

Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Ford N. et al. (2012) Chronic hepatitis C treatment outcomes in low- and middle-income countries: a systematic review and meta-analysis. Bulletin of the World Health Organization, 90(7):540-550.			
Date of Review:	February 9, 2015			
Reviewer(s):	Christine Hu			
Part A				
Category:	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
Best Practice/Intervention:	Focus: Hepatitis C <input checked="" type="checkbox"/> Hepatitis C/HIV <input type="checkbox"/> Other: _____ Level: Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ Target Population: <u>HCV patients treated in low- and middle-income countries</u> Setting: Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ Country of Origin: <u>Switzerland</u> Language: English <input checked="" type="checkbox"/> French <input checked="" type="checkbox"/> Other: <u>Chinese, Spanish, Russian, Arabic</u>			
Part B				
	YES	NO	N/A	COMMENTS
<i>Is the best practice/intervention a meta-analysis or primary research?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	meta-analysis; systematic review to assess effectiveness of treatments for HCV infection in low and middle income countries
<i>The best practice/intervention has utilized an evidence-based approach to assess:</i>				
<i>Efficacy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Effectiveness</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Primary outcome: SVR rate Secondary outcomes: end-of-treatment responses, adverse events resulting in treatment interruption, modification or discontinuation, the proportion of patients lost to follow-up, and mortality

<i>The best practice/intervention has been evaluated in more than one patient setting to assess:</i>				
<i>Efficacy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Effectiveness</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	93 studies with a total of 12213 patients included in analysis

	YES	NO	N/A	COMMENTS
<i>The best practice/intervention has been operationalized at a multi-country level:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	studies covered 17 counties
<i>There is evidence of capacity building to engage individuals to accept treatment/diagnosis</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	All articles are observational studies
<i>There is evidence of outreach models and case studies to improve access and availability</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Are the best practices/methodology/results described applicable in developed countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Are the best practices/methodology/results described applicable in developing countries?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	HCV treatment in developing countries are difficult given the high cost and difficult access of medication
<i>Evidence of manpower requirements is indicated in the best practice/intervention</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Juried journal reports of this treatment, intervention, or diagnostic test have occurred</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Bulletin of the World Health Organization</i>
<i>International guideline or protocol has been established</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention is easily accessed/available electronically</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Free to download from http://www.who.int/en/
<i>Is there evidence of a cost effective analysis? If so, what does the evidence say?</i> Please go to Comments section	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>How is the best practice/intervention funded?</i> Please got to Comments section	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not funded

<i>Other relevant information:</i> <hr/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	- Effectiveness of HCV treatment in low and middle income countries are similar to those in developed countries
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Chronic hepatitis C treatment outcomes in low- and middle-income countries: a systematic review and meta-analysis

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Objective To assess the effectiveness of treatment for hepatitis C virus (HCV) infection in low- and middle-income countries and identify factors associated with successful outcomes.

Methods We performed a systematic review and meta-analysis of studies of HCV treatment programmes in low- and middle-income countries. The primary outcome was a sustained virological response (SVR). Factors associated with treatment outcomes were identified by random-effects meta-regression analysis.

Findings The analysis involved data on 12 213 patients included in 93 studies from 17 countries. The overall SVR rate was 52% (95% confidence interval, CI: 48–56). For studies in which patients were predominantly infected with genotype 1 or 4 HCV, the pooled SVR rate was 49% (95% CI: 43–55). This was significantly lower than the rate of 59% (95% CI: 54–64) found in studies in which patients were predominantly infected with other genotypes ($P=0.012$). Factors associated with successful outcomes included treatment with pegylated interferon and ribavirin, infection with an HCV genotype other than genotype 1 or 4 and the absence of liver damage or human immunodeficiency virus infection at baseline. No significant difference in the SVR rate was observed between weight-adjusted and fixed-dose ribavirin treatment. Overall, 17% (95% CI: 13–23) of adverse events resulted in treatment interruption or dose modification, but only 4% (95% CI: 3–5) resulted in treatment discontinuation.

