

# Hepatitis D virus dual infection increased the risk of hepatocellular carcinoma compared with hepatitis B virus mono infection: A meta-analysis

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#### Abstract

**Background:** Hepatitis delta virus (HDV) is a defective virus that relies on the supply of hepatitis B surface antigen (HBsAg) from hepatitis B virus (HBV) to assemble HDV virions and infect hepatocytes. However, controversy remains in whether the presence of HDV increases the risk of hepatocellular carcinoma (HCC). Our aim is to evaluate the influence of HDV on the risk of HCC through a systematic review and meta-analysis.

**Methods:** A review of all English-language literature was conducted in the major medical databases using the subject search terms "hepatocellular carcinoma," "liver cancer," "hepatic tumor," and "hepatitis delta." A meta-analysis of the qualifying publications was then performed.

**Results:** The meta-analysis included 21 studies, which revealed a significantly higher risk of HCC among patients with HDV/HBV dual infection (odds ratio [OR] = 2.08, 95% confidence interval [CI], 1.37-3.14, p < 0.01) compared with those with HBV monoinfection. Those with HDV/HBV dual infection remained at higher risk of HCC in the subgroup analysis, irrespective of the status of hepatitis C virus (HCV) or human immunodeficiency virus (HIV) coinfection and in different ethnicities. The HCC risk remained higher in patients with HDV/HBV dual infection with heterogeneous fibrosis stage (OR=2.04, 95% Cl, 1.31-3.17, p < 0.01). The difference in the risk of HCC between HDV/HBV dual infection and HBV monoinfection was not statistically significant in patients with cirrhosis or advanced fibrosis (OR=1.84, 95% Cl, 0.48-7.02, p = 0.37). However, this subgroup comprised only two studies. **Conclusion:** HDV and HBV dual infection significantly increase the risk of HCC development compared with HBV monoinfection.

Keywords: Dual infection; Hepatitis B; Hepatitis delta; Hepatocellular carcinoma; Superinfection

#### **1. INTRODUCTION**

Hepatitis delta virus (HDV) is a defective virus that relies on the supply of hepatitis B surface antigen (HBsAg) from hepatitis B

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virus (HBV) to assemble HDV virions and infect hepatocytes.<sup>1,2</sup> HDV infection can present as coinfection or superinfection. Coinfection is defined as a concurrent infection of HBV and HDV, whereas superinfection is when HDV infection is superimposed on chronic HBV infection.<sup>2</sup>

Chronic HDV infection is associated with more severe liver injury and a higher risk of fulminant hepatitis and fibrosis progression compared with those with HBV monoinfection.<sup>3-6</sup> HDV infection may lead to a high risk of hepatocellular carcinoma (HCC) development and high mortality rate in patients with compensated cirrhosis.<sup>7</sup> In a 28-year study, persistent replication of HDV resulted in cirrhosis, liver decompensation, HCC, and liver-related mortality.<sup>8</sup> In an Italian study, patients with HDV-related HCC were significantly younger than patients without HDV infection, which indicated that HDV infection may be associated with more rapid progression of disease.<sup>9</sup>

HDV infected noncirrhotic patients who had higher levels of HDV RNA were more likely to develop cirrhosis and HCC.<sup>10,11</sup> Coexisting HDV and HBV were reported to increase HCC risk compared with HBV monoinfection in some studies.<sup>12-18</sup> In contrast, several articles suggest that the risk of HCC is similar in patients with HDV dual infection and HBV monoinfection.<sup>19-25</sup> However, HDV is still regarded as a group 3 agent that are unclassifiable with respect to their carcinogenicity for humans in the International Agency for Research on Cancer (IARC).<sup>26</sup>

It has been debated whether dual infection of HDV is more likely to cause HCC than HBV monoinfection. Therefore, we performed a systematic review and meta-analysis to estimate the risk of HBV and HDV dual infections regarding the development of HCC.

### 2. METHODS

#### 2.1. Search methodology and study selection

A literature research was conducted according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analyzes (PRISMA) statement. We searched PubMed, Embase, and the Cochrane Database of Systematic Reviews for articles that were published up to December 2019 using the medical subject heading terms "hepatocellular carcinoma," "hepatitis delta," "hepatitis D," "liver cancer," and "hepatic tumor." The search was limited to English-language literature.

Articles were screened for full text review base on the titles and abstracts. Furthermore, we manually searched the reference lists of the retrieved articles to increase the numbers of possibly relevant articles. Two authors independently looked for all the retrieved papers and assessed their eligibility for inclusion in the present study. Discordant opinions were resolved by consensus with the other coauthors.

#### 2.2. Inclusion and exclusion criteria

We included case control studies, cohort studies, and cross-sectional studies in the meta-analysis. The inclusion criteria were: (1) articles published in full length, (2) inclusion of both HDV/ HBV dual infection and HBV monoinfection, and (3) availability of information about HDV and HBV seroprevalence and the incidence of hepatocellular carcinoma (HCC). HDV infection was defined as a positive result for hepatitis delta virus antibody (anti-HDV Ab), and HBV infection was defined as a positive result for hepatitis B surface antigen (HBsAg).

The exclusion criteria were as follows: (1) review articles, (2) lack of a non-HCC control group or HBV monoinfection group for comparison, and (3) incomplete data on the number of cases, controls, and percentage of positive anti-HDV.

The risk of bias was assessed by two authors independently (T.E. Chang and C.W. Su) using the Newcastle-Ottawa Scale (NOS), which evaluates the quality of nonrandomized studies through the selection of the study individuals, comparability of the study groups, ascertainment of the outcome, and the adequacy of follow up.

#### 2.3. Statistical analysis

All statistical analyses were performed using Review Manager version 5.3.5 (RevMan for Windows, 2014; The Cochrane Collaboration, Oxford, United Kigdom). The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the association between the incidence of HCC and HDV/HBV dual infection using a random effect model. Heterogeneity between studies was recognized with a cutoff value of  $\geq$ 50% using I<sup>2</sup> statistics or *p* < 0.10 with the  $\chi^2$  test for Cochran Q statistics. If significant heterogeneity was found, subgroup analyses were performed. Funnel plots were used to assess the publication bias, and subgroup analyses were performed due to high heterogeneity, including coinfection of HCV or HIV, fibrosis status, different ethnic population, study designs, year of study, antiviral treatment, and coinfection or superinfection of HDV.

#### **3. RESULTS**

#### 3.1. Search results

A total of 897 citations were identified following the initial main database search. After reviewing abstracts and titles duplicates and unrelated articles were excluded, which left 42 articles. Full-text reviews were performed, and 21 articles were removed according to the exclusion criteria.<sup>7,12-25,27-32</sup> Finally, 21 studies were eligible for the meta-analysis (Fig. 1).

Among the 21 studies, five involved patients with HDV and HBV coinfection, two involved patients with HDV superinfection only, and four involved both coinfection and superinfection patients. Most studies used anti-HDV antibody as the diagnostic method for HDV infection, while two studies used both intrahepatic delta antigen and serum anti-HDV antibody to make the diagnosis (Table 1).

Eight studies involved patients with HIV or HCV coinfection, while four excluded patients with HIV or HCV infection. Two studies included only patients with cirrhosis or advanced fibrosis, and 12 studies involved patients with all stages of fibrosis.

Most of the studies did not indicate whether the included cohorts had received nucleos(t)ide analogue or interferon treatment, the quantitative viral loads, dominant genotypes of HBV and HDV, and the rate of HBsAg clearance (Table 2). The median NOS of enrolled studies was 6 (4–10). Eight of the 21 enrolled studies had a low risk of bias with NOS > 7.

## 3.2. Comparison of the HCC risk between HBV/HDV dual infection and HBV mono infection

The 21 included studies enrolled 18,497 patients, including 2560 with HDV/HBV dual infections and 15,937 with HBV monoinfection. The risk of HCC was significantly higher in the HDV/HBV dual infection group (OR = 2.08, 95% CI, 1.37-3.14, p < 0.01) with high heterogeneity (I<sup>2</sup> = 69%, p < 0.01) (Fig. 2A). The funnel plot was symmetrical, which suggests a lower likelihood of publication bias (Fig. 2B).

## 3.3. Subgroup analysis stratified by the status of virus coinfection, ethnicities, and the stage of liver fibrosis

We grouped the enrolled studies according to whether they looked at concurrent HIV or HCV coinfection, cirrhosis, or advanced fibrosis at baseline, the ethnic populations, and study designs. The HCC risk remained higher in HDV/HBV dual infection group among patients with concurrent HIV or HCV infection (OR = 1.85, 95% CI, 1.13-3.03, p < 0.01) and patients without concurrent HIV and HCV infection (OR = 4.19, 95% CI, 2.64-6.63, p < 0.01) (Fig. 3A). A significant subgroup difference was noted (p=0.02).

When stratified by the status of liver fibrosis, there was no significant difference in the risk of HCC between HDV/HBV dual infection and HBV monoinfection groups among patients with cirrhosis or advanced fibrosis at baseline (OR =1.84, 95% CI, 0.48-7.02, p = 0.37). However, only two studies fit this subgroup. The HCC risk remained significantly higher in patients with HDV/HBV dual infection with respect to heterogeneous fibrosis stage (OR = 1.79, 95% CI, 1.10-2.92, p = 0.02) (Fig. 3B). No significant subgroup difference was found (p = 0.97).

As for ethnic populations, the risks of HCC were significantly higher in the HDV/HBV dual infection group than in the HBV monoinfection group among Caucasians (OR = 1.97, 95% CI, 1.23-3.16, p < 0.01) and Asians (OR = 3.45, 95% CI, 1.41-8.45, p < 0.01). But the difference was less significant in Africans (OR = 2.01, 95% CI, 0.73-5.51, p = 0.18) (Fig. 3C). To be recorded, Govindarajan et al. listed the risk of HCC in different ethnic populations.<sup>22</sup> Thus, the case numbers presented in this subgroup analysis were numbers for Caucasians only. In cohort studies (OR = 2. 36, 95% CI, 1.56-3.58, p < 0.01), the HDV/HBV group had significantly higher risk of HCC compared with the

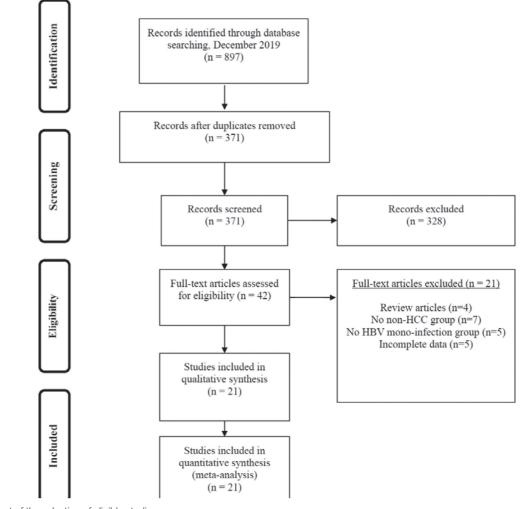


Fig. 1 Flow chart of the selection of eligible studies.

monoinfection group. The risk of HCC did not significantly differ between the two groups in case control studies (OR = 9.03, 95% CI, 0.44-187.0, p=0.15) and cross-sectional studies (OR = 0.76, 95% CI, 0.25-2.34, p=0.64) (Fig. 3D).

Since the periods of the enrolled studies had a wide range, subgroup analysis based on the year of publication was performed. There were trends of an increased risk of HCC development among the dual infection group in the studies before 1990 (OR=1.40, 95% CI, 0.32-6.18, p=0.65), between 1991 and 2000 (OR=1.89, 95% CI, 0.79-4.55, p=0.15), and between 2001 and 2010 (OR=1.57, 95% CI, 0.89-2.79, p=0.12), but without statistical significance. Increased HCC risk was found in the dual infection group among studies published between 2011 and 2019 (OR=2.54, 95% CI, 1.37-3.14, p<0.01) (Fig. 3E).

Most of the enrolled studies did not mention about antiviral treatment. One study only included patients without antiviral treatment. In the two studies that included only patients who received nucleos(t)ides analogues, a tendency of increased HCC risk was found in the dual infection group compared with the monoinfection group, although the difference was not statistically significant (OR = 2.01, 95% CI, 0.80-5.10, p = 0.14). The risk of HCC significantly increased in the dual infection group in the subgroups that enrolled patients who received interferon or nucleos(t)ides analogues (OR = 1.81, 95% CI, 1.18-2.79, p < 0.01) (Fig. 3F). However, both subgroups enrolled only small numbers, and the results should be interpreted carefully.

The risk of HCC did not significantly increase in patients with superinfection (OR = 1.61, 95% CI, 0.70-3.67, p = 0.26). Instead, the risk of HCC development significantly increased in studies of HDV coinfection (OR = 1.74, 95% CI, 1.23-2.48, p < 0.01) and studies including both coinfection and superinfection (OR = 5.11, 95% CI, 2.21-11.79, p < 0.01). However, there were still nine studies that did not declare the mode of HDV infection in the article.

#### 4. DISCUSSION

Whether HDV infection increases the risk of HCC development more than HBV monoinfection is still under active debate. This meta-analysis demonstrated that the risk of HCC was higher in the HBV/HDV dual-infected group. The subgroup analysis further demonstrated that the HDV/HBV dual infection remained a significant higher risk for HCC in the presence of HCV or HIV coinfection and in various ethnicities. The risk was less apparent in patients who already presented with cirrhosis or advanced fibrosis.

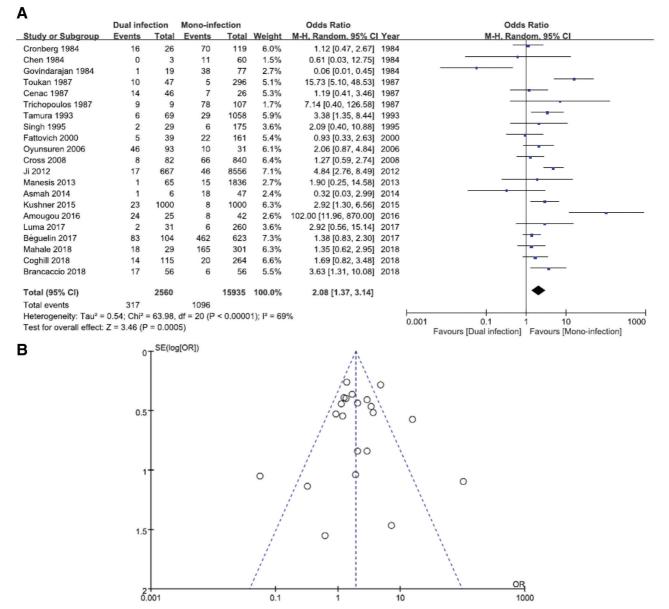
Our results were generally consistent with a previous metaanalysis by Alfaiate et al.<sup>33</sup> The difference between these two meta-analyses may be caused by the search strategy and the selection criteria. The discrepancy in the number of studies may result in different results in the analysis. Nevertheless, our study provided subgroup analyses of different aspects, including fibrosis stage and different ethnic populations.

