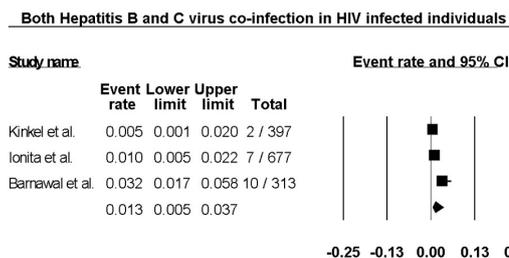


Figure 4. Prevalence of both HBV and HCV co-infection among HIV positive individuals

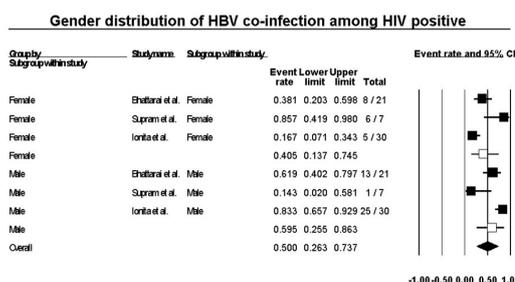


Figure 5. Gender distribution of HBV co-infection among HIV positive individuals

B. Marital status

Analysis on marital status of HBV co-infection among HIV positive individuals showed 76.1% (95% CI: 30.1-96.0;  $I^2: 52.7$ ) were married and 23.8% (95% CI: 4.0-69.9;  $I^2: 52.7$ ) were unmarried (fig. 6).

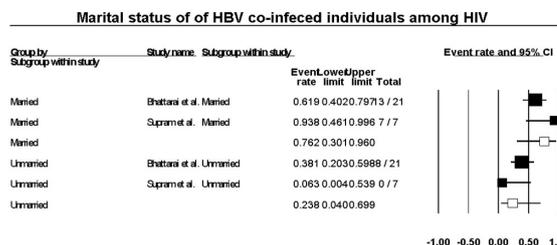


Figure 6. Marital status of HBV co-infection among HIV positive individuals

C. IVDU

Analysis on IVDU among HBV co-infected HIV-positive individuals showed 43.6% (95% CI: 3.8-93.8;  $I^2: 92.3$ ) had a history of IVDU (fig. 7).

4.3. Distribution of HCV co-infection among HIV positive individuals

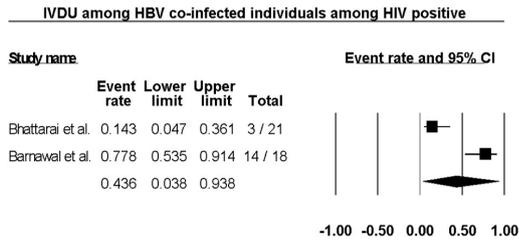


Figure 7. IVDU status of HBV co-infection among HIV positive individuals

A. Gender distribution

Analysis on gender distribution of HCV co-infection among HIV positive individuals showed 11.6% (95% CI: 4.6-26.4; I<sup>2</sup>: 77.3) were female and 88.3% (95%CI: 73.6-95.4; I<sup>2</sup>: 77.3) were male (fig. 8).

Gender distribution of HCV co-infection among HIV positive individuals

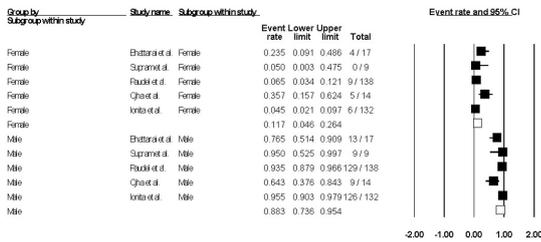


Figure 8. Gender distribution of HCV co-infection among HIV positive individuals

B. Marital status

Analysis on marital status of HCV co-infection among HIV positive individuals showed 63.6% (95% CI: 55.4-71.1; I<sup>2</sup>: 12.6) were married and 35.8% (95% CI: 25.9-47.1; I<sup>2</sup>: 37.4) were unmarried (fig. 9).

Marital status of Hepatitis C virus co-infected HIV patients

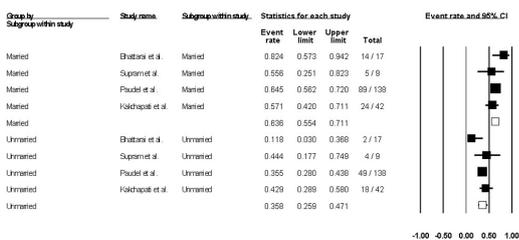


Figure 9. Marital status of HCV co-infection among HIV positive individuals

C. Literacy status

Analysis on literacy status of HCV co-infection among HIV positive individuals showed 91.5% (95% CI: 68.6-98.1; I<sup>2</sup>: 82.3) were literate and 8.5% (95% CI: 1.9-31.4; I<sup>2</sup>: 82.3) were illiterate (fig. 10).