Conclusion The outcomes of treatment for HCV infection in low- and middle-income countries were similar to those reported in high-income countries.

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

Introduction

Hepatitis C virus (HCV) infection is a growing public health concern. Globally an estimated 180 million people, or roughly 3% of the world's population, are currently infected.¹ The burden of disease is greatest in developing countries: the highest reported prevalences are in China (3.2%), Egypt (22%) and Pakistan (4.8%).²

In light of the above, the need to improve access to care and treatment for patients with a chronic HCV infection is receiving increasing attention. A recent report by the World Hepatitis Alliance revealed that 80% of 135 countries surveyed regarded hepatitis B or C virus infection as an urgent public health issue.³ In 2010, the World Health Assembly adopted a resolution to “support or enable an integrated and cost-effective approach to the prevention, control and management of viral hepatitis considering the linkages with associated coinfection such as HIV”.⁴

Most of the disease burden associated with HCV infection results from the development of chronic liver disease, sometimes leading to end-stage liver disease (cirrhosis), and standardized mortality ratios for liver-related death are 16- to 46-fold higher in infected individuals than in the general population.^{5–7} The complications of cirrhosis include liver failure, hepatocellular carcinoma and death.^{8,9} Approximately 20% of HCV-infected patients will experience complications.^{10–12} Successful treatment can improve liver fibrosis and cirrhosis,

help prevent hepatocellular carcinoma and even clear the virus.¹³ Treatment can also contribute to disease prevention by reducing the reservoir of infected individuals who can transmit the virus.

Despite the benefits of treatment, there is reluctance to making it more widely available in resource-limited settings because of fears that treatment success rates will be low and because treatment is complex, costly and produces side-effects.¹⁴ In addition, outcomes are often poor in patients coinfecting with the human immunodeficiency virus (HIV).¹⁵

We performed a systematic review and meta-analysis of reported treatment outcomes in HCV-infected patients in low- and middle-income countries. The aims were to assess the feasibility of providing treatment for HCV infection in less well-resourced settings and to identify factors associated with successful treatment outcomes.

Methods

The PubMed and Embase databases were searched for articles on observational studies that reported sustained virological response (SVR) rates in adult patients with chronic HCV infection and that were performed in a low- or middle-income country, as defined by The World Bank classification.¹⁶ Both cohort studies and case series including 10 or more patients were considered for inclusion. An SVR was defined as the

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(Submitted: 7 October 2011 – Revised version received: 28 December 2011 – Accepted: 3 January 2012 – Published online: 3 February 2012)

absence of detectable HCV in blood 24 weeks after the completion of antiviral therapy.

The databases were searched using a predefined protocol (Appendix A, available at: http://www.msfactcess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/AIDS_MedJourn_HCVtreatmentReview_ENG_2011.pdf) using the terms *hepatitis C*, *HCV*, *treatment*, *therapy*, *interferon*, *sustained virological response* and *SVR*. In addition, the bibliographies of relevant articles were reviewed. Preliminary searches were carried out independently by two of the study authors, who decided whether a publication was eligible for inclusion in the systematic review by evaluating its title using predefined criteria. If there was any uncertainty, all the study authors were consulted to reach a consensus on eligibility.

Because the aim of the systematic review was to describe the outcomes of HCV treatment administered within a clinical programme, we included observational cohort studies that reported treatment outcomes and excluded studies with an experimental design. We also excluded studies that reported outcomes in specific patient groups, such as patients with comorbid conditions, with prior treatment, or with known treatment resistance. However, because of concerns about HCV infection in HIV-infected individuals, studies on patients coinfecting with HIV were included in the review.

Data extraction

Our primary outcome of interest was the SVR rate. Secondary outcomes included end-of-treatment responses, adverse events resulting in treatment interruption, modification or discontinuation, the proportion of patients lost to follow-up, and mortality. A patient was defined as having an end-of-treatment response if HCV ribonucleic acid was undetectable at the completion of treatment.

