Effectiveness of generic direct-acting agents for the treatment of hepatitis C: systematic review and meta-analysis

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Systematic reviews

Abstracts in العربية, 中文, Français, Русский and Español at the end of each article.

Introduction

An estimated 70 million people worldwide are chronically infected by the hepatitis C virus (HCV).1 The clinical presentation of HCV infection can vary from minimal fibrosis to cirrhosis and its complications.2 The disease is one of the most frequent reasons for liver transplantation and more than 1 million deaths were due to HCV infection in 2013,3 most of which were related to cirrhosis and hepatocellular carcinoma.4 A sustained virological response to treatment has been associated with lower rates of liver-related complications,5 better quality of life,6 and a shorter waiting list for liver transplantation.7

The introduction of direct-acting antiviral agents has revolutionized the treatment of chronic hepatitis C – all-oral, interferon-free regimens have been shown to be highly effective.8 In 2016, the World Health Organization (WHO) outlined strategies for eliminating HCV infection and for reducing the number of viral hepatitis-related deaths by 65% by 2030.9 However, the use of direct-acting agents has had a substantial economic impact in several countries due to high drug costs. Nevertheless, the adoption of a test-and-treat-all strategy is cost-effective and has been shown to be essential for reaching global treatment goals.8 Access to direct-acting agents varies widely across the world.10 Several countries have provided access with minimal co-payments or have negotiated large discounts with the pharmaceutical industry to provide universal treatment for everyone living with HCV.11 Despite the availability of highly effective therapeutic regimens, however, WHO’s target of eliminating HCV infection by 2030 will probably be difficult to achieve for several reasons, including:

(i) the high rate of new infections; (ii) HCV-infected individuals remaining untreated due to a lack of screening; (iii) patent restrictions that affect generic medicines; and (iv) the high price of direct-acting agents in middle-income countries with large HCV epidemics.12 Generic versions of direct-acting agents could be provided at a much lower cost than brand-name medicines and could contribute to eradicating HCV infection in coming years. Optimally, generic HCV direct-acting agents should be prequalified by WHO.13

Our hypothesis was that generic direct-acting agents are highly effective for the treatment of hepatitis C. Generic agents should be considered in resource-constrained settings for decreasing the burden of liver disease in HCV-infected patients.

Methods

We performed a systemic search of the PubMed®, Embase®, Scopus and LILACS (Literatura Latino Americana em Ciências da Saúde) databases to 31 August 2018, without language restrictions. The search string was: [“sofosbuvir” OR “sovaldi” OR “simeprevir” OR “olysio” OR “daclatasvir” OR “daklinza” OR “ledipasvir” OR “harvoni” OR “elbasvir” OR “grazoprevir” OR “zepatier” OR “velpatasvir” OR “epclusa” OR “direct-acting agents”] AND [“hepatitis C” OR “HCV”] AND [“Generic” OR “Drug substitution” OR “Therapeutic equivalency”]. Table 1, Table 2 and Box 1 describe the study inclusion and exclusion criteria.
This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. 13 The quality of the studies included was appraised using the National Institute of Health’s quality assessment tool (i.e. the DerSimonian–Laird model (i.e. the DerSimonian–Laird random-effects model (i.e. the DerSimonian–Laird random-effects model). 13 The following study types were excluded: (i) studies of HCV prevalence or screening; and (ii) clinical trials or cohort studies that evaluated the effectiveness of brand-name direct-acting agents only.

Table 1. Study inclusion criteria, systematic review and meta-analysis of generic direct-acting agents for treating hepatitis C

| Characteristic | Inclusion criteria | Notes |
|---------------|-------------------|-------|
| Study population | People living with a chronic HCV infection | None |
| Study intervention | Treatment of HCV infection using generic direct-acting agents | Table 2 lists eligible drugs and their licensed doses and Box 1 lists eligible treatment regimens |
| Comparison treatment | Either: (i) brand-name direct-acting agents for HCV infection; or (ii) no comparator treatment | The following study types were excluded: (i) studies of HCV prevalence or screening; and (ii) clinical trials or cohort studies that evaluated the effectiveness of brand-name direct-acting agents only |
| Study outcome | Sustained virological response 12 weeks after the end of treatment | The outcome used in intention-to-treat and per-protocol analyses was the eradication of HCV virus, as indicated by a sustained virological response 12 weeks after the end of treatment |
| Study design | Randomized or open-label clinical trials and real-life cohort studies | The following study types were eligible for inclusion: (i) randomized or open label clinical trials that compared the effectiveness of generic and brand-name direct-acting agents for the treatment of HCV infection; and (ii) cohort studies that reported the effectiveness of generic direct-acting agents for HCV eradication |

HCV: hepatitis C virus.

Table 2. Eligible drugs, systematic review and meta-analysis of generic direct-acting agents for treating hepatitis C

| Drug | Formulation | Brand name |
|------|-------------|------------|
| Sofosbuvir | Tablets containing 400 mg | Sovaldi® |
| Simeprevir | Capsules containing 150 mg | Olysio® |
| Daclatasvir | Tablets containing 30 or 60 mg | Daklinza® |
| Sofosbuvir–ledipasvir combination | Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir | Harvoni® |
| Sofosbuvir–velpatasvir combination | Tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir | Epclusa® |
| Grazoprevir–elbasvir combination | Tablets containing 100 mg of grazoprevir and 50 mg of elbasvir | Zepatier® |

Box 1. Eligible drug treatment regimes, systematic review and meta-analysis of generic direct-acting agents for treating hepatitis C, 2019

- Sofosbuvir and daclatasvir, with or without ribavirin for 12 or 24 weeks.
- Sofosbuvir and simeprevir, with or without ribavirin for 12 or 24 weeks.
- Sofosbuvir–daclatasvir combination, with or without ribavirin for 12 or 24 weeks.
- Sofosbuvir–ledipasvir combination, with or without ribavirin for 8 or 12 weeks.
- Sofosbuvir–velpatasvir combination, with or without ribavirin for 12 weeks.
- Grazoprevir–elbasvir combination, with or without ribavirin for 12 weeks.

The quality of the studies included was appraised using the National Institute of Health’s quality assessment tool for observational cohort and cross-sectional studies. 13 This tool’s 14-item checklist was designed to focus on factors important for evaluating a study’s internal validity. Studies were rated as being of good, fair or poor quality. Those with 0 to 6, 7 to 10, or 11 or more “yes” responses to the 14 items were considered as having a high, moderate or low risk of bias, respectively.

Statistical analysis

Our primary outcome was the pooled proportions of treated patients with sustained virological response for generic direct-acting agents, reported with a 95% confidence interval (CI). In addition, where data were available, we performed a meta-analysis of proportions using a random-effects model (i.e. the DerSimonian–Laird statistical method).
Results

Study characteristics

The database and manual searches identified 341 and 4 records, respectively. Subsequent screening of titles and abstracts led to 19 studies being eligible for inclusion in the meta-analysis (Fig. 1).23–41 These 19 published full articles reported sustained virological response proportions for generic direct-acting agents in a total of 57,433 individuals and all except one were published in English.38 The studies were performed in seven territories – Egypt (seven studies), India (three studies), China (four studies), the Islamic Republic of Iran (two studies), Argentina (one study) and Chile (one study) – and one was a multiregional study in Australia, eastern Europe and South-East Asia (Table 3; available at: http://www.who.int/bulletin/volumes/98/3/19-231522). Four studies compared the effectiveness of generic and brand-name direct-acting agents.23,24,32,38 Patients were treated with generic versions of: (i) sofosbuvir and ribavirin; (ii) sofosbuvir and daclatasvir, with or without ribavirin; (iii) sofosbuvir and ledipasvir, with or without ribavirin; or (iv) sofosbuvir and velpatasvir. Cirrhosis was identified by liver biopsy, liver stiffness measurement, serological biomarkers, clinical signs or imaging. Generic direct-acting agents originated from Egypt (nine studies), India (seven studies), the Islamic Republic of Iran (two studies), Argentina (one study) and Bangladesh (two studies), though one study had multiregional sources (Table 4; available at: http://www.who.int/bulletin/volumes/98/3/19-231522).

