Burden of Tuberculosis and Hepatitis Coinfection among People Living with HIV in Nepal: A Systematic Review and Meta-analysis

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Running Head: TB and Hepatitis Coinfection in PLHIV in Nepal

Abstract

People living with HIV (PLHIV) are prone to tuberculosis (TB) and hepatitis coinfections which cause substantial burden on morbidity and mortality. However, data on the burden of HIV coinfection from a specific low- and middle-income country are limited. To address this gap in evidence, a meta-analysis of published literature and country surveillance report was conducted to estimate the burden of TB, hepatitis B (HBV) and hepatitis C (HCV) co-infection among PLHIV in Nepal. Twenty-three studies including 5,900 PLHIV were included in the meta-analysis. The pooled prevalence of HIV-TB, HIV-HBV and HIV-HCV co-infection was 19% (95% CI, 10-28%), 3% (2-5%) and 19% (4-33%) respectively. Low CD4 cell count (pooled odds ratio [OR] 4.38, 95% CI 1.11-17.25), smoking (3.07, 1.48-6.37) and alcohol drinking (3.12, 1.52-6.43) were significantly correlated with HIV-TB coinfection. The odds of HCV coinfection was greater in PLHIV, who were male (5.39, 1.54-18.89) and drug users (166.26, 15.94-1734.44). PLHIV who were on antiretroviral therapy had a reduced risk of HCV coinfection (0.49, 0.36-0.66) than the genal PLHIV population. The burden of TB and hepatitis coinfection among PLHIV in Nepal was high. Regular screening of PLHIV for coinfections and prompt initiation of treatment are essential to reduce the transmission of infection and improve quality of life.

Keywords: HIV; coinfection; prevalence; systematic review; meta-analysis; Nepal

Introduction

Human Immunodeficiency Virus (HIV) continues to be a significant global public health issue, with an estimated 38 million people living with HIV (PLHIV) in 2019 (1). In recent years, due to the improved effectiveness of and increased access to antiretroviral therapy (ART), PLHIV are living longer and healthy lives than ever before (2, 3). Despite such progress and global attempts to implement treatment-as-prevention programmes every year (4), a significant proportion of PLHIV continues to die from HIV-related coinfections (5). Tuberculosis (TB) remains the most common opportunistic disease and cause of premature death among HIV infected individuals, with an estimated 208,000 deaths globally in 2019 (6, 7). Since HIV weakens the immune system, PLHIV are at least 20 times more likely to develop TB than people without HIV (8). Among HIV infected individuals, hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfections are not uncommon due to the shared risk of transmission. The global prevalence rates of HCV and HBV coinfections among PLHIV are estimated to be 2.4% and 7.6% respectively (9, 10), however this may still be underestimated (11).

Although considerable progress in addressing HIV-TB, HIV-HBV and HIV-HCV coinfections have been made by developed nations, the majority of the low- and middle-income countries (LMICs) have not achieved the global targets. LMICs are still facing an overwhelming burden of the HIV epidemic in terms of an increasing number of people living with HIV/AIDS, attributed in part to minimal access to treatment and services availability (12, 13).

In 2019, the prevalence of HIV was estimated at over 29,000 in Nepal, with a concentrated epidemic in specific sub-populations; people who inject drugs (PWID), men who have sex with men, transgender people, male- and female sex workers, and male labour migrants as well as their spouses (14). In 2017, Nepal's national HIV programme implemented the "test and treat" policy which provided ART to all PLHIV regardless of the CD4 counts. In line with the World Health Organization's recommendations, all patients with advanced HIV disease in Nepal are offered a package of interventions including screening, treatment and/or prophylaxis

for major opportunistic infections, ART and adherence support. Following the national HIV testing and treatment guideline (15), PLHIV with TB are immediately treated for TB, followed by ART as soon as possible. Among PLHIV with HCV, treating both HIV and HCV infections is a priority. However, clinical stabilisation of HIV with ART is advisable before initiating HCV treatment among those with HCV mono-infection. The national treatment protocol recommends treatment of HIV/HBV coinfection with tenofovir disoproxil fumarate (TDF) with lamivudine (3TC) or emtricitabine (FTC).