Each cohort was divided into categories in accordance with the following discrete clinical variables: (i) whether standard or pegylated interferon was administered, irrespective of the type of interferon; (ii) whether fixed-dose or weight-adjusted ribavirin was administered; (iii) whether treatment lasted less than 24 weeks or longer; (iv) whether fewer than or more than 50% of patients in the study cohort were HIV-positive (HIV+); (v) whether fewer than or

more than 50% of patients in the study cohort were infected with genotype 1 or 4 (these genotypes are associated with a poor response to treatment); and (vi) whether fewer than or more than 50% of patients in the study cohort had bridging fibrosis, an indicator of the extent of liver damage, at baseline. In addition, information was also sought on the presence of the interleukin-28B gene polymorphism, which is an important determinant of treatment success.

The methodological quality of the studies included in the systematic review was assessed on the basis of the study design (i.e. retrospective or prospective), the reporting of disease status at baseline, the proportion of patients who completed treatment, and consideration of potential confounding. Finally, information on sources of funding were extracted to give an indication of the potential replicability and sustainability of the treatment programme. Any uncertainty surrounding the data was resolved by contacting the study authors.

Statistical analysis

Point estimates and 95% confidence intervals (CIs) were derived for all outcomes. The SVR rates were calculated on an intention-to-treat basis, with all patients who initiated therapy being included in the denominator of the calculation. The variance in the raw proportion was stabilized using a Freeman–Tukey-type arcsine square-root transformation¹⁷ and these proportions were pooled using a DerSimonian–Laird random-effects model.¹⁸ The τ^2 statistic was calculated to assess the proportion of the overall variation that was attributable to between-study heterogeneity.^{19,20} Since pooling proportions can yield high rates of heterogeneity, we explored the potential influence of clinical and programmatic covariates that had been identified a priori through random-effects method-of-moments meta-regression²¹ and univariate subgroup analyses. Subgroup analyses were used to assess the potential influence of the following covariates: treatment regimen, HIV status, HCV genotype, liver damage at baseline, level of economic development of the study region, geographical location of the study region and study design (i.e. prospective or retrospective). All reported *P*-values are two-sided and significance was set at $P \leq 0.05$. All analyses were performed using Stata version 11 (StataCorp. LP, College Station, United States of America).

Results

Study characteristics

Our search found 1216 articles. After evaluation, 93 studies, which involved a total of 12 213 patients, met our inclusion criteria and were carried through to the meta-analysis (Fig. 1). Although the studies covered 17 countries, some were more frequently represented: there were 19 studies from Brazil, 17 from Pakistan, 13 from Egypt, 12 from China and 10 from India.

Around half of the studies (i.e. 46 studies involving 5995 patients) included patients who were predominantly infected with HCV genotype 1 or 4. Ten studies failed to adequately report on viral genotype. Patients were treated with ribavirin and interferon in 86 studies, while interferon alone was given in 7 studies: pegylated interferon was administered in 52 and standard interferon was used in 44. The extent of liver damage at baseline was reported in 33 studies, together comprising 2407 patients. In addition, although 54 studies gave details of patients' HIV status, only 3, which included 105 patients in total, reported outcomes among HIV-infected individuals. Two studies included data on outcomes in patients with and without the interleukin-28B gene polymorphism.

