

## **Supplementary Material**

**Direct-acting antivirals and the risk of hepatitis B reactivation in hepatitis B and C co-infected patients: A systematic review and meta-analysis**

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# I. Supplementary Materials and Methods

## 1. Search strategy and results

### 1-1. Ovid-Medline (Ovid MEDLINE(R) ALL 1946 to August 25, 2020

No.	Keywords	Results
1	exp Hepatitis C, Chronic/	24430
2	chronic adj5 (hepatitis C or hepacivirus* or hcv).mp.	36077
3	1 OR 2	36077
4	exp Antiviral agents/	357256
5	exp Protease Inhibitors/	203080
6	exp Nucleic acid synthesis inhibitors/	162317
7	(direct* acting anti?viral*) or DAA or ((protease or polymerase) adj3 inhibitor*).mp.	69366
8	(ledipasvir OR sofosbuvir OR elbasvir OR grazoprevir OR velpatasvir OR voxilaprevir OR glecaprevir OR pibrentasvir OR ombitasvir OR paritaprevir OR ritonavir OR dasabuvir OR simeprevir OR boceprevir OR telaprevir OR asunaprevir OR daclatasvir OR Harvoni OR Zepatier OR Epclusa OR Vosevi OR Mavyret OR Maviret OR 'Holkira Pak' OR 'Viekira Pak' OR Viekirax OR Exviera OR Technivie OR Galexos OR Sovaldi OR Victrelis OR Incivek OR Incivo OR Olysio OR Sunvepra OR Daklinza).mp.	12541
9	4 or 5 or 6 or 7 or 8	680628
10	3 and 9	18531
11	(Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or clinical trial, phase i.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or randomized controlled trial.pt. or multicenter study.pt. or clinical trial.pt. or exp Clinical Trials as topic/ or (clinical adj trial\$).tw. or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. or PLACEBOS/ or placebo\$.tw. or randomly allocated.tw. or (allocated adj2 random\$).tw.) not (case report.tw. or letter/ or historical article/)	1610881
12	Epidemiologic Studies/ or exp Case Control Studies/ or exp Cohort Studies/ or Case-control.tw. or (cohort adj (study or studies)).tw. or Cohort analy\$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/	3041720
13	11 OR 12	4234029
14	10 AND 13	7978
15	animals/ not (human/ and animals/)	4694218
16	14 NOT 15	7969

17	limit 16 to yr="2010 -Current"	4716
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## 1-2. OVID-Embase 1974 to 2020 August 25

No.	Keywords	Results
1	exp Chronic Hepatitis C/	11108
2	chronic adj5 (hepatitis C or hepacivirus* or hcv).mp.	46284
3	1 OR 2	46284
4	exp Antivirus agent/	994602
5	exp Proteinase Inhibitor/	382195
6	exp Nucleic acid synthesis inhibitor/	413
7	(direct* acting anti?viral*) or DAA or ((protease or polymerase) adj3 inhibitor*).mp.	78454
8	(ledipasvir OR sofosbuvir OR elbasvir OR grazoprevir OR velpatasvir OR voxilaprevir OR glecaprevir OR pibrentasvir OR ombitasvir OR paritaprevir OR ritonavir OR dasabuvir OR simeprevir OR boceprevir OR telaprevir OR asunaprevir OR daclatasvir OR Harvoni OR Zepatier OR Epclusa OR Vosevi OR Mavyret OR Maviret OR "Holkira Pak" OR "Viekira Pak" OR Viekirax OR Exviera OR Technivie OR Galexos OR Sovaldi OR Victrelis OR Incivek OR Incivo OR Olysio OR Sunvepra OR Daklinza).mp.	43047
9	4 or 5 or 6 or 7 or 8	1305661
10	3 and 9	28135
11	(Clinical Trial/ OR Randomized Controlled Trial/ OR controlled clinical trial/ OR multicenter study/ OR Phase 3 clinical trial/ OR Phase 4 clinical trial/ OR exp RANDOMIZATION/ OR Single Blind Procedure/ OR Double Blind Procedure/ OR Crossover Procedure/ OR PLACEBO/ OR randomi?ed controlled trial\$.tw. OR rct.tw. OR (random\$ adj2 allocat\$.tw. OR single blind\$.tw. OR double blind\$.tw. OR ((treble or triple) adj blind\$.tw. OR placebo\$.tw. OR Prospective Study/) not (Case Study/ OR case report.tw. OR abstract report/ or letter/ OR Conference proceeding.pt. OR Conference abstract.pt. OR Editorial.pt. OR Letter.pt. OR Note.pt.)	1749593
12	Clinical study/ OR Case control study OR Family study/ OR Longitudinal study/ OR Retrospective study OR (Prospective study/ not Randomized controlled trials/) OR Cohort analysis/ OR (Cohort adj (study or studies)).mp. OR (Case control adj (study or studies)).tw. OR (follow up adj (study or studies)).tw. OR (observational adj (study or studies)).tw. OR (epidemiologic\$ adj (study or studies)).tw. OR (cross sectional adj (study or studies)).tw.	2815140
13	11 OR 12	4004982
14	10 AND 13	9051
15	animals/ not (human/ and animals/)	896577