D. ART status

Analysis on ART status of HCV co-infection among HIV positive individuals showed 40.8% (95% CI: 32.1-50.1; I<sup>2</sup>: 57.8) were not on ART and 59.2% (95% CI: 49.9-67.9; I<sup>2</sup>: 57.8) were on ART (fig. 11).

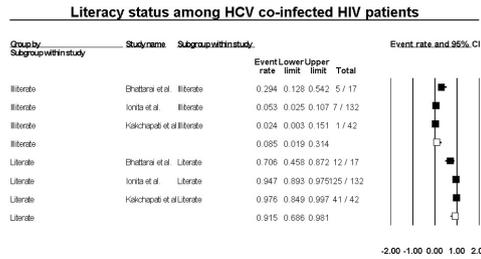


Figure 10. Literacy status of HCV co-infection among HIV positive individuals

ART status among HCV coinfecting HIV patients

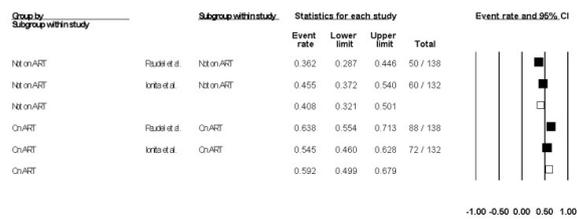


Figure 11. ART status of HCV co-infection among HIV positive individuals

E. IVDU status

Analysis on IVDU status of HCV co-infection among HIV positive individuals showed 92.2% (95% CI: 84.9-96.1; I<sup>2</sup>: 67.9) had a history of IVDU (fig. 12). Sensitivity analysis performed by excluding individual studies did not show significant differences (Supplementary file 2, fig. 4).

IVDU among HCV co-infected HIV patients

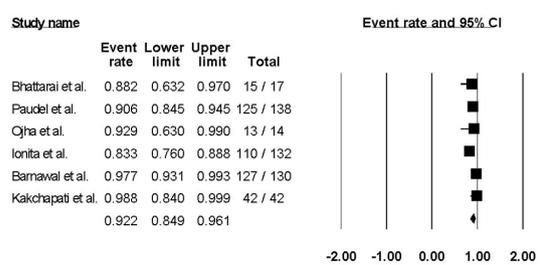


Figure 12. IVDU status of HCV co-infection among HIV-positive individual

DISCUSSION

As per our knowledge, this is the first systematic review and meta-analysis of the prevalence estimates of hepatitis B and hepatitis C co-infection in patients with HIV in Nepal. This study could help estimate the burden of HBV and HCV among HIV patients in Nepal, and the findings of this study could be used in public health interventions and policy making.

The hepatitis B prevalence estimates for the included studies ranged from the highest of 9.1% (95% CI: 4.1-18.8%) to the lowest of 3.2% (95% CI: 1.5-6.6%) among HIV patients. There are a total of 5 studies reporting HBsAg prevalence among 1853 HIV patients. The pooled HBV

prevalence was 4.6% (95% CI: 3.7-5.6%;  $I^2$ :34.1) among HIV positive patients.

The hepatitis C prevalence estimates for the included studies ranged from the highest of 64.6% (95% CI: 52.3-75.2%) to the lowest of 2.9% (95% CI: 1.8-4.7%) among HIV patients. There are a total of 8 studies reporting HCV prevalence among 3653 HIV patients. The pooled HCV prevalence was 19.7% (95% CI: 10.8-33.0;  $I^2$ :97.6) among HIV positive patients. The finding is in contrast to a global systematic review and meta-analysis conducted by Platt et al. who reported HIV-HCV co-infection in 2.4% (IQR 0.8-5.8) within the general population.<sup>22</sup> They also revealed that the odds of HCV infection were six times higher in people living with HIV (5.8, 95% CI 4.5-7.4) than their HIV-negative counterparts. The high prevalence of HCV in people with HIV might be due to overlapping modes of transmission, especially IVDU.

HIV infected individuals are also more likely to have HBV or HCV or both than the general population.<sup>23</sup> We discovered HBV and HCV co-infection in HIV affected individual from 3 studies which showed 1.3% (95% CI: 0.5-3.7;  $I^2$ :77.2) co-infection rate. The lowest prevalence was 0.5 % (95% CI: 0.1-2%) and the highest prevalence was 3.2% (95% CI: 1.7-5.8%). The pooled prevalence is much lower than two meta-analyses conducted in China (2.7% and 3.5%).<sup>24,25</sup> These viruses, despite differences in the nature and extent of transmission, are transmitted through unsafe IVDU, syringe sharing, repeated injections, high-risk sexual activity, mother-to-child transmission during pregnancy or birth, receiving contaminated blood and blood products, and the use of non-sterile medical equipment.<sup>26</sup>