Study quality was good in 37% (7/19), fair in 26% (5/19) and poor in 37% (7/19) and the risk of bias was low in 26% (5/19) and high in 75% (14/19). The likelihood of bias was low in 26% (5/19) and high in 21% (4/19). Three studies used WHO prequalified medicines or medicines listed for use in mass-treatment programmes by the Expert Review Panel of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Table 4).23 In addition, another three studies used generic direct-acting agents whose bioequivalence with the original versions had previously been demonstrated in pharmacokinetics studies.

Sustained virological response

Overall

The pooled proportion of patients with sustained virological response for generic direct-acting agents overall was 98% (95% CI: 97–99; $I^2 = 94.1\%$) in per-protocol analyses (18 studies including 57,249 patients; Fig. 2) and 96% (95% CI: 93–98; $I^2 = 68.1\%$) in intention-to-treat analyses (8 studies including 1420 patients; Fig. 3). The likelihood of a sustained virological response with brand-name medicines was similar to that with generic direct-acting agents (RR: 1.00; 95% CI: 0.98–1.02; $F = 0.00\%$) in the four studies (including 1026 patients) that compared the two types of direct-acting agent (Fig. 4). Among the 55,778 patients treated with sofosbuvir and daclatasvir, with or without ribavirin, the pooled proportion was 98% (95% CI: 97–99; $I^2 = 96.1\%$) in per-protocol analyses (Fig. 5; avail-
Fig. 2. Sustained virological response to hepatitis C treatment by generic direct-acting agents, per-protocol analysis, systematic review and meta-analysis, 2019

| Author, year | Treated (no.) | Sustained virological responsea (no.) | % | Weight | Sustained virological responsea, % (95% CI) |
|--------------|---------------|-------------------------------------|---|--------|---------------------------------|
| Yakoot et al. 2016 | 48 | 46 | 3.10 | 96 (86–99) |
| Hill et al. 2017 | 250 | 247 | 6.90 | 99 (97–100) |
| Menat et al. 2017 | 94 | 92 | 4.65 | 99 (95–99) |
| Nagai et al. 2017 | 29 | 29 | 2.15 | 100 (99–100) |
| Sharfi et al. 2017 | 30 | 29 | 2.21 | 97 (83–99) |
| Vergas et al. 2017 | 26 | 25 | 1.98 | 96 (81–99) |
| Yakoot et al. 2017 | 118 | 117 | 5.20 | 99 (95–100) |
| Zeng et al. 2017 | 187 | 186 | 6.28 | 97 (94–98) |
| Abozeid et al. 2018 | 395 | 388 | 7.44 | 98 (96–99) |
| El-Nahas et al. 2018 | 133 | 133 | 5.49 | 99 (96–100) |
| Elsharkawy et al. 2018 | 36186 | 35663 | 9.76 | 100 (97–100) |
| Gupta et al. 2018 | 393 | 376 | 7.73 | 99 (99–100) |
| Kumar et al. 2018 | 71 | 71 | 3.97 | 97 (95–99) |
| Liu et al. June 2018 | 226 | 223 | 6.70 | 99 (96–100) |
| Liu et al. September 2018 | 508 | 493 | 8.12 | 97 (95–99) |
| Li et al. 2018 | 137 | 135 | 5.56 | 99 (95–100) |
| Omar et al. 2018 | 18378 | 17473 | 9.73 | 97 (95–99) |
| Shousha et al. 2018 | 40 | 39 | 2.73 | 98 (87–100) |
| **Overall (I² = 94.1%, P = 0.00)** | 100.00 | | | | 98 (97–99) |

CI: confidence interval.  
* A sustained virological response 12 weeks after the end of treatment.

Fig. 3. Sustained virological response to hepatitis C treatment by generic direct-acting agents, intention-to-treat analysis, systematic review and meta-analysis, 2019

| Author, year | Treated (no.) | Sustained virological responsea (no.) | % | Weight | Sustained virological responsea, % (95% CI) |
|--------------|---------------|-------------------------------------|---|--------|---------------------------------|
| Yakoot et al. 2016 | 50 | 46 | 8.14 | 92 (81–97) |
| Menat et al. 2017 | 100 | 92 | 11.61 | 92 (85–96) |
| Nagai et al. 2017 | 29 | 29 | 5.71 | 100 (88–100) |
| Yakoot et al. 2017 | 120 | 117 | 12.50 | 98 (93–99) |
| Zeng et al. 2017 | 192 | 186 | 14.60 | 97 (93–99) |
| Liu et al. June 2018 | 228 | 223 | 15.28 | 98 (93–99) |
| Liu et al. September 2018 | 517 | 493 | 17.74 | 95 (93–97) |
| Marciano et al. 2018 | 184 | 164 | 14.42 | 89 (84–93) |
| **Overall (I² = 68.1%, P = 0.00)** | 100.00 | | | | 96 (93–98) |

CI: confidence interval.  
* A sustained virological response 12 weeks after the end of treatment.

The generic version of the pan-genotypic regimen of sofosbuvir and velpatasvir, the proportion was 98% (95% CI: 95–99) and 99% (95% CI: 97–100), respectively. Subgroups

A single study exclusively included individuals with cirrhosis, 31 11 studies included patients with and without cirrhosis, two excluded cirrhotic patients and five did not report the prevalence of cirrhosis. Of the eight studies that reported proportions of sustained virological response in patients with cirrhosis, seven reported proportions for cirrhotic and noncirrhotic patients separately. The pooled proportion for patients without and with cirrhosis was 98% (95% CI: 97–99; I² = 34.2%; 7 studies; 1199 patients; Fig. 7; available at: http://www.who.int/bulletin/volumes/98/3/19-231522). The likelihood of a sustained virologi-
Fig. 4. Relative risk of a sustained virological response to hepatitis C treatment by brand-name versus generic direct-acting agents, systematic review and meta-analysis, 2019

| Author, year | % Weight | RR (95% CI) |
|--------------|----------|-------------|
| Vargas et al. 2017 | 4.40 | 1.00 (0.91–1.10) |
| Abozeid et al. 2018 | 61.59 | 1.00 (0.98–1.02) |
| El-Nahhas et al. 2018 | 15.44 | 0.99 (0.96–1.01) |
| Marcuno et al. 2018 | 18.57 | 1.02 (0.95–1.10) |
| Overall (I² = 0%); P = 0.725 | 100.00 | 1.00 (0.98–1.02) |

CI: confidence interval; RR: relative risk.