16	14 NOT 15	9051
17	limit 16 to yr="2010 -Current"	<b>5985</b>

### 1-3. Cochrane Register of Controlled Trials (CENTRAL), 2020.8.25.

No.	Keywords	Results
1	[Hepatitis C, Chronic] explode all trees	1952
2	chronic near/5 (hepatitis C or hepacivirus* or hcv)	11679
3	#1 OR #2	11679
4	MeSH descriptor: [Antiviral Agents] explode all trees	8183
5	MeSH descriptor: [Protease Inhibitors] explode all trees	7032
6	MeSH descriptor: [Nucleic Acid Synthesis Inhibitors] explode all trees	1047
7	(direct* acting anti?viral*) or DAA or ((protease or polymerase) near/3 inhibitor*)	4293
8	(ledipasvir OR sofosbuvir OR elbasvir OR grazoprevir OR velpatasvir OR voxilaprevir OR glecaprevir OR pibrentasvir OR ombitasvir OR paritaprevir OR ritonavir OR dasabuvir OR simeprevir OR boceprevir OR telaprevir OR asunaprevir OR daclatasvir OR Harvoni OR Zepatier OR Epclusa OR Vosevi OR Mavyret OR Maviret OR ‘Holkira Pak’OR ‘Viekira Pak’OR Viekirax OR Exviera OR Technivie OR Galexos OR Sovaldi OR Victrelis OR Incivek OR Incivo OR Olysio OR Sunvepra OR Daklinza)	4560
9	#4 or #5 or #6 or #7 or #8	18905
10	#3 and #9	3266
11	#10 with Publication Year from 2010 to 2020, in Trials	<b>2063</b>

### 1-4. KMBase

No.	Keywords	Results
1	(“hepatitis C” OR hepacivirus OR HCV) AND (“direct acting antiviral” OR DAA)	44
2	(“hepatitis C” OR hepacivirus OR HCV) AND (ledipasvir OR sofosbuvir OR elbasvir OR grazoprevir OR velpatasvir OR voxilaprevir OR glecaprevir OR pibrentasvir OR ombitasvir OR paritaprevir OR ritonavir OR dasabuvir OR simeprevir OR boceprevir OR telaprevir OR asunaprevir OR daclatasvir OR Harvoni OR Zepatier OR Epclusa OR Vosevi OR Mavyret OR Maviret OR “Holkira Pak”OR “Viekira Pak”OR Viekirax OR Exviera	30