		Dual ii	Dual infection	Monoinfection	fection		Coinfaction or			
	Country	HCC	Total	HCC	Total	Study design	superinfection	Diagnostic method of HDV	Genotype	Viral load
Chen 1984 <sup>21</sup>	Taiwan	0	с	1	60	Cross sectional	Uncertain	Intrahepatic delta antigen and anti-HDV	No data	No data
Govindarajan 198422	SU	<del>, -</del>	19	38	27	Cross sectional	Uncertain	Intrahepatic delta antigen and anti-HDV	No data	No data
Cronberg 1984 <sup>23</sup>	Senegal	16	26	20	119	Cross sectional	Uncertain	Anti-HDV	No data	No data
Cenac 1987 <sup>29</sup>	Niger	14	46	7	26	Retrospective	Superinfection	Anti-HDV	No data	No data
Toukan 198712	Japan	10	47	2	296	Prospective	Both included	Anti-HDV	No data	No data
Trichopoulos 198713	Greece	6	6	78	107	Case-control	Uncertain	Anti-HDV	No data	No data
Tamura 1993 <sup>14</sup>	Japan	9	69	29	1058	Prospective	Superinfection	Anti-HDV	No data	No data
Singh 1995 <sup>15</sup>	India	2	29	9	175	Cross sectional	Both included	Anti-HDV	No data	No data
Fattovich 20007	Italy	Ŋ	39	22	161	Retrospective	Superinfection	Anti-HDV	No data	Tested HBV DNA,
										no quantitated data
Oyunsuren 2006 <sup>30</sup>	Mongolia	46	93	10	31	Prospective	Co-infection	Anti-HDV and HDV RNA	88.7% HBV carrier	Tested,
									were genotype D	no quantitated data
Cross 2008 <sup>24</sup>	N	œ	82	99	840	Retrospective	Co-infection	Total HDV antibody, anti-HDV IgM. No HDV RNA.	No data	No data
Ji 2012 <sup>16</sup>	Sweden	17	667	46	8556	Retrospective	Both included	Used Swedish Hospital Discharge Register and	No data	No data
								Outpatient Registry (by ICD-7 code)		
Manesis 2013 <sup>25</sup>	Greece	-	65	15	1836	Prospective	Both included	Anti-HDV and HDV RNA	No data	Tested HBV DNA
Asmah 2014 <sup>27</sup>	Ghana	-	9	18	47	Cross sectional	Uncertain	Anti-HDV	No data	No data
Kushner 201517	SU	23	1000*	œ	1000	Retrospective	Co-infection	Anti-HDV and HDV RNA	No data	Tested HBV DNA
Amougou 2016 <sup>18</sup>	Cameroon	24	25	œ	42	Case-control	Uncertain	Anti-HDV	No data	Yes
Béguelin 2017 <sup>31</sup>	Switzerland	83	104	462	623	Prospective	Uncertain	Anti-HDV for screening, then HDV RNA	HDV: 94.3% genotype 1;	No data
								were checked (stored samples)	Dual infection: most	
									genotype D HBV	
Luma 2017 <sup>19</sup>	Cameroon	2	31	9	260	Cross-sectional	Uncertain	Anti-HDV antibody and HDV RNA	No data	Both HBV and HDV viral load
										presented with median level
Brancaccio 2018 20	Italy	17	56	9	56	Prospective	Uncertain	Anti-HDV antibody and HDV RNA	No data	Both HBV and HDV viral load
										presented with median level
Mahale 201832	Gambia	18	29	165	301	Case control	Co-infection	Anti-HDV antibody and HDV RNA	HDV: 70.6% genotype 5,	Tested, no quantitate data
Codhill 2018 <sup>28</sup>	Australia	14	115	20	264	Retrospective	Co-infection	Anti-HDV	29.4% genotype 1 No data	No data

HCC = hepatocellular carcinoma; HBV= hepatitis B virus; HCV= hepatitis C virus; HDV= hepatitis delta virus; ICD= International Classification of Diseases.

Chen 1984 <sup>21</sup> Govindarajan 1984 <sup>22</sup>	HIV/HCV cointection	Cirrhosis/fibrosis	<b>Cirrhosis at the time of HCC diagnosis</b>	Antiviral treatment	HBsAg loss
Govindarajan 1984 <sup>22</sup>	No data	No data	Uncertain	No data	No data
	No data	All cirrhosis in HCC group; 56% cirrhosis in control group	Yes	No data	No data
Cronberg 1984 <sup>23</sup>	No data	Yes, unknown proportion	Uncertain	No data	No data
Cenac 1987 <sup>29</sup>	No data	Yes, unknown proportion	Uncertain	No data	No data
Toukan 1987 <sup>12</sup>	No data	Yes, unknown proportion	Uncertain	No data	No data
Trichopoulos 1987 <sup>13</sup>	No data	55.6% HDV (+) HCC patients had cirrhosis; 60.3% HDV (-) HCC patients had cirrhosis	Uncertain	No data	No data
Tamura 199314	No data	Yes, unknown proportion	Uncertain	No data	No data
Singh 1995 <sup>15</sup>	No data	Yes, unknown proportion	Uncertain	No data	No data
Fattovich 20007	Yes	All compensated cirrhosis	Median interval between entry and HCC development:	Patients with anti-viral treatment	No data
			Anti-HUV(+)/HBeAg(-): / 5 monuns Anti-HDV/_//HBeAn(-): / 8	auring tonow up were excluded	
			months		
			Anti-HDV/-//HReAr(+)· 40 months		
			5-vear cumulative HCC risk:		
			Anti-HDV(+)/HBeAn(-): 13%		
			Anti-HDV(=)/HBeAg(=): 2%		
Ovunsuren 2006 <sup>30</sup>	Yes	No data	Uncertain	No data	No data
Cross 2008. <sup>24</sup>	Yes	22 natients had circhosis. 8 of 22 had HCC	Uncertain	IFN-hased treatment: 2 patients	No data
Ji 2012 <sup>16</sup>	HIV/HCV co-infection excluded	No data	No data	No data	No data
Manesis 2013 <sup>25</sup>	HIV/HCV co-infection excluded	Yes unknown nronortion	Baseline cirrhosis: 145 (7.3) in HBV mono-infection	46 HDV natients received antiviral treatment	No data
			and 16 (19.8) in HDV co-infection	40 patients received IFN-based therapy	100 0414
Asmah 2014 <sup>27</sup>	No data	Yes. unknown proportion	Known HCC when included	No data	No data
Kushner 2015 <sup>17</sup>	59% anti-HDV positive patients	Yes, unknown proportion	Uncertain	7 (9.6%) HDV patients received IFN-based treatment;	No data
	have HCV			30 (41%) HBV patients received NA.	
Amougou 2016 <sup>18</sup>	23 HCC patients with positive anti-HCV	No data	Uncertain	No data	No data
Béauelin 2017 <sup>31</sup>	All HIV infected. 70% with HCV	Yes. unknown proportion	Cirrhosis as the primary outcomes	Tenofovir for HBV suppression	No data
			(liver disease related death)		
Luma 2017 <sup>19</sup>	HIV/HCV co-infection excluded	Yes, fibrosis stages were documented	Uncertain	No data	No data
Brancaccio 2018 20	HIV/HCV co-infection excluded	Yes, all cirrhosis or advanced fibrosis	All cirrhosis or advanced fibrosis	Entecavir or Tenofovir	HBsAg
			when included		loss: 4
Mahale 201832	Yes	No data	Uncertain	No data	No data
Coghill 2018 <sup>28</sup>	Yes	Yes, unknown proportion	Uncertain	7 (8%) HDV carrier had treatment; 182 (48.5%) HBV carrier received treatment for HBV	No data

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HDV is a defective virus that needs hepatitis B surface antigen (HBsAg) for the assembly of virions, secretion, and infection of hepatocytes.<sup>2</sup> After invading the host cell, the replication of HDV can carry on without the presence of HBV proteins.<sup>34</sup> HDV superinfection is more likely to become a chronic disease. Chronic HDV infection may accelerate liver fibrosis.<sup>3-6</sup> Enduringly detectable HDV viremia was suggested to have a higher rate of progression to liver cirrhosis and hepatic decompensation.<sup>5,11</sup>

The interaction between HBV and HDV and the factors associated with disease progression during chronic infection has been examined. HDV may trigger an antiviral immune response and suppress the replication of HBV.<sup>35</sup> HDV viremia was associated with the HBsAg level and did not correlate with biochemical activity or histological severity.<sup>36,37</sup>

Our previous study reported that the levels of HDV and HBV viremia varied over time, and the predominance of the viruses

fluctuated at different times.<sup>37,38</sup> The presence of HBV or HDV viremia was associated with lower remission rates.<sup>39</sup> Although in most cases, HBV was suppressed and presented with low viremia, there were still cases that presented with HBV reactivation during chronic dual infection.

Furthermore, the carcinogenesis of HCC involves both direct and indirect mechanisms. Immune clearance of infected hepatocytes and regeneration of liver promote HCC in patients with chronic hepatitis B or C.<sup>40,41</sup> The pathogenesis of HDV-associated HCC has yet to be elucidated. HDV might promote HCC development via modifying signaling pathways that may accelerate liver fibrosis and modulate immune response.<sup>35,41-49</sup> The large hepatitis delta antigen (LHDAg) can promote liver fibrosis and HCC.<sup>35,42-44</sup> LHDAg may induce oxidative stress and stimulate nuclear factor kappa B (NF-κB) that sustain inflammation in the microenvironment, which may lead to HCC development.<sup>35,45-47</sup> Small hepatitis delta antigen (s-HDAg) could downregulate the

