

Protocol:
Systematic Review and Meta-analysis of Hepatitis C
Treatments for Non-Pregnant, Treatment-Naïve Adults

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This systematic review protocol was registered with the
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Prevention Guidelines Division Project Team:

Francesca Reyes Domingo (lead investigator); Alejandra Jaramillo Garcia; Mitulika Chawla; Kate Morissette; Nathalie Holmes

CTFPHC Working Group Members:

Roland Grad (Chair); Alejandra Jaramillo (Co-Chair); Brett Thombs; Maria Bacchus; Richard Birtwhistle; Scott Klarenbach; Harminder Singh; Francesca Reyes.

CADTH:

George Wells (lead author of original treatment review); Sumeet Singh

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PROSPERO Registration Number: CRD42015029513

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Section I. Purpose and Background

The Hepatitis C virus (HCV) is a virus that attacks the liver and can cause liver disease.¹ It is estimated that 3% of the world's population has a chronic hepatitis C virus infection.² In 2011, it was estimated that 0.64% of Canadians, or approximately 220,000 persons, had chronic HCV infection, but that 44% of cases were not diagnosed.³ Individuals living with undiagnosed HCV infection remain infectious and can potentially transmit the virus to others through blood-to-blood contact.¹

An initial screening test is conducted to detect HCV antibodies in the blood. If the screening test is positive, an additional blood test is conducted to detect HCV RNA in the blood to confirm current infection with HCV.¹ Currently, there are no national or provincial screening programs in Canada for HCV infection.⁴ In 2009, the College of Family Physicians of Canada and the Public Health Agency of Canada recommended that anyone with risk behaviours or potential exposures to HCV and those with clinical clues that raise suspicion of possible HCV infection receive testing.⁵ However, evidence suggested that risk-factor based testing have failed to identify a large proportion of infected people, possibly due to inaccurate reporting of risk-status by patients or lack of time and expertise necessary to conduct a proper risk assessment by health providers.⁶ So in 2012, the Canadian Liver Foundation issued a statement recommending that all adults born between 1945 and 1975 be tested once for HCV infection.⁷

Treatment of HCV infection is through antiviral therapy and effectiveness is often evaluated by sustained virological response (SVR), or undetectable serum levels of HCV RNA, after a defined period post-treatment.⁸ Until 2011, the standard of care for treatment of chronic HCV infection was pegylated interferon alpha + ribavirin (PR) administered for 48 weeks⁹, resulting in SVR rates between 40%-80% depending on the HCV genotype of the patient.¹⁰ Since then, the standard of care has changed due to regulatory approvals for use of direct-acting antivirals (DAAs) such as boceprevir, telaprevir, simeprevir and sofosbuvir, which, in combination with PR, offer substantial improvement in SVR rates compared to PR alone.^{10,11} Besides improvements in SVR rates, some newer treatments are interferon-free, resulting in fewer side effects, or are all-oral treatments that reduce the burden on patients compared to injection-based treatments.¹²

The purpose is to conduct a systematic review of published research evidence on the effectiveness and harms of Hepatitis C treatment in treatment-naïve non-pregnant adults that will provide part of the evidence required for the Canadian Task Force on Preventive Health Care to develop recommendations on screening for hepatitis C infection.

Section II. Research Questions

The key questions for this review are as follows:

KQ1) What is the comparative clinical benefit of treatment regimens for patients diagnosed with chronic hepatitis C (CHC) infection (genotype 1 to 6) who are treatment naïve?

KQ2) What are the frequency of harms associated with treatment regimens for patients diagnosed with chronic hepatitis C (CHC) infection (genotype 1 to 6) who are treatment naïve?

Eligibility Criteria

The inclusion and exclusion criteria that will be used to select studies to answer the key questions of this review are summarized in Table 1.