Table 5. Effect of cirrhosis on the likelihood of a sustained virological response* to generic direct-acting agents in patients with hepatitis C, meta-analysis, 2019

| Studya | No. of patients with a response/no. treated | RR (95% CI) | Study weighting (%) |
|--------|------------------------------------------|-------------|---------------------|
| | Without cirrhosis | With cirrhosis | |
| Yakoot et al., 2016b | 37/37 | 9/11 | 1.19 (0.90–1.58) | 1.87 |
| Nagral et al., 2017b | 22/22 | 3/4 | 1.20 (0.77–1.87) | 0.88 |
| Zeng et al., 2017b | 125/129 | 61/63 | 1.00 (0.95–1.06) | 11.00 |
| Abozeid et al., 2018b | 245/247 | 143/148 | 1.03 (0.99–1.06) | 24.00 |
| Gupta et al., 2018b | 248/259 | 128/134 | 1.00 (0.96–1.05) | 22.64 |
| Liu et al., 2018b | 173/175 | 49/52 | 1.05 (0.98–1.12) | 10.14 |
| Liu et al., 2018b | 330/331 | 172/187 | 1.06 (1.01–1.11) | 29.47 |
| Pooled datac | 1180/1190 | 565/599 | 1.03 (1.01–1.06) | 100.00 |

CI: confidence interval; RR: relative risk.

* A response was defined as a sustained virological response 12 weeks after the end of treatment.
*b The Merat et al.33 study was not included in this subanalysis because it involved only patients with cirrhosis.
*c The I² value for between-study heterogeneity was 0.0% (P = 0.435).

Sensitivity analysis

Our sensitivity analysis showed that heterogeneity was lower in studies performed in Asia than in Egypt (Fig. 12). In addition, we found that heterogeneity was lower in studies of patients with cirrhosis (Fig. 8) and when studies were stratified by quality (Fig. 13); available at: http://www.who.int/bulletin/volumes/98/3/19-231522) or risk of bias (Fig. 14; available at: http://www.who.int/bulletin/volumes/98/3/19-231522).

Discussion

Through a systematic review and meta-analysis approach, we derived pooled proportions of sustained virological response in patients treated for HCV infection using generic direct-acting agents. We found that generic direct-acting agents were highly effective. The overall pooled proportion of patients with a sustained virological response was 98% in real-life observational studies that included over 57 000 individuals, which was similar to that reported for brand-name direct-acting agents in large, real-life, observational cohort studies around the world.8,44,45 In particular, we found that a sustained virological response with generic direct-acting agents was similar to brand-name medicines. Additionally, in sensitivity analyses, we found that sustained virological response was also high with specific regimens, such as sofosbuvir with daclatasvir and sofosbuvir with ledipasvir. Although neither an HIV coinfection nor previous treatment was associated with a high treatment failure, the presence of cirrhosis at baseline was associated with a significantly lower sustained virological response in patients treated...
with generic direct-acting agents. The results of this study can help in the elaboration of public health strategies for using generic direct-acting agents to treat HCV infection.

Our study findings have implications for achieving the goal of eliminating HCV infection by 2030. Universal access to direct-acting agents is essential for decreasing viral transmission as well as for reducing mortality and the risk of liver-related complications associated with chronic hepatitis C worldwide. However, HCV treatment has entailed a substantial financial burden, especially as direct-acting agents are expensive. The nominal price of a 12-week course of sofosbuvir ranges from $6766 in Brazil to $64680 in the United States. In contrast, a course of a generic direct-acting agent regimen can be produced for approximately $200 per patient in countries such as Egypt and India.

The production of generic direct-acting agents has been challenged in various local intellectual property jurisdictions because some pharmaceutical components may still be patented. In most countries, local drug regulatory authorities can approve the marketing of a generic version of a patented drug only after the relevant patent has expired, generally after 20 years. In several countries, local intellectual property offices have evaluated requests to cancel patent claims previously granted to pharmaceutical companies, thereby opening up the possibility that affordable generic versions of direct-acting agents could be produced. Opposition pharmaceutical companies have defended their patents and, in the meantime, have collaborated with local companies to produce authorized versions of generic medicines for HCV treatment. The cost of these authorized versions will most likely exceed that of generic direct-acting agents produced by independent companies. Authorized, generic versions of sofosbuvir–ledipasvir and sofosbuvir–velpatasvir combinations were expected to be available in the United States in 2019 at a cost of $24000 per treatment course.

Our study has limitations. First, there was high between-study heterogeneity for pooled overall proportions of sustained virological response. High heterogeneity might have resulted from differences in the ethnic or clinical characteristics of study participants. Most studies were conducted either in Egypt, where most patients have an HCV genotype-4 infection, or in various parts of Asia. Our sensitivity analysis showed that the region where the study took place and characteristics of patients and study design influenced the heterogeneity. Second, there was a lack of a pooled proportion of patients with a sustained virological response for pan-genotypic interferon-free regimens. We acknowledge that few studies included patients treated with sofosbuvir and velpatasvir, or patients with an HIV–HCV coinfection. Most studies included in our analysis were real-life cohort studies in-

### Table: Sustained virological response to hepatitis C treatment with generic direct-acting agents, by geographical location, systematic review and meta-analysis, 2019

| Author, year | Treated (no.) | Sustained virological response (no.) | % Weight | Sustained virological response, % (95% CI) |
|--------------|---------------|-------------------------------------|----------|-------------------------------------------|
| Egypt        |               |                                     |          |                                           |
| Yakoot et al. 2016 | 48             | 46                                   | 3.10     | 96 (86–99)                                |
| Yakoot et al. 2017 | 118            | 117                                  | 5.26     | 99 (95–100)                               |
| Abdel et al. 2018 | 395            | 388                                  | 7.74     | 98 (96–99)                                |
| El-Nahhas et al. 2018 | 133          | 133                                  | 5.49     | 100 (97–100)                              |
| Elsharkawy et al. 2018 | 36186        | 35863                                | 9.76     | 98 (96–98)                                |
| Omar et al. 2018 | 18378         | 17473                                | 9.73     | 95 (95–95)                                |
| Shousha et al. 2018 | 40             | 39                                   | 2.73     | 98 (96–96)                                |
| Subtotal (I² = 97.8%, P = 0.00) | 43.75 |                                    |          | 98 (96–99)                                |
| Asia         |               |                                     |          |                                           |
| Meraz et al. 2017 | 94             | 92                                   | 4.65     | 98 (95–99)                                |
| Nagpal et al. 2017 | 29             | 29                                   | 2.75     | 100 (98–99)                               |
| Shariati et al. 2017 | 30            | 29                                   | 2.21     | 97 (83–99)                                |
| Zeng et al. 2017 | 187            | 186                                  | 6.28     | 99 (97–100)                               |
| Gupta et al. 2018 | 393            | 376                                  | 7.73     | 96 (95–97)                                |
| Kumar et al. 2018 | 71             | 71                                   | 3.97     | 100 (95–100)                              |
| Liu et al. June 2018 | 226          | 223                                  | 6.70     | 99 (96–100)                               |
| Liu et al. September 2018 | 508       | 493                                  | 8.12     | 97 (95–98)                                |
| Li et al. 2018 | 137            | 135                                  | 5.56     | 99 (95–100)                               |
| Subtotal (I² = 43.0%, P = 0.08) | 47.37 |                                    |          | 98 (97–99)                                |
| Other        |               |                                     |          |                                           |
| Hill et al. 2017 | 250            | 247                                  | 6.90     | 99 (97–100)                               |
| Vergara et al. 2017 | 26             | 25                                   | 1.98     | 96 (81–99)                                |
| Heterogeneity between groups: P = 0.80 |          |                                      | 100.00   |                                           |
| Overall (I² = 94.1%, P = 0.00) |          |                                      | 98 (97–99) |
The main strength of our study is the large number of patients in real-life scenarios included in the meta-analysis. This large sample size enabled us to estimate the pooled overall proportion of patients with a sustained virological response rates and proportions for different direct-acting agent regimens and for the presence of conditions such as cirrhosis. Moreover, we were able to perform sensitivity analyses that explored the effect on pooled estimates of geographical location, study quality and clinical and demographic characteristics.