	Dual in		Mono-in			Odds Ratio		Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95%	CI Year	M-H, Random, 95% Cl
1.2.1 HIV/HCV co-inf								
Fattovich 2000	5	39	22	161	8.0%	0.93 [0.33, 2.6		
Oyunsuren 2006	20	42	10	31	8.5%	1.91 [0.73, 5.0	-	-
Cross 2008 Kushner 2015	8	82	66	840	10.0%	1.27 [0.59, 2.74	-	
	23 24	1000	8	1000		2.92 [1.30, 6.5		
Amougou 2016 Béguelin 2017	24	25 104	o 462	42 623		102.00 [11.96, 870.0 1.38 [0.83, 2.3	-	
Coghill 2018	14	104	402	264	10.4%	1.69 [0.82, 3.4	-	+
Mahale 2018	18	29	165	301	9.9%	1.35 [0.62, 2.9		
Subtotal (95% CI)	10	1436	100	3262	71.9%	1.85 [1.13, 3.03		◆
Total events	195		761				-	
Heterogeneity: Tau <sup>2</sup> =	= 0.30; Chi	<sup>2</sup> = 19.21,	df = 7 (P	= 0.008);	l² = 64%			
Test for overall effect:	Z = 2.44	(P = 0.01)						
1.2.2 No HIV/HCV co	-infection							
Ji 2012	17	667	46	8556	11.7%	4.84 [2.76, 8.4	2012	
Manesis 2013	1	65	15	1836	3.5%	1.90 [0.25, 14.5	-	
Luma 2017	2	31	6	260	4.8%	2.92 [0.56, 15.14	-	
Brancaccio 2018	17	56	6	56	8.1%	3.63 [1.31, 10.0		
Subtotal (95% CI)		819		10708	28.1%	4.19 [2.64, 6.63	]	•
Total events	37		73					
Heterogeneity: Tau <sup>2</sup> =				0.77); l <sup>2</sup> :	= 0%			
Test for overall effect:	Z = 6.11	P < 0.000	001)					
Total (95% CI)		2255		13970	100.0%	2.25 [1.45, 3.49	0	◆
Total events	232		834					
Heterogeneity: Tau <sup>2</sup> =				e = 0.001)	; l² = 65%			0.002 0.1 1 10 50
3	Dual infe		ono-infect			Odds Ratio		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
3	Dual infed Events	tion Me Total E	ono-infect		ight M-I	Odds Ratio I, Random, 95% Cl Yea	r	
Study or Subgroup	Dual infed Events	tion Me Total E	ono-infect	Total We	ight M-H 7.1%			Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018	Dual infector Events vanced fibr	tion Mo <u>Total E</u> rosis at ba 39 56	ono-infect vents aseline	Total We 161 7 56 7	7.1%	H, Random, 95% Cl Yea 0.93 [0.33, 2.63] 200 3.63 [1.31, 10.08] 201	D	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl)	Dual infec Events vanced fibr 5 17	ction Mo <u>Total E</u> rosis at ba 39	ono-infect ivents aseline 22 6	Total We 161 7 56 7	7.1%	H, Random, 95% Cl Yea	D	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events	Dual infer Events vanced fibr 5 17 22	tion Mo Total E rosis at ba 39 56 95	ono-infect vents aseline 22 6 28	Total We 161 7 56 7 217 14	7.1% 7.2% 4.3%	H, Random, 95% Cl Yea 0.93 [0.33, 2.63] 200 3.63 [1.31, 10.08] 201	D	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0	Dual infec Events vanced fibr 5 17 22 0.65; Chi <sup>2</sup> =	tion Mo <u>Total E</u> osis at ba 39 56 95 3.36, df =	ono-infect vents aseline 22 6 28	Total We 161 7 56 7 217 14	7.1% 7.2% 4.3%	H, Random, 95% Cl Yea 0.93 [0.33, 2.63] 200 3.63 [1.31, 10.08] 201	D	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2	Dual infec Events vanced fibr 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P	tion Mo <u>Total E</u> rosis at ba 39 56 95 3.36, df = = 0.37)	ono-infect vents aseline 22 6 28 1 (P = 0.0)	Total We 161 7 56 7 217 14	7.1% 7.2% 4.3%	H, Random, 95% Cl Yea 0.93 [0.33, 2.63] 200 3.63 [1.31, 10.08] 201	D	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fit	Dual infector vanced fibin 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrh 16	tion M. <u>Total E</u> rosis at ba 39 56 95 3.36, df = = 0.37) notic stage 26	ono-infect vents aseline 22 6 28 1 (P = 0.0)	Total         We           161         7           56         7           217         14           7); I <sup>2</sup> = 709         119	7.1% 7.2% 4.3%	H, Random, 95% Cl Yea 0.93 [0.33, 2.63] 200 3.63 [1.31, 10.08] 201	3	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984	Dual infer Events vanced fibr 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrh 16 1	Stion         Min           Total         E           rosis at ba         39           56         95           3.36, df =         =           = 0.37)	ono-infect iseline 22 6 28 1 (P = 0.0 es 70 38	Total         We           161         7           56         7           217         14           7); $I^2 = 70$ ?           119         8           77         3	7.1% 7.2% 4.3% % 8.0% 3.3%	<ul> <li>H. Random, 95% Cl Yea</li> <li>0.93 [0.33, 2.63] 200</li> <li>3.63 [1.31, 10.08] 201</li> <li>1.84 [0.48, 7.02]</li> <li>1.84 [0.48, 7.02]</li> <li>1.12 [0.47, 2.67] 198</li> <li>0.06 [0.01, 0.45] 198</li> </ul>	0 3 4 -	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fit Cronberg 1984 Govindarajan 1984 Cenac 1987	Dual infer Events vanced fibu 5 17 22 0.65; Chi <sup>2</sup> = 2 0.90 (P brottic/cirrr 16 1 1	tion M <u>Total E</u> osis at ba 39 56 95 3.36, df = = 0.37) otic stage 26 19 46	ono-infect ivents aseline 22 6 28 1 (P = 0.0 28 5 70 38 7	Total         We           161         7           56         7           217         14           7); I <sup>2</sup> = 70%         14           119         8           77         3           26         6	7.1% 7.2% 4.3% % 8.0% 8.3% 5.9%	<ul> <li>H. Random, 95% Cl Yea</li> <li>0.93 [0.33, 2.63] 200</li> <li>3.63 [1.31, 10.08] 201</li> <li>1.84 [0.48, 7.02]</li> <li>1.12 [0.47, 2.67] 198</li> <li>0.06 [0.01, 0.45] 198</li> <li>1.19 [0.41, 3.46] 198</li> </ul>	2) 33	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous filt Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987	Dual infer Events vanced fibu 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrr 16 1 14 9	Construction         Mm           Total         E           tosis at ba         39           56         95           3.36, df =         =           = 0.37)	ono-infect <u>vents</u> sseline 22 6 28 1 (P = 0.0 95 70 38 7 78	Total         We           161         7           56         7           217         14           7); $I^2 = 70$ ?           119         8           77         3           26         6           107         2	7.1% 7.2% 4.3% % 3.0% 3.3% 5.9% 2.0%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         1.84           1.12 [0.47, 2.67]         198           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198	) 3 4 4 7 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2 1.3.2 Heterogenous fit Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987	Dual infec Events vanced fibi 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrr 16 1 1 4 9 9	tion M. <u>Total E</u> tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47	ono-infect ivents 22 6 28 1 (P = 0.0 8 7 7 8 7 7 8 5	Total         We           161         7           56         7           217         14           7); I <sup>2</sup> = 70%         14           77); I <sup>2</sup> = 70%         2           119         8           77         3           26         6           107         2           296         6	7.1% 7.2% 4.3% % 8.0% 3.3% 5.9% 2.0% 5.6%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         1.84           1.12 [0.47, 2.67]         198           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           15.73 [5.10, 48.53]         198	1 1 7 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fit Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Tamura 1993	Dual infer Events vanced fibu 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrr 16 1 14 9	Construction         Mm           Total         E           tosis at ba         39           56         95           3.36, df =         =           = 0.37)	ono-infect ivents 22 6 28 1 (P = 0.0 8 7 7 8 7 7 8 5	Total         We           161         7           56         7           217         14           7); I² = 70%           119         8           77         3           26         6           107         2           296         6           1058         7	7.1% 7.2% 4.3% % 3.0% 3.3% 5.9% 2.0%	I. Random, 95% CI Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         1.84           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           1.19 [0.41, 3.46]         198           1.573 [5.10, 48.53]         198           3.38 [1.35, 8.44]         199	1 4 7 7 3	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Tamura 1993 Singh 1995	Dual infec Events vanced fibi 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrh 16 1 14 9 10 6	tion M. <u>Total E</u> osis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69	ono-infect ivents 22 6 28 1 (P = 0.0) 28 7 38 7 78 5 29	Total         We           161         7           56         7           217         14           7); $l^2 = 70^9$ 119         8           77         3           26         6           107         2           296         6           1058         7           175         4	7.1% 7.2% 4.3% % 3.0% 3.3% 5.9% 2.0% 3.6% 7.8%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         1.84           1.12 [0.47, 2.67]         198           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           15.73 [5.10, 48.53]         198	1 4 7 7 7 3 5	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Tamura 1993 Singh 1995 Cross 2008	Dual infer Events vanced fibr 5 17 22 20.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrh 16 1 14 9 10 6 2	Stion         M.           Total         E           rosis at ba         39           56         95           3.36, df =         =           = 0.37)	ono-infect ivents 22 6 28 1 (P = 0.0 8 7 7 8 5 29 6 6 6 6	Total         We           161         7           56         7           217         14           7); $l^2 = 70^9$ 119         8           77         3           26         6           107         2           296         6           1058         7           175         4           840         8	7.1% .2% 4.3% % 3.0% 3.3% 5.9% 2.0% 5.6% 6.6% 6.8%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         1.84           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           15.73 [5.10, 48.53]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199	0 3 4 4 7 7 7 7 3 5 3	Odds Ratio
Study or Subgroup           1.3.1 All cirrhosis/adv           Fattovich 2000           Brancaccio 2018           Subtotal (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> = 0           Test for overall effect: Z           1.3.2 Heterogenous filt           Cronberg 1984           Govindarajan 1984           Cenac 1987           Toichapoulos 1987           Toukan 1983           Singh 1995           Cross 2008           Manesis 2013	Dual infec Events vanced fibi 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrh 16 1 14 9 10 6 2 8 1 1 1	tion M. <u>Total E</u> tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69 29 82 65 6	ono-infect ivents 22 6 28 1 (P = 0.0) 28 7 7 8 7 7 8 5 29 6 66 15 18	Total         We           161         7           56         7           217         14           7); I² = 70%           119         8           77         3           26         6           107         2           108         7           107         2           1058         7           175         4           840         8           1836         32	7.1% 7.2% 4.3% % 8.0% 3.3% 3.9% 2.0% 3.6% 7.8% 4.4% 8.6% 3.3% 2.9%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         198           0.06 [0.01, 0.45]         198           1.19 [0.47, 3.46]         198           7.14 [0.40, 126.58]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200	0 3 4 4 7 7 7 3 5 3 3 3	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Toukan 1987 Tamura 1993 Singh 1995 Cross 2008 Manesis 2013 Asmah 2014 Kushner 2015	Dual infer Events vanced fibu 5 17 22 20.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 1 14 9 10 6 2 8 1 1 1 2 2 3	Stion         M.           Total         E           rosis at ba         39           56         95           3.36, df =         =           0.37)         0           otic stage         26           19         46           9         47           69         29           82         65           6         1000	ono-infect vents sseline 22 6 28 1 (P = 0.0 8 7 70 38 7 7 8 5 29 6 6 66 15 18 8	Total         We           161         7           56         7           217         14           7); I <sup>2</sup> = 709         2           119         8           206         6           107         2           296         6           1058         7           11058         3           1836         3           47         2           1000         8	7.1% .22% 4.3% % 8.0% 3.3% 5.9% 7.8% 4.4% 8.6% 7.8% 4.4% 3.3% 2.9% 3.4%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         1.84           1.12 [0.47, 2.67]         198           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           15.73 [5.10, 48.53]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.032 [0.03, 2.99]         201           2.92 [1.30, 6.56]         201	1	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Tamura 1993 Singh 1995 Cross 2008 Masmah 2014 Kushner 2015 Béguelin 2017	Dual infer Events vanced fibi 5 17 22 2.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 14 9 10 6 2 8 1 1 1 23 83	tion M. <u>Total E</u> tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69 29 82 65 6 1000 104	ono-infect vents 22 6 28 1 (P = 0.0 28 7 7 8 5 29 6 6 6 6 6 15 18 8 4 62	Total         We           161         7           56         7           217         14           7); I² = 70%           119         8           77         3           26         6           107         2           296         6           1078         77           175         4           840         8           1836         3           47         2           1000         8           623         100	7.1% 7.2% 4.3% % 8.0% 8.9% 2.0% 5.6% 7.8% 7.8% 8.6% 8.6% 8.3% 2.9% 8.4% 0.1%	H. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         201           1.9 [0.47, 2.67]         198           1.19 [0.47, 3.46]         198           1.19 [0.41, 3.46]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.90 [0.25, 14.58]         201           0.32 [0.03, 2.99]         201           1.38 [0.83, 2.30]         201	4 — 7 7 7 3 3 3 4 5 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous filt Cronberg 1984 Govindarajan 1984 Cenac 1987 Toichopoulos 1987 Toichopoulos 1987 Toukan 1987 Tamura 1993 Singh 1995 Cross 2008 Manesis 2013 Asmah 2014 Kushner 2015 Béguelin 2017 Luma 2017	Dual infer Events vanced fibs 5 17 22 2.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 1 14 9 10 6 2 8 1 1 1 2 8 8 3 2	tion M. <u>Total E</u> tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69 29 82 65 6 1000 104 31	ono-infect ivents 22 6 28 1 (P = 0.0 28 7 70 38 7 7 8 5 29 6 66 15 18 8 66 15 18 8 462 6	Total         We           161         7           56         7           217         14           7); I²         70;           119         8           77         3           26         6           107         2           296         6           1075         4           1836         3           47         2           1000         8           623         10           260         4	7.1% 7.2% 4.3% % 8.0% 8.9% 8.0% 8.6% 8.8% 8.8% 8.8% 8.8% 8.8% 8.8% 8.4% 9.1% 4.4%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         1.84           1.12 [0.47, 2.67]         198           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.90 [0.25, 14.58]         201           0.32 [0.33, 2.99]         201           1.38 [0.83, 2.30]         201           2.92 [1.30, 6.65]         201	5 3 4 7 7 7 3 3 3 4 5 7 7 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Govindarajan 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Toukan 1987 Toukan 1985 Cross 2008 Manesis 2013 Asmah 2014 Kushner 2015 Béguelin 2017 Luma 2017 Coghill 2018	Dual infer Events vanced fibi 5 17 22 2.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 14 9 10 6 2 8 1 1 1 23 83	tion M. <u>Total E</u> tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69 29 82 65 6 1000 104	ono-infect vents iseline 22 6 28 1 (P = 0.0 8 70 38 7 78 5 29 6 66 66 15 15 18 8 462 6 20	Total         We           161         7           56         7           217         14           7); I² = 70%           119         8           77         3           266         6           107         2           296         6           1058         7           175         4           840         8           1836         3           47         2           260         4           260         4           260         4	7.1% 7.2% 4.3% % 8.0% 8.9% 2.0% 5.6% 7.8% 7.8% 8.6% 8.6% 8.3% 2.9% 8.4% 0.1%	H. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         201           1.9 [0.47, 2.67]         198           1.19 [0.47, 3.46]         198           1.19 [0.41, 3.46]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.90 [0.25, 14.58]         201           0.32 [0.03, 2.99]         201           1.38 [0.83, 2.30]         201	5 3 4 7 7 7 3 3 3 4 5 7 7 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/ adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Toukan 1987 Tous 1983 Singh 1995 Cross 2008 Manesis 2013 Asmah 2014 Kushner 2015 Béguelin 2017 Luma 2017 Coghill 2018 Subtotal (95% Cl)	Dual infer Events vanced fibs 5 17 22 2.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 1 14 9 10 6 2 8 1 1 1 2 8 8 3 2	tion M. <u>Total E</u> tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69 29 47 69 29 82 65 6 1004 31 115	ono-infect vents iseline 22 6 28 1 (P = 0.0 8 70 38 7 78 5 29 6 66 66 15 15 18 8 462 6 20	Total         We           161         7           56         7           217         14           7); I² = 70%           119         8           77         3           266         6           107         2           296         6           1058         7           175         4           840         8           1836         3           47         2           260         4           260         4           260         4	7.1% 7.2% 4.3% % 8.0% 3.3% 3.9% 5.6% 7.8% 4.4% 8.6% 3.3% 2.9% 3.4% 0.1% 4.4% 3.9%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         200           1.84 [0.48, 7.02]         200           1.84 [0.48, 7.02]         198           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           15.73 [5.10, 48.53]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.90 [0.25, 14.58]         201           0.32 [0.03, 2.99]         201           2.92 [1.30, 6.56]         201           1.69 [0.82, 3.48]         201	5 3 4 7 7 7 3 3 3 4 5 7 7 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous filt Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Tamura 1993 Singh 1995 Cross 2008 Manesis 2013 Asmah 2014 Kushner 2015 Béguelin 2017 Luma 2017 Coghill 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0	Dual infer Events vanced fibs 5 17 22 2.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 1 4 9 10 6 2 8 1 1 1 2 3 8 3 2 14 190 0.47; Chi <sup>2</sup> =	tion M. Total E tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69 29 82 65 6 1000 104 31 115 1648 36.21, df =	ono-infect vents aseline 22 6 28 1 (P = 0.0 28 70 38 7 78 5 29 6 66 15 18 8 462 6 20 8 8 462 6 20 8 46 20 8 46 20 46 46 20 46 46 20 47 47 47 47 47 47 47 47 47 47	Total         We           161         7           56         7           217         14           7); l² = 70%           119         8           77         3           26         6           107         2           296         6           1075         4           840         8           623         100           260         4           264         8           6728         8	7.1% 7.2% 4.3% % 8.0% 8.0% 2.0% 5.6% 7.8% 7.8% 8.6% 3.3% 2.9% 8.6% 3.3% 2.9% 3.4% 3.1% 4.4% 3.9% 5.7%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         200           1.84 [0.48, 7.02]         200           1.84 [0.48, 7.02]         198           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           15.73 [5.10, 48.53]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.90 [0.25, 14.58]         201           0.32 [0.03, 2.99]         201           2.92 [1.30, 6.56]         201           1.69 [0.82, 3.48]         201	5 3 4 7 7 7 3 3 3 4 5 7 7 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Tamura 1993 Singh 1995 Cross 2008 Manesis 2013 Asmah 2014 Kushner 2015 Béguelin 2017 Luma 2017 Coghill 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	Dual infer Events vanced fibs 5 17 22 2.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 1 4 9 10 6 2 8 1 1 1 2 3 8 3 2 14 190 0.47; Chi <sup>2</sup> =	ction         M.           Total         E           rosis at ba         39           56         95           3.36, df =         =           0.37)         1000           otic stage         26           19         46           9         47           69         29           82         65           1000         104           31         115           1648         36.21, df =           0.02)         =	ono-infect vents aseline 22 6 28 1 (P = 0.0) 28 70 38 7 78 5 29 6 66 15 18 8 462 6 20 828 = 13 (P = 0) 15 15 18 8 462 6 20 15 18 8 462 6 20 10 10 10 10 10 10 10 10 10 1	Total         We           161         7           56         7           217         14           7); I <sup>2</sup> = 709           119         8           77         32           6         107           296         6           1058         7           175         4           840         8           623         100           264         8           6728         8           .00006); I <sup>2</sup> .	7.1% 7.2% 4.3% % 3.0% 3.3% 5.9% 2.0% 5.6% 7.8% 7.8% 4.4% 3.6% 3.3% 5.9% 5.4% 0.1% 4.4% 3.9% 5.7% = 64%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         201           1.9 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.90 [0.25, 14.58]         201           0.32 [0.33, 2.90]         201           2.92 [1.30, 6.56]         201           1.38 [0.83, 2.30]         201           1.69 [0.82, 3.48]         201           1.79 [1.10, 2.92]         201	5 3 4 7 7 7 3 3 3 4 5 7 7 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Tamura 1993 Singh 1995 Cross 2008 Manesis 2013 Asmah 2014 Kushner 2015 Béguelin 2017 Luma 2017 Coghill 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z Total (95% Cl)	Dual infer Events vanced fibs 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 14 9 10 6 2 8 1 1 23 83 2 14 190 0.47; Chi <sup>2</sup> = 2 = 2.32 (P	tion M. Total E tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69 29 82 65 6 1000 104 31 115 1648 36.21, df =	ono-infect vents aseline 22 6 28 1 (P = 0.0) 28 70 38 7 78 5 29 6 66 15 18 8 462 6 20 828 = 13 (P = 0.0) 29 6 15 18 8 462 6 20 15 18 8 462 6 20 10 10 10 10 10 10 10 10 10 1	Total         We           161         7           56         7           217         14           7); l² = 70%           119         8           77         3           26         6           107         2           296         6           1075         4           840         8           623         100           260         4           264         8           6728         8	7.1% 7.2% 4.3% % 3.0% 3.3% 5.9% 2.0% 5.6% 7.8% 7.8% 4.4% 3.6% 3.3% 5.9% 5.4% 0.1% 4.4% 3.9% 5.7% = 64%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         200           1.84 [0.48, 7.02]         200           1.84 [0.48, 7.02]         198           0.06 [0.01, 0.45]         198           1.19 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           15.73 [5.10, 48.53]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.90 [0.25, 14.58]         201           0.32 [0.03, 2.99]         201           2.92 [1.30, 6.56]         201           1.69 [0.82, 3.48]         201	5 3 4 7 7 7 3 3 3 4 5 7 7 7	Odds Ratio
Study or Subgroup 1.3.1 All cirrhosis/adv Fattovich 2000 Brancaccio 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.3.2 Heterogenous fil Cronberg 1984 Govindarajan 1984 Cenac 1987 Trichopoulos 1987 Toukan 1987 Tamura 1993 Singh 1995 Cross 2008 Manesis 2013 Asmah 2014 Kushner 2015 Béguelin 2017 Luma 2017 Coghill 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	Dual infer Events vanced fibs 5 17 22 0.65; Chi <sup>2</sup> = 2 = 0.90 (P brotic/cirrf 16 1 1 4 9 10 6 2 8 1 1 1 23 83 2 14 190 0.47; Chi <sup>2</sup> = 2 = 2.32 (P	tion M. Total E tosis at ba 39 56 95 3.36, df = = 0.37) totic stage 26 19 46 9 47 69 29 82 65 6 1000 104 31 115 1648 36.21, df = = 0.02) 1743	ono-infect vents seline 22 6 28 1 (P = 0.0 8 7 7 8 5 29 6 6 6 15 18 8 4 6 20 4 6 20 4 8 28 8 8 4 6 20 4 8 20 6 5 29 8 1 8 8 4 6 20 7 7 8 5 29 8 6 8 7 7 8 5 29 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	Total         We           161         7           56         7           217         14           7); I² = 709           119         8           77         3           26         6           107         2           296         6           107         2           296         6           107         2           296         6           107         2           296         6           1000         8           623         1000           66728         8           0.0006); I²         100           6945         100	7.1% 7.2% 4.3% % 8.0% 8.9% 8.0% 8.6% 8.8% 8.6% 8.8% 8.6% 8.8% 8.4% 9.1% 4.4% 8.9% 5.7% = 64%	1. Random, 95% Cl Yea           0.93 [0.33, 2.63]         200           3.63 [1.31, 10.08]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         201           1.84 [0.48, 7.02]         201           1.9 [0.41, 3.46]         198           7.14 [0.40, 126.58]         198           3.38 [1.35, 8.44]         199           2.09 [0.40, 10.88]         199           1.27 [0.59, 2.74]         200           1.90 [0.25, 14.58]         201           0.32 [0.33, 2.90]         201           2.92 [1.30, 6.56]         201           1.38 [0.83, 2.30]         201           1.69 [0.82, 3.48]         201           1.79 [1.10, 2.92]         201	5 3 4 7 7 7 3 3 3 4 5 7 7 7	Odds Ratio M-H, Random, 95% Cl

**Fig. 3** A, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of HCV or HIV co-infection. Events denote patients with HCC. B, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of advanced fibrosis or cirrhosis. Events denote patients with HCC. C, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of different ethnic populations. Events denote patients with HCC. D, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of different ethnic populations. Events denote patients with HCC. D, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of different ethnic populations. Events denote patients with HCC. D, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of different study design. Events denote patients with HCC. E, Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of antiviral treatment. Events denote patients with HCC. G Odds ratio of hepatitis delta infection to HCC by the subgroup analysis of antiviral treatment. Events denote patients with HCC. C = confidence interval; M-H = Mantel-Haenszel; IFN = interferon; NA = nucleos(t)ides analogues.