Table 1 - Inclusion and Exclusion Criteria- Treatment questions (KQ1 and KQ2)

	Inclusion	Exclusion
Population	Treatment-naïve non-pregnant adults <i>* For studies wherein data on only treatment-naïve patients cannot be extracted, study populations comprised of at least 80% treatment-naïve individuals will also be included.</i>	Post-transplant patients; people with HIV; hemodialysis patients; people with occupational exposure
Interventions	Treatment (any that is currently available for use in Canada and any emerging regimens that are anticipated to become available in Canada by February 2016) of HCV for all genotypes (1-6)	
Comparators	KQ1: PR48 (Pegylated interferon plus ribavirin for 48 weeks) <i>* For single arm trials, pre-established baseline/historical SVR rates will be used as comparator.</i>	
Outcomes	KQ1: <i>Long-term outcomes:</i> Mortality (hepatic & all cause), Cirrhosis, Hepatocellular carcinoma, Hepatic decompensation, Need for liver transplantation, Quality of life (all scales reported) <i>Intermediate outcomes:</i> Reduced HCV transmission, Sustained virological response, Improvement in liver histology. KQ2: Withdrawal due to adverse events, Psychological adverse events, Neutropenia, Flu-like symptoms, Anemia, rash	
Settings	Settings where treatment for HCV is commonly or may be performed (e.g., specialized centers)	
Study designs	Randomized or non-randomized, controlled or uncontrolled, interventional studies.	
Language	English	
Search	No limits	

timeframe		
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Section III: Methods

To evaluate the evidence on treatment for HCV infection, the following will be completed: (1) conduct a literature search using a systematic search strategy OR conduct an update of a previous systematic search strategy; (2) review and select studies for analysis using pre-defined inclusion and exclusion criteria; (3) extract data from included studies; (4) assess the methodological quality of each study using validated tools; and (5) synthesize and evaluate the strength and quality of the evidence on each outcome of interest.

Two reviewers will extract and verify data. The quality of evidence for each outcome will be assessed separately by two evaluators using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolkit. Additional information is reported in the Data Extraction and Quality Assessments section.

The systematic review to address key questions related to treatment (KQ6 to 7) will be conducted by the Prevention Guidelines Division at PHAC. The systematic review will follow the methodology as recommended in the GRADE¹³ and Cochrane¹⁴ methods for systematic reviews.

Literature Search Strategy

The full search strategies are reported in Appendix A and B.

In 2015, CADTH conducted a systematic review on the efficacy and safety of Hepatitis C regimens that were either currently approved for use in Canada, or were considered to have a high likelihood of regulatory approval in Canada by February 2016, and were of clinical relevance due to their inclusion in either a Canadian or US guideline.¹¹ Since these are the same Hepatitis C regimens of interest for the CTFPHC treatment review, it was decided that the CADTH literature search strategy will be used for this review (Appendix A). For retrieval of articles published up until February 4, 2015, the list of articles that were eligible for full-text article screening (n=238) in the CADTH Therapeutic Review will be assessed further for possible inclusion. For retrieval of articles published since then, a recreation of the search strategy used for the CADTH Therapeutic Review on Drugs for Chronic Hepatitis C Infection: Clinical Review July 2015¹¹ will be conducted by a Health Canada librarian, while an update of the search strategy for grey literature would be conducted by a scientific officer from the PGD project team (Appendix B).

Study Selection

Two reviewers will independently screen abstracts relevant to the research questions. Full texts of potentially relevant articles will be retrieved and independently assessed by two reviewers for possible inclusion based on the pre-determined selection criteria outlined in TABLE 1. Consensus will be required for inclusion. Conflicts at this level will be resolved by discussion between the two reviewers. A third team member will be consulted to resolve any continued disagreements. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.¹⁵

Data Extraction and Quality Assessments

For each included study, two independent reviewers will extract data about the population, intervention, comparator(s), study design, results, and primary conclusions. Each reviewer will verify the accuracy and completeness of the other's data extraction. Disagreements will be resolved through discussion and/or third party consultation if consensus cannot be reached. We will contact study authors for missing or incomplete data, as necessary.