In conclusion, we found that the proportion of patients treated with generic direct-acting agents with sustained virological response was high. The proportion was also high in patients treated with sofosbuvir and daclatasvir, and with sofosbuvir and ledipasvir, and in those with cirrhosis or an HIV coinfection. Recent cost-effectiveness studies of generic direct-acting agents in India suggest that their use can reduce costs, especially if pan-genotypic regimens are used (though efficacy estimates for brand-name medicines were used in these studies). Our results corroborate these economic analyses by showing that the effectiveness of generic and brand-name direct-acting agents is indeed the same. Future cost-effectiveness analyses are needed to investigate the specific characteristics of different countries and regions. Nevertheless, generic direct-acting agents are effective and should be considered in public health strategies for HCV elimination.

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通用直接药物治疗丙型肝炎的效果：系统评审和元分析

目的 通过开展系统评审和元分析，比较使用通用直接药物和品牌药物治疗丙型肝炎病毒（HCV）感染的疗效。

方法 我们搜索了在线数据库中报告的使用直接药物进行HCV治疗12周后的持续病毒性应答方面的研究。我们从意向性治疗和按方案分析中得出了治疗后表现的持续病毒性应答的概率。此外，我们还使用现有数据的随机效果模型（DerSimonian－Laird）计算了品牌药物和通用直接药物的持续病毒性应答的总相对风险（RR）。通过I²统计对研究间异质性进行了评估。

结果 我们确定了19份研究，涉及来自8个国家或地区的57433名个体。显示出持续病毒性应答的患者的比例为：意向性治疗：RR = 1.03；95%CI：0.81–1.29；11份研究；按方案分析：RR = 0.97；95%CI：0.89–1.05；18份研究。

结论 通用直接药物治疗丙型肝炎的效果：系统评审和元分析

摘要

Efficacité des antiviraux à action directe génériques pour le traitement de l’hépatite C. revue systématique et méta-analyse

Objective Comparer l’efficacité des antiviraux à action directe génériques et des médicaments de marque pour traiter l’infection par le virus de l’hépatite C (VHC) à l’aide d’une revue systématique et d’une métanalyse.

Méthodes Nous avons recherché dans les bases de données en ligne des études qui décrivaient une réponse virologique à l’aide d’un modèle de données de prises de décision de DerSimonian－Laird calculée par l’utilisation de logiciels spécialisés. Nous avons utilisé la statistique de I² pour l’analyse de la hétérogénéité entre les études.

Résultats Nous avons identifié 19 études portant sur un total de 57433 personnes réparties dans huit territoires ou régions. Les proportions totales combinées de patients présentant une réponse virologique à l’aide de ces données étaient de 98% (IC à 95% : 93–98; 8 études; I² = 94,1%) dans les analyses per protocole et 96% (IC à 95% : 93–98; 8 études; I² = 68,1%) dans les analyses en intention de traiter. La probabilité d’une réponse virologique à l’aide de ces données était sensiblement plus élevée chez les patients sans cirrhose que chez ceux ayant une cirrhose (RR : 1,03; IC à 95% : 1,01–1,06; 7 études), mais elle n’était pas significativement affectée par la prise d’un traitement antérieur (3 études) ou par une co-infection par le virus de l’immunodéficience humaine (3 études).

Conclusion Les antiviraux à action directe génériques sont très efficaces pour traiter l’hépatite C. Les médicaments génériques devraient être envisagés en cas de ressources limitées afin de réduire la charge des affections hépatiques chez les patients infectés par l’hépatite C.
Resumen

Eficacia de los antivirales genéricos de acción directa para el tratamiento de la hepatitis C: revisión sistemática y metanálisis

Objetivo
Comparar la eficacia de los antivirales genéricos de acción directa y los medicamentos de marca para el tratamiento de la infección por el virus de la hepatitis C (VHC) mediante la realización de una revisión sistemática y un metaanálisis.

Métodos
Se realizaron búsquedas en las bases de datos en línea de estudios que notificaron respuestas virológicas sostenidas 12 semanas después del final del tratamiento contra el VHC con antivirales genéricos de acción directa. Se derivaron las proporciones agrupadas de los pacientes tratados con una respuesta virológica sostenida de los análisis por intención de tratar y por protocolo. Además, se calculó el riesgo relativo (RR) agrupado de un medicamento de marca de respuesta virológica sostenida versus antivirales genéricos de acción directa mediante un modelo de efectos aleatorios (DerSimonian–Laird) a partir de los datos disponibles. Se evaluó la heterogeneidad entre los estudios mediante la estadística I².

Resultados
Se identificaron 19 estudios con un total de 57.433 individuos de ocho territorios o regiones. Las proporciones generales agrupadas de pacientes con una respuesta virológica sostenida fueron del 98 % (intervalo de confianza del 95 %: 97–99; 18 estudios; I² = 94,1 %) en los análisis por protocolo y del 96 % (IC del 95 %: 93–98; 8 estudios; I² = 68,1 %) en los análisis por intención de tratar. La probabilidad de una respuesta virológica sostenida con medicamentos de marca fue similar a la de los antivirales genéricos de acción directa (RR: 1,00; IC del 95 %: 0,98–1,02; I² = 0,0 %). La probabilidad de una respuesta virológica sostenida fue significativamente mayor en los pacientes sin cirrosis que con cirrosis (RR: 1,03; IC del 95 %: 1,01–1,05; 7 estudios), pero no se vio afectada significativamente por el tratamiento previo (3 estudios) o la coinfección por el virus de la inmunodeficiencia humana (3 estudios).

Conclusión
Los antivirales genéricos de acción directa son altamente efectivos para el tratamiento de la hepatitis C. Los antivirales genéricos deben ser considerados en entornos con recursos limitados para disminuir la carga de la enfermedad hepática en pacientes infectados por el VHC.

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## Table 3. Characteristics of included studies in the systematic review and meta-analysis of generic direct-acting agents for treating hepatitis C, 2016–2018

| Study | Location | Multicentre study | Study period | Comparison with brand-name direct-acting agent treatment regimen | Treatment duration, weeks | Method of cirrhosis diagnosis | No. of patients | No. (%) of patients with specific HCV genotypesa | No. (%) of male patients | No. (%) of previously treated patients | No. (%) of patients with cirrhosis | No. (%) of patients with an HIV coinfection |
|-------|-----------|-------------------|--------------|---------------------------------------------------------------|--------------------------|-------------------------------|----------------|-----------------------------------------------|----------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Yakoot et al., 2016 | Egypt | Yes | ND | No | SOF and RBV | 12 or 24 | FIB-4 or APRI | 50 | genotype 4: 50 (100) | 26 (52) | 12 (24) | 11 (22) | 0 (0) |
| Hill et al., 2017 | Multiregional (Australia, Eastern Europe and South-East Asia) | Yes | ND | No | (i) SOF and DCV; and (ii) SOF–LDV combination | ND | ND | 250 | ND | ND | ND | ND | ND |
| Merat et al., 2017 | Iran (Islamic Republic of) | No | Sep 2015 to Nov 2015 | No | SOF–DCV combination and RBV | 12 | Liver biopsy, liver stiffness measurement, clinical signs or imaging | 100 | genotype 1: 56 (56); genotype 3: 44 (44) | 65 (65) | ND | 100 (100) | 0 (0) |
| Nagral et al., 2017 | India | Yes | ND | No | (i) SOF and DCV ± RBV; and (ii) SOF–LDV combination ± RBV | 12 or 24 | Liver stiffness measurement, clinical signs or imaging | 29 | genotype 1: 17 (55); genotype 3: 12 (41) | 16 (55) | 7 (24) | 6 (21) | 0 (0) |
| Sharafi et al., 2017 | Iran (Islamic Republic of) | No | ND | No | SOF–LDV combination ± RBV | 12 or 24 | Liver stiffness measurement, clinical signs or imaging | 30 | genotype 1: 29 (97); genotype 4: 1 (3) | 22 (73) | 18 (60) | 16 (53) | 0 (0) |
| Vargas et al., 2017 | Chile | Yes | Jun 2013 to May 2017 | Yes | (i) SOF and DCV ± RBV; and (ii) SOF–LDV combination ± RBV | ND | Liver biopsy, liver stiffness measurement, clinical signs or imaging | 76 | ND | ND | ND | ND | ND |
| Yakoot et al., 2017 | Egypt | ND | ND | No | SOF and DCV | 8 or 12 | Liver stiffness measurement, FIB-4 or APRI | 120 | genotype 4: 120 (100) | 48 (40) | 29 (24) | 0 (0) | 0 (0) |
| Zeng et al., 2017 | China | ND | ND | No | SOF–LDV combination ± RBV | 8 or 12 | Liver stiffness measurement, clinical signs or imaging | 192 | genotype 1: 192 (100) | 38 (20) | ND | 63 (33) | 0 (0) |