Study or Subaroup	Dual infe Events		Mono-inf Events		Weight	Odds Ratio	l Voar			lds Ratio Ind <u>om, 95% Cl</u>	
Study or Subgroup 1.4.1 Caucasians	Events	rotar	Events	rotal	weight	M-H, Random, 95% Cl	reaf		м-п, Ка	100/11, 35 /0 GI	
Govindarajan 1984	0	14	7	29	1.5%	0.10 [0.01, 1.95]	1004				
		9	78	107					_		
Trichopoulos 1987	9				1.5%	7.14 [0.40, 126.58]					
Fattovich 2000	5	39	22	161	5.4%						
Cross 2008	8	82	66	840	6.6%	1.27 [0.59, 2.74]				-	
Ji 2012	17	667	46	8556	7.5%	4.84 [2.76, 8.49]	2012				
Manesis 2013	1	65	15	1836	2.6%	1.90 [0.25, 14.58]	2013				
Kushner 2015	23	1000	8	1000	6.4%	2.92 [1.30, 6.56]	2015				
Béguelin 2017	83	104	462	623	7.7%	1.38 [0.83, 2.30]	2017			+	
Brancaccio 2018	17	56	6	56	5.5%	3.63 [1.31, 10.08]					
Coghill 2018	14	115	20	264	6.8%	1.69 [0.82, 3.48]				<b></b>	
Subtotal (95% CI)	14	2151	20	13472	51.7%	1.97 [1.23, 3.16]	2010			•	
		2131	-	13472	51.770	1.37 [1.23, 3.10]				•	
Total events	177		730								
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2				0.008); I	<sup>2</sup> = 60%						
1.4.2 Asians											
Chen 1984	0	3	11	60	1.4%	0.61 [0.03, 12.75]	1004				
	-	-									
Toukan 1987	10	47	5	296	5.1%	15.73 [5.10, 48.53]					
Tamura 1993	6	69	29	1058	6.0%	3.38 [1.35, 8.44]			_	-	
Singh 1995	2	29	6	175	3.4%	2.09 [0.40, 10.88]			-		
Oyunsuren 2006	46	93	10	31	6.2%	2.06 [0.87, 4.84]	2006				
Subtotal (95% CI)		241		1620	22.1%	3.45 [1.41, 8.45]					
Total events	64		61							[	
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2				0.04); l <sup>2</sup>	= 60%						
1.4.3 Africans	,		·								
Cronberg 1984	16	26	70	119	6.2%	1.12 [0.47, 2.67]	1984		-	<b></b>	
Cenac 1987	14	46	70	26	5.3%	1.19 [0.41, 3.46]			-		
Asmah 2014	1	6	18	47	2.3%	0.32 [0.03, 2.99]					
Amougou 2016	24	25	8	42	2.4%	102.00 [11.96, 870.00]					
Luma 2017	2	31	6	260	3.4%	2.92 [0.56, 15.14]					
Mahale 2018	18	29	165	301	6.6%	1.35 [0.62, 2.95]	2018				
Subtotal (95% CI)		163		795	26.2%	2.01 [0.73, 5.51]					
Total events	75		274								
Heterogeneity: Tau <sup>2</sup> = <sup>4</sup> Test for overall effect: 2			df = 5 (P =	0.002); I	<sup>2</sup> = 74%						
Total (95% CI)		2555		15887	100.0%	2.18 [1.48, 3.22]				•	
Total events	316		1065								
Heterogeneity: Tau <sup>2</sup> = 0	0 44 Chi2 -	- 55 75		< 0.0001	) 12 = 64%			0.001			100
Test for subgroup differ	rences: Ch	i <sup>2</sup> = 1.21,	, df = 2 (P	= 0.55), I	<sup>2</sup> = 0%			'		n] Favours [Mono-infection	
					<sup>2</sup> = 0%	Odds Ratio			Q		
Study or Subgroup	Dual infe Events	ction	, df = 2 (P Mono-inf Events	ection		Odds Ratio M-H, Random, 95% Cl	l Year			Ids Ratio andom, 95% CI	
Study or Subgroup 1.5.1 Cross sectional	Dual infe Events study	ction Total	Mono-inf Events	ection Total	Weight	M-H, Random, 95% C				lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984	Dual infe Events study 1	ction Total 19	Mono-inf Events 38	ection Total 77	Weight 2.7%	M-H, Random, 95% C	1984			lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984	Dual infe Events study 1 16	rction Total 19 26	Mono-inf Events 38 70	Total 77 119	Weight 2.7% 6.0%	M-H, Random, 95% C 0.06 [0.01, 0.45] 1.12 [0.47, 2.67]	1984 1984			lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984	Dual infe Events study 1 16 0	Total 19 26 3	Mono-inf Events 38 70 11	ection Total 77 119 60	Weight 2.7% 6.0% 1.5%	M-H, Random, 95% C 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75]	1984 1984 1984			lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984	Dual infe Events study 1 16	rction Total 19 26	Mono-inf Events 38 70	Total 77 119	Weight 2.7% 6.0%	M-H, Random, 95% C 0.06 [0.01, 0.45] 1.12 [0.47, 2.67]	1984 1984 1984			lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995	Dual infe Events study 1 16 0	Total 19 26 3	Mono-inf Events 38 70 11	ection Total 77 119 60	Weight 2.7% 6.0% 1.5%	M-H, Random, 95% C 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75]	1984 1984 1984 1995	<		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Asmah 2014	Dual infe Events study 1 16 0 2	rction Total 19 26 3 29	Mono-inf Events 38 70 11 6	rotal 77 119 60 175	Weight 2.7% 6.0% 1.5% 3.6%	M-H, Random, 95% C 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88]	1984 1984 1984 1995 2014	<		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Asmah 2014 Luma 2017	Dual infe Events study 1 16 0 2 1	tion Total 19 26 3 29 6	Mono-inf Events 38 70 11 6 18	77 77 119 60 175 47	Weight 2.7% 6.0% 1.5% 3.6% 2.4%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99]	1984 1984 1984 1995 2014	<		lds Ratio	
Study or Subgroup 15.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI)	Dual infe Events study 1 16 0 2 1 2	19 26 3 29 6 31	Mono-inf Events 38 70 11 6 18 6	77 119 60 175 47 260	<b>Weight</b> 2.7% 6.0% 1.5% 3.6% 2.4% 3.6%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14]	1984 1984 1984 1995 2014	<		lds Ratio	-
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 1	Dual infe Events study 1 16 0 2 1 2 22 1.07; Chi <sup>2</sup> =	tion <u>Total</u> 19 26 3 29 6 31 114 = 12.38, 6	Mono-inf Events 38 70 11 6 18 6 18 6 149	ection Total 77 119 60 175 47 260 738	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14]	1984 1984 1984 1995 2014	<		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2	Dual infe <u>Events</u> study 1 16 0 2 1 2 1.07; Chi <sup>2</sup> = 2 2 2 2 2 2 2 2 2 2 2 2 1.07; Chi <sup>2</sup> =	tion <u>Total</u> 19 26 3 29 6 31 114 = 12.38, 6	Mono-inf Events 38 70 11 6 18 6 18 6 149	ection Total 77 119 60 175 47 260 738	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14]	1984 1984 1984 1995 2014	<		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.5.2 Case-control stu	Dual infe Events study 1 16 0 2 1 2 22 1.07; Chi <sup>2</sup> = Z = 0.47 (P Jdy	tion Total 19 26 3 29 6 31 114 = 12.38, = 0.64)	Mono-inf Events 38 70 11 6 18 6 18 6 149 df = 5 (P =	ection Total 77 119 60 175 47 260 738 0.03); I <sup>2</sup>	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% = 60%	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34]	1984 1984 1984 1995 2014 2017	<		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.5.2 Case-control stu Trichopoulos 1987	Dual infe <u>Events</u> study 1 16 0 2 1 2 1.07; Chi <sup>2</sup> = 2 2 2.0.47 (P 3 2 2 1.07; Chi <sup>2</sup> = 0.47 (P 3 2 2 1.07; Chi <sup>2</sup> = 0.47 (P 1.07) 2 1.07; Chi <sup>2</sup> = 0.04 (P 1.07) 2 0 0 0 0 0 0 0 0 0 0 0 0 0	rection Total 19 26 3 29 6 31 114 = 12.38, ( = 0.64) 9	Mono-inf Events 38 70 11 6 18 6 18 6 149 df = 5 (P =	ection Total 77 119 60 175 47 260 738 0.03); I <sup>2</sup> 107	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% = 60%	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58]	1984 1984 1985 2014 2017	<		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect 2 1.5.2 Case-control stu Trichopoulos 1987 Amougou 2016	Dual infe <u>Events</u> study 1 1 6 0 2 1 2 22 1.07; Chi <sup>2</sup> = Z = 0.47 (P ady 9 24	retion 19 26 3 29 6 31 114 = 12.38, ( = 0.64) 9 25	Mono-inf Events 38 70 11 6 18 6 149 df = 5 (P = 78 8	ection Total 77 119 60 175 47 260 738 0.03); I <sup>2</sup> 107 42	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% = 60% 1.7% 2.6%	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.56] 102 00 [11.96, 870.00]	1984 1984 1995 2014 2017 1987 2016	<		lds Ratio	
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Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 1 Tichopoulos 1987 Amougou 2016 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: 2 Test for overall effect: 2 1.5.2 Case-control study	Dual infe Events study 1 16 0 2 1 2 22 1.07; Chi <sup>2</sup> = 2 2 2 2 2 2 2 2 2 2 2 2 2	State         State           19         26         3           29         6         3           31         114         114           = 12.38, 8         9         25           29         63         3           = 15.75, 5         -         -	Mono-inf <u>Events</u> 38 70 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P =	ection Total 77 119 60 175 47 260 738 0.03); I <sup>2</sup> 0.03); I <sup>2</sup> 107 42 301 450	Weight 2.7% 6.0% 1.5% 2.4% 3.6% 19.8% = 60% 1.7% 2.6% 6.3% 10.6%   <sup>2</sup> = 87%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00]	1984 1984 1984 1995 2014 2017 1987 2016 2018	<		lds Ratio	
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Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.5.2 Case-control stud Trichopoulos 1987 Amougou 2016 Mahale 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 6 Test for overall effect: 2 1.5.3 Cohort study Toukan 1987 Cenac 1987	$\begin{array}{c} \mbox{Dual infe} \\ \hline \mbox{Events} \\ \mbox{study} \\ 1 \\ 16 \\ 0 \\ 2 \\ 1 \\ 2 \\ 22 \\ 1.07; \mbox{Chi}^2 = \\ 2 = 0.47 \ (P \\ 9 \\ 24 \\ 18 \\ 6.09; \mbox{Chi}^2 = \\ 51 \\ 6.09; \mbox{Chi}^2 = \\ 1.42 \ (P \\ 10 \\ 14 \\ \end{array}$	ction Total 19 26 3 3 3 1 114 = 12.38, 8, 6 31 114 = 0.64) 9 25 29 6 5 29 5 29 5 5 29 5 5 29 5 47 47 46	Mono-inf <u>Events</u> 38 70 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 5 7	ection <u>Total</u> 77 119 60 175 47 738 738 107 42 301 450 0.003); I <sup>2</sup> 450 0.0004); 2966 266 266	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% = 60% 1.7% 2.6% 6.3% 10.6%   <sup>2</sup> = 87% 5.1% 5.3%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 12.76] 2.09 [0.40, 126] 9.292 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46]	1984 1984 1995 2014 2017 1987 2016 2018	٠ <u>ـ</u>		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect 2 1.5.3 Cohort study Toukan 1987 Cenac 1983	$\begin{array}{c} \textbf{Dual infe} \\ \hline \textbf{Events} \\ \textbf{study} \\ 1 \\ 16 \\ 0 \\ 2 \\ 11 \\ 2 \\ 22 \\ 107; Chi^2 = \\ 24 \\ 18 \\ 5.09; Chi^2 = \\ 14 \\ 6 \\ \end{array}$	ction           Total           19           26           3           29           6           31           114           =12.38, 8, 92           9           25           29           63           =           114           =           9           25           29           63           =           0.64)           9           25           29           63           =           0.15)           47           46           69	Mono-inf Events 38 70 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 5 7 29	ection <u>Total</u> 77 119 60 00 175 47 7260 738 0.003); l <sup>2</sup> 107 42 301 450 0.0004); 2296 266 266 266 266 266 1058	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% = 60% 1.7% 2.6% 6.3% 10.6% 10.6% 5.1% 5.1% 5.9%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.38, 8.44]	1984 1984 1995 2014 2017 1987 2016 2018 1987 1987 1987	<b>←</b>		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect 2 1.5.2 Case-control stu Trichopoulos 1987 Amougou 2016 Mahale 2018 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = 1 Total events Heterogeneity: Tau <sup>2</sup> = 1 1.5.3 Cohort study Toukan 1987 Cenac 1987 Tamura 1993 Fattovich 2000	$\begin{array}{c} \mbox{Dual infe} \\ \hline \mbox{Events} \\ \mbox{study} \\ 1 \\ 1 \\ 6 \\ 2 \\ 1 \\ 2 \\ 1.07; \mbox{Chi}^2 = \\ 22 \\ 1.07; \mbox{Chi}^2 = \\ 22 \\ 1.07; \mbox{Chi}^2 = \\ 1.07; \mbox{Chi}^2 = \\ 1.07; \mbox{Chi}^2 = \\ 1.42; \mbox{Prime} \\ 1.42; \mbox{Prime} \\ 1.43; \mbox{Prime} \\ 1.44; \mbox$	ction           Total           19           26           31           114           = 12.38,           9           26           29           6           31           114           9           25           29           63           53           63           53           63           54           63           63           63           63           47           46           69           39	Mono-inf Events 388 700 111 6 188 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 5 7 29 22	ection <u>Total</u> 77 119 60 175 47 260 0.0.03); I <sup>2</sup> 107 42 30 0.0.03); I <sup>2</sup> 260 0.0004); 296 266 1058 161 105 105 105 105 105 105 105 10	Weight. 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% = 60% 1.7% 6.3% 10.6% 1.7% 5.1% 5.3% 5.9%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.88 [1.35, 8.16], 3.8, 2.63]	1984 1984 1995 2014 2017 1987 2016 2018 1987 1987 1987 1993 2000	<b>+</b> ــــــــــــــــــــــــــــــــــــ		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Chen 1984 Singh 1995 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 1 Tichopoulos 1987 Amougou 2016 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 6 Test for overall effect: 2 1.5.2 Case-control stut Trichopoulos 1987 Amougou 2016 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 6 Test for overall effect: 2 1.5.3 Cohort study Toukan 1987 Canac 1987 Tamura 1993 Fattovich 2000 Oyunsuren 2006	$\begin{array}{c} \mbox{Dual infe} \\ \mbox{Events} \\ \mbox{study} \\ 1 \\ 16 \\ 0 \\ 2 \\ 1 \\ 1 \\ 2 \\ 22 \\ 1.07; \mbox{Chi}^2 = \\ 22 \\ 1.07; \mbox{Chi}^2 = \\ 22 \\ 1.07; \mbox{Chi}^2 = \\ 1.07; \mbox{Chi}^2 = \\ 1.03; \mbox{Chi}^2 = \\ 1.03; \mbox{Chi}^2 = \\ 1.04; C$	Total           Total           19           26           3           29           6           31           114           =           229           6           31           114           9           92           63           =           15.75, f.           47           46           69           39           93	Mono-inf Events 38 700 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 251 df = 2 (P = 5 7 29 22 10	ection <u>Total</u> 77 119 60 175 47 260 738 0.0.03); I <sup>2</sup> 107 42 301 450 0.0004); 296 266 1058 161 155 1058 161 131	Weight 2.7% 6.0% 1.5% 3.6% 3.6% 19.8% = 60% 1.7% 2.6% 2.6% 19.8% 10.6% 10.5% 10.5% 10.5% 10.5% 10.5% 10.5% 10.5% 10.5% 10.5% 10.5% 10.6% 10.5% 10.6% 1	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.35, 8.44] 0.39 [0.33, 2.65] 2.06 [0.87, 4.84]	1984 1984 1995 2014 2017 1987 2016 2018 1987 1987 1993 2000 2006	<b>٠</b> ــــ		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Cronberg 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.5.2 Case-control study Trichopoulos 1987 Amougou 2016 Mahale 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 6 Test for overall effect: 2 1.5.3 Cohort study Toukan 1987 Cenac 1987 Tamura 1993 Fattovich 2000 Oyunsuren 2006 Cross 2008	$\begin{array}{c} \textbf{Dual infe} \\ \hline \textbf{Events} \\ \textbf{study} \\ 1 \\ 16 \\ 0 \\ 2 \\ 1 \\ 2 \\ 22 \\ 1.07; Chi2 = \\ 24 \\ 18 \\ 51 \\ 6.09; Chi2 = \\ 51 \\ 6.09; Chi2 = \\ 10 \\ 14 \\ 6 \\ 5 \\ 46 \\ 8 \\ \end{array}$	Total           Total           19           26           31           114           = 12.38, 8           9           26           29           6           31           114           = 12.38, 8           = 15.75, 100           46           69           39           9           33           9           46           69           39           382	Mono-inf Events 38 70 11 6 18 8 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 5 7 29 22 10 66	ection <u>Total</u> 77 119 60 175 47 280 738 60 03); l <sup>2</sup> 450 0.0004); 2966 266 266 266 1058 161 31 840	$\begin{array}{c} \textbf{Weight} \\ 2.7\% \\ 6.0\% \\ 1.5\% \\ 3.6\% \\ 2.4\% \\ 2.6\% \\ 19.8\% \\ 2.6\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 2.6\% \\ 10.6\% \\ 10.6\% \\ 5.1\% \\ 5.3\% \\ 5.4\% \\ 5.4\% \\ 6.1\% \\ 6.4\% \end{array}$	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 2.09 [0.40, 10.88] 0.32 [0.33, 2.75] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.56] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.38, 8.44] 0.33 [0.32, 2.63] 2.6 [0.87, 4.84] 1.27 [0.59, 2.74]	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1987 1987 1983 2000 2006 2008	¢		lds Ratio	
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Study or Subgroup           1.5.1 Cross sectional           Govindarajan 1984           Cronberg 1984           Chen 1984           Singh 1995           Asmah 2014           Luma 2017           Subbotal (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> = 1           Tichopoulos 1987           Amougou 2016           Subbotal (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> = 6           Test for overall effect: 2           1.5.2 Case-control stud           Thichopoulos 1987           Amougou 2016           Bubtotal (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> = 6           Test for overall effect: 2           1.5.3 Cohort study           Toukan 1987           Crons 2006           Cross 2008           Ji 2012           Manesis 2013           Kushner 2015           Béguelin 2017	$\begin{array}{c} \mbox{Dual infe} \\ \hline \mbox{Events} \\ \mbox{study} \\ 1 \\ 16 \\ 0 \\ 2 \\ 1 \\ 1 \\ 2 \\ 22 \\ 1.07; Chi^2 = \\ 2 \\ 2 \\ 1.07; Chi^2 = \\ 2 \\ 2 \\ 2 \\ 1.07; Chi^2 = \\ 1.07; Chi^2 =$	Section           Total           19           26           3           29           63           114           114           114           9           25           29           63           31           114           9           25           29           63           50           63           114           9           25           29           63           114           14           14           14           47           667           657           1000           104	Mono-inf Events 38 700 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 78 8 165 251 df = 2 (P = 5 7 29 22 10 66 66 466 15 8 8	Total           777           119           60           175           47           260           738           800.03); I <sup>2</sup> 107           42           107           42           00.03); I <sup>2</sup> 107           42           00           296           26           1058           161           31           840           8556           1836           1000           623	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% = 60% 1.7% 6.3% 10.6% 1.7% 6.3% 5.9% 5.4% 5.4% 6.4% 5.4% 6.4% 7.3%	M-H, Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.35, 8.44] 0.33 [0.33, 2.63] 2.26 [0.87, 4.84] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58] 2.92 [1.30, 6.56] 1.38 [0.38, 2.30]	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1987 1987 1993 2000 2006 2008 2012 2013 2015	¢,		lds Ratio	