Two reviewers will independently assess the quality of each included study using the assessment tool that is most appropriate. Quality assessment will involve a two-step process: first we will critically appraise the methodological quality of all comparative studies; next we will assess the strength and quality of the evidence on each outcome of interest. We will use the AMSTAR tool¹⁶ to critically appraise all systematic reviews and meta-analyses; the Cochrane Risk of Bias tool¹⁴ for RCTs, the Newcastle-Ottawa Scale¹⁷ for Non-Randomized Studies of Interventions¹⁸ as appropriate. A modified version of the Drummond Checklist will be used to assess disease-progression modelling studies.¹⁹ The critical appraisal of qualitative studies will follow criteria outlined in the CASP checklist: http://media.wix.com/ugd/dded87_29c5b002d99342f788c6ac670e49f274.pdf

We will use the GRADE system¹³ to assess the strength and quality of the evidence for all outcomes ranked by the CTFPHC working group members and the patient sample as critical or important.

Analysis Plan

Each study design will be analyzed separately (i.e., data from randomized and non-randomized control studies will not be quantitatively pooled with data from observational studies). Separate analyses will be conducted on data from observational studies with controls (for both benefits and harms) and without controls (for harms only). Data on sustained virological response (SVR) from single arm trials will be compared to historical rates and rates obtained from the comparator group (PR48) of the controlled studies analyses conducted in this review.

The methodological, clinical and statistical heterogeneity will be assessed within the GRADE domains (i.e., directness across studies, risk of bias, and consistency). We will do a sensitivity analysis based on risk of bias rating (high, unclear, low) for primary outcomes of interest and number needed to treat and number needed to harm will be calculated based on Cochrane's recommended method.¹⁴ To assess for publication bias, funnel plots will be created pending sufficient number of studies for inclusion (minimum 10 studies).

Data Analysis

The Cochrane Review Manager software version 5.3 will be used for meta-analyses of the pooled data for the outcomes of interest. Randomized and non-randomized study designs will be analyzed separately. Analyses of dichotomous outcomes such as frequency of harms will be summarized using relative risks (RRs) and 95% confidence intervals (CIs), and analyses of continuous outcomes will be summarized using differences in means and 95% CIs. When different scales are used, analyses of continuous outcomes will be summarized as standardised mean differences (SMD) with 95% CIs.

For outcomes of benefits of treatment for HCV, further sub-group and sensitivity analyses will be conducted where possible to evaluate statistical stability and effect on statistical heterogeneity. The Cochran's Q ($\alpha=0.05$) will be employed to detect statistical heterogeneity and the I^2 statistic will be used to quantify the magnitude of statistical heterogeneity between studies.¹⁴

Section IV: Planned Schedule and Timeline

- Draft protocol: November 2015
- Final Protocol: November 2015
- Draft Evidence Review: January 2016
- Final Evidence Review: March 2016

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Appendix A: Search Strategy (up until February 2015)

Treatment

(Source: CADTH Therapeutic Review on Drugs for Chronic Hepatitis C Infection: Clinical Review July 2015¹¹)

OVERVIEW

Interface: Ovid
Databases: Embase 1974 to present
MEDLINE Daily and MEDLINE 1946 to present
MEDLINE In-Process & Other Non-Indexed Citations
EBM Reviews - Cochrane Central Register of Controlled Trials
December 2014
Note: Subject headings have been customized for each database.
Duplicates between databases were removed in Ovid.
Date of Search: February 4, 2015
Alerts: Bi-weekly search updates until project completion
Study Types: No study design filters used
Limits: Date limit: None
Language limit: English
Conference abstracts: excluded
Animal filter used

SYNTAX GUIDE

/ At the end of a phrase, searches the phrase as a subject heading
.sh At the end of a phrase, searches the phrase as a subject heading
exp Explode a subject heading
* Before a word, indicates that the marked subject heading is a primary topic;
or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj Requires words are adjacent to each other (in any order)
.ti Title
.ab Abstract
.hw Heading Word; usually includes subject headings and controlled vocabulary
.nm Name of Substance Word
.ot Original title
.pt Publication type
.rn CAS registry number
pmez Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd Ovid database code; Embase 1974 to present, updated daily
cctr Ovid database code; Cochrane Central Register of Controlled Trials

