Prevalence of hepatitis B and C in HIV-infected patients: a meta-analysis

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BACKGROUND: **Hepatitis C virus (HCV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV) share similar routes of transmission by sexual intercourse or drug use by parenteral injection, so coinfection is common. This study aimed to determine the prevalence of coinfection with either HCV or HBV in patients infected with HIV.**

DATA SOURCES: **A meta-analysis was performed to quantify HBV coinfection with HCV in HIV patients. Published studies in the English and Chinese language medical literature involving cohorts of HIV patients concomitantly infected with HBV and/or HCV were collected from the PubMed database, ISI Web of Science, the Cochrane library clinical trials registry, CNKI (China National Knowledge Infrastructure) and Google Scholar, for relevant articles before November 2009. The search was conducted with the following key words: hepatitis C, HCV, hepatitis B, HBV, human immunodeficiency virus, HIV, and coinfection. Data were extracted from relevant studies by two investigators. RevMan 5.0 software was used to perform the meta-analysis.**

RESULTS: **We identified 22 studies involving 17 664 patients. Substantial differences in the HCV rate compared to the HBV rate in HIV patients were found in the overall analysis [odds ratio (OR)=3.00; 95% confidence interval (CI) 1.90-4.73]. A subgroup analysis showed similar results in a European group, but not in Asian or African groups. However, a meta-analysis between HIV+HBV+HCV+ and HIV+HBV+HCV- patients showed no significant difference (OR=0.91; 95% CI 0.57-1.45). Although subgroup analysis still lacked essential differences, different regions seemed to have different patterns.**

CONCLUSIONS: **HCV-HIV coinfection is more frequent than HBV-HIV coinfection overall. However, HCV infection does not affect the prevalence of HBV infection in HIV-positive patients.**

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KEY WORDS: **hepatitis B virus; hepatitis C virus; human immunodeficiency virus; coinfection; meta-analysis**

Introduction

Worldwide, an estimated 33 million people are infected with the human immunodeficiency virus (HIV).[1] As hepatitis C virus (HCV), hepatitis B virus (HBV) and HIV share similar routes of transmission by sexual intercourse or drug use by parenteral injection, coinfection is common. Infection with HIV has significant impact on the natural history of patients with hepatitis virus infection. Coinfection with HBV can accelerate the damage incurred by the liver, resulting in a prolonged elevation of ALT,[2] shortening the period before cirrhosis,[3] and increasing the risk of developing hepatocellular carcinoma (HCC). Similar results of HCV-HIV coinfection have also been reported.[4-6] Moreover, compared to HIV mono-infection, HIV patients with HBV or HCV coinfection have higher liver-related mortality rates,[7] even when antiretroviral therapies are used.[8] Several studies[9, 10] showed that HCV increases the risk of HBV infection in patients with HIV. However, others found the opposite result.[11, 12]

The prevalence of HIV-HBV or HIV-HCV coinfection has been reported, and some studies provide evidence that the prevalence of HBV is higher than that of HCV in HIV-positive patients.[13, 14] However, others have derived conflicting results.[15] Furthermore, the effect of one virus upon another in HIV-infected patients is still controversial. To describe the infection rates of HBV and HCV in persons with HIV and to determine whether one of these liver viruses has an influence on the infection rate of another, we performed a meta-analysis.

Methods

Selection of studies

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Published studies in the English and Chinese language medical literature involved cohorts of HIV patients concomitantly infected with HBV and/or HCV. The studies were identified by searching the PubMed database, ISI Web of Science, CNKI (China National Knowledge Infrastructure) and Google Scholar, for relevant articles before November 2009 using a search criterion combination of the following key words: hepatitis C, HCV, hepatitis B, HBV, human immunodeficiency virus, HIV, and coinfection. To maximize the number of studies for our analysis, we also combined the above key words.

Inclusion and exclusion criteria

All identified studies were screened, and the articles were selected by reviewing their titles and/or abstracts. Two observers independently reviewed the full texts of the remaining articles. We excluded studies that 1) were not published at full length; 2) included no more than 20 participants; and 3) had no control group. When participant recruitment overlapped by more than 30% in two or more articles by the same author(s), the one with the largest population of participants or most recently published was selected. HIV infection was defined by a positive result in HIV enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blotting assay. 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); this was confirmed by ELISA or enzyme immunoassay (EIA). HCV infection was defined by a HCV ELISA-positive result and confirmed by polymerase chain reaction (PCR) or recombinant immunoblot assay.