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Study or Subgroup           1.5.1 Cross sectional           Govindarajan 1984           Cronberg 1984           Chen 1984           Singh 1995           Asmah 2014           Luma 2017           Subtotal (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> = 1           Tichopoulos 1987           Amougou 2016           Mahale 2018           Subtotal (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> = 6           Test for overall effect: 2           1.5.2 Cose-control stud           Total events           Heterogeneity: Tau <sup>2</sup> = 6           Test for overall effect: 2           1.5.3 Cohort study           Toukan 1987           Cenac 1987           Tamura 1993           Fattovich 2000           Oyunsuren 2006           Cross 2008           Ji 2012           Manesis 2013           Kushner 2015           Béguelin 2017           Brancaccio 2018           Cophill 2018	$\begin{array}{c} \mbox{Dual infe} \\ \hline \mbox{Events} \\ \mbox{study} \\ 1 \\ 16 \\ 0 \\ 2 \\ 1 \\ 1 \\ 2 \\ 22 \\ 1.07; Chi^2 = \\ 2 \\ 2 \\ 1.07; Chi^2 = \\ 2 \\ 2 \\ 2 \\ 1.07; Chi^2 = \\ 1.07; Chi^2 =$	Total           19         26           3         3           29         6           31         114           114         114           9         25           29         63           = 15.75, 5, 5, 5, 5, 5, 75, 6, 39           63         39           93         82           63         667           65         1000           104         56           100         104           56         115	Mono-inf Events 38 700 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 78 8 165 251 df = 2 (P = 5 7 29 22 10 66 66 466 15 8 8	Total           777           119           60           175           47           260           738           107           42           107           42           107           42           107           42           107           42           107           42           107           42           107           42           60           0.0004);           296           61           1058           1108           0.0004);           296           1058           108           0.0004);           296           108           0.0004);           296           108           0.0004);           296           108           0.0004);           296           108           0.0006           118           0.0006           10000	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% 10.8%10.8% 10.8% 10.8% 10.8% 10.8% 10.8%10.8% 10.8% 10.8% 10.8% 10.8%10.8% 10.8%10.8% 10.8% 10.8% 10.8% 10.8% 10.8%10.8% 10.8% 10.8% 10.8%	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.38, 8.44] 1.27 [0.59, 2.74] 4.84 [2.76, 8.49] 1.90 [0.25, 14.58] 2.92 [1.36, 556] 1.38 [0.83, 2.30] 3.63 [1.31, 10.6, 553] 1.69 [0.32, 3.48] 1.90 [0.22, 14.58] 1.90 [0.	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1993 2000 2006 2008 2000 2008 2012 2013 2015 2017	¢		lds Ratio	
Study or Subgroup 1.5.1 Cross sectional Govindarajan 1984 Cronberg 1984 Singh 1995 Asmah 2014 Luma 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.5.2 Case-control stut Trichopoulos 1987 Amougou 2016 Mahale 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 6 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 2 1.5.3 Cohort study Toukan 1987 Cenac 1987 Tamura 1983 Fattovich 2000 Oyunsuron 2006 Cross 2008 Ji 2012 Manesis 2013 Kushner 2015 Béguelin 2017 Brancaccio 2018	Dual infe Events study 1 16 0 2 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Total           19           26           31           114           =           12.38, 8, 31           =           9           25           29           63           =           15.75, 5, 5, 66           9           63           29           63           39           39           82           667           765           10000           104           56	Mono-inf Events 38 70 11 6 18 8 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 22 20 10 66 46 46 15 8 8 462 6	Total           77           119           60           175           47           260           738           0.033); I <sup>2</sup> 107           42           301           450           0.0004);           2296           26           31           344           356	$\begin{array}{c} \textbf{Weight} \\ 2.7\% \\ 6.0\% \\ 1.5\% \\ 3.6\% \\ 2.6\% \\ 3.6\% \\ 2.6\% \\ 6.3\% \\ 19.8\% \\ 6.3\% \\ 5.1\% \\ 5.1\% \\ 5.4\% \\ 6.4\% \\ 7.1\% \\ 6.3\% \\ 6.3\% \\ 7.3\% \\ 6.5\% \\ 5.5\% \end{array}$	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 2.09 [0.40, 10.88] 0.32 [0.33, 2.75] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.38, 8.44] 0.33 [0.32, 2.43] 2.65 [0.87, 4.84] 1.27 [0.59, 2.74] 4.84 [2.76, 8.49] 1.90 [0.25, 14.58] 2.92 [1.30, 6.56] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08]	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1993 2000 2006 2008 2000 2008 2012 2013 2015 2017	¢		lds Ratio	
Study or Subgroup           1.5.1 Cross sectional           Govindarajan 1984           Cronberg 1984           Chen 1984           Singh 1995           Asmah 2014           Luma 2017           Subbotal (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> = 1           1.5.2 Case-control stud           Trichopoulos 1987           Amougou 2016           Mahale 2018           Subtotal (95% Cl)           Total events           Heterogeneity: Tau <sup>2</sup> = 6           Test for overall effect: 2           1.5.3 Cohort study           Toukan 1987           Cenac 1987           Tamura 1993           Fattovich 2000           Oyunsuren 2006           Cross 2008           Ji 2012           Manesis 2013           Béguelin 2017           Brancaccio 2018           Cophill 2018	Dual infe Events study 1 16 0 2 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Total           19         26           3         3           29         6           31         114           114         114           9         25           29         63           = 15.75, 5, 5, 5, 5, 5, 75, 6, 39           63         39           93         82           63         667           65         1000           104         56           100         104           56         115	Mono-inf Events 38 70 11 6 18 8 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 22 20 10 66 46 46 15 8 8 462 6	Total           777           119           60           175           47           260           738           107           42           107           42           107           42           107           42           107           42           107           42           107           42           107           42           60           0.0004);           296           61           1058           1108           0.0004);           296           1058           108           0.0004);           296           108           0.0004);           296           108           0.0004);           296           108           0.0004);           296           108           0.0006           118           0.0006           10000	Weight 2.7% 6.0% 1.5% 3.6% 2.4% 3.6% 19.8% 10.8%10.8% 10.8% 10.8% 10.8% 10.8% 10.8%10.8% 10.8% 10.8% 10.8% 10.8%10.8% 10.8%10.8% 10.8% 10.8% 10.8% 10.8% 10.8%10.8% 10.8% 10.8% 10.8%	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.38, 8.44] 1.27 [0.59, 2.74] 4.84 [2.76, 8.49] 1.90 [0.25, 14.58] 2.92 [1.36, 556] 1.38 [0.83, 2.30] 3.63 [1.31, 10.6, 553] 1.69 [0.32, 3.48] 1.90 [0.22, 14.58] 1.90 [0.	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1993 2000 2006 2008 2000 2008 2012 2013 2015 2017	¢		lds Ratio	
Study or Subgroup           1.5.1 Cross sectional           Govindarajan 1984           Cronberg 1984           Chen 1984           Singh 1995           Asmah 2014           Luma 2017           Subbotal (95% Cl)           Total events           Heterogeneity: Tau* = 1           Tichopoulos 1987           Amougou 2016           Mahale 2018           Subtotal (95% Cl)           Total events           Heterogeneity: Tau* = 6           Test for overall effect: 2           1.5.2 Case-control stud           Trichopoulos 1987           Amougou 2016           Guardant (95% Cl)           Total events           Heterogeneity: Tau* = 1           Featorich 2000           Oyunsuren 2006           Cross 2008           Ji 2012           Manesis 2013           Kushner 2015           Béguelin 2017           Brancaccio 2018           Subtotal (95% Cl)           Total events           Heterogeneity: Tau* = 0	$\begin{array}{c} \textbf{Dual infe}\\ \hline \textbf{Events}\\ \textbf{study}\\ 1\\ 16\\ 0\\ 2\\ 1\\ 1\\ 2\\ 22\\ 1.07; Chi^2 = \\ 2\\ 2\\ 1.07; Chi^2 = \\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 1.07; Chi^2 = \\ 1.07; Chi^2 =$	store         store           19         26           3         29           6         31           114         114           114         114           9         25           29         63           = 15.75, 100         29           63         31           = 15.75, 100         23           667         65           10000         104           56         667           102         333           = 31.47,         31.47,	Mono-inf Events 38 700 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 78 8 165 251 1 df = 2 (P = 78 8 165 251 29 22 10 66 66 66 66 66 66 66 66 66 66 66 66 66	ection Total 777 119 60 0738 47 260 738 107 42 206 738 107 42 0.0004); 107 42 0.0004); 2266 266 266 266 1058 161 840 8556 1840 8556 1840 8556 100 2266 266 266 266 266 266 266	$\begin{array}{l} \textbf{Weight} \\ 2.7\% \\ 6.0\% \\ 1.5\% \\ 3.6\% \\ 1.5\% \\ 3.6\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 10.6\% \\ 19.8\% \\ 10.6\% \\ 1$	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.38, 8.44] 0.33 [0.33, 2.63] 2.06 [0.87, 4.84] 1.27 [0.59, 2.74] 4.84 [2.76, 8.49] 1.90 [0.25, 14.58] 2.92 [1.30, 6.56] 1.38 [0.83, 2.30] 3.63 [1.1, 10.08] 1.69 [0.82, 3.48] 2.36 [1.56, 3.58]	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1993 2000 2006 2008 2000 2008 2012 2013 2015 2017	¢		lds Ratio	
Study or Subgroup           1.5.1 Cross sectional           Govindarajan 1984           Cronberg 1984           Chen 1984           Singh 1995           Asmah 2014           Luma 2017           Subtotal (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 1           Test for overall effect: 2           1.5.2 Case-control stud           Trichopoulos 1987           Amougou 2016           Mahale 2018           Subtotal (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 6           Test for overall effect: 2           1.5.2 Cohort study           Toukan 1987           Conac 1987           Tamura 1983           Fattovich 2000           Oyunsuren 2006           Cross 2008           Ji 2012           Manesis 2013           Kushner 2015           Béguelin 2017           Brancaccio 2018           Cophill 2018           Subtotal (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = (           Total events           Subtotal (95% CI)           Total events           <	$\begin{array}{c} \textbf{Dual infe}\\ \hline \textbf{Events}\\ \textbf{study}\\ 1\\ 16\\ 0\\ 2\\ 1\\ 1\\ 2\\ 22\\ 1.07; Chi^2 = \\ 2\\ 2\\ 1.07; Chi^2 = \\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 1.07; Chi^2 = \\ 1.07; Chi^2 =$	Total           19         26           3         29         6           31         114         114           114         114         114           9         25         29         63           = 15.75, 5, 5, 5, 5, 5, 5, 5, 75, 6, 667         65         99         93           82         2667         657         1000         104         56           102         2383         22         31, 47, 7         4         4         4           5         667         657         339         32         33         32         33         32         34         34         35         36         37         36         36         36         36         36         36         36         36         36         36         36         36         36         36         36         36         36         36         36         37         36         36	Mono-inf Events 38 700 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 78 8 165 251 1 df = 2 (P = 78 8 165 251 29 22 10 66 66 66 66 66 66 66 66 66 66 66 66 66	ection Total 777 119 60 738 47 260 738 0.0.03); l <sup>2</sup> 107 42 206 60 301 450 0.0004); 296 62 1058 106 1050 623 56 264 14747 = 0.0009	$\begin{array}{l} \textbf{Weight} \\ 2.7\% \\ 6.0\% \\ 1.5\% \\ 3.6\% \\ 1.9.8\% \\ 19.8\% $	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.88 [1.35, 8.44] 0.93 [0.32, 2.63] 2.06 [0.87, 8.84] 1.27 [0.52, 2.74] 4.84 [2.76, 8.49] 1.90 [0.25, 1.36, 56] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 1.69 [0.82, 3.48] 2.36 [1.56, 3.58]	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1993 2000 2006 2008 2000 2008 2012 2013 2015 2017	¢		lds Ratio	
Study or Subgroup           1.5.1 Cross sectional           Govindarajan 1984           Cronberg 1984           Chen 1984           Singh 1995           Asmah 2014           Luma 2017           Subtotal (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 1           Tichopoulos 1987           Amougou 2016           Mahalae 2018           Subtotal (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 1           Heterogeneity: Tau <sup>2</sup> = 2           Test for overall effect: 2           1.5.3 Cohort study           Toukan 1987           Cenac 1987           Tamura 1993           Fattovich 2000           Oyunsuren 2006           Cross 2008           J 2012           Manesis 2013           Kushner 2015           Beiguelin 2017           Brancacio 2018           Subtotal (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 1           Test for overall effect: 2           Test for overall effect: 2           Total (95% CI)	$\begin{array}{c} \textbf{Dual infe} \\ \hline \textbf{Events} \\ \textbf{study} \\ 1 \\ 16 \\ 0 \\ 2 \\ 1 \\ 1 \\ 2 \\ 22 \\ 1.07; Chi2 = \\ 2 \\ z = 0.47 (P \\ 1 \\ 18 \\ 5 \\ 5 \\ c = 1.42 (P \\ 10 \\ 14 \\ 6 \\ 5 \\ 46 \\ 8 \\ 17 \\ 1 \\ 23 \\ 83 \\ 17 \\ 14 \\ 2.44 \\ 0.33; Chi2 = 4.04 (P \\ z = 4.04 (P \\ z = 4.04 (P \\ z = 1.42 + 1.15 \\ z = 1.15 + 1.15 \\ z$	store         store           19         26           3         29           6         31           114         114           114         114           9         25           29         63           = 15.75, 100         23           667         667           667         655           10000         104           56         667           102         383           = 31.47,         31.47,	Mono-inf Events 38 70 11 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 22 10 66 46 5 7 7 29 22 10 66 46 5 15 8 8 462 20 696 df = 11 (P 1)	ection Total 777 119 60 738 47 260 738 0.0.03); l <sup>2</sup> 107 42 206 60 301 450 0.0004); 296 62 1058 106 1050 623 56 264 14747 = 0.0009	$\begin{array}{l} \textbf{Weight} \\ 2.7\% \\ 6.0\% \\ 1.5\% \\ 3.6\% \\ 1.5\% \\ 3.6\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 19.8\% \\ 10.6\% \\ 19.8\% \\ 10.6\% \\ 1$	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.38, 8.44] 0.33 [0.33, 2.63] 2.06 [0.87, 4.84] 1.27 [0.59, 2.74] 4.84 [2.76, 8.49] 1.90 [0.25, 14.58] 2.92 [1.30, 6.56] 1.38 [0.83, 2.30] 3.63 [1.1, 10.08] 1.69 [0.82, 3.48] 2.36 [1.56, 3.58]	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1993 2000 2006 2008 2000 2008 2012 2013 2015 2017	¢		lds Ratio	
Study or Subgroup           1.5.1 Cross sectional           Govindarajan 1984           Cronberg 1984           Chen 1984           Singh 1995           Asmah 2014           Luma 2017           Subtotal (95% CI)           Total events           Heterogeneity: Tau² = 1           Test for overall effect: 2           Inchopoulos 1987           Amougou 2016           Subtotal (95% CI)           Total events           Heterogeneity: Tau² = 1           Heterogeneity: Tau² = 2           Test for overall effect: 2           1.5.3 Cohort study           Toukan 1987           Cenac 1987           Tamura 1993           Fattovich 2000           Oyunsuren 2006           Cross 2008           Ji 2012           Manesis 2013           Kushner 2015           Béguelin 2017           Brancacio 2018           Coghill 2018           Subtotal (95% CI)	Dual infe Events study 1 16 0 2 1 2 1.07; Chi <sup>2</sup> = 2 2 1.07; Chi <sup>2</sup> = 2 4 1.07; Chi <sup>2</sup> = 2 4 1.07; Chi <sup>2</sup> = 1.07; Chi <sup>2</sup> = 1.07; Chi <sup>2</sup> = 1.07; Chi <sup>2</sup> = 1.07; Chi <sup>2</sup> = 2 4 1.07; Chi <sup>2</sup> = 1.07; Chi <sup>2</sup> = 2 4 1.07; Chi <sup>2</sup> = 1.07; Chi <sup>2</sup> = 2 4 1.07; Chi <sup>2</sup> = 2 4 1.02; Chi <sup>2</sup> = 2 4 2 4 1.02; Chi <sup>2</sup> = 2 4 2 4 2 4 2 4 2 4 2 4 4 2 4 4 2 4 4 2 4 4 2 4 4 2 4 4 4 4 4 5 4 5 4 5 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5	Total           19         26           3         29           6         31           11         14           14         14           14         14           14         14           14         14           14         14           14         14           14         14           14         14           9         25           63         29           63         38           9         38           667         65           1000         104           56         115           2383         31.47, r           <	Mono-inf Events 38 70 011 6 18 6 149 df = 5 (P = 78 8 165 251 df = 2 (P = 5 7 29 22 29 22 29 22 29 22 20 66 64 64 6 15 8 462 6 20 696 df = 11 (P 1) 1096	ection Total 777 119 60 0738 47 260 738 107 42 301 450 0.0004); 2296 266 266 266 1058 161 311 840 8556 1336 14747 = 0.0009 15935	Weight 2.7% 6.1.5% 1.5% 3.6% 19.8% 19.8% 19.8% 19.8% 19.8% 19.8% 19.8% 10.6% 5.1% 5.3% 5.9% 5.1% 5.3% 6.3% 6.3% 10.6% 10.	M-H. Random, 95% Cl 0.06 [0.01, 0.45] 1.12 [0.47, 2.67] 0.61 [0.03, 12.75] 2.09 [0.40, 10.88] 0.32 [0.03, 2.99] 2.92 [0.56, 15.14] 0.76 [0.25, 2.34] 7.14 [0.40, 126.58] 102.00 [11.96, 870.00] 1.35 [0.62, 2.95] 9.03 [0.44, 187.00] 15.73 [5.10, 48.53] 1.19 [0.41, 3.46] 3.38 [1.35, 8.44] 0.33 [0.33, 2.63] 2.06 [0.87, 4.84] 1.27 [0.52, 2.74] 4.84 [2.76, 8.49] 2.92 [1.30, 6.56] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 1.69 [0.82, 3.48] 2.36 [1.57, 3.14]	1984 1984 1984 1995 2014 2017 1987 2016 2018 1987 1993 2000 2006 2008 2000 2008 2012 2013 2015 2017	¢		lds Ratio	