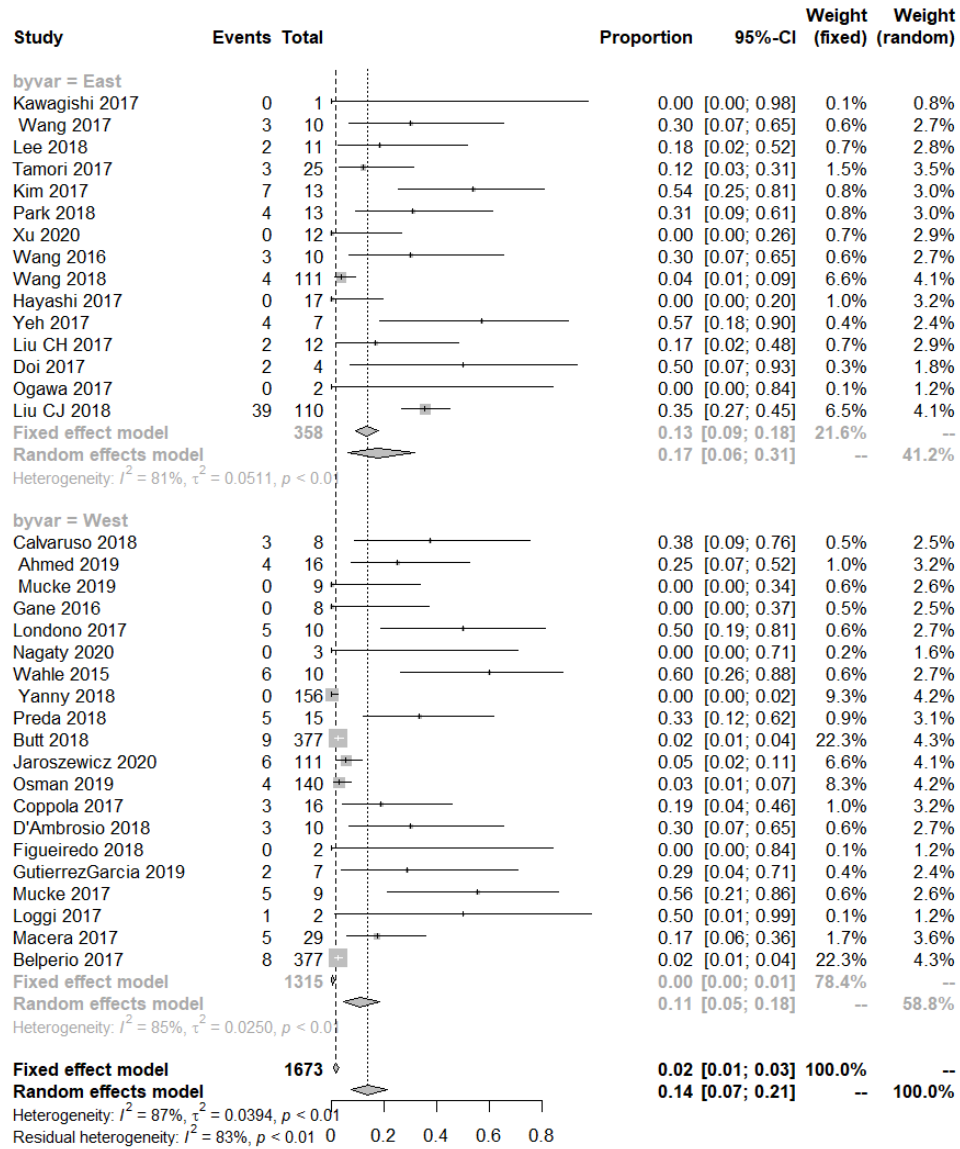
	OR Technivie OR Galexos OR Sovaldi OR Victrelis OR Incivek OR Incivo OR Olysio OR Sunvepra OR Daklinza)	
	<b>Overall results after excluding duplicates</b>	<b>61</b>
1	("hepatitis C" OR hepacivirus OR HCV) AND "direct acting antiviral"	65
2	("hepatitis C" OR hepacivirus OR HCV) AND DAA	41
3	(ledipasvir OR sofosbuvir OR elbasvir OR grazoprevir OR velpatasvir OR voxilaprevir OR glecaprevir OR pibrentasvir OR ombitasvir OR paritaprevir OR ritonavir OR dasabuvir OR simeprevir OR boceprevir OR telaprevir OR asunaprevir OR daclatasvir OR Harvoni OR Zepatier OR Epclusa OR Vosevi OR Mavyret OR Maviret OR "Holkira Pak" OR "Viekira Pak" OR Viekirax OR Exviera OR Technivie OR Galexos OR Sovaldi OR Victrelis OR Incivek OR Incivo OR Olysio OR Sunvepra OR Daklinza)	55
4	(([ALL=C 형 간염] OR [ALL=C 형간염]) AND ([ALL=항바이러스제] OR [ALL=항 바이러스제]))	14
	<b>Overall results after excluding duplicates</b>	<b>120</b>