(continues...)
| Study | Location          | No. of patients | No. (%) of patients with specific HCV genotypes | No. (%) of male patients | No. (%) of previously treated patients | No. (%) of patients with cirrhosis | No. (%) of patients with an HIV coinfection |
|-------|-------------------|-----------------|-----------------------------------------------|--------------------------|----------------------------------------|---------------------------------|-------------------------------------------|
| Abozeid et al., 2018<sup>23</sup> | Egypt | No | Jan 2016 to Dec 2017 | Yes | (i) SOF and DCV ± RBV, and (ii) SOF–LDV combination ± RBV | 12 or 24 | 395 | ND | 226 (57) | 27 (7) | 148 (37) | ND |
| El-Nahaas et al., 2018<sup>24</sup> | Egypt | No | ND | Yes | SOF and DCV ± RBV | 12 | 234 | ND | 139 (59) | 50 (21) | 61 (26) | 0 (0) |
| Elsharkawy et al., 2018<sup>25</sup> | Egypt | Yes | Oct 2015 to Mar 2016 | No | SOF and DCV ± RBV | 12 | ND | 36 186 | ND | ND | ND | ND |
| Gupta et al., 2018<sup>26</sup> | India | No | May 2015 to Jan 2017 | No | (i) SOF and RBV, (ii) SOF and DCV ± RBV, and (iii) SOF–LDV combination ± RBV | 12 or 24 | 393 | genotype 1: 83 (21); genotype 3: 310 (79) | ND | ND | ND | 0 (0) |
| Kumar et al., 2018<sup>28</sup> | India | ND | Sep 2015 to Feb 2017 | No | (i) SOF and RBV; (ii) SOF and DCV; and (iii) SOF–LDV combination | 12 or 24 | 71 | genotype 1: 44 (62); genotype 3: 27 (38) | 54 (76) | 13 (18) | 17 (24) | ND |
| Liu et al., 2018<sup>29</sup> | Taiwan, China | No | Aug 2016 to Apr 2017 | No | SOF–VEL combination ± RBV | 12 | 228 | genotype 1: 113 (50); genotype 2: 89 (39); genotype 3: 7 (3); genotype 4: 3 (1) | 137 (60) | 58 (25) | 52 (23) | 69 (30) |
| Liu et al., 2018<sup>30</sup> | Taiwan, China | Yes | May 2016 to Jun 2017 | No | (i) SOF and RBV; (ii) SOF–DCV combination ± RBV; (iii) SOF–LDV combination ± RBV, and (iv) SOF–VEL combination ± RBV | 12 or 24 | 517 | genotype 1: 297 (57); genotype 2: 185 (36); genotype 3: 8 (2); genotype 4: 2 (1) | 252 (49) | 147 (28) | 187 (36) | 61 (12) |

(continues . . .)
| Study          | Location | Multicentre study | Study period | Comparison with brand-name direct-acting agent | Generic direct-acting agent treatment regimen | Treatment duration, weeks | Method of cirrhosis diagnosis | No. of patients | No. (%) of patients with specific HCV genotypesa | No. (%) of male patients | No. (%) of previously treated patients | No. (%) of patients with cirrhosis | No. (%) of patients with an HIV coinfection |
|---------------|----------|-------------------|--------------|-----------------------------------------------|-----------------------------------------------|----------------------------|-----------------------------|----------------|-----------------------------------------------|-------------------------------|---------------------------------------|-------------------------------|----------------------------------------|
| Li et al., 2018 | China    | Yes               | Jun 2015 to Dec 2016 | No (i) SOF and RBV; (ii) SOF and DCV ± RBV; and (iii) SOF–LDV combination ± RBV | 12 or 24                                      | Clinical signs or imaging | 137                        | genotype 1: 44 (32); genotype 2: 3 (2); genotype 3: 71 (52) | 110 (80)                              | ND                                      | 26 (19)                              | 137 (100)                     |
| Marciano et al., 2018 | Argentina | Yes               | Mar 2016 to Jun 2016 | No (i) SOF and RBV; and (ii) SOF and DCV ± RBV | 12 or 24                                      | Liver biopsy, liver stiffness measurement, clinical signs or imaging | 321                        | genotype 1: 240 (75); genotype 2: 27 (8); genotype 3: 47 (15); genotype 4: 7 (2) | 189 (59)                              | 136 (42)                               | 292 (91)                              | 58 (18)                        |
| Omar et al., 2018 | Egypt    | Yes               | Nov 2015 to Dec 2015 | No                                             | 12                                             | Liver stiffness measurement or FIB-4 | 18 378                      | genotype 4: 40 (100)                                             | 17 (43)                               | ND                                      | 0 (0)                                  | 0 (0)                          |
| Shousha et al., 2018 | Egypt    | ND                | Feb 2017 to Jul 2017 | No                                             | 8 or 12                                        | Liver stiffness measurement | 40                         | genotype 4: 40 (100)                                             | 17 (43)                               | ND                                      | 0 (0)                                  | 0 (0)                          |

APRI: aspartate aminotransferase-to-platelet ratio index; DCV: daclatasvir; FIB-4: fibrosis-4 score; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LDV: ledipasvir; ND: not determined; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir.

a The number of patients with specific HCV genotypes does not always equal the total number of patients because data on HCV genotype were missing for some patients in a few studies.
Table 4. Generic medicines used, systematic review and meta-analysis of generic direct-acting agents for treating hepatitis C, 2019