Sharing of equipment used for IVDU causes substantial disease burden. Transmission via contaminated injection paraphernalia of blood-borne viruses, including HIV, HBV and HCV, is a leading contributor to morbidity and mortality as a consequence of IVDU.<sup>27</sup> In our study, we found that 43.6% (95% CI: 3.8-93.8;  $I^2$ : 92.3) of HIV-HBV co-infected patients and 92.2% (95% CI: 84.9-96.1;  $I^2$ : 67.9) of HIV-HCV co-infected persons had history of IVDU use. According to a meta-analysis, the prevalence of HBV among IVDU in HIV patients was 8% (95% CI: 5-13%), and that of HCV was 72% (95% CI: 59-83%).<sup>26</sup> A similar study conducted in Mozambique suggested that co-infections of HIV/HBV, HIV/HCV and HIV/HBV/HCV were identified in 13.1% (95% CI: 7.2-18.9), 29.5% (95% CI: 22.2-36.8) and 9.2% (95% CI: 3.7-14.7) of IVDU, respectively.<sup>28</sup> In a recent meta-analysis by Platt et al. the rate of HCV co-infection was reported to be 82.4% in IVDU with HIV.<sup>22</sup> Another study concluded that individuals with HIV and hepatitis C had a greater odds of injection drug use (adjusted odds ratio 9.7; 95% confidence interval 6.0-15.5).<sup>29</sup> A meta-analysis conducted among prisoners globally concluded that IVDU had 6 times the prevalence of HIV (pooled prevalence ratio (PPR) = 6.0, 95% CI: 3.8, 9.4), 8 times the prevalence of hepatitis C virus (PPR = 8.1, 95% CI: 6.4, 10.4), and 2 times the prevalence of

hepatitis B virus (PPR = 2.0, 95% CI: 1.5, 2.7) compared with non-injecting prisoner populations.<sup>30</sup> Globally it has been estimated that 17.8% (10.8-24.8) of IVDU are living with HIV, 52.3% (42.4-62.1) are HCV positive, and 9.1% (5.1-13.2) are HBV positive.<sup>31</sup> The increased risk of co-infection with HIV-HBV and HIV-HCV among IV drug users is alarming and highlights the need to spread awareness about various risks of drug abuse and focus in rehabilitation.

Gender distribution of HBV co-infection among HIV positive individuals showed 40.5% (95%CI: 13.7-74.5;  $I^2$ : 77.6) were female and 59.5% (95% CI: 25.5-86.3;  $I^2$ : 77.6) were male. Similarly, among HIV-HCV co-infection group, 11.6% (95% CI: 4.6-26.4;  $I^2$ : 77.3) were female and 88.3% (95% CI: 73.6-95.4;  $I^2$ : 77.3) were male. A Malaysian study observed that there is a high prevalence of HIV-HBV co-infection in males 76 (11.4%) as compared to females 10 (1.5%) ( $p = 0.002$ ).<sup>32</sup> Similarly, a meta-analysis conducted in Singapore also concluded that HIV-HBV co-infection was significantly higher in males as compared to females (8% vs 3.2%,  $p = 0.014$ ).<sup>33</sup> However, a study conducted in Nigeria concluded that the triple infection and both co-infections were preponderant among females than males.<sup>34</sup> A meta-analysis conducted in New York City revealed that 70-80% of HBV/HCV co-infection with HIV population were male.<sup>35</sup> The male predominance in both HBV and HCV might be attributed to the fact that males are more involved in high-risk behavior like IVDU.<sup>32,33</sup> The analysis on marital status of HIV-HBV and HIV-HCV co-infected population showed that a high prevalence of infection is seen in married population as compared to unmarried.

The determination of co-infection of HBV and HCV among HIV patients is important given the increased complications and the effect on treatment on patients with co-infections. People with triple infections have worse virological response than infection with HIV alone, and greater risks of disseminating their disease to other high-risk population.<sup>36,37</sup> Therefore, knowledge about possible co-infection is important for any clinician in deciding potential treatment and predicting prognosis. Because these viral infections share common modes of transmission, targeted approaches to reduce IVDU, unprotected sexual intercourse, and so on would help curb all of them. The concerned authorities should focus on the high-risk population and push for routine screening as well as programs to increase awareness about potential hazards of IVDU, unprotected sexual contact with multiple partners, receiving contaminated blood through blood transfusions, and so on as well as extension of needle exchange programs (NEP).

Our study is the first to pool the prevalence of co-infection of HBV, HCV and HIV. We included nine studies in Nepal among high risk populations. However, most of these studies were conducted in the narrow geographical location and among the high-risk population. Hence, it may be difficult to generalize the findings of our study across the

entire population. Another limitation was the presence of high heterogeneity due to difference in individual studies and their patient population. Still, our findings of high rates of co-infection of HIV, HCV and HBV among IV drug users are significant.

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## CONCLUSION

The pooled prevalence of HBV, HCV, and HBV+HCV infections were 4.6%, 19.7% and 1.3% respectively among HIV positive patients. It is, therefore, necessary to screen for HBV and HCV co-infection in people diagnosed with HIV and high-risk populations. IVDU remains the most reported risk factor among all the risk factors for co-infections with HBV and HCV in patients with HIV. The findings of the review would shed light on future policy measures to control the spread of these infections.

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