The second edition of Nepal's National HIV Strategic Plan (NHSP) 2016-2021 is entirely aligned with the global commitment of test and treat approach 90-90-90. Subsequently, in line with national commitment and NHSP, Nepal has made substantial progress in reducing HIV, TB and hepatitis infection as part of the Sustainable Development Goals in recent years (16). Despite these significant signs of progress, the global target of 90-90-90 is still far from being achieved since infections with TB, HBV and HCV are now emerging as an increasing cause of morbidity and mortality in HIV infected persons, more specifically in resource-limited settings like Nepal. Tuberculosis is one of the leading causes of death among PLHIV in Nepal, accounting for 23% of total HIV-related deaths in 2020 (17). Likewise, HCV, along with HBV, is considered a growing public health problem in the South-East Asia region (18), and Nepal is not an exception; where in 2016, around 130,000 individuals were infected by HCV (19). The convergence of these infectious diseases poses a significant burden to public health and healthcare systems, particularly in a low-resource nation like Nepal.

Furthermore, there is a need to establish a comprehensive understanding of the national burden of TB and hepatitis coinfection among PLHIV and inform national screening programmes and clinical management. Therefore, we undertook this review to provide an overall prevalence of HIV-TB, HIV-HBV and HIV-HCV coinfections and associated risk factors in Nepal.

Methods

This review was conducted and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure the search process's quality and adequate reporting (20).

Data Sources and Searches

We searched for articles published from inception to November 2020 using the electronic database PubMed, EMBASE, AMED, MEDLINE (Ovid), Cochrane CENTRAL, PsychINFO, and Nepal Journal Online (NepJOL). After reviewing the titles and abstracts, the reference list of included studies was examined manually to identify further eligible studies. Additionally, free text searching was performed using Google scholar. The search comprised of a combination of keywords HIV ('human immunodeficiency virus', or 'HIV'), coinfection ('tuberculosis', 'TB', 'hepatitis B', 'HBV', 'hepatitis C', 'HCV', 'coinfection', or 'opportunistic infection') and 'Nepal' (see Appendix A for detailed search strategy).

Study Selection

Following the database search and removal of duplicate records, three authors independently screened titles and abstracts for inclusion. We included observational studies that reported estimates of (or sufficient information to derive) the prevalence of tuberculosis or hepatitis B or/ and hepatitis C among HIV positive individuals. Included studies were limited to primary research reports and those conducted in Nepal. We excluded studies that (i) purposively selected PLHIV with TB or hepatitis coinfection; (ii) did not report TB or hepatitis seroprevalence; (iii) did not mention the TB, HBV or HCV diagnostic assays used; or (iii) were conferences reports, research letters, editorials, or commentaries.

A positive TB case was defined by a positive result of Acid-Fast Bacillus (AFB) stained smear or clinical or radiological traits (chest X-ray) suggestive of TB. HBV infection was defined by a positive result of HBV infection markers: hepatitis B surface antigen (HBsAg), hepatitis B e

antigen (HBeAg), anti-hepatitis B surface antibody (HBsAb), and anti-hepatitis B core antibody (HBcAb) as confirmed by ELISA or enzyme immunoassay (EIA). HCV infection was defined by a positive result of the anti-HCV Ab test and confirmed by ELISA or EIA.

Studies identified as potentially eligible or those without an abstract had their full text retrieved, and full texts of the studies were assessed by two reviewers independently. Any discrepancies were resolved through discussion and in consultation with a third reviewer. In some cases, one study resulted in multiple publications. In such a case, we included the most recently published paper with the complete data.

Assessment of Methodological Quality

The methodological quality of included studies was assessed using an adapted version of the risk of bias tool for prevalence studies, developed by Hoy et al. (21) independently by two reviewers. This tool was based on ten criteria, and each criterion was worth 1 point; for each item, score 1 indicates low risk, and score 0 shows high risk. Based on the number of Hoy et al. criteria met, studies were categorised into high (0-5), moderate (6-8) or low (9-10) risk of methodological bias (see Appendix B, Table S1). A third reviewer compared the assessment and highlighted the disagreements between two reviewers, which were resolved through discussion between the three reviewers. All studies, regardless of their methodological quality, were included. Nineteen studies had a moderate risk of bias (score of 6-8), and four studies had a low risk of bias (score of 9-10).