Searches

- 1 (incivek or incivo or telaprevir* or telapravir* or teleprvir* or teleprevir* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950).ti,ab.
- 2 *telaprevir/
- 3 (boceprevir* or bocepravir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab.
- 4 *boceprevir/
- 5 (sofosbuvir* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI

- 7976 or PSI7976 or Sovaldi or Virunon).ti,ab.
- 6 *sofosbuvir/
- 7 (simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab.
- 8 *simeprevir/
- 9 (ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab.
- 10 *ledipasvir/
- 11 (paritaprevir* or veruprevir* or ABT 450* or ABT450*).ti,ab.
- 12 *paritaprevir/ or *veruprevir/
- 13 (ombitasvir* or ABT 267 or ABT267).ti,ab.
- 14 *ombitasvir/
- 15 (dasabuvir* or ABT 333 or ABT333).ti,ab.
- 16 *dasabuvir/
- 17 (daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab.
- 18 *daclatasvir/
- 19 (asunaprevir* or Sunvepra or BMS 650032 or BMS650032).ti,ab.
- 20 *asunaprevir/
- 21 (grazoprevir* or MK 5172 or MK5172).ti,ab.
- 22 *grazoprevir/
- 23 (elbasvir* or MK 8742 or MK8742).ti,ab.
- 24 *elbasvir/
- 25 (beclabuvir* or BMS 791325 or BMS791325).ti,ab.
- 26 *beclabuvir/
- 27 (GS5816 or GS 5816).ti,ab.
- 28 (ABT-530 or ABT530).ti,ab.
- 29 (Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab.
- 30 or/1-29
- 31 30 use oemezd
- 32 31 not conference abstract.pt.
- 33 (incivek or incivo or telaprevir* or telapravir* or telepravir* or teleprevir* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950).ti,ab,ot,sh,hw,rn,nm.
- 34 (402957-28-2 or 569364-34-7 or 655M5O3W0U).rn,nm.
- 35 (boceprevir* or bocepravir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab,ot,sh,hw,rn,nm.
- 36 (394730-60-0 or 89BT58KELH).rn,nm.
- 37 (sofosbuvir* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or Sovaldi or Virunon).ti,ab,ot,sh,hw,rn,nm.
- 38 (1190307-88-0 or WJ6CA3ZU8B).rn,nm.
- 39 (simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab,ot,sh,hw,rn,nm.
- 40 (923604-59-5 or 9WS5RD66HZ).rn,nm.
- 41 (ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab,ot,sh,hw,rn,nm.
- 42 (1256388-51-8 or 013TE6E4WV).rn,nm.
- 43 (paritaprevir* or veruprevir* or ABT 450* or ABT450*).ti,ab,ot,sh,hw,rn,nm.
- 44 (1216941-48-8 or OU2YM37K86).rn,nm.
- 45 (ombitasvir* or ABT 267 or ABT267).ti,ab,ot,sh,hw,rn,nm.
- 46 (1258226-87-7 or 2302768XJ8).rn,nm.
- 47 (dasabuvir* or ABT 333 or ABT333).ti,ab,ot,sh,hw,rn,nm.
- 48 (1132935-63-7 or DE54EQW8T1).rn,nm.
- 49 (daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab,ot,sh,hw,rn,nm.
- 50 (1009119-64-5 or LI2427F9CI).rn,nm.
- 51 (asunaprevir* or Sunvepra or BMS 650032 or BMS650032).ti,ab,ot,sh,hw,rn,nm.
- 52 (630420-16-5 or S9X0KRJ00S).rn,nm.
- 53 (grazoprevir* or MK 5172 or MK5172).ti,ab,ot,sh,hw,rn,nm.