| Study and generic direct-acting agents used | Commercial name | Manufacturer | Quality assessment |
|--------------------------------------------|-----------------|--------------|--------------------|
|                                            |                 | WHO prequalification | Listed by the Global Fund’s Expert Review Panel | Other |
|                                            |                 |                          |                                 |       |
| Yakoot et al., 2016*                       | SOF (400 mg)    | Gratisovir®             | No                               | No     |
|                                            | SOF (400 mg)    | Pharco Pharmaceutical (Egypt) European Egyptian Pharmaceutical Industries (Egypt) | No (reference: HP003) | No     |
| Hill et al., 2017*                         | SOF (400 mg), DCV (60 mg), LDV (90 mg) | Numerous Direct-acting agents from 24 different companies, 34% from Cipla Ltd (Egypt) and 30% from Hetero Laboratory Ltd (India) | Yes (SOF from Cipla Ltd and Hetero Laboratory Ltd) | Yes (DCV from Cipla Ltd and Hetero Laboratory Ltd) | No     |
| Merat et al., 2017*                        | SOF–DCV combination (400/60 mg) | Sovodak® Fanavar Rojan Mohaghegh Darou (Islamic Republic of Iran) | No | No | No |
| Nagral et al., 2017*                       | SOF (400 mg), DCV (60 mg), SOF–LDV combination (400/90 mg) | Not reported All direct-acting agents manufactured in India | ND | ND | ND |
| Sharafi et al., 2017*                      | SOF–LDV combination (400/90 mg) | Sobopasvir® Sobhan Medicine Trade Development Co. (Islamic Republic of Iran) | No | No | No |
| Vargas et al., 2017*                       | SOF (400 mg), DCV (60 mg), SOF–LDV combination (400/90 mg) | Not reported Most direct-acting agents manufactured in India | ND | ND | ND |
| Yakoot et al., 2017*                       | SOF (400 mg)    | Gratisovir®             | No                               | No     |
|                                            | DCV (60 mg)     | Daktavira®              | No                               | No     |
|                                            | Pharco Pharmaceutical (Egypt) European Egyptian Pharmaceutical Industries (Egypt) | No | No | No |
|                                            | MPH-ViroPack-Plus® Marcyl Pharmaceutical Industries (Egypt) | No | No | No |
|                                            |                   | Bioequivalence shown for SOF–LDV combination versus Harvoni® |       |       |
| El-Nahaas et al., 2018*                    | SOF (400 mg)    | Sofolanork®             | No                               | No     |
|                                            | DCV (60 mg)     | Mash Premiere (Egypt)    | No                               | No     |
|                                            |                   | Mash Premiere (Egypt)    | No | No | No |
| Elsharkawy et al., 2018*                   | SOF (400 mg), DCV (60 mg) | Not reported All direct-acting agents manufactured in Egypt | ND | ND | ND |
| Gupta et al., 2018*                        | SOF (400 mg)    | Hepcvir® Cipla Ltd (Egypt) | Yes (reference: HP004) | ND     |

(continues . . )
Systematic reviews

Generic direct-acting agents for hepatitis C

| Study and generic direct-acting agents used | Commercial name | Manufacturer | Quality assessment |
|-------------------------------------------|-----------------|--------------|--------------------|
| DCV (60 mg)                               | Hepdaci*        | Cipla Ltd (Egypt)* | Yes (reference: HP008) |
| SOF–LDV combination (400/90 mg)           | Not reported    | The direct-acting agent combination was manufactured in India* | No |
| **Kumar et al., 2018**                     |                 |              | ND                 |
| SOF (400 mg), DCV (60 mg), SOF–LDV combination (400/90 mg) | Not reported | All direct-acting agents manufactured in India | ND |
| **Liu et al., 2018**                       |                 |              | ND                 |
| SOF–VEL combination (400/100 mg)          | Sofosvel*       | Beacon Pharmaceuticals (Bangladesh) | No |
| **Liu et al., 2018**                       |                 |              | No                 |
| SOF (400 mg)                              | Hepcinat*       | Natco Pharma (India) | No |
| **Marciano et al., 2018**                 |                 |              | No                 |
| SOF–DCV combination (400/60 mg)           | Darvoni*        | Beacon Pharmaceuticals (Bangladesh) | No |
| SOF–LDV combination (400/90 mg)           | Hepcinat-LP*    | Natco Pharma (India) | No |
| SOF–LDV combination (400/90 mg)           | Ledifos*        | Hetero Laboratory Ltd (India) | No |
| SOF–VEL combination (400/100 mg)          | Velpanat*       | Natco Pharma (India) | No |
| SOF–VEL combination (400/100 mg)          | Velasof*        | Hetero Laboratories Ltd (India) | No |
| **Li et al., 2018**                       |                 |              | No                 |
| SOF (400 mg), DCV (60 mg), SOF–LDV combination (400/90 mg) | Not reported | All direct-acting agents manufactured in India | ND |
| **Omar et al., 2018**                      |                 |              | ND                 |
| SOF (400 mg), DCV (60 mg)                 | Probirase*      | Laboratorios Richmond SACIF (Argentina) | No |
| **Shousha et al., 2018**                  |                 |              | No                 |
| SOF–LDV combination (400/90 mg)           | MPI-Vitopack Plus* | Marcyrl Pharmaceutical Industries (Egypt) | No |

DCV: daclatasvir; Global Fund: Global fund to Fight AIDS, Tuberculosis and Malaria; LDV: ledipasvir; NA: not applicable; ND: not determined; SOF: sofosbuvir; VEL: velpatasvir.

* The generic drug was produced by Cipla Ltd in collaboration with the Bristol-Myers Squibb Co. through the Medicines Patent Pool.

** The SOF–LDV combination was produced by Indian companies using voluntary manufacturing licences from Gilead Sciences Inc.

† In this study, patients received generic sofosbuvir (Probirase*) and brand-name daclatasvir (Daklinza*) from the Bristol-Myers Squibb Co.

( . . . continued)
Fig. 5. **Sustained virological response to hepatitis C treatment with generic sofosbuvir and daclatasvir, with or without ribavirin, systematic review and meta-analysis, 2019**

| Author              | Treated (no.) | Sustained virological response (no.) | %       | Weight | Sustained virological responsea, % (95% CI) |
|---------------------|--------------|--------------------------------------|---------|--------|-------------------------------------------|
| Hill et al. 2017    | 146          | 143                                  | 8.64    |        | 98 (94–99)                               |
| Merat et al. 2017   | 100          | 92                                   | 7.30    |        | 92 (85–96)                               |
| Nagral et al. 2017  | 12           | 12                                   | 1.63    |        | 100 (76–100)                             |
| Yakovtsev et al. 2017 | 118      | 117                                  | 7.89    |        | 99 (95–100)                              |
| Abozaid et al. 2018 | 315          | 308                                  | 11.00   |        | 98 (95–99)                               |
| El-Nahaas et al. 2018 | 133        | 133                                  | 8.32    |        | 100 (97–100)                             |
| Elsharkawy et al. 2018 | 36186     | 35363                                | 14.37   |        | 98 (98–98)                               |
| Gupta et al. 2018   | 178          | 171                                  | 9.31    |        | 96 (92–98)                               |
| Kumar et al. 2018   | 19           | 19                                   | 2.40    |        | 100 (83–100)                             |
| Liu et al. September 2018 | 123   | 119                                  | 8.04    |        | 97 (92–99)                               |
| Li et al. 2018      | 86           | 86                                   | 6.76    |        | 100 (96–100)                             |
| Omar et al. 2018    | 18378        | 17473                                | 14.33   |        | 95 (95–95)                               |
| Overall (I² = 95.9%, P = 0.00) |              |                                       | 100.00  |        | 98 (97–99)                               |

CI: confidence interval.

* A sustained virological response 12 weeks after the end of treatment.

Fig. 6. **Sustained virological response to hepatitis C treatment with generic sofosbuvir and ledipasvir, with or without ribavirin, systematic review and meta-analysis, 2019**

| Author              | Treated (no.) | Sustained virological response (no.) | %       | Weight | Sustained virological responsea, % (95% CI) |
|---------------------|--------------|--------------------------------------|---------|--------|-------------------------------------------|
| Hill et al. 2017    | 104          | 104                                  | 12.96   |        | 100 (96–100)                             |
| Nagral et al. 2017  | 17           | 17                                   | 5.15    |        | 100 (82–100)                             |
| Sharifi et al. 2017 | 30           | 29                                   | 7.44    |        | 97 (83–99)                               |
| Zeng et al. 2017    | 187          | 186                                  | 14.99   |        | 99 (97–100)                              |
| Abozaid et al. 2018 | 80           | 80                                   | 11.88   |        | 100 (95–100)                             |
| Gupta et al. 2018   | 57           | 32                                   | 8.39    |        | 86 (72–94)                               |
| Kumar et al. 2018   | 26           | 26                                   | 6.82    |        | 100 (87–100)                             |
| Liu et al. September 2018 | 135  | 130                                  | 13.94   |        | 96 (92–98)                               |
| Li et al. 2018      | 49           | 47                                   | 9.68    |        | 96 (86–99)                               |
| Shousha et al. 2018 | 40           | 39                                   | 8.74    |        | 98 (87–100)                               |
| Overall (I² = 59.2%, P = 0.01) |              |                                       | 100.00  |        | 99 (96–100)                               |

CI: confidence interval.