Data Extraction

Using a standardised pro forma, two reviewers extracted data from the included studies. A third reviewer checked the data extraction and highlighted the disagreement between the two reviewers. Any such discrepancies were resolved through discussion between the three reviewers. Data extraction included details of the study such as the first author's name, the year of publication, information on study type, population sampled, study period, sample size,

type of coinfection (TB, HBV or HCV), outcome (prevalence rate), study results for the outcomes of interest (adjusted or unadjusted odds ratios [ORs], raw data) along with associated risk factors of coinfection (s). We chose to use unadjusted ORs preferentially if these data were available.

Data Synthesis and Statistical Analysis

We used a random-effects model to estimate pooled prevalence rate with 95% confidence intervals (CIs) (22). The Mantel-Haenszel random-effects model was used to estimate the summary odds ratio and 95 % CIs from the included studies. I^2 statistics of >50% and Q chi-squared test ≤0.10 were employed to assess the heterogeneity between the studies. The effect sizes of risk factors composed of heterogeneous studies were calculated using the random-effects model. The effect sizes of non-heterogeneous studies were estimated using the fixed-effects model (23). At least two eligible studies per risk factor were needed for the risk factor meta-analysis.

Estimations of publication bias were examined by Egger's weighted regression method and funnel plot.(24) Asymmetry of funnel plot and a p-value of less than 0.05 was considered indicative of statistically significant publication bias. All analyses were performed with the *meta package* (25) of R statistical software version 4.0.2 (26). Prevalence rates were reported with the corresponding 95% CI. We performed sensitivity analyses comparing the data from studies with the methodological quality score to assess the robustness of crude findings. Forest plots were used to assess publication bias. Where a significant association was observed, sensitivity analysis was performed to assess the robustness of the result. For this at least two eligible studies were needed.

To estimate the burden, the number of TB, HBV and HCV infections in PLHIV, we used the 2020 data from the UNAIDS (27) and the National Centre for AIDS and STD Control (NCASC) Nepal (17), which gives the number of PLHIV.

Results

Search Results

The literature search identified 868 potentially relevant records, with an additional 140 records identified through other sources. After removing the duplicates, 356 studies were screened by titles and abstracts and 103 full-text studies were reviewed, with 23 articles included (Figure 1).

Characteristics of Included Studies

Of the 23 studies, 11 reported TB, 11 were HBV and/or HCV, and one study reported both TB and HCV coinfection in PLHIV. The number of study participants ranged from 49 to 1807 (Table 1). One study included only male participants (28). The proportion of female participants in 22 studies ranged from 4.8% to 53.3%. Of the 23 studies, 20 were cross-sectional studies, and 3 were retrospective in design. There were 5,900 study participants; 3,404 with HIV-TB infection, 1,887 with HIV-HBV infection and 2,343 HIV-HCV infections (Table 1).

Prevalence of Coinfections in PLHIV

The prevalence of HIV-TB co-infection ranged from 5% (29, 30) to 35% (31), and pooled prevalence was 19% (95% CI: 10%- 28%) across 11 included studies. The pooled prevalence of HIV-HBV co-infection in 7 studies was 3% (95% CI: 2%-5%). The prevalence of HIV-HCV co-infection ranged between 2% (32) and 65% (28), and pooled prevalence was 19% (95% CI, 4%-33%). Heterogeneity between studies reporting the prevalence of HIV-TB (I^2=97%, p<0.01) and HIV-HCV co-infections (I^2=98%, p<0.01) was high. While low heterogeneity between studies reporting HIV-HBV co-infection (I^2=45%, p<0.1) was observed (Figure 2).

Estimates of National Cases of TB, HBV and HCV Infection in PLHIV

Using our pooled prevalence of TB, HBV and HCV infection in PLHIV and the data on the estimated number of PLHIV in Nepal from the UNAIDS and NCACS reports (17, 27), we estimated that there were 5,700 (95% CI, 3,000 – 8,400) cases of TB, 900 (95% CI, 600 – 1,500) cases of HBV and 5,700 (95% CI, 1,200 – 9,900) cases of HCV in Nepal.

Coinfection Risk Factors

We estimate the pooled OR to examine the association of risk factors with coinfections (Table 2). The risk factors that had a significant association with HIV-TB co-infection were a male gender (pooled OR 1.25, 95% CI:1.03-1.51), younger age (less than 30 years) (OR 0.58, 95% CI: 0.48-0.69), CD4 T-lymphocytes count less than 200 cells/μ (OR 4.38, 95% CI: 1.11-17.25), smoker (OR 3.07, 95% CI: 1.48-6.37) and alcohol drinker (OR 3.12, 95% CI: 1.52-6.43).