Data extraction

Two of us were responsible to data extraction and others checked the results and arbitrated discrepancies. The results were converted to odds ratio (OR). We used those adjusted for the greatest number of potential confounders when risk estimates were presented.

Assessment of study quality

We used a 12-point scoring system to rate the quality of the retrieved studies, and this was carried out by two independent investigators. The score was based on the factors (study design, patient number, source of population and detection method), which are used for the evaluation of the quality of our included studies. The studies were classified into three levels that represented their quality. A higher score indicated better quality.

Sensitivity analysis and publication bias

Sensitivity analysis was performed by removing trial(s) to evaluate whether the remaining studies were affected in terms of statistical significance. Publication bias was evaluated by using funnel plots and the Egger's test.[16]

Statistical analysis

Analyses were made with Review Manager (version 5.0 Cochrane Collaboration, Oxford, UK). The significance was measured at $P<0.05$. Significant heterogeneity was measured at $P<0.10$. Significant publication biases were measured at $P<0.10$. The Egger's test was performed using STATA software (version 10.0, Stata Corp., College Station, TX, USA).

Results

Selected studies

After searching the database, a total of 22 studies were identified and screened for retrieval. Of these studies, five were from Italy,[9, 12, 17-19] two from France,[20, 21] two from Spain,[11, 22] one each from China, Germany, the USA, Greece, Iran, Nigeria, Thailand, Malawi, Australia, India and Kenya,[13-15, 23-30] and two from two or more countries or regions.[10, 31] The characteristics of the 22 studies are given in Table.

Extraction process

In a total of 221 studies identified, 84 not involving the three viruses or mainly focusing on other viruses or diseases were excluded after reviewing their titles. Sixty-eight studies were excluded after reviewing their abstracts 9 contained fewer than 20 patients and 59 lacked relevant data. After a full text review, 47 studies were excluded: 21 lacked control groups or a triple infection group, 16 lacked full text, 8 were not written in English or Chinese, and 2 focused on other fields (such as HBV genotype-related analysis or DNA analysis). The remaining 22 studies[9-15, 17-31] were included in the analysis.

Study quality

The number of patients participating in the studies ranged from 72 to 5472. Their mean age was 27.2 to 43 years. Most of the patients were men. Of the 22 cohort studies, 10 were retrospective in design, 11 were prospective, and one was a cross-study. There were 5486 patients with HCV infection, 1630 with HBV infection and 18 959 with HIV infection.

Table. Characteristics of studies included in the meta-analysis

Reference	Study design	Continent, Country or Region	Age (mean, yr)	Gender (male %)	Total patients infected with HIV+ HBV+ HCV-/ HIV+ HBV+ HCV+	Quality score (12)
Ockenga et al. 1997[24]	Prospective	Germany	37	81	22/4	⩾8
Pallas et al. 1999[11]	Prospective	Spain	27.2	93.9	5/135	⩾8
Dimitrakopoulos et al. 2000[13]	Retrospective	Greece	32	88	122/5	5-7
De Luca et al. 2002[18]	Prospective	Italy	33	75	46/44	5-7
Bonnet et al. 2002[20]	Retrospective	France	36	72	22/10	⩽4
Law et al. 2003[14]	Retrospective	Thailand	32.3	52	60/3	⩽4
Lincoln et al. 2003[29]	Retrospective	Australia	Unclear	94	101/38	5-7
Almond et al. 2004[17]	Cross-sectional	Italy	40	73.2	2/4	5-7
Meraviglia et al. 2004[19]	Prospective	Italy	40.7	75.4	25/27	5-7
He et al. 2006[15]	Retrospective	China	35.6	60.2	3/7	5-7
Guitton et al. 2006[21]	Retrospective	France	43	71	72/26	5-7
Palacios et al. 2006[22]	Retrospective	Spain	39	77	25/18	5-7
Filippini et al. 2007[9]	Retrospective	Italy	37.2	58.4	4/5	⩽4
Zhou et al. 2007[10]	Prospective	Asia and Pacific region	37	73	171/153	5-7
Forbi et al. 2007[26]	Prospective	Nigeria	20-64	46	37/13	5-7
Harania et al. 2008[23]	Prospective	Kenya	39.5	55	26/1	5-7
Nyirenda et al. 2008[27]	Prospective	Malawi	35	39	31/2	5-7
Tedaldi et al. 2008[28]	Prospective	USA	ND	ND	120/14	⩾8
Solomon et al. 2008[30]	Longitudinal cohort, prospective	India	35	99.7	24/25	5-7
Landes et al. 2008[31]	Retrospective	Western and Central Europe, Ukraine	27.6	0	30/21	5-7
Morsica et al. 2009[12]	Prospective	Italy	36	82	18/21	5-7
Mohsen et al. 2009[25]	Retrospective	Iran	Unclear	91.6	57/31	5-7

ND: not noted in study; Unclear: containing patients not within our consideration.