54 (1350462-55-3 or 1350514-68-9 or 4O2AB118LA or 8YE81R1X1J).rn,nm.
 55 (elbasvir* or MK 8742 or MK8742).ti,ab,ot,sh,hw,rn,nm.
 56 (1370468-36-2 or 632L571YDK).rn,nm.
 57 (beclabuvir* or BMS 791325 or BMS791325).ti,ab,ot,sh,hw,rn,nm.
 58 (958002-33-0 or MYW1X5CO9S).rn,nm.
 59 (GS5816 or GS 5816).ti,ab,ot,sh,hw,rn,nm.
 60 (ABT-530 or ABT530).ti,ab,ot,sh,hw,rn,nm.
 61 (Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab,ot,sh,hw,rn,nm.
 62 or/33-61
 63 62 use pmez,cctr
 64 32 or 63
 65 exp animals/
 66 exp animal experimentation/ or exp animal experiment/
 67 exp models animal/
 68 nonhuman/
 69 exp vertebrate/ or exp vertebrates/
 70 or/65-69
 71 exp humans/
 72 exp human experimentation/ or exp human experiment/
 73 or/71-72
 74 70 not 73
 75 64 not 74
 76 75 use cctr
 77 76 not Journal: conference abstract.pt.
 78 75 use pmez,oomezd
 79 limit 78 to english language
 80 77 or 79
 81 remove duplicates from 80

OTHER DATABASES

PubMed	Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov)	Same keywords, limits used as per MEDLINE search. Search limited to completed trials with study results.

Grey Literature

Date of Search:	February 2015
Keywords:	Hepatitis C, telaprevir, boceprevir, simeprevir, sofosbuvir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, daclatasvir, asunaprevir, grazoprevir, elbasvir, beclabuvir, GS-5816 and ABT-530
Limits:	No date limit, English only

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)

Appendix B: Search Strategy (February 2015 to November 2015)

Drugs for Chronic Hepatitis C Infection

Search conducted by the Health Canada Library (Update – February 4, 2015 to November 18, 2015)

Database(s): **Embase** 1974 to 2015 November 18

Search Strategy:

#	Searches	Results
1	(incivek or incivo or telaprevir* or telaprevir* or teleprevir* or teleprevir* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950).ti,ab.	2644
2	*telaprevir/	1333
3	(boceprevir* or boceprevir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab.	1817
4	*boceprevir/	842
5	(sofosbuvir* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or Sovaldi or Virunon).ti,ab.	1227
6	*sofosbuvir/	674
7	(simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab.	686
8	*simeprevir/	301
9	(ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab.	321
10	*ledipasvir/	65
11	(paritaprevir* or veruprevir* or ABT 450* or ABT450*).ti,ab.	226
12	*paritaprevir/ or *veruprevir/	27
13	(ombitasvir* or ABT 267 or ABT267).ti,ab.	210
14	*ombitasvir/	42
15	(dasabuvir* or ABT 333 or ABT333).ti,ab.	201
16	*dasabuvir/	86
17	(daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab.	536
18	*daclatasvir/	272
19	(asunaprevir* or Sunvepra or BMS 650032 or BMS650032).ti,ab.	217

20	*asunaprevir/	129
21	(grazoprevir* or MK 5172 or MK5172).ti,ab.	117
22	*grazoprevir/	15
23	(elbasvir* or MK 8742 or MK8742).ti,ab.	63
24	*elbasvir/	13
25	(beclabuvir* or BMS 791325 or BMS791325).ti,ab.	55
26	*beclabuvir/	19
27	(GS5816 or GS 5816).ti,ab.	19
28	(ABT-530 or ABT530).ti,ab.	7
29	(Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab.	24
30	or/1-29	5154
31	30 not conference abstract.pt.	2463
32	limit 31 to (human and english language)	1988
33	remove duplicates from 32	1849
34	2015\$.dd,em.	1906041
35	33 and 34	703