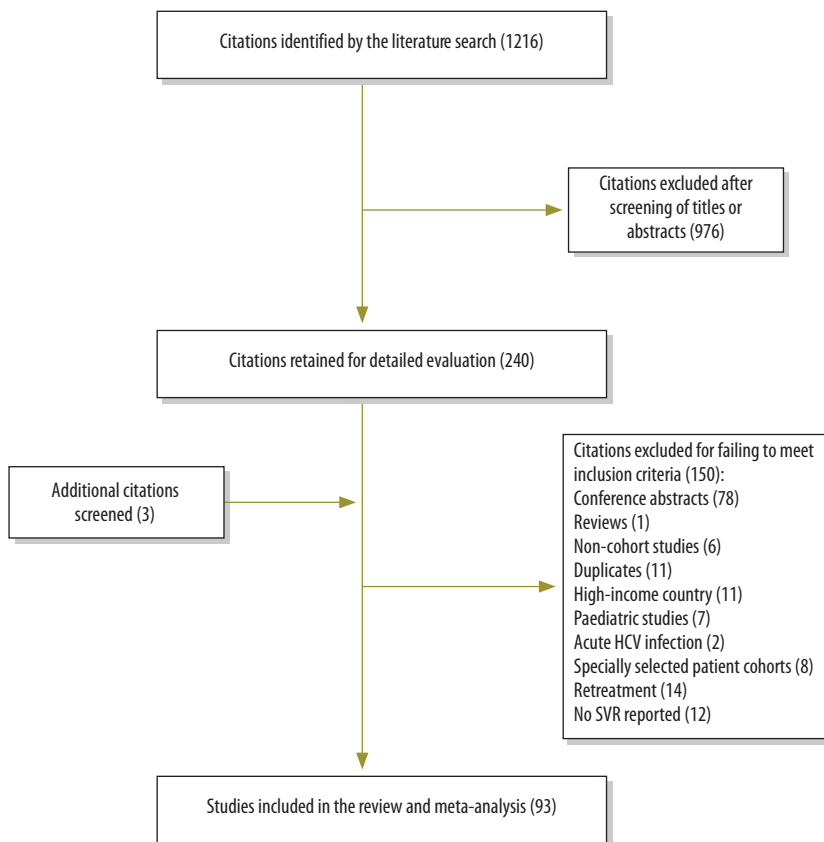
We judged the quality of the studies included in the meta-analysis to be moderate. The majority (i.e. 65 studies) reported prospectively collected data, 72 detailed disease progression at baseline, 77 considered potential confounding factors and 89 stated that $\geq 80\%$ of patients completed treatment.

Of the 29 studies that reported sources of funding, 18 were supported by national government funds, 4 received pharmaceutical industry funding, 1 was supported by an international research grant, 1 by a charitable grant and 5 stated that the study received no specific funding. A table summarizing each study's characteristics is available in Appendix B, at: http://www.msfactcess.org/sites/default/files/MSF_assets/CAME/Access_Data_StudyCharacteristics_ENG_2012.pdf.

Study outcomes

Overall, 52% (95% CI: 48–56) of patients achieved an SVR. However, the between-study heterogeneity in the SVR rate was high (τ^2 : 410), as expected for observational data. For studies in which

Fig. 1. Selection of studies on chronic hepatitis C treatment in low- and middle-income countries



HCV, hepatitis C virus; SVR, sustained virological response.

patients were predominantly infected with HCV genotype 1 or 4, the proportion of patients who achieved an SVR ranged from 4% (95% CI: 1–9)²² to 79% (95% CI: 66–89)²³ and the pooled proportion was 49% (95% CI: 43–55). For studies in which patients were predominantly infected with HCV genotypes other than 1 or 4, the SVR rate ranged from 16% (95% CI: 10–24)²⁴ to 86% (95% CI: 77–93)²⁵ and the pooled proportion of these patients who achieved an SVR was 59% (95% CI: 54–64), which was significantly higher than among patients infected with HCV genotype 1 or 4 ($P=0.012$). Since the treatment duration was found to be collinear with viral genotype, it was not considered in the analysis.

Fig. 2 summarizes how the SVR rate was influenced by HCV treatment, viral genotype, liver damage at baseline, HIV status, the level of economic development and the geographical location of the study region. Univariate meta-regression analysis showed that the proportion of patients who achieved an SVR var-

ied significantly with the formulation of the interferon administered (i.e. standard or pegylated), ribavirin use, viral genotype, the severity of liver damage at baseline, HIV status and the level of economic development of the study region (Table 1). Viral genotype and HIV status were still found to be significantly associated with the SVR rate on multivariate analysis, but other factors were not. Further, subgroup analyses showed that the best outcomes were achieved in studies in which patients were either predominantly HIV-negative (HIV⁻), predominantly infected with an HCV genotype other than 1 or 4, or treated with ribavirin. The proportion of patients who achieved an SVR in the 20 studies that included patients with all three of these characteristics ranged from 45% (95% CI: 34–55)⁷⁰ to 78% (95% CI: 61–91)⁷¹ and the pooled proportion was 65% (95% CI: 61–68). The presence of the interleukin-28B polymorphism was associated with a high SVR rate in the two studies which reported relevant data.^{26,72}