HCV+HIV+ versus HBV+HIV+

Substantial differences in the HCV rate compared to the HBV rate in HIV patients were found according to an overall analysis (OR=3.00; [95% CI 1.90-4.73, $P<0.00001$] heterogeneity $P<0.00001$, $I^2=96\%$) (Fig. 1). However, some factors might lead to the significant heterogeneity, for example, ethnicity. We then performed a subgroup analysis by ethnicity.

The subgroup analysis showed that the prevalence of HCV in the European group was higher than that of HBV in HIV-positive patients (OR=4.08; [95% CI 2.24-7.44, $P<0.00001$] heterogeneity $P<0.00001$, $I^2=95\%$), while in the Asian (OR=1.96; [95% CI 0.35-10.82, $P=0.44$] heterogeneity $P<0.00001$, $I^2=95\%$) and African (OR=2.7; [95% CI 0.61-11.88, $P=0.19$] heterogeneity $P<0.00001$, $I^2=96\%$) groups, that was not the case (Fig. 2). The results implied that regional diversity should be taken into account.

We further carried out a sensitive analysis by trial(s) exclusion. We excluded the publication(s) with statistically significant heterogeneity and repeated the analysis. In the overall summary estimates, the European and Asian groups did not demonstrate a statistically significant change after the exclusion (overall: from eight studies,[11, 12, 20, 21, 23-25, 29] OR=2.48; [95% CI 2.13-2.88, $P<0.00001$] heterogeneity $P=0.14$, $I^2=36\%$); European: from six studies[11, 12, 17, 20, 21, 24] OR=2.44; [95% CI 1.95-3.04, $P<0.00001$] heterogeneity $P=0.16$, $I^2=38\%$). The heterogeneity of the African group could not be eliminated. Publication bias was evaluated, and forest plots and Egger's test suggested no evidence of publication bias (Egger's test: overall $P=0.425$; European $P=0.936$; African $P=0.312$; and Asian $P=0.798$).

HIV+HBV+HCV+ versus HIV+HBV+HCV-

Because of the high prevalence of HCV in HIV-infected patients, we then asked whether HCV infection affected the prevalence of HBV in HIV-infected patients. No significant differences were seen in the overall analysis of HIV+HBV+HCV+ compared to HIV+HBV+HCV- in the meta-analysis (OR=0.91; [95% CI 0.57-1.45, $P=0.69$] heterogeneity $P<0.00001$, $I^2=91\%$). As the heterogeneity was significant, we then performed a subgroup analysis and still could not identify any relationship between these two groups in the European (OR=1.09; [95% CI 0.58-2.07, $P=0.79$] heterogeneity