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(incivek or incivo or telaprevir* or telaprevir* or teleprevir* or teleprevir* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950).ti,ab,ot,sh,hw,rn,nm.	1306
2	(402957-28-2 or 569364-34-7 or 655M5O3W0U).rn,nm.	740
3	(boceprevir* or boceprevir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520).ti,ab,ot,sh,hw,rn,nm.	798
4	(394730-60-0 or 89BT58KELH).rn,nm.	503
5	(sofosbuvir* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or Sovaldi or Virunon).ti,ab,ot,sh,hw,rn,nm.	646
6	(1190307-88-0 or WJ6CA3ZU8B).rn,nm.	254

7	(simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad).ti,ab,ot,sh,hw,rn,nm.	334
8	(923604-59-5 or 9WS5RD66HZ).rn,nm.	146
9	(ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796).ti,ab,ot,sh,hw,rn,nm.	155
10	(1256388-51-8 or 013TE6E4WV).rn,nm.	52
11	(paritaprevir* or veruprevir* or ABT 450* or ABT450*).ti,ab,ot,sh,hw,rn,nm.	95
12	(1216941-48-8 or OU2YM37K86).rn,nm.	0
13	(ombitasvir* or ABT 267 or ABT267).ti,ab,ot,sh,hw,rn,nm.	91
14	(1258226-87-7 or 2302768XJ8).rn,nm.	0
15	(dasabuvir* or ABT 333 or ABT333).ti,ab,ot,sh,hw,rn,nm.	81
16	(1132935-63-7 or DE54EQW8T1).rn,nm.	0
17	(daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza).ti,ab,ot,sh,hw,rn,nm.	283
18	(1009119-64-5 or LI2427F9CI).rn,nm.	0
19	(asunaprevir* or Sunvepra or BMS 650032 or BMS650032).ti,ab,ot,sh,hw,rn,nm.	109
20	(630420-16-5 or S9X0KRJ00S).rn,nm.	0
21	(grazoprevir* or MK 5172 or MK5172).ti,ab,ot,sh,hw,rn,nm.	40
22	(1350462-55-3 or 1350514-68-9 or 4O2AB118LA or 8YE81R1X1J).rn,nm.	0
23	(elbasvir* or MK 8742 or MK8742).ti,ab,ot,sh,hw,rn,nm.	25
24	(1370468-36-2 or 632L571YDK).rn,nm.	0
25	(beclabuvir* or BMS 791325 or BMS791325).ti,ab,ot,sh,hw,rn,nm.	24
26	(958002-33-0 or MYW1X5CO9S).rn,nm.	0
27	(GS5816 or GS 5816).ti,ab,ot,sh,hw,rn,nm.	3
28	(ABT-530 or ABT530).ti,ab,ot,sh,hw,rn,nm.	0
29	(Viekira or Viekirax or Exviera or Holkira or Harvoni).ti,ab,ot,sh,hw,rn,nm.	20
30	or/1-29	2395
31	30 not (conference abstract or Journal: conference abstract).pt.	2395

32	limit 31 to (english language and humans)	1630
33	remove duplicates from 32	1433
34	2015\$.dc,ed.	1516769
35	33 and 34	428

Database(s): **COCHRANE LIBRARY**

Search Strategy as searched in <http://onlinelibrary.wiley.com/cochranelibrary/search/advanced>:

#	Searches	Results
1	(incivek or incivo or telaprevir* or telaprevir* or teleprevir* or teleprevir* or VX-950 or VX950 or LY-570310 or LY570310 or MP-424 or MP424 or VRT-111950 or VRT111950) all text	236
2	(boceprevir* or boceprevir* or victrelis or sch 503034 or sch503034 or ebp 520 or ebp520) all text	182
3	(sofosbuvir* or GS 7977 or GS7977 or PSI 7977 or PSI7977 or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or Sovaldi or Virunon) all text	146
4	(simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos or Olysio or Sovriad) all text	80
5	(ledipasvir* or GS-5885 or GS5885 or WHO 9796 or WHO9796) (Word variations have been searched) all text	55
6	(paritaprevir* or veruprevir* or ABT 450* or ABT450*) (Word variations have been searched) all text	66
7	(ombitasvir* or ABT 267 or ABT267) (Word variations have been searched) all text	54
8	(dasabuvir* or ABT 333 or ABT333) (Word variations have been searched) all text	52
9	(daclatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or Daklinza) all text	73
10	(asunaprevir* or Sunvepra or BMS 650032 or BMS650032) all text	45
11	(grazoprevir* or MK 5172 or MK5172) (Word variations have been searched) all text	20
12	(elbasvir* or MK 8742 or MK8742) (Word variations have been searched) all text	12