End-of-treatment responses were recorded in 49 studies. The pooled estimate of the proportion of patients who achieved an end-of-treatment response was higher: (i) for those who were HIV⁻ than for those who were HIV⁺, at 74% versus 52%, respectively; (ii) for those who received ribavirin than for those who did not, at 69% versus 51%, respectively; and (iii) for those who received pegylated rather than standard interferon, at 73% versus 62%, respectively. Overall, 53% (95% CI: 47–58) of patients who achieved an end-of-treatment response went on to achieve an SVR. This rate was significantly greater in patients who were treated with pegylated interferon (i.e. 57%; 95% CI: 52–63) than in those who received standard interferon (i.e. 47%; 95% CI: 38–56) and in those who were HIV⁻ (i.e. 59%; 95% CI: 53–64) than in those who were HIV⁺ (i.e. 35%; 95% CI: 30–40). However, neither viral genotype ($P=0.2$), ribavirin treatment ($P=0.6$) nor liver damage at baseline ($P=0.4$) influenced the proportion that went on to achieve an SVR.

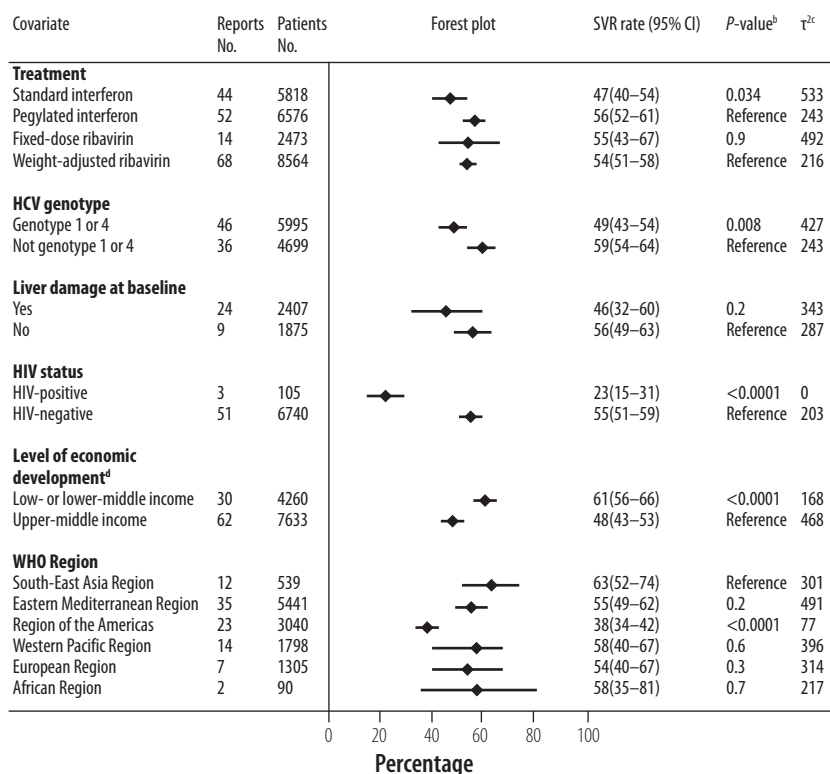
Adverse events that resulted in treatment interruption or dose modification were reported in 16 studies and were experienced by 17% (95% CI: 13–23) of patients in these studies. The drug regimen had no significant effect on the proportion of these adverse events. Adverse events that resulted in treatment termination were reported in 39 studies and were experienced by 4% of patients (95% CI: 3–5). These adverse events were significantly more common in patients who were taking weight-adjusted ribavirin than in those taking fixed-dose ribavirin (4% versus 2%, respectively; $P<0.0001$). Table 2 lists the most serious adverse events that led to treatment discontinuation in individual studies.