Fig. 3 Continued.

	Dual infe		Mono-inf		Wolaht	Odds Ratio	Vear		Odds Ratio
Study or Subgroup I.6.1 Before 1990	Events	rotar	Events	rotal	veight	M-H. Random. 95% Cl	rear		M-H. Random. 95% Cl
Cronberg 1984	16	26	70	119	6.0%	1.12 [0.47, 2.67]	1984		
Govindarajan 1984	1	19	38	77	2.7%	0.06 [0.01, 0.45]	1984	<u> </u>	
Chen 1984	0	3	11	60	1.5%	0.61 [0.03, 12.75]	1984		
Frichopoulos 1987	9	9	78	107	1.7%	7.14 [0.40, 126.58]			
Cenac 1987 Foukan 1987	14 10	46 47	7	26 296	5.3% 5.1%	1.19 [0.41, 3.46] 15.73 [5.10, 48.53]			
Subtotal (95% CI)	10	150	5	685	22.3%	1.40 [0.32, 6.18]	1907		
Total events	50		209						
Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z			if = 5 (P <	0.0001);	I <sup>2</sup> = 83%				
1.6.2 1991-2000									
Famura 1993	6	69	29	1058	5.9%	3.38 [1.35, 8.44]			
Singh 1995 Fattovich 2000	2	29 39	6 22	175 161	3.6%	2.09 [0.40, 10.88] 0.93 [0.33, 2.63]			
Subtotal (95% CI)	5	137	22	1394	14.8%	1.89 [0.79, 4.55]	2000		-
Total events	13		57						
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z			= 2 (P = 0	0.18); I <sup>2</sup> =	43%				
1.6.3 2001-2010									
Dyunsuren 2006	46	93	10	31	6.1%	2.06 [0.87, 4.84]			
Cross 2008 Subtotal (95% CI)	8	82 175	66	840 871	6.4% 12.5%	1.27 [0.59, 2.74] 1.57 [0.89, 2.79]	2008		•
Fotal events	54		76	071	12.070	1.57 [0.05, 2.75]			-
Heterogeneity: Tau <sup>2</sup> = 0		0.68, df		0.41); I <sup>2</sup> =	0%				
Test for overall effect: Z									
1.6.4 2011-2019 Ji 2012	17	667	46	8556	7.1%	4.84 [2.76, 8.49]	2012		
Manesis 2013	1	65	15	1836	2.7%	1.90 [0.25, 14.58]			
Asmah 2014	1	6	18	47	2.4%	0.32 [0.03, 2.99]	2014		
Kushner 2015	23	1000	8	1000	6.3%	2.92 [1.30, 6.56]			
Amougou 2016 Béguelin 2017	24 83	25 104	8 462	42 623	2.6% 7.3%	102.00 [11.96, 870.00] 1.38 [0.83, 2.30]			
uma 2017	2	31	462	260	3.6%	2.92 [0.56, 15.14]			
Coghill 2018	14	115	20	264	6.6%	1.69 [0.82, 3.48]			
Mahale 2018	18	29	165	301	6.3%	1.35 [0.62, 2.95]			
Brancaccio 2018 Subtotal (95% CI)	17	56 2098	6	56 12985	5.5% 50.4%	3.63 [1.31, 10.08] 2.54 [1.47, 4.40]	2018		-
Fotal events	200	2050	754	12505	30.4%	2.54 [1.47, 4.40]			-
Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z	.46; Chi <sup>2</sup> =		if = 9 (P =	0.0006);	l² = 69%				
	0.00 (P		~	15005	100.0%	0.00/4.07.0.4.5			
Total (95% CI)		2560		15935	100.0%	2.08 [1.37, 3.14]			-
Fotal events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z Fest for subgroup differe	= 3.46 (P ences: Chi	= 0.0005 <sup>2</sup> = 1.62,	5) df = 3 (P	= 0.65), l				0.01	0.1 1 10 1 Favours [Dual infection] Favours [Mono-infection]
Fotal events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z Fest for subgroup differe	.54; Chi <sup>2</sup> = = 3.46 (P	= 0.0008 <sup>2</sup> = 1.62, oction	if = 20 (P 5)	= 0.65), I fection	<sup>2</sup> = 0%	% Odds Ratio <u>M-H, Random, 95% C</u>	I Year		
Total events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z Fest for subgroup differe Study or Subgroup 1.7.1 Untreated	54; Chi <sup>2</sup> = = 3.46 (P ences: Chi Dual infe Events	= 0.0005 <sup>2</sup> = 1.62, oction Total	df = 20 (P 5) df = 3 (P Mono-in Events	= 0.65), F fection Total	² = 0% Weight	Odds Ratio M-H. Random. 95% C			Favours [Dual infection] Favours [Mono-infection] Odds Ratio
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Fotal events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z Fest for subgroup differe Study or Subgroup 1.7.1 Untreated Fattovich 2000 Subtotal (95% CI)	54; Chi <sup>2</sup> = = 3.46 (P ences: Chi Dual infe Events	= 0.0005 <sup>2</sup> = 1.62, oction Total	df = 20 (P 5) df = 3 (P Mono-in Events	= 0.65), F fection Total	² = 0% Weight	Odds Ratio M-H. Random. 95% C			Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events Teleforgeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z Fest for subgroup differe Study or Subgroup 1.7.1 Untreated Fattovich 2000 Subtotal (95% CI) Total events Heterogeneity: Not app	54; Chi <sup>2</sup> = = 3.46 (P ences: Chi Dual infe Events 5 5	= 0.0005 <sup>2</sup> = 1.62, totion Total 39 39	df = 20 (P 5) df = 3 (P Mono-in Events 22	= 0.65), F fection Total 161	<sup>2</sup> = 0% <u>Weight</u> 5.4%	Odds Ratio 			Favours [Dual infection] Favours [Mono-infection] Odds Ratio
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Fotal events leterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: Z Fest for subgroup differe Study or Subgroup 1.7.1 Untreated Fattovich 2000	1.54; Chi <sup>2</sup> = 2 = 3.46 (P ences: Chi Dual infe Events 5 5 5 5 5 5 5 5 5 5 5 5 5	= 0.0005 <sup>2</sup> = 1.62, <u>ction</u> <u>Total</u> 39 39 39 - = 0.89)	df = 20 (P 5) df = 3 (P Mono-in Events 22	= 0.65), F fection Total 161	<sup>2</sup> = 0% <u>Weight</u> 5.4%	Odds Ratio <u>M-H, Random, 95% C</u> 0.93 [0.33, 2.63] 0.93 [0.33, 2.63]	2000		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
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Total events -leterogeneity: Tau <sup>2</sup> = 0 fees for overall effect: Z feest for subgroup differe 	1.54; Chi <sup>2</sup> = = 3.46 (P ences: Chi Dual infe Events 5 5 5 5 6 6 83 17 100	= 0.0005 <sup>2</sup> = 1.62, <b>ction</b> <b>Total</b> 39 39 39 - = 0.89) <b>mly</b> 104 56 160	ff = 20 (P 5) df = 3 (P <u>Mono-in</u> <u>Events</u> 22 22 22 462 6 468	= 0.65), F fection Total 161 161 623 56 679	2 = 0% Weight 5.4% 5.4% 5.4% 7.3% 5.5% 12.8%	Odds Ratio M-H, Random, 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08]	2000		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events Total events Total events Test for overall effect: Z Test for subgroup differd Study or Subgroup 1.7.1 Untreated Fattovich 2000 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = C Test for overall effect: Z Test for overall effect: Z	1.54; Chi <sup>2</sup> = = 3.46 (P ences: Chi Dual infe Events 5 5 5 5 5 5 5 6 83 17 100 0.30; Chi <sup>2</sup> : Z = 1.48 (P	= 0.0005 <sup>2</sup> = 1.62, <u>cction</u> <u>Total</u> <u>39</u> <u>39</u> = 0.89) mly 104 56 <b>160</b> = 2.77, d	ff = 20 (P 5) df = 3 (P <u>Mono-in</u> <u>Events</u> 22 22 22 462 6 468	= 0.65), F fection Total 161 161 623 56 679	2 = 0% Weight 5.4% 5.4% 5.4% 7.3% 5.5% 12.8%	Odds Ratio M-H, Random, 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08]	2000		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
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Total events Total events Total events Test for overall effect: Z Test for subgroup differd T.7.1 Untreated T.7.1 Untreated Tattovich 2000 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = C Test for overall effect: Z T.3. JFN + NA (partial Cross 2008 Manesis 2013	1.54; Chi <sup>2</sup> = = 3.46 (P ences: Chi Dual Infe Events 5 5 10 10 10 0.30; Chi <sup>2</sup> ; 2 = 1.48 (P 1) 8 1	= 0.0005 <sup>2</sup> = 1.62, <b>Total</b> 39 39 = 0.89) <b>inly</b> 104 56 160 = 2.77, d = 0.14) 82 65	ff = 20 (P 5) df = 3 (P Mono-in: <u>Events</u> 22 22 462 6 468 f = 1 (P = 66 15	= 0.65), F fection Total 161 161 623 56 679 0.10); P = 840 1836	<sup>2</sup> = 0% <u>Weight</u> 5.4% 5.4% 5.4% 7.3% 5.5% 12.8% = 64% 6.4% 2.7%	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58]	2000 2017 2018 2008 2013		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events -leterogeneity: Tau <sup>2</sup> = 0 feas for overall effect: Z feas for osubgroup differd 	1.54; Chi <sup>₽</sup> = = 3.46 (P ences: Chi Dual infe Events 5 5 licable Z = 0.14 (P alogues c 83 17 100 0.30; Chi <sup>2</sup> Z = 1.48 (P ) 8	= 0.0005 <sup>2</sup> = 1.62, <b>rection</b> <b>Total</b> 39 39 = 0.89) 104 56 160 = 2.77, d = 0.14) 82	ff = 20 (P 5) df = 3 (P Mono-in: <u>Events</u> 22 22 22 462 6 468 f = 1 (P = 665 8	= 0.65), F fection Total 161 161 623 56 679 0.10); I <sup>2</sup> = 840	<sup>2</sup> = 0% <u>Weight</u> 5.4% 5.4% 7.3% 5.5% 12.8% = 64% 6.4%	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74]	2000 2017 2018 2008 2013		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
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Total events Total events Test for overall effect: Z Test for subgroup differd Study or Subgroup 1.7.1 Untreated Fattovich 2000 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z 1.7.2 Nucleos(t)ide an Béguelin 2017 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = C Test for overall effect: Z 1.7.3 IFN + NA (partial Cross 2008 Manesis 2013 Subtotal (95% CI) Total events Subtotal (95% CI) Total (95% CI) Total (95% CI) Total (95% CI) Total (95% CI) Total events	1.54; Chi <sup>2</sup> = 3.46 (P ences: Chi Dual infe Events 5 5 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2	= 0.0003 = 1.62, totion Total 39 39 = 0.89) 104 56 160 = 2.77, d 104 265 1000 115	ff = 20 (P 5) df = 3 (P Mono-in: <u>Events</u> 22 22 462 6 468 f = 1 (P = 66 15 8 20 109	= 0.65), F fection 161 161 161 161 001 0.10); I <sup>2</sup> = 840 1836 1000 264 3940	2 = 0% Weight 5.4% 5.4% 5.4% 5.5% 12.8% = 64% 6.4% 2.7% 6.3% 6.6% 22.0%	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58] 2.92 [1.30, 6.56]	2000 2017 2018 2008 2013 2015		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events -leterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z Test for subgroup differd - - - - - - - - - - - - -	1.54; Chi <sup>2</sup> = 3.46 (P ences: Chi Dual infe Events 5 5 5 5 5 5 5 5 5 5 5 5 5	= 0.0009 = 1.62, totion Total 39 39 = 0.89) 104 56 160 = 2.77, d = 0.14) 82 65 1000 115 1262 = 2.21, d	ff = 20 (P 5) 6 df = 3 (P 6 df = 3 (P 7 df = 3 (P) 7 df = 3 (P)	= 0.65), F fection 161 161 161 161 001 0.10); I <sup>2</sup> = 840 1836 1000 264 3940	2 = 0% Weight 5.4% 5.4% 5.4% 5.5% 12.8% = 64% 6.4% 2.7% 6.3% 6.6% 22.0%	Odds Ratio M-H, Random, 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.68] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58] 2.92 [1.30, 5.65] 1.69 [0.22, 3.48]	2000 2017 2018 2008 2013 2015		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events teterogeneity: Tau <sup>2</sup> = 0 test for overall effect: Z test for subgroup differd <b>Study or Subgroup</b> <b>1.7.1 Untreated</b> <b>1.7.1 Untreated</b> <b>1.7.1 Untreated</b> <b>1.7.2 Untreated</b> <b>1.7.2 Untreated</b> <b>1.7.2 Nucleos(1)</b> Total events Heterogeneity: Not app Test for overall effect: Z <b>1.7.2 Nucleos(1)</b> <b>1.7.3 IFN + NA</b> (partial <b>Cross 2008</b> Manesis 2013 Kushner 2015 Coghil 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = C <b>1.7.3 IFN + NA</b> (partial <b>Cross 2008</b> Manesis 2013 Coghil 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = C <b>1.7.4 Unknown</b>	1.54; Chi <sup>2</sup> = 3.46 (P = 3.46 (P) ennces: Chi Dual infin <u>Events</u> 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	= 0.0004 = 1.62, ction Total 39 39 = 0.89) 104 56 160 = 2.77, d = 0.14) 82 65 1010 1262 = 2.21, d = 0.007	ff = 20 (P 5) 5) 6) 70 Mono-im Events 22 22 462 6 468 8 20 20 9 109 9 f = 3 (P = )	= 0.65), I <u>Total</u> 161 161 161 161 161 161 161 16	* = 0% Weight 5.4% 5.4% 5.5% 5.5% 5.5% 6.4% 6.4% 6.3% 6.6% 2.7% 6.3% 6.6% 2.20%	Odds Ratio M-H, Random, 95% C 0,93 [0.33, 2,63] 0,93 [0.33, 2,63] 1,38 [0,83, 2,30] 3,63 [1,31, 10,08] 2,01 [0,80, 5,10] 1,27 [0,59, 2,74] 1,90 [0,25, 14,58] 2,292 [1,30, 6,56] 1,69 [0,82, 3,48] 1,81 [1,18, 2,79]	2000 2017 2018 2013 2015 2018		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