13	(beclabuvir* or BMS 791325 or BMS791325) all text	17
14	(GS5816 or GS 5816) all text	7
15	(Viekira or Viekirax or Exviera or Holkira or Harvoni) all text	2
16	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	704
17	[Animals] explode all	7358
18	[Animal Experimentation] explode all	4
19	[Models, Animal] explode all	355
20	[Vertebrates] explode all	5939
21	#17 or #18 or #19 or #20	7412
22	#16 not #21	703
23	#16 not #21 Limit=Online Publication Date from Feb2015 to Nov 2015	11

Database(s): **ClinicalTrials.gov**

Search Strategy as searched in clinicaltrials.gov:

#	Searches	Results
1	incivek OR incivo OR telaprevir* OR telaprevir* OR teleprevir* OR teleprevir* OR VX-950 OR VX950 OR LY-570310 OR LY570310 OR MP-424 OR MP424 OR VRT-111950 OR VRT111950 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	5
2	boceprevir* OR boceprevir* OR victrelis OR "sch 503034" OR sch503034 OR "ebp 520" OR ebp520 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	14
3	sofosbuvir* OR "GS 7977" OR GS7977 OR "PSI 7977" OR PSI7977 OR "PSI 7851" OR PSI7851 OR "PSI 7976" OR PSI7976 OR Sovaldi OR Virunon Completed Studies With Results updated from 02/04/2015 to 11/30/2015	15
4	simeprevir* OR TMC435 OR "TMC 435" OR TMC435350 OR "TMC 435350" OR Galexos OR Olysio OR Sovriad Completed Studies With Results updated from 02/04/2015 to 11/30/2015	2
5	ledipasvir* OR GS-5885 OR GS5885 OR "WHO 9796" OR WHO9796 Completed Studies With Results updated from 02/04/2015 to	5

	11/30/2015	
6	paritaprevir* OR veruprevir* OR "ABT 450*" OR "ABT450*" Completed Studies With Results updated from 02/04/2015 to 11/30/2015	0
7	ombitasvir* OR "ABT 267" OR ABT267 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	8
8	dasabuvir* OR "ABT 333" OR ABT333 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	7
9	daclatasvir* OR "BMS 790052" OR BMS790052 OR "EBP 883" OR EBP883 OR Daklinza Completed Studies With Results updated from 02/04/2015 to 11/30/2015	15
10	asunaprevir* OR Sunvepra OR "BMS 650032" OR BMS650032 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	0
11	grazoprevir* OR "MK 5172" OR MK5172 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	0
12	elbasvir* OR "MK 8742" OR MK8742 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	0
13	beclabuvir* OR "BMS 791325" OR BMS791325 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	0
14	GS5816 OR "GS 5816" Completed Studies With Results updated from 02/04/2015 to 11/30/2015	0
15	ABT-530 OR ABT530 Completed Studies With Results updated from 02/04/2015 to 11/30/2015	0
16	Viekira OR Viekirax OR Exviera OR Holkira OR Harvoni Completed Studies With Results updated from 02/04/2015 to 11/30/2015	9
17	or/1-16	80

Search conducted by a Scientific Officer from the PGD project team

Grey Literature

Date of Search: November 20, 2015

Keywords: Hepatitis C, telaprevir, boceprevir, simeprevir, sofosbuvir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, daclatasvir, asunaprevir, grazoprevir, elbasvir, beclabuvir, GS-5816 and ABT-530

Limits: From February 2015 to November 2015, English only

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching”

(<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)