Overall, 39 studies reported losses to follow-up. The rate was generally low and the pooled proportion of patients reported as lost to follow-up was 4% (95% CI: 3–4). In addition, mortality was also low: less than 1% (95% CI: 0.1–1) of patients were reported to have died during the observation period.

Discussion

Our systematic review found many reports of HCV treatment programmes in low- and middle-income countries involving substantial numbers of patients.

Fig. 2. Sustained virological response^a rate in patients with a chronic hepatitis C virus infection in low- and middle-income countries, by treatment, disease, patient and study covariates



CI, confidence interval; HIV, human immunodeficiency virus; HCV, hepatitis C virus; SVR, sustained virological response; WHO, World Health Organization.

^a A sustained virological response was defined as the absence of detectable hepatitis C virus (HCV) in blood 24 weeks after the completion of antiviral therapy.

^b P-values were derived using the χ^2 test for the difference between reference and comparison groups.

^c The Tau-squared (τ^2) statistic indicates the degree to which the overall variation in the sustained virological response rate was attributable to between-study heterogeneity.

^d The level of economic development of the study country was categorized using the World Bank classification.¹⁶

They indicated that the programmes had been successful. Notably, most of the studies that gave information on funding sources reported funding from domestic public sources. This observation is consistent with recent survey data indicating that partial or total government funding is available for hepatitis treatment in 69% of countries worldwide and in more than 50% of countries in all WHO regions except the WHO African Region.³ We found that overall 52% of patients treated in low- and middle-income countries achieved an SVR, which is similar to the rate reported in high-income countries. For example, in developed countries, the average SVR rate observed in clinical trials of patients with HCV genotype 1 infections after 48 weeks of treatment with pegylated interferon and weight-adjusted ribavirin ranged from 45% to 48%, while it ranged from 22% to 31% after 24 weeks of treatment.¹¹⁶

As found in other studies, the most important determinants of treatment success were infection with an HCV genotype other than 1 or 4, the absence of liver damage at baseline, an HIV– status and treatment with pegylated interferon and ribavirin.¹¹⁶ The geographical variations in outcomes we observed were probably due to a combination of these factors. Although, as expected, treatment with pegylated interferon and ribavirin was associated with better outcomes than treatment with other regimens, the use of weight-adjusted rather than fixed-dose ribavirin offered no observable advantage. Moreover, despite reports that HCV treatment is associated with significant side-effects, only 4% of patients included in our meta-analysis discontinued treatment because of adverse events. The observation that clinical rather than geographical factors were the most important determinants

of treatment success suggests that good outcomes can be achieved with current regimens in resource-limited settings and offers support to calls for better access to diagnosis and treatment in these settings.¹¹⁷

We used a broad search strategy that attempted to capture evidence from many different settings. Consequently, we were able to compile a large meta-analytical data set that enabled us to assess the influence on treatment success of numerous patient, treatment and disease characteristics. However, the way in which studies reported information on potential determinants of treatment success was inconsistent and limited our ability to assess their relative contributions. For example, although we identified a substantial number of studies from countries with a relatively high burden of both HIV and HCV infection, only three reported outcomes among patients coinfecting with the two viruses. In addition, few data were available on adherence to treatment, another important determinant of treatment success. The influence of the interleukin-28B gene polymorphism, which is also known to affect responses to treatment, was also poorly reported, probably because of limited resources. Future studies should report data on factors known to influence outcomes, particularly those in underrepresented regions, notably Africa, and in underrepresented populations, notably HIV+ patients and people who inject drugs.