* A sustained virological response 12 weeks after the end of treatment.
Fig. 7. **Sustained virological response in patients without cirrhosis to hepatitis C treatment with generic direct-acting agents, systematic review and meta-analysis, 2019**

| Author               | Treated (no.) | Sustained virological response (no.) | %   | Weight | Type of analysis | Sustained virological response, % (95% CI) |
|----------------------|---------------|--------------------------------------|-----|--------|------------------|------------------------------------------|
| Yakoot et al. 2016  | 37            | 37                                   | 4.81|        | Per-protocol     | 100 (91–100)                             |
| Nagral et al. 2017  | 22            | 22                                   | 3.02|        | Per-protocol     | 100 (85–100)                             |
| Zeng et al. 2017    | 129           | 125                                  | 13.12|       | Intention-to-treat analysis (ITT) | 97 (92–99)                              |
| Abozeid et al. 2018 | 247           | 245                                  | 19.75|        | Per-protocol     | 99 (97–100)                             |
| Gupta et al. 2018   | 259           | 248                                  | 20.27|        | Per-protocol     | 96 (93–98)                              |
| Liu et al. June 2018| 175           | 173                                  | 16.09|        | Intention-to-treat analysis (ITT) | 99 (96–100)                             |
| Liu et al. September 2018 | 330 | 321                                  | 22.95|        | Intention-to-treat analysis (ITT) | 97 (95–99)                              |
| Overall (I²=34.2%, P=0.17) |              |                                      | 100.00|       |                  | 98 (97–99)                              |

CI: confidence interval.

* A sustained virological response 12 weeks after the end of treatment.

Fig. 8. **Sustained virological response in patients with cirrhosis to hepatitis C treatment with generic direct-acting agents, systematic review and meta-analysis, 2019**

| Author, year | Treated (no.) | Sustained virological response (no.) | %   | Weight | Type of analysis | Sustained virological response, % (95% CI) |
|--------------|---------------|--------------------------------------|-----|--------|------------------|------------------------------------------|
| Yakoot et al. 2016 | 11            | 9                                    | 2.15|        | Per-protocol     | 82 (52–95)                              |
| Merat et al. 2017 | 94            | 92                                   | 14.47|       | Per-protocol     | 98 (93–99)                              |
| Nagral et al. 2017 | 4             | 4                                    | 0.86|        | Per-protocol     | 100 (51–100)                             |
| Zeng et al. 2017    | 63            | 61                                   | 10.42|       | Intention-to-treat analysis (ITT) | 97 (89–99)                              |
| Abozeid et al. 2018 | 148           | 143                                  | 20.37|        | Per-protocol     | 97 (92–99)                              |
| Gupta et al. 2018   | 134           | 128                                  | 18.97|        | Per-protocol     | 96 (91–98)                              |
| Liu et al. June 2018 | 52            | 49                                   | 8.84|        | Intention-to-treat analysis (ITT) | 94 (84–98)                              |
| Liu et al. September 2018 | 187 | 172                                  | 23.92|        | Intention-to-treat analysis (ITT) | 92 (87–95)                              |
| Overall (I²=18.0%, P=0.29) |              |                                      | 100.00|       |                  | 97 (95–98)                              |

CI: confidence interval.

* A sustained virological response 12 weeks after the end of treatment.

Table 6. **Effect of previous treatment on the likelihood of a sustained virological response* to generic direct-acting agents in patients with hepatitis C, meta-analysis, 2019**

| Study               | No. of patients with a response/no. treated | RR (95% CI) | Study weighting (%) |
|---------------------|---------------------------------------------|-------------|---------------------|
|                     | Treatment-naive/Previously treated          |             |                     |
| Abozeid et al., 2018 | 362/368                                     | 26/27       | 1.02 (0.95–1.10)    | 14.51 |
| Liu et al., 2018    | 166/170                                     | 57/58       | 0.99 (0.95–1.04)    | 25.46 |
| Liu et al., 2018    | 353/370                                     | 140/147     | 1.00 (0.96–1.06)    | 60.03 |
| Pooled data*       | 881/908                                     | 223/232     | 1.00 (0.97–1.03)    | 100.00 |

CI: confidence interval; RR: relative risk.

* A response was defined as a sustained virological response 12 weeks after the end of treatment.

* The I² value for between-study heterogeneity was 0.0% (P=0.810).
Systematic reviews

Generic direct-acting agents for hepatitis C

Hugo Perazzo et al.

Fig. 9. Sustained virological response in treatment-naïve patients to hepatitis C treatment with generic direct-acting agents, systematic review and meta-analysis, 2019

| Author, year     | Treated (no.) | Sustained virological responsea (no.) | % | Type of analysis                   | Sustained virological responsea, % (95% CI) |
|------------------|---------------|-------------------------------------|---|-----------------------------------|---------------------------------------------|
| Abozeid et al. 2018 | 368           | 352                                 | 36.50 | Per-protocol analysis         | 98 (96–99)                                  |
| Liu et al. June 2018 | 170           | 166                                 | 26.93 | Intention-to-treat analysis (ITT) | 98 (94–99)                                  |
| Liu et al. September 2018 | 370         | 353                                 | 36.56 | Intention-to-treat analysis (ITT) | 95 (93–97)                                  |
| Overall (I²=64.0%, P=0.06) |              | 100.00                             |     |                                  | 97 (95–99)                                  |

CI: confidence interval.
* A sustained virological response 12 weeks after the end of treatment.

Fig. 10. Sustained virological response in previously treated patients to hepatitis C treatment with generic direct-acting agents, systematic review and meta-analysis, 2019

| Author, year     | Treated (no.) | Sustained virological responsea (no.) | % | Type of analysis                   | Sustained virological responsea, % (95% CI) |
|------------------|---------------|-------------------------------------|---|-----------------------------------|---------------------------------------------|
| Abozeid et al. 2018 | 27            | 26                                  | 11.78 | Per-protocol analysis         | 96 (82–99)                                  |
| Liu et al. June 2018 | 58            | 57                                  | 25.05 | Intention-to-treat analysis (ITT) | 98 (91–100)                                 |
| Liu et al. September 2018 | 147         | 140                                 | 63.17 | Intention-to-treat analysis (ITT) | 95 (90–98)                                  |
| Overall (I²= 0.0%, P= 0.65) |              | 100.00                             |     |                                  | 97 (94–99)                                  |

CI: confidence interval.
* A sustained virological response 12 weeks after the end of treatment.