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<sup>100</sup> <sup>125</sup> <sup>125</sup> <sup>126</sup> <sup>127</sup> <sup>127</sup> <sup>127</sup> <sup>128</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup>	ff = 20 (P 5) 5) 6) 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	= 0.65), I fection Total 161 161 161 161 161 161 161 161 161 16	<ul> <li><sup>2</sup> = 0%</li> <li>Weight</li> <li>5.4%</li> <li>5.4%</li> <li>5.5%</li> <li>5.5%</li> <li>12.8%</li> <li>6.4%</li> <li>6.4%</li> <li>6.4%</li> <li>6.6%</li> <li>6.6%</li> <li>2.7%</li> </ul>	Odds Ratio M-H. 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Total events -leterogeneity: Tau <sup>2</sup> = 0 fees for overall effect: Z fees for subgroup differed 	<pre>1.54, Ch<sup>2</sup> = i = 3.64 (C) = i = 3.64 (C) Dual infer Events 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5</pre>	= 0.0005 = 1.62, = 1.62, = 1.62, = 1.62, = 1.62, = 0.089) = 0.89) 104 56 160 = 0.14) 82 65 1000 115 1262 = 2.21, d = 0.007 19 3 3	ff = 20 (P 5) 5) 6) 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	= 0.65), I fection Total 161 161 161 161 161 161 000 0,10); P = 840 0,10); P = 840 1836 1000 264 3940 0,53); P = 777 60	<ul> <li>P = 0%</li> <li>Weight</li> <li>5.4%</li> <li>5.4%</li> <li>5.5%</li> <li>5.5%</li> <li>12.8%</li> <li>6.4%</li> <li>6.4%</li> <li>2.7%</li> <li>6.6%</li> <li>22.0%</li> <li>2.7%</li> <li>1.5%</li> </ul>	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58] 2.82 [1.30, 6.56] 1.69 [0.82, 3.48] 1.81 [1.18, 2.79] 0.06 [0.01, 0.45] 0.61 [0.03, 12.75]	2000 2017 2018 2013 2015 2018 1984		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events ieterogeneity: Tau <sup>2</sup> = 0 fest for overall effect: Z fest for subgroup differd <b>Study or Subgroup</b> <b>1.7.1 Untreated</b> <b>Fatovich 2000</b> Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z <b>1.7.2 Nucleos(t)ide an</b> Böguelin 2017 <b>Fancaccio 2018</b> Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = C Test for overall effect: Z <b>1.7.3 IFN + NA (partial</b> Cross 2008 Manesis 2013 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = C Test for overall effect: Z Test for overall effect: Z Test for overall effect: Z <b>1.7.4 Unknown</b> Govindarajan 1984 Chen 1984	L 54, Ch <sup>2</sup> = 3, 64 = 3, 64 (P L 54, 64) = 5 5 5 5 5 5 5 5 5 5 5 5 5 5	= 0.0000 <sup>2</sup> = 1.62, <sup>3</sup> = 1.62, <sup>3</sup> = 1.62, <sup>3</sup> = 1.62, <sup>3</sup> = 0.89) <sup>104</sup> <sup>56</sup> <sup>160</sup> <sup>104</sup> <sup>56</sup> <sup>160</sup> <sup>105</sup> <sup>100</sup> <sup>125</sup> <sup>125</sup> <sup>126</sup> <sup>127</sup> <sup>127</sup> <sup>127</sup> <sup>128</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> 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<sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup> <sup>129</sup>	ff = 20 (P 5) 5) 6) 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	= 0.65), I fection Total 161 161 161 161 161 161 161 161 161 16	<ul> <li><sup>2</sup> = 0%</li> <li>Weight</li> <li>5.4%</li> <li>5.4%</li> <li>5.5%</li> <li>5.5%</li> <li>12.8%</li> <li>6.4%</li> <li>6.4%</li> <li>6.4%</li> <li>6.6%</li> <li>6.6%</li> <li>2.7%</li> </ul>	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58] 2.92 [1.30, 6.65] 1.69 [0.22, 3.48] 1.81 [1.18, 2.79] 0.06 [0.01, 0.45]	2000 2017 2018 2008 2013 2015 2018 1984 1984 1984		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events leterogeneity: Tau <sup>2</sup> = 0 lest for overall effect: Z lest for overall effect: Z lest for subgroup differd <b>Study or Subgroup</b> <b>1.7.1 Untreated</b> <b>1.7.1 Untreated</b> <b>1.7.1 Untreated</b> <b>1.7.2 Nucleos(1)</b> Total events Heterogeneity: Not app Test for overall effect: Z <b>1.7.2 Nucleos(t)ide an</b> Béguelin 2017 <b>Tanacacio</b> 2018 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z <b>1.7.3 IFN + NA (partial</b> <b>Cross 2008</b> Manesis 2013 Kushner 2015 Coghill 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 <b>1.7.4 Unknown</b> Govindarajan 1984 Cronberg 1984 Trichopoulos 1987 Conac 1987	L 54, Ch <sup>2</sup> = 3, 64 = 3, 54 (P) Dual Inferences: Chi Dual Inferences: Chi 5 5 5 5 5 5 5 5 5 10 100 00, 00, Chi <sup>2</sup> P 1 4 4 6 0 10 10 0 0, 00, Chi <sup>2</sup> P 2 = 2, 70 (P) 1 1 1 1 1 1 1 1 1 1 1 1 1	= 0.0000 + 0.0000 + 0.00000 + 0.000000000	$\begin{array}{c} \mathrm{if} = 20 \ (\mathrm{P} \\ \mathrm{i}) \\ $	= 0.65), I <u>Total</u> 161 161 161 161 161 161 161 16	2 = 0% Weight 5.4% 5.4% 5.4% 5.5% 5.5% 6.4% 6.4% 6.4% 6.6% 6.6% 6.6% 6.6% 5.2.0%	Odds Ratio M-H, Random, 95% C 0,93 [0,33, 2,63] 0,93 [0,33, 2,63] 1.38 [0,83, 2,30] 3.63 [1,31, 10,08] 2.01 [0,80, 5,10] 1.27 [0,59, 2,74] 1.90 [0,25, 14,68] 2.92 [1,30, 6,56] 1.69 [0,82, 3,48] 1.81 [1,18, 2,79] 0.06 [0,01, 0,45] 0.61 [0,03, 12,75] 1.12 [0,47, 2,67] 7.74 [0,40, 126,58] 1.19 [0,41, 3,46]	2000 2017 2018 2013 2015 2013 2015 2018 1984 1984 1987 1987		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events leterogeneity: Tau <sup>2</sup> = 0 feas for overall effect: Z feas for osubgroup differd leterogeneity: Not app Tatovich 2000 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z 1.7.2 Nucleos(t)ide an Biguelin 2017 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Total overall Heterogeneity: Tau <sup>2</sup> = 0 Tast for overall effect: Z 1.7.3 IFN + NA (partial Cross 2008 Mannesis 2013 Kushner 2015 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.7.4 Unknown Govindaraign 1984 Cronberg 1984 Cronberg 1987 Cenac 1987 Cenac 1987 Cenac 1987 Cenac 1987	L 54, Ch <sup>2</sup> = 3, 66 = 3, 66 (P L 54, 67) = 10, 50 L 5 5 5 5 5 5 5 5 5 5 5 5 5 5	= 0.0005 * = 1.62, * = 1.62, 39 39 39 = 0.89) 104 56 160 = 2.77, d 15 1262 = 0.014) 115 1262, = 0.007 19 3 26 9 9 9 46	ff = 20 (P 5) 5) 6) 7 7 7 7 7 7 5	= 0.65), II Total 161 161 161 161 161 161 161 16	2 = 0% Weight 5.4% 5.4% 5.4% 7.3% 5.5% 6.4% 6.4% 2.7% 6.3% 6.4% 22.0% 2.7% 6.3% 6.0% 1.5% 5	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 1458] 2.82 [1.30, 6.65] 1.69 [0.82, 3.48] 1.81 [1.18, 2.79] 0.06 [0.01, 0.45] 0.61 [0.03, 12.75] 1.12 [0.47, 2.67] 7.14 [0.40, 126.58] 1.73 [51.04, 85.33]	2000 2017 2018 2013 2015 2018 1984 1984 1984 1987 1987		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events teterogeneity: Tau <sup>2</sup> = 0 test for overall effect: Z test for subgroup differd <b>Study or Subgroup</b> <b>1.7.1 Untreated</b> <b>1.7.1 Untreated</b> <b>1.7.1 Untreated</b> <b>1.7.2 Nucleos(1)</b> Total events Heterogeneity: Not app Test for overall effect: Z <b>1.7.2 Nucleos(1)</b> <b>1.7.2 Nucleos(1)</b> <b>1.7.3 IFN + NA</b> (post) <b>1.7.3 Untreation</b> <b>1.7.3 IFN + NA</b> (post) <b>1.7.3 IFN + NA</b> (post) <b>1.7.3 Untreation</b> <b>1.7.3 IFN + NA</b> (post) <b>1.7.3 IFN + NA</b> (post) <b>1.7.4 Untreation</b> <b>1.7.4 Untreation</b> <b>1.7.5</b> <b>1.7.4 Untreation</b> <b>1.7.6</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untertial</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untertial</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untreation</b> <b>1.7.7 Untertial</b> <b>1.7.7 Untertial</b>	5.45, Ch <sup>2</sup> := 3.46 (P := 3.46 (P Dual Infe Events 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	$\begin{array}{l} = 0.0000 \\ = 0.0000 \\ = 2.77, d\\ = 0.89) \\ = 0.89) \\ = 0.89) \\ 104 \\ 56 \\ 160 \\ = 0.14) \\ 82 \\ 65 \\ 1262 \\ = 2.21, d\\ 100 \\ 115 \\ 1262 \\ = 2.21, d\\ 0.007 \\ 19 \\ 3 \\ 26 \\ 6 \\ 9 \\ 9 \\ 46 \\ 47 \\ 69 \end{array}$	$\begin{array}{c} \mathrm{ff}=20\ (P\\ \mathrm{ff}=20\ (P\\ \mathrm{ff}=3\ (P\ (P\\ \mathrm{ff}=3\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P$	= 0.65), I fection 161 161 161 161 161 161 161 16	2 = 0% Weight 5.4% 5.4% 5.4% 5.5% 5.5% 6.4% 6.4% 6.6% 6.6% 6.6% 6.6% 6.6% 5.3% 5.3% 5.5%	Odds Ratio M-H, Random, 95% C 0,93 [0.33, 2,63] 0,93 [0.33, 2,63] 1,38 [0.83, 2,30] 3,63 [1,31, 10,08] 2,01 [0,80, 5,10] 1,27 [0,59, 2,74] 1,90 [0,25, 14,58] 2,82 [1,30, 6,56] 1,69 [0,82, 3,48] 1,81 [1,18, 2,79] 0,06 [0,01, 0,45] 0,61 [0,03, 12,75] 1,12 [0,47, 2,67] 7,14 [0,40, 126,58] 1,19 [0,41, 3,46] 15,73 [5,10, 48,53] 3,38 [15, 5, 8,44]	2000 2017 2018 2013 2015 2018 1984 1984 1984 1984 1984 1984 1984		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
Total events leterogeneity: Tau <sup>2</sup> = 0 fest for overall effect: Z fest for subgroup differd fest for overall effect: Z fest for subgroup 1.7.1 Untreated Fattoxich 2000 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z 1.7.2 Nucleos(t)de an Biguelin 2017 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Est for overall effect: Z 1.7.3 IFN + NA (partial Cross 2008 Manesis 2013 Kushner 2015 Cophill 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.7.4 Unknown Govindarajan 1984 Chen 1984 Cronberg 1984 Trichopoulos 1987 Cenac 1987 Taulura 1983 Singh 1995	L 54, Ch <sup>2</sup> = 3, 64 = 3, 64 (P L 54, 64) = 10, 54 (C) =	$\begin{array}{l} = 0.0005\\ = 1.62,\\ \\ \hline \\ = 1.62,\\ \\ \hline \\ = 1.62,\\ \\ \hline \\ = 0.89)\\ 104\\ 56\\ 160\\ = 0.14)\\ \\ 100\\ = 2.77,\\ \\ d = 0.14)\\ \\ \\ 1262\\ = 2.21,\\ \\ d = 0.007\\ \\ \hline \\ 19\\ 3\\ 26\\ 9\\ 46\\ 47\\ 69\\ 9\\ 46\\ 47\\ 69\\ 9\\ 29\\ \end{array}$	$\begin{array}{c} \mathrm{if} = 20 \ (P \\ \mathrm{i}) \\ $	= 0.65), II Total 161 161 161 161 161 161 161 16	P = 0% Weight 5.4% 5.4% 5.4% 5.5% 5.5% 12.8% 6.4% 6.4% 2.7% 6.3% 6.3% 6.3% 6.4% 2.7% 1.5% 2.7% 5.3% 5.3% 5.1% 5.3% 5.3% 3.6%	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58] 2.82 [1.30, 6.65] 1.69 [0.22, 3.48] 1.81 [1.18, 2.79] 0.06 [0.01, 0.45] 0.61 [0.03, 12.75] 1.12 [0.47, 2.67] 7.14 [0.40, 126.88] 1.19 [0.41, 3.46] 1.573 [5.10, 48.53] 3.38 [1.35, 8.44] 2.09 [0.40, 10.88]	2000 2017 2018 2013 2015 2018 1984 1984 1984 1987 1987 1987 1987 1995		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
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Total events teterogeneity: Tau <sup>2</sup> = 0 test for overall effect: Z test for subgroup differd <b>Study or Subgroup</b> <b>Study or Subgroup</b> <b>Subtors</b> <b>Study or Subgroup</b> <b>Subtors</b> <b>Study or Subtors</b> <b>Study or Subtors</b> <b>Stu</b>	L 54, Ch <sup>2</sup> = 3, 64 = 3, 64 (P L 54, 64 (P)) = 1, 14 (P L 54, 64 (P)) = 1, 14 (P = 1, 14 (P = 1, 14 (P)) = 1, 14 (P = 1, 14 (P)) = 1, 14 (P) = 1, 14 (	$ = 0.0002 \\ = 1.62, \\ \hline total \\ = 0.189 \\ \hline total \\ = 0.189 \\ \hline total \\ = 0.189 \\ \hline total \\ = 0.180 \\ \hline total \\ = 0.180 \\ \hline total \\ = 0.007 \\ \hline $	$\begin{array}{c} \mathrm{ff}=20\ (P\\ \mathrm{ff}=20\ (P\\ \mathrm{ff}=20\ (P\\ \mathrm{ff}=1\ (P\ (P\\ \mathrm{ff}=1\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P$	= 0.65), I fection 161 161 161 161 161 161 161 161 161 16	2 = 0% Weight 5.4% 5.4% 5.4% 5.4% 5.4% 5.4% 6.4% 2.7% 6.6% 2.7% 6.6% 2.7% 6.6% 5.3% 5.9% 5.9% 5.9%	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58] 2.92 [1.30, 6.56] 1.69 [0.82, 3.48] 1.81 [1.18, 2.79] 0.06 [0.01, 0.45] 0.61 [0.03, 12.75] 1.12 [0.47, 2.67] 7.14 [0.40, 126.88] 1.73 [5.10, 42.58] 3.38 [1.35, 8.44] 2.09 [0.40, 10.88] 1.73 [5.10, 42.58] 3.38 [1.35, 8.44] 2.09 [0.40, 10.88] 1.57 [5.10, 42.58] 3.08 [1.35, 8.44] 2.09 [0.57, 4.84] 3.03 [1.35, 1.64] 3.03 [1.35, 0.62, 2.95] 2.28 [1.18, 4.44]	2000 2017 2018 2013 2015 2018 1984 1984 1984 1987 1987 1987 1987 1987 2016 2012 2014 2014		Favours [Dual infection] Favours [Mono-infection] Odds Ratio
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Total events teterogeneity: Tau <sup>2</sup> = 0 test for overall effect: Z test for subgroup differd <b>Study or Subgroup</b> <b>Study or Subgroup</b> <b>Subtors</b> <b>Study or Subgroup</b> <b>Subtors</b> <b>Study or Subtors</b> <b>Study or Subtors</b> <b>Stu</b>	L 54, Ch <sup>2</sup> = 3, 64 = 3, 64 (P L 54, 64 (P)) = 1, 14 (P L 54, 64 (P)) = 1, 14 (P = 1, 14 (P = 1, 14 (P)) = 1, 14 (P = 1, 14 (P)) = 1, 14 (P) = 1, 14 (	$ = 0.0002 e^2 = 1.62, \\ e^2 = 1.62, \\ e^2 = 1.62, \\ e^2 = 1.62, \\ e^2 = 0.89) \\ e^3 = 0.007 \\ e^3 $	$\begin{array}{c} \mathrm{ff}=20\ (P\\ \mathrm{ff}=20\ (P\\ \mathrm{ff}=20\ (P\\ \mathrm{ff}=1\ (P\ (P\\ \mathrm{ff}=1\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P\ (P$	= 0.65), i Total Total 161 161 161 161 161 161 161 161 161 16	2 = 0% Weight 5.4% 5.4% 5.4% 5.4% 5.4% 5.4% 6.4% 2.7% 6.6% 2.7% 6.6% 2.7% 6.6% 5.3% 5.9% 5.9% 5.9%	Odds Ratio M-H. Random. 95% C 0.93 [0.33, 2.63] 0.93 [0.33, 2.63] 1.38 [0.83, 2.30] 3.63 [1.31, 10.08] 2.01 [0.80, 5.10] 1.27 [0.59, 2.74] 1.90 [0.25, 14.58] 2.92 [1.30, 6.56] 1.69 [0.82, 3.48] 1.81 [1.18, 2.79] 0.06 [0.01, 0.45] 0.61 [0.03, 12.75] 1.12 [0.47, 2.67] 7.14 [0.40, 126.88] 1.73 [5.10, 42.58] 3.38 [1.35, 8.44] 2.09 [0.40, 10.88] 1.73 [5.10, 42.58] 3.38 [1.35, 8.44] 2.09 [0.40, 10.88] 1.57 [5.10, 42.58] 3.08 [1.35, 8.44] 2.09 [0.57, 4.84] 3.03 [1.35, 1.64] 3.03 [1.35, 0.62, 2.95] 2.28 [1.18, 4.44]	2000 2017 2018 2013 2015 2018 1984 1984 1984 1987 1987 1987 1987 1987 2016 2012 2014 2014		Favours [Dual infection] Favours [Mono-infection] Odds Ratio