#### 1-5. RISS

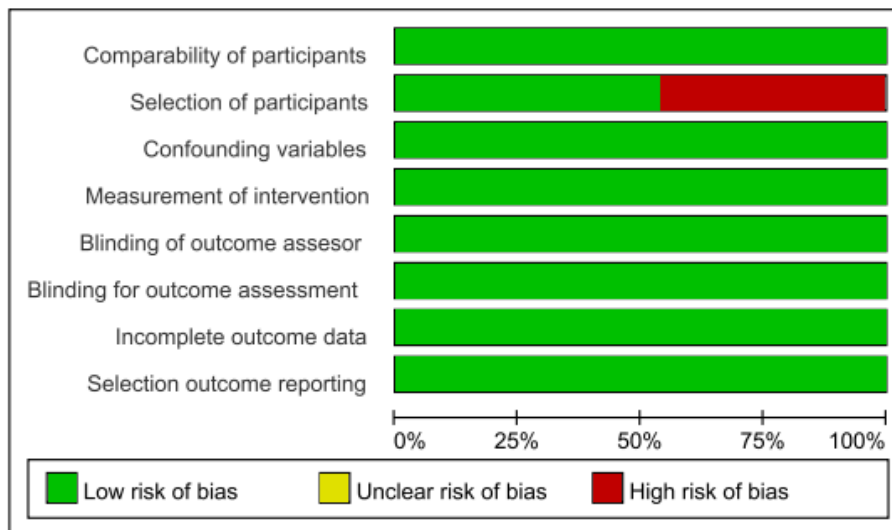
No.	Keywords	Results
1	("hepatitis C" OR hepacivirus OR HCV) AND "direct acting antiviral"	159
2	("hepatitis C" OR hepacivirus OR HCV) AND DAA	189
3	(ledipasvir OR sofosbuvir OR elbasvir OR grazoprevir OR velpatasvir OR voxilaprevir OR glecaprevir OR pibrentasvir OR ombitasvir OR paritaprevir OR ritonavir OR dasabuvir OR simeprevir OR boceprevir OR telaprevir OR asunaprevir OR daclatasvir OR Harvoni OR Zepatier OR Epclusa OR Vosevi OR Mavyret OR Maviret OR "Holkira Pak" OR "Viekira Pak" OR Viekirax OR Exviera OR Technivie OR Galexos OR Sovaldi OR Victrelis OR Incivek OR Incivo OR Olysio OR Sunvepra OR Daklinza)	1
4	C 형 간염 AND 항 바이러스제	1
5	C 형간염 AND 항바이러스제	15
	<b>Overall results after excluding duplicates</b>	<b>240</b>