Table 7. Effect of an HIV coinfection on the likelihood of a sustained virological responsea to generic direct-acting agents in patients with hepatitis C, meta-analysis, 2019

| Studyb                      | No. of patients with a response/ no. treated | RR (95% CI) | Study weighting (%) |
|-----------------------------|-----------------------------------------------|-------------|                     |
|                             | With an HCV monoinfection                      | With an HIV–HCV coinfection |         |             |
| Liu et al., 2018            | 156/159                                       | 67/69       | 1.01 (0.97–1.06)    | 47.31   |
| Liu et al., 2018            | 434/456                                       | 59/61       | 0.98 (0.94–1.04)    | 52.69   |
| Pooled datac                | 590/615                                       | 126/130     | 1.00 (0.96–1.03)    | 100.00  |

CI: confidence interval; HCV: hepatitis C virus; HIV: human immunodeficiency virus; RR: relative risk.

* A response was defined as a sustained virological response 12 weeks after the end of treatment.

b The Li et al. study was not included in this subanalysis because it involved only patients with an HIV–HCV coinfection.

c The F value for between-study heterogeneity was 0.0% (P=0.842).

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Systematic reviews
Generic direct-acting agents for hepatitis C

**Fig. 11.** Sustained virological response in patients with an HIV coinfection to hepatitis C treatment with generic direct-acting agents, systematic review and meta-analysis, 2019

| Author, year | Treated (no.) | Sustained virological response* (no.) | % | Weight | Type of analysis | Sustained virological response*, % (95% CI) |
|--------------|---------------|---------------------------------------|---|--------|-----------------|-------------------------------------------|
| Liu et al. June 2018 | 69 | 67 | 25.88 | Intention-to-treat analysis (ITT) | 97 (86–99) |
| Liu et al. September 2018 | 61 | 59 | 22.91 | Intention-to-treat analysis (ITT) | 97 (89–99) |
| Li et al. 2018 | 137 | 115 | 51.21 | Per-protocol analysis | 99 (95–100) |
| **Overall ($I^2 = 0.0\%, P = 0.61$)** | **100.00** | | | | **98 (96–99)** |

CI: confidence interval; HIV: human immunodeficiency virus.
* A sustained virological response 12 weeks after the end of treatment.

**Fig. 13.** Sustained virological response to hepatitis C treatment with generic direct-acting agents, by study quality, systematic review and meta-analysis, 2019

| Author, year | Treated (no.) | Sustained virological response* (no.) | % | Weight | Sustained virological response*, % (95% CI) |
|--------------|---------------|---------------------------------------|---|--------|-------------------------------------------|
| Good | | | | | |
| Zeng et al. 2017 | 187 | 186 | 6.28 | | 99 (97–100) |
| Abouzaid et al. 2018 | 395 | 388 | 7.74 | | 98 (96–99) |
| Gupta et al. 2018 | 393 | 376 | 7.73 | | 96 (93–97) |
| Liu et al. June 2018 | 226 | 223 | 6.70 | | 99 (96–100) |
| Liu et al. September 2018 | 508 | 493 | 8.12 | | 97 (95–98) |
| Li et al. 2018 | 137 | 115 | 5.56 | | 99 (95–100) |
| Subtotal ($I^2 = 54.08\%, P = 0.05$) | | | | | 42.13 |
| Fair | | | | | |
| Menat et al. 2017 | 94 | 92 | 4.65 | | 98 (93–99) |
| Yakoot et al. 2017 | 118 | 117 | 5.20 | | 99 (95–100) |
| El-Nahaas et al. 2018 | 133 | 133 | 5.49 | | 100 (97–100) |
| Elsharkawy et al. 2018 | 35186 | 33563 | 9.76 | | 98 (98–98) |
| Kumar et al. 2018 | 71 | 71 | 3.97 | | 100 (95–100) |
| Subtotal ($I^2 = 57.65\%, P = 0.05$) | | | | | 29.06 |
| Poor | | | | | |
| Yakoot et al. 2016 | 48 | 46 | 3.10 | | 99 (97–100) |
| Hill et al. 2017 | 250 | 247 | 6.90 | | 96 (88–95) |
| Nagral et al. 2017 | 29 | 29 | 2.15 | | 99 (97–100) |
| Sharafi et al. 2017 | 30 | 29 | 2.21 | | 100 (88–100) |
| Vargas et al. 2017 | 26 | 25 | 1.98 | | 97 (83–99) |
| Omar et al. 2018 | 18178 | 17473 | 9.73 | | 96 (81–99) |
| Shousha et al. 2018 | 40 | 39 | 2.73 | | 95 (95–95) |
| Subtotal ($I^2 = 54.75\%, P = 0.04$) | | | | | 28.81 |
| Heterogeneity between groups: $P = 0.164$ | | | | | 100.00 |
| **Overall ($I^2 = 94.1\%, P = 0.001$)** | | | | | **98 (97–99)** |

CI: confidence interval.
* A sustained virological response 12 weeks after the end of treatment.
Notes: The quality of each study was rated as good, fair or poor (see main text for details).
### Table 1.

**Sustained virological response to hepatitis C treatment with generic direct-acting agents, by risk of study bias, systematic review and meta-analysis, 2019**

| Author, year | Treated (no.) | Sustained virological response (no.) | % | Weight | Sustained virological response, % (95% CI) |
|--------------|---------------|-------------------------------------|---|--------|-------------------------------------------|
| **Low risk of bias** |               |                                     |   |        |                                           |
| Zeng et al. 2017 | 187           | 186                                 | 6.28 |        | 99 (97–100)                               |
| Abozeid et al. 2018 | 395           | 388                                 | 7.74 |        | 98 (96–99)                                |
| Gupta et al. 2018 | 393           | 376                                 | 7.73 |        | 96 (93–97)                                |
| Liu et al. June 2018 | 226           | 223                                 | 6.70 |        | 96 (93–97)                                |
| Liu et al. September 2018 | 508           | 493                                 | 8.12 |        | 97 (95–98)                                |
| Li et al. 2018 | 137           | 135                                 | 5.56 |        | 99 (95–100)                               |
| **Subtotal (I² = 54.08%, P = 0.05)** |               |                                     | 82.13 |        | 98 (97–99)                                |
| **Moderate risk of bias** |               |                                     |   |        |                                           |
| Yakoot et al. 2016 | 48            | 46                                  | 3.10 |        | 96 (86–99)                                |
| Merat et al. 2017 | 94            | 92                                  | 4.65 |        | 98 (91–99)                                |
| Naqvi et al. 2017 | 29            | 29                                  | 2.15 |        | 100 (88–100)                              |
| Sharif et al. 2017 | 30            | 29                                  | 2.21 |        | 97 (83–99)                                |
| Vargas et al. 2017 | 26            | 25                                  | 1.98 |        | 96 (81–99)                                |
| Yakoot et al. 2017 | 118           | 117                                 | 5.20 |        | 99 (95–100)                               |
| El-Rahaei et al. 2018 | 133           | 133                                 | 5.49 |        | 100 (97–100)                              |
| Elsharkawy et al. 2018 | 30186       | 30563                               | 9.76 |        | 98 (98–98)                                |
| Kumar et al. 2018 | 71            | 71                                  | 3.97 |        | 100 (95–100)                              |
| Shousha et al. 2018 | 40            | 39                                  | 2.73 |        | 98 (87–100)                               |
| **Subtotal (I² = 28.14%, P = 0.19)** |               |                                     | 41.24 |        | 98 (98–100)                               |
| **High risk of bias** |               |                                     |   |        |                                           |
| Hill et al. 2017 | 250           | 247                                 | 6.90 |        | 99 (97–100)                               |
| Omar et al. 2018 | 18378         | 17473                               | 9.73 |        | 95 (95–95)                                |
| **Overall (I² = 94.1%, P = 0.00)** | | | 100.00 | | 98 (97–99) |

CI: confidence interval.

* A sustained virological response 12 weeks after the end of treatment.

Notes: The risk of bias in each study was rated as low, moderate or high (see main text for details).