However, the male gender was not significantly associated with the HIV-HBV coinfection (OR 0.88, 95% CI: 0.11-7.17). The risk factors that had a significant association with HCV coinfection were male gender (OR 5.39, 95% CI: 1.54-18.89), people who inject drug (OR 166.26, 95% CI: 15.94-1734.44) and taking antiretroviral therapy (OR 0.49, 95% CI: 0.36-0.66). We observed greater heterogeneity in some risk factors for HBV and HCV coinfection (Table 2).

Evaluation of Publication Bias

We generated funnel plots to assess publication bias of the prevalence rate. For the overall prevalence of HIV-TB and HIV-HBV prevalence rates, the asymmetry observed in the funnel plot was minimal (See Appendix C, Figure S1). We also assessed funnel plot asymmetry using the Egger's linear regression test. Looking at the funnel plot of HIV-TB prevalence (Figure S1), there was a slight evidence of publication bias in terms of smaller studies with minor effect sizes missing at the bottom left corner. Furthermore, Egger's regression test for publication bias for HIV-TB was nonsignificant (z=-0.9612, p=0.827) indicating no evidence of publication

bias. No publication bias was obverted in the prevalence estimates for HIV-HBV (z=1.111, p=0.402). However, publication bias was observed in the estimates of HIV-HCV prevalence rates (z=7.572, p=0.029).

Sensitivity Analyses

We performed sensitivity analyses of the coinfection prevalence rates by applying a fixed-effects model, and we found similar prevalence rates between random-effects and fixed-effect models in the overall analysis. We also assessed the prevalence rates by methodological quality. Among the 19 studies with moderate risk of bias (score of 6-8), the pooled prevalence rate of HIV-TB coinfection (22%, 95% CI: 12%-32%) was higher, and the prevalence rate of HIV-HCV was low (13%, 95% CI: 2%-24%). However, the HIV-HBV prevalence rate was similar (3%, 95% CI: 1%-5%). The remaining 4 studies (28, 33-35) with a low risk of methodological bias (score >8), had a higher prevalence rate of HIV-HCV (42%, 95% CI: 0%-100%), lower rate of HIV-TB (7%, 95% CI: 0%-21%), and similar rates for HIV-HBV (4%, 95% CI: 3%-6%) co-infection (see Appendix C, Figure S2-S4).

Discussion

Overall, our analysis revealed that the prevalence of HIV-HCV coinfection was more frequent than but not significantly different from HIV-TB and HIV-HBV coinfection, suggesting that HIV patients appeared to be at greater risk for both HCV and TB infection in Nepal. The prevalence of HIV-TB coinfection (19%) was considerably higher than the 2018 Nepal TB HIV Sentinel Survey finding, i.e. 9.9% (36). Likewise, our estimates of HIV-HCV prevalence (19%) was higher than the WHO estimates for Nepal (2-15%) (37) and was about five times higher than the HIV-HCV prevalence reported in other South Asian countries (38). The studies included in this review were primarily conducted in the (tertiary) hospitals, partly explaining the higher prevalence rates. However, the pooled prevalence of HBV infection among PLHIV (3%, 95% CI 2-5%) is significantly lower than the prevalence rate (8.4%) reported by Leumi et al.(39) in the WHO Southeast Asia region.

Our findings of the significant risk factor of HIV-TB coinfection (being a male, younger adult, CD4 value of <200, tobacco smokers, and alcohol drinkers) and HIV-HCV corroborate previously published evidence that low CD4 cell count and PWID are significantly associated with the development and severity of TB (40, 41) and HCV (10) respectively. The odds of HCV coinfection among PWIDs were higher (175, 50-611) than Platt et al.'s (10) study. In their global systematic review, Platt et al. reported lower odds (6.0, 95% CI 4.2-8.7) of HIV-HCV coinfection among PWID. This considerable variation is likely to be due to the small number of studies included in our analysis. The shared transmission routes of both HIV and HCV viruses, unsafe injecting behaviours, larger numbers of injecting partners are believed to be the most common factors that place PWIDs at such an immense risk for HCV transmission (42).