## II. Supplementary Figures

### (1) The risk of HBV reactivation by area

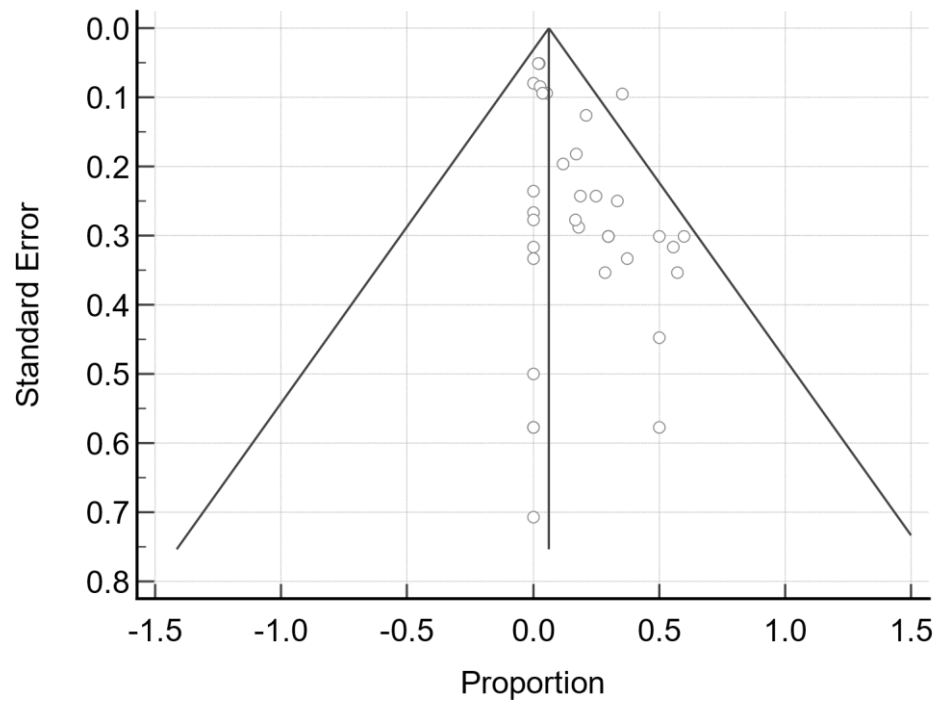


## (2) Risk of bias



	Comparability of participants	Selection of participants	Confounding variables	Measurement of intervention	Blinding of outcome assessor	Blinding for outcome assessment	Incomplete outcome data	Selection outcome reporting
Ahmed 2019	+	+	+	+	+	+	+	+
Ancha 2017	+	+	+	+	+	+	+	+
Belperio 2017	+	+	+	+	+	+	+	+
Butt 2018	+	+	+	+	+	+	+	+
Calvaruso 2018	+	+	+	+	+	+	+	+
Coppola 2017	+	+	+	+	+	+	+	+
D'Ambrosio 2018	+	+	+	+	+	+	+	+
Doi 2017	+	+	+	+	+	+	+	+
Figueiredo 2018	+	+	+	+	+	+	+	+
Gane 2016	+	+	+	+	+	+	+	+
GutierrezGarcia 2019	+	+	+	+	+	+	+	+
Hayashi 2017	+	+	+	+	+	+	+	+
Jaroszewicz 2020	+	+	+	+	+	+	+	+
Kawagishi 2017	+	+	+	+	+	+	+	+
Kim 2017	+	+	+	+	+	+	+	+
Lee 2018	+	+	+	+	+	+	+	+
Liu CH 2017	+	+	+	+	+	+	+	+
Liu CJ 2018	+	+	+	+	+	+	+	+
Loggi 2017	+	+	+	+	+	+	+	+
Londono 2017	+	+	+	+	+	+	+	+
Macera 2017	+	+	+	+	+	+	+	+
Mucke 2017	+	+	+	+	+	+	+	+
Mucke 2019	+	+	+	+	+	+	+	+
Nagaty 2020	+	+	+	+	+	+	+	+
Ogawa 2017	+	+	+	+	+	+	+	+
Osman 2019	+	+	+	+	+	+	+	+
Park 2018	+	+	+	+	+	+	+	+
Preda 2018	+	+	+	+	+	+	+	+
Sulkowski 2016	+	+	+	+	+	+	+	+
Tahir 2019	+	+	+	+	+	+	+	+
Tamori 2017	+	+	+	+	+	+	+	+
Tang 2017	+	+	+	+	+	+	+	+
Wahle 2015	+	+	+	+	+	+	+	+
Wang 2016	+	+	+	+	+	+	+	+
Wang 2017	+	+	+	+	+	+	+	+
Wang 2018	+	+	+	+	+	+	+	+
Xu 2020	+	+	+	+	+	+	+	+
Yanny 2018	+	+	+	+	+	+	+	+
Yeh 2017	+	+	+	+	+	+	+	+

**(3) Funnel plot for analysis publication bias.**



Egger's test: p value 0.0002