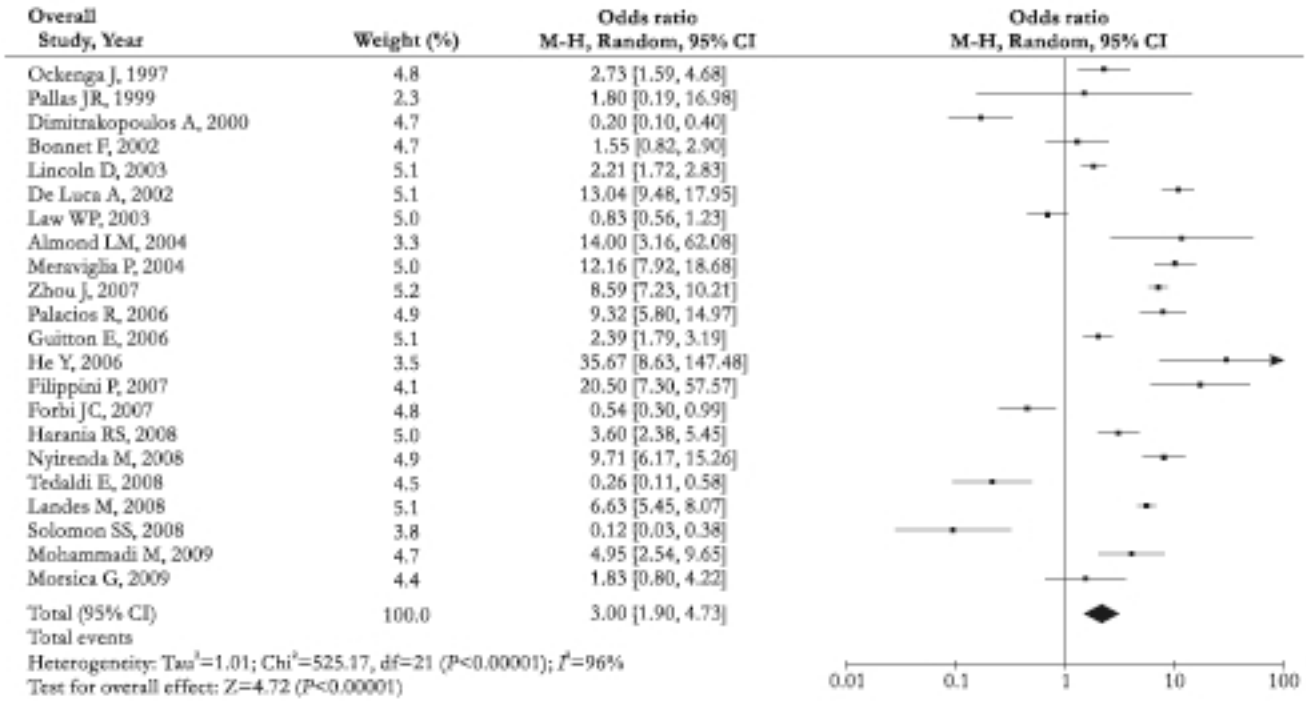

Fig. 1. HCV+ HIV+ versus HBV+ HIV+(overall).