We found that the odds of HCV coinfection decreased almost half for those PLHIV on ART, suggesting ART could be beneficial to lower the threat posed by HCV among PLHIV. However, for that to happen, ART has to be started before HCV coinfection since existing coinfection can complicate ART delivery by increasing the risk of drug-induced hepatoxicity and thus influencing the selection of drugs acting dually against HIV and HCV infection (43). Substance use such as drugs, alcohol consumption and cigarette smoking were associated with TB infection among PLHIV, consistent with previous studies conducted in Ethiopia and South India (44, 45). In line with previous studies (46-48), in our study, the male gender was a significant determinant of HIV-TB and HIV-Hepatitis C infection relative to females. Surprisingly, we found a higher prevalence of HBV infection in females than in the general PLHIV population, which contradicts the previously reported study (49).

To the best of our knowledge, this was the first systematic review and meta-analysis to synthesise the existing evidence on the prevalence and risk factors of TB and Hepatitis (HBV or HCV) coinfection among HIV-infected people in Nepal. Key strengths of our review are the comprehensive search of published literature, including the NEPJOL, and the inclusion of common coinfections in PLHIV. Despite this, some limitations do exist in our study. The main

limitation of this study was the considerable heterogeneity in the studies in terms of study design, population sampling approach and data collection methods. The quality of studies was also variable, and most studies were of moderate to high risk of bias. Second, due to limited studies, the effect sizes could not be calculated for all risk factors, and the pooled ORs had wide CIs. We only included risk factors that are reported in two or more studies. Further, well-designed population-based studies examining HIV and coinfections would provide better estimates in order to delineate the additive burden, contribution on mortality, early diagnosis and management. Nevertheless, reporting the burden of TB, HBV and HCV coinfection among PLHIV in Nepal is critical in developing strategies to overcome the overall burden posed by HIV.

In this meta-analysis, we found relatively higher TB and HCV infections among PLHIV in Nepal. Preventive interventions such as risk-stratified screening, testing and treating and behavioural interventions are needed for TB and hepatitis control efforts. Besides, strengthening health systems to promote regular ART and integrating TB, hepatitis and HIV prevention, diagnosis and treatment services at a single site would help reduce the burden of TB and hepatitis infection among PLHIV and improve quality of life.

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Figure Legend

Figure 1. Flow chart of included studies

Figure 2: The pooled prevalence (proportion) of TB, HBV and HCV co-infection among PLHIV. Black Diamond: pooled prevalence.

480 **Table 1. Characteristics of studies included in the meta-analysis**

Author, year	Setting	Study design and target population	Sample size (n)	Female participants, n (%)	Mean age (years)	Prevalence of Coinfection, n (%)			Quality score[(a)]
						TB	HBV	HCV	
Ghimire et al. (31)	Hospital	Cross-sectional; OPD attending patients suspected of TB/HIV	81	18 (22.2)	—, range 11-80 years	28 (35%)			Moderate
Dhungana et al. (50)	Hospital and HIV/AIDS care centres	Cross-sectional; HIV infected people	100	34 (34.0)	31, range 11-60	23 (23%)			Moderate
Ghimire et al. (51)	Blood transfusion centre	Cross-sectional; blood donors who tested HIV positive	49	—	—, range 18-60 years		4 (8%)		Moderate
Karki et al. (52)	Blood transfusion centre	Cross-sectional; blood donors who tested HIV positive	65	7 (10.7)	—, range 18-60			7 (11%)	Moderate
Sharma et al. (53)	Hospital and HIV/AIDS care centres	Cross-sectional; PLHIV	150	50 (33.3)	26.2, range 1-60	15 (10%)			Moderate
Poudel et al. (54)	Hospital	Cross-sectional, PLHIV	66	30 (45.5)	—, range 11-60	18 (27%)			Moderate
Verma et al. (29)	HIV care centres	Cross-sectional, HIV infected drug users	62	3 (4.8)	—, range 11-50	3 (5%)			Moderate
Dhungana et al. (33)	Hospital and HIV/AIDS care centres	Cross-sectional, HIV infected people	394	169 (42.9)	—, range 1-60	32 (8%)			Low
Tiwari et al. (55)	Hospital (NPHL)	Cross-sectional, HIV infected people	1807	616 (34.1)	—, median 30	585 (32%)			Moderate
Verma et al. (34)	HIV care canters	Cross-sectional, HIV infected people	184	74 (40.2)	—, range 1-60	11 (6%)			Low
Ojha et al. (56)	Hospital (NPHL)	Cross-sectional, HIV infected people	105	40 (38.1)	—, nr			14 (13%)	Moderate
Bohara (30)	Hospital	Cross-sectional, HIV infected people visiting ART clinic	103	57 (53.3)	—, range 1-60	5 (5%)			Moderate
Poudyal et al. (57)	Hospital	Cross-sectional, PLHIV attending microbiology lab for CD4 cell counting	336	56 (16.7)	34.2	72 (21%)			Moderate
Bista et al. (58)	Hospital	Retrospective, OPD and IPD patients undergoing screening for	165	35 (21.2)	—		2 (1%)	29 (18%)	Moderate