Fig. 3 Continued.

	Dual infe	ction	Mono-inf	ection		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	Year	M-H. Random, 95% Cl
1.8.1 Superinfection								
Cenac 1987	14	46	7	26	5.3%	1.19 [0.41, 3.46]	1987	
Tamura 1993	6	69	29	1058	5.9%	3.38 [1.35, 8.44]		
Fattovich 2000	5	39	22	161	5.4%	0.93 [0.33, 2.63]		
Subtotal (95% CI)		154		1245	16.6%	1.61 [0.70, 3.67]		
Total events	25		58					
Heterogeneity: Tau <sup>2</sup> =		4 03 dt		0 13)· I <sup>2</sup> =	50%			
Test for overall effect:			2 ()		0070			
1.8.2 Co-infection								
Oyunsuren 2006	46	93	10	31	6.1%	2.06 [0.87, 4.84]	2006	
Cross 2008	8	82	66	840	6.4%	1.27 [0.59, 2.74]		
Kushner 2015	23	1000	8	1000	6.3%	2.92 [1.30, 6.56]		
Mahale 2018	18	29	165	301	6.3%			
Coghill 2018	18	115	20	264	6.6%	1.35 [0.62, 2.95] 1.69 [0.82, 3.48]		
Subtotal (95% CI)	14	1319	20	264	5.6% 31.6%	1.69 [0.82, 3.48]	2018	◆
Total events	109		269					
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =	= 2.79, di	f=4 (P=0	0.59); l <sup>2</sup> =	= 0%			
Test for overall effect:								
1.8.3 Both included								
Toukan 1987	10	47	5	296	5.1%	15.73 [5.10, 48.53]	1987	
Singh 1995	2	29	6	175	3.6%	2.09 [0.40, 10.88]		
Ji 2012	17	667	46	8556	7.1%	4.84 [2.76, 8.49]		
Manesis 2013	1	65	15	1836	2.7%	1.90 [0.25, 14.58]		
Subtotal (95% CI)		808	10	10863	18.5%	5.11 [2.21, 11.79]	2010	
Total events	30		72					
Heterogeneity: Tau <sup>2</sup> =		5.88 d		0.12): I <sup>2</sup> =	49%			
Test for overall effect:					4070			
1.8.4 Uncertain								
Chen 1984	0	3	11	60	1.5%	0.61 [0.03, 12.75]	1984	
Cronberg 1984	16	26	70	119	6.0%	1.12 [0.47, 2.67]		
Govindarajan 1984	1	19	38	77	2.7%	0.06 [0.01, 0.45]		←
				. /	L.1 /0	0.00 [0.01, 0.40]	1004	
Trichonoulos 1987	0	0	78	107	1 7%	7 14 10 40 126 581	1987	
	9	9	78 18	107	1.7%	7.14 [0.40, 126.58]		
Asmah 2014	1	6	18	47	2.4%	0.32 [0.03, 2.99]	2014	
Asmah 2014 Amougou 2016	1 24	6 25	18 8	47 42	2.4% 2.6%	0.32 [0.03, 2.99] 102.00 [11.96, 870.00]	2014 2016	
Asmah 2014 Amougou 2016 Béguelin 2017	1 24 83	6 25 104	18 8 462	47 42 623	2.4% 2.6% 7.3%	0.32 [0.03, 2.99] 102.00 [11.96, 870.00] 1.38 [0.83, 2.30]	2014 2016 2017	
Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017	1 24 83 2	6 25 104 31	18 8 462 6	47 42 623 260	2.4% 2.6% 7.3% 3.6%	0.32 [0.03, 2.99] 102.00 [11.96, 870.00] 1.38 [0.83, 2.30] 2.92 [0.56, 15.14]	2014 2016 2017 2017	
Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017 Brancaccio 2018	1 24 83	6 25 104	18 8 462	47 42 623	2.4% 2.6% 7.3%	0.32 [0.03, 2.99] 102.00 [11.96, 870.00] 1.38 [0.83, 2.30]	2014 2016 2017 2017	
Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017 Brancaccio 2018 Subtotal (95% CI)	1 24 83 2	6 25 104 31 56	18 8 462 6	47 42 623 260 56	2.4% 2.6% 7.3% 3.6% 5.5%	0.32 (0.03, 2.99) 102.00 [11.96, 870.00] 1.38 (0.83, 2.30) 2.92 [0.56, 15.14] 3.63 [1.31, 10.08]	2014 2016 2017 2017	
Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017 Brancaccio 2018 Subtotal (95% CI) Total events	1 24 83 2 17 153	6 25 104 31 56 279	18 8 462 6 6 697	47 42 623 260 56 1391	2.4% 2.6% 7.3% 3.6% 5.5% 33.2%	0.32 (0.03, 2.99) 102.00 [11.96, 870.00] 1.38 (0.83, 2.30) 2.92 [0.56, 15.14] 3.63 [1.31, 10.08]	2014 2016 2017 2017	
Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> =	1 24 83 2 17 153 1.25; Chi <sup>2</sup> =	6 25 104 31 56 279	18 8 462 6 6 697	47 42 623 260 56 1391	2.4% 2.6% 7.3% 3.6% 5.5% 33.2%	0.32 (0.03, 2.99) 102.00 [11.96, 870.00] 1.38 (0.83, 2.30) 2.92 [0.56, 15.14] 3.63 [1.31, 10.08]	2014 2016 2017 2017	
Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	1 24 83 2 17 153 1.25; Chi <sup>2</sup> =	6 25 104 31 56 279	18 8 462 6 6 697	47 42 623 260 56 1391 0.0001);	2.4% 2.6% 7.3% 3.6% 5.5% 33.2%	0.32 (0.03, 2.99) 102.00 [11.96, 870.00] 1.38 (0.83, 2.30) 2.92 [0.56, 15.14] 3.63 [1.31, 10.08]	2014 2016 2017 2017	
Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Total (95% CI)	1 24 83 2 17 153 1.25; Chi <sup>2</sup> =	6 25 104 31 56 279 = 31.85, 6 = 0.25)	18 8 462 6 6 697	47 42 623 260 56 1391 0.0001);	2.4% 2.6% 7.3% 3.6% 5.5% 33.2%	0.32 [0.03, 2.99] 102.00 [11.96, 870.00] 1.38 [0.83, 2.30] 2.92 [0.56, 15.14] 3.63 [1.31, 10.08] 1.72 [0.68, 4.37]	2014 2016 2017 2017	
Trichopoulos 1987 Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> =	1 24 83 2 17 153 1.25; Chi <sup>2</sup> = Z = 1.14 (P 317	6 25 104 31 56 279 = 31.85, = 0.25) 2560	18 8 462 6 6 6 97 df = 8 (P <	47 42 623 260 56 1391 : 0.0001); 15935	2.4% 2.6% 7.3% 3.6% 5.5% 33.2% ; l <sup>2</sup> = 75% 100.0%	0.32 [0.03, 2.99] 102.00 [11.96, 870.00] 1.38 [0.83, 2.30] 2.92 [0.56, 15.14] 3.63 [1.31, 10.08] 1.72 [0.68, 4.37] 2.08 [1.37, 3.14]	2014 2016 2017 2017	
Asmah 2014 Amougou 2016 Béguelin 2017 Luma 2017 Brancaccio 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>Total (95% CI)</b> Total events	1 24 83 2 17 153 1.25; Chi <sup>2</sup> = Z = 1.14 (P 317 0.54; Chi <sup>2</sup> =	6 25 104 31 56 279 = 31.85, ( = 0.25) 2560 = 63.98, (	18 8 462 6 6 6 7 df = 8 (P < 1096 df = 20 (P	47 42 623 260 56 1391 : 0.0001); 15935	2.4% 2.6% 7.3% 3.6% 5.5% 33.2% ; l <sup>2</sup> = 75% 100.0%	0.32 [0.03, 2.99] 102.00 [11.96, 870.00] 1.38 [0.83, 2.30] 2.92 [0.56, 15.14] 3.63 [1.31, 10.08] 1.72 [0.68, 4.37] 2.08 [1.37, 3.14]	2014 2016 2017 2017	0.01 0.1 1 10 100 Favours [experimental] Favours [control]

Fig. 3 Continued.

expression of glutathione S-transferase P1 (GSTP1), and potentially lead to tumor growth.<sup>48</sup> Nevertheless, the direct evidence for the oncogenicity of HDV is still lacking.

HBV and HCV are oncogenic agents for HCC.<sup>26</sup> HIV is believed to increase the risk of HCC in HBV or HCV coinfected patients.50 HIV coinfection may reduce the rate of viral clearance and promote chronic infection due to defective immunity. To minimize the confounding effects of HCV or HIV infection, we performed a subgroup analysis. The results showed that the risk of HCC development was higher in the HDV/HBV dual infection group in both subgroups. The cohorts excluding HCV or HIV infection had a higher Odds ratio of risk to develop HCC. The presence of HCV or HIV may contribute to HCC risk in both the HDV-infected and the non-HDV-infected group, which may underestimate the influence of HDV. Furthermore, the level of HDV/HIV viremia, antiviral treatment, and the length of infection may affect the results. Besides, some confounding factors of HCC had not been adjusted, including alcohol consumption, primary biliary cholangitis, autoimmune hepatitis, and metabolic dysfunction-associated fatty liver disease. It needs further prospective study to elucidate this issue.

It is difficult to define whether the development of HCC was generated from cirrhosis or triggered directly by HDV infection. Fattovich et al. assessed the influence of hepatitis delta in compensated cirrhotic patients and revealed an increased risk of HCC among HDV-infected patients.<sup>7</sup> A later study enrolled patients with advanced fibrosis or cirrhosis revealed that the rates of death, liver transplantation, liver decompensation, and HCC were significantly higher among HDV-infected patients than HBV monoinfected patients after reached HBV DNA suppression with nucleos(t)ide analogue.<sup>20</sup> However, the subgroup analysis showed no significant difference between HDV/HBV dual infection and HBV monoinfection among patients with advanced fibrosis and cirrhosis. This is not surprising because cirrhosis is a high-risk factor for HCC development.

The time sequence of the development of cirrhosis and HCC was difficult to identify in most of the included studies. Although superinfection of HDV is more likely to be associated with chronic liver disease, the HCC risk did not increase among superinfected patients in the subgroup analysis.<sup>7,14,29</sup> The impact of HDV infection on HCC risk among patients in different stages of liver disease should be further examined.

Persistent HDV viremia was reported to be associated with cirrhosis and HCC in previous studies.<sup>10,11</sup> However, only few studies had documented the level of HDV and HBV viremia,<sup>19,20</sup> or recorded as detectable or undetectable viral loads.<sup>7,17,18,25,30,32</sup>

A subgroup analysis of varying activity of HBV or HDV could not be performed due to inadequate information. Similarly, an analysis for different genotypes of HBV and HDV was not done because lack of the necessary data.

In addition, two of the studies included only patients that received nucleos(t)ide analogue for HBV suppression, and both studies suggested that HDV infection affected HCC development.<sup>20,32</sup> Most of the included studies did not have any record of antiviral treatment. HDV/HBV dual infection did not increase the risk of HCC when patients received nucleos(t)ide analogues.<sup>20,31</sup> Although the activity of viral replication and interaction between HBV and HDV may be crucial for HCC, there was not enough information for analyze.

Subgroup analyses according to the publication year revealed an increased risk of HCC development in the HDV/ HBV dual infection group, but only in studies between 2011 and 2019. The cohorts in the studies between 2011 and 2019 were not significantly older or had more advanced liver disease comparing to earlier studies. Yet, the studies published between 2011 and 2019 were mainly cohort studies with a median research time span of 13 years (0.5–27 years) and prospective studies with a median follow-up of 4.3 years (4.2–8.7 years). In contrast, the studies published earlier were mainly cross-sectional studies, or cohort studies with shorter follow-up intervals. These were smaller studies that may not reflect the relationship of HDV infection and HCC in general populations.

There were limitations to this meta-analysis. First, there were inestimable confounding factors of HCC in the enrolled studies. Nearly half of the enrolled studies did not reveal the status of HCV and HIV infection. Second, as mentioned, the viral loads of HBV and HDV were not accurately assessed in most of the studies. We could not assess whether the enrolled patients were inactive carriers with high or low HDV viremia. Third, not all HBV carriers were tested for anti-HDV or HDV RNA, which may lead to underestimation of the HDV infected population. Fourth, the rate of HBsAg clearance was not documented in most of the studies, and it is left to be answered whether the HCC risk remains high in those who have suppressed HBV activity. Fifth, the percentage of HCC cases were varied in the enrolled studies, which may be related to selection bias of these studies. Thus, the data of meta-analysis should be carefully interpretated.

In conclusion, HDV does increase the risk of HCC compared with HBV monoinfection. However, the HCC risk was less apparent in HDV/HBV dual infections if the patients had advanced liver fibrosis or cirrhosis.

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