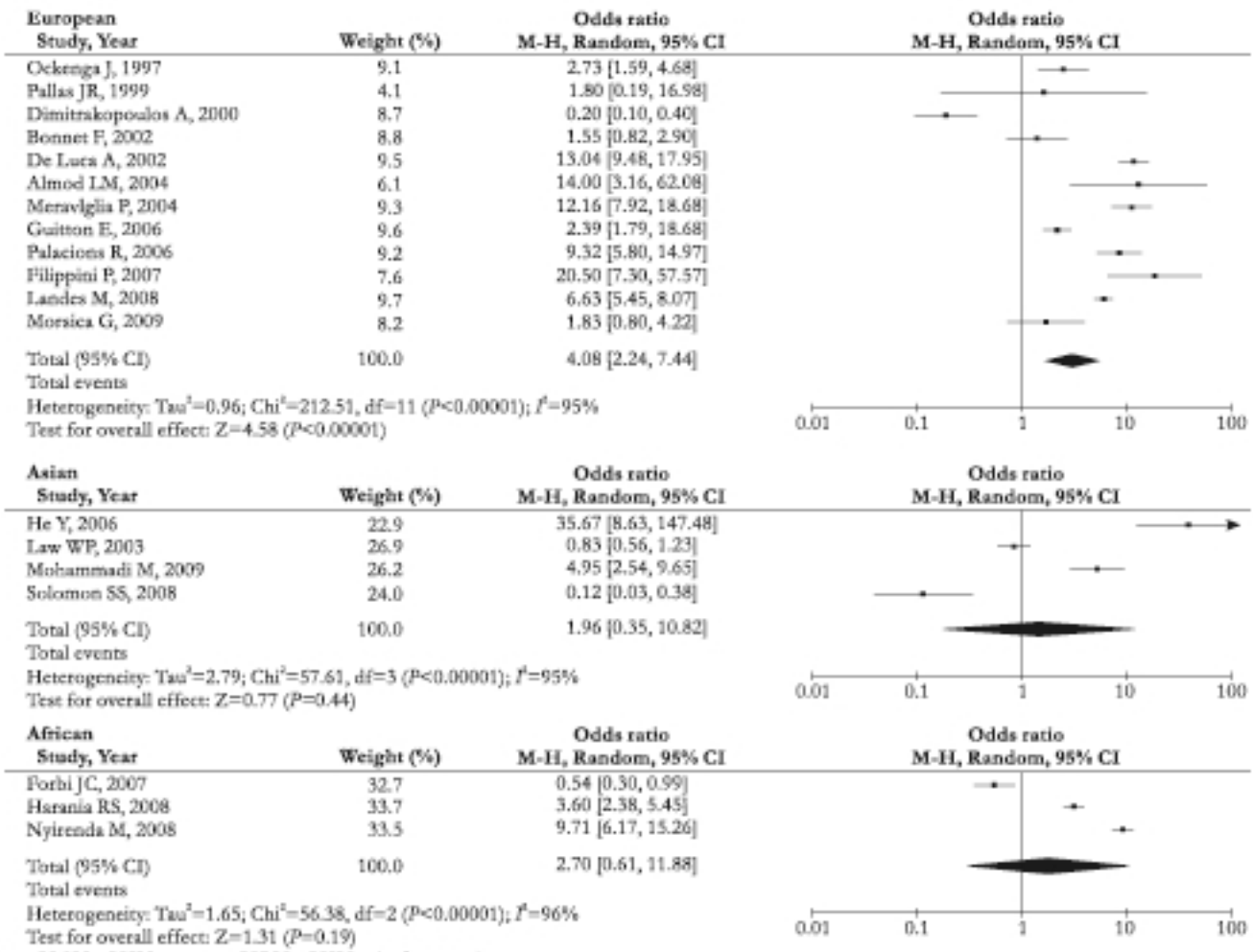

Fig. 2. HCV+ HIV+ versus HBV+ HIV+ (subgroup).

$P<0.00001$, $I^2=82\%$), Asian (OR=0.29; [95% CI 0.04-1.99, $P=0.21$] heterogeneity $P<0.00001$, $I^2=95\%$) and African groups (OR=1.77; [95% CI 0.90-3.47, $P=0.1$] heterogeneity $P=0.55$, $I^2=0\%$).

Sensitive analysis and publication bias

We then performed a sensitive analysis. The summary estimates for overall, and for the European and Asian groups did not change with any statistical significance after the exclusion (overall: from sixteen studies,[9-11, 14, 17-21, 23-27, 30, 31] OR=1.01; [95% CI 0.87-1.18, $P=0.90$] heterogeneity $P=0.10$, $I^2=33\%$; European: from eight studies,[9, 11, 12, 17-19] OR=1.15 [95% CI 0.78-1.70, $P=0.47$] heterogeneity $P=0.15$, $I^2=35\%$; Asian: from three studies,[14, 15, 30] OR=0.91; [95% CI 0.56-1.48, $P=0.70$] heterogeneity $P=0.10$, $I^2=56\%$). The heterogeneity of the African group could not be eliminated. We did not find any evidence of a publication bias from forest plots and Egger's test (Egger's test: overall $P=0.798$; European $P=0.633$; African $P=0.822$; and Asian $P=0.127$).

Discussion

In this study, our meta-analysis examined the prevalence of coinfection with either HBV or HCV in patients infected with HIV. The overall analysis showed that HCV-HIV coinfection was more frequent than HBV-HIV coinfection, indicating that patients with HIV seemed to have a higher risk of HCV infection. This outcome might be due to sex, age, ethnicity, occupation, marital status[25] and injection of drug use.[11, 30] We performed subgroup analyses by ethnicity using available data. Similar results were obtained in the European group, but not in the Asian or African groups. Ethnicity is a potential reason for differences in standard of living, habits and customs. In addition, medical resources, sanitation, and the development of therapy vary, and these factors should be considered. In this meta-analysis we found that a higher frequency of HCV infection does not impact a patient's susceptibility to HBV infection, a result that is similar to that of a previous study.[27]

There are several potential limitations in this meta-analysis. First, the possibility of information and selection biases and unidentified confounders cannot be completely excluded, while not all regions of the world were included. Second, because our search strategy only focused on articles in English and Chinese, some potential high-quality data written in other languages were excluded, and this might cause a significant bias. Third, factors including different methodologies of study design, numbers of patients in cohorts, and publication bias may have caused the heterogeneity in the meta-analysis; caution should be taken when generalizing the results.

As ethnicity may largely affect the prevalence of any of the three viruses, several measures should be taken. Doubling the HBV vaccine may be used in regions with large HBV-infected populations, as in China, for better responses and higher $CD4^+$ cell counts.[32, 33] Blood safety should be granted more attention in Africa, where blood transfusion is the most common route of transmitting these diseases. People with unsafe sexual relationships and addiction to drug injection should always be careful because all of these viruses can be transmitted by sexual intercourse and injection drug use. In addition, the replication of HBV and HCV in HIV patients should be actively monitored when receiving antiviral therapy, and this monitoring system should be a part of clinical care in case of reactivation of latent infection.[34, 35]

In summary, our data showed that patients with HIV have a higher risk of HCV infection than those of HBV infection. Periodic liver checkups are required for a better therapeutic strategy. Meanwhile, more attention should be paid to the prevention of such liver diseases in HIV-infected patients according to their ethnicities.

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