Author, year	Setting	Study design and target population	Sample size (n)	Female participants, n (%)	Mean age (years)	Prevalence of Coinfection, n (%)			Quality score[(a)]
						TB	HBV	HCV	
		HbsAg, anti-HCV and anti-HIV antibody							
Paudel et al. (59)	Kathmandu valley	Cross-sectional, PLHIV	319	136 (42.6)	35.6, range 20-60			138 (43%)	Moderate
Khushbu et al. (60)	Hospital	Cross-sectional, confirmed HIV/AIDS patients with/without respiratory symptoms	121	35 (28.9)	—	48 (40%)			Moderate
Supram et al. (61)	Hospital	Retrospective; Patients screened for HIV for those undergoing surgery	218	85 (39.0)	—, nr		7 (3%)	9 (4%)	Moderate
Baral et al. (62)	Hospital	Cross-sectional; Patient attending hospital for HIV test	104	35 (33.7)	—, range 0-70		6 (6%)		Moderate
Bhusal et al. (63)	Hospital	Cross-sectional; PLHIV visiting OPD and medical IPD	55	17 (30.9)	35.85			6 (11%)	Moderate
Ionita et al. (35)	ART treatment centres	Cross-sectional; PLHIV undergoing ART therapy	677	330 (48.7)	—, nr		30 (4%)	132 (19%)	Low
Kakchapati et al. (28)	Community (major cities)	Cross-sectional, Male IDUs who tested HIV positive	65	0 (0)	—, nr			42 (65%)	Low
Mahato et al. (32)	Hospital	Cross-sectional; OPD patients screened for HIV and co-infections	95	35 (36.8)	28.94, range 2-89		3 (3%)	2 (2%)	Moderate
Bhattarai et al. (64)	Hospital	Retrospective, PLHIV	579	159 (27.5)	39.13		21 (4%)	17 (3%)	Moderate

AIDS: acquired immune deficiency syndrome; ART: antiretroviral therapy; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IDU: injecting drug user; IPD: inpatient department; nr: not reported OPD: outpatient department; PLHIV: people living with HIV; TB: tuberculosis.

(a) Quality assessment checklist for prevalence studies (adapted from Hoy et al. (21)) was used.

483 **Table 2: The effect size of risk factors for HIV co-infections**

Coinfection	Risk factors	n	Odds ratio (95% CI)	Heterogeneity test				Analysed model
				tau^2	Q (df)	p	I^2 (%)	
Tuberculosis	Male gender	8	1.25 (1.03-1.51)	0.000	3.84 (7)	0.798	0.0	Fixed
	CD4 cell count <200	5	4.38 (1.11-17.25)	0.950	86.03 (4)	<0.0001	95.4	Random
	Younger age	8	0.58 (0.48-0.69)	0.000	6.72 (7)	0.458	0.0	Fixed
	ART therapy	2	1.25 (0.40-3.94)	0.000	0.66 (1)	0.417	0.0	Fixed
	PWID	2	1.18 (0.98-1.42)	0.000	0.24 (1)	0.624	0.0	Fixed
	Smoker	3	3.07 (1.48-6.37)	0.000	1.03 (2)	0.598	0.0	Fixed
	Alcoholic	3	3.12 (1.52-6.43)	0.000	0.32 (2)	0.852	0.0	Fixed
Hepatitis B	Male gender	5	0.88 (0.11-7.17)	1.890	17.54 (4)	0.002	77.2	Random
Hepatitis C	Male gender	8	5.39 (1.54-18.89)	1.524	48.92 (7)	<0.0001	85.7	Random
	ART therapy	2	0.49 (0.36-0.66)	0.000	0.29 (1)	0.588	0.0	Fixed
	PWID	3	166.26 (15.94-1734.44)	0.527	7.12 (2)	0.029	71.9	Random

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