Furthermore, the substantial heterogeneity in results we observed between studies limited the validity of this analysis, as it made it more difficult to determine the magnitude of the relative influence of individual factors on treatment success. In addition, we may have missed some studies because we searched a limited number of databases and our review excluded studies that reported outcomes in patients who were coinfecting with a non-HIV agent that may have influenced treatment outcomes, such as the hepatitis B virus. Finally, our analysis was also limited by inconsistent reporting of secondary outcomes. Future studies should report rapid virological responses, end-of-treatment responses, adverse events and losses to follow-up. Data on rapid virological responses would help inform decisions on whether to shorten treatment.¹¹⁴

Given these limitations, our review should not be taken as representative of

Table 1. Effect of treatment, disease, patient and study covariates on the sustained virological response^a rate in patients with a chronic hepatitis C virus infection in low- and middle-income countries, by meta-regression analysis

Covariate	No. of re-ports ^b	Univariate analysis		Multivariate analysis	
		β coefficient (95% CI)	P-value	β coefficient (95% CI)	P-value
Treatment regimen					
Standard interferon ^{22,24,26-69}	44	-10.6 (-18.0 to -3.1)	0.006	-7.8 (-16.6 to 0.9)	0.07
Pegylated interferon ^{35,36,39,33,36,61,63,65,67,70-115}	52	Reference	NA	Reference	NA
Ribavirin not administered ^{23,37,40,50,56,64,85}	7	27.5 (13.8 to 41.2)	<0.0001	1.6 (-21.8 to 18.6)	0.9
Ribavirin administered ^{24-36,38,39,41-49,51,53-55,57-63,66-84,86-93,95-100,102-115}	86	Reference	NA	Reference	NA
Fixed-dose ribavirin ^{2,2,63,145,146,158,60,66,69,71,80,82,84,97}	14	1.2 (-8.5 to 10.9)	0.8	ND	ND
Weight-based ribavirin ^{25,27-30,32,33,35,36,38,39,41,42,44,47-49,51-55,57,59,61-63,65,67,68,72-79,81,83,86-93,95,96,98-115}	68	Reference	NA	ND	ND
HCV genotype					
Genotype 1 or 4 ^{2,22,63,43,7-39,54-57,63,65,67-69,72,73,76-83,85,86,88,90-94,96,97,100-107,109-111,114,115}	46	-10.2 (-17.7 to -2.5)	0.01	-11.9 (-23.8 to 0)	0.005
Not genotype 1 or 4 ^{4,2,5,27-29,32,33,35,36,41-47,50-53,58,62,66,70,71,74,75,84,87,89,95,108,110,112,113}	36	Reference	NA	Reference	NA
Liver damage at baseline					
Yes ^{3,33,43,65,55,57,58,63,65-67,69,70,75,76,79,87,88,90,92,93,95,101,104,105,115}	24	-12.2 (-23.2 to -1.3)	0.03	ND	ND
No ^{2,51,64,78,98-100,108,110}	9	Reference	NA	ND	ND
HIV status					
HIV-positive ^{73,76,104}	3	-32.4 (-50.5 to -14.2)	0.001	-28.9 (-45.9 to -11.9)	0.001
HIV-negative ^{27,28,31,32,34-36,39,41,43,44,46,50-52,54,55,58,63,65,67-73,75,76,78,80,82,83,85-87,89-96,98-100,102,104-106,108,111-115}	51	Reference	NA	Reference	NA
Economic level of study region^c					
Low- or lower-middle income ^{25,27-33,36,41-43,45-48,51-53,58,62,66,71,74,75,84,87,89,105,108}	30	-13.0 (-20.7 to -5.2)	0.001	-6.7 (-19.4 to 6.0)	0.3
Upper-middle income ^{22,24,26,34,35,37-40,44,49,50,53-57,59-61,63-65,67-70,72,73,76-83,85,86,88,90-93,95-104,106,107,109-115}	62	Reference	NA	Reference	NA
Study design					
Prospective ^{22,24,25,28-32,34,35,37-39,41,43-45,47-53,55,57,58,62,66,69-75,77-80,82,84-86,88,90-93,95-102,104,105,107,108,110-112,115}	65	-2.6 (-11 to 5.7)	0.5	ND	ND
Retrospective ^{26,27,33,36,40,42,46,52,54,56,59-61,63-65,67,68,76,81,83,87,89,103,106,109,113,114}	28	Reference	NA	ND	ND

CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, not applicable; ND, not determined.

^a A sustained virological response was defined as the absence of detectable hepatitis C virus (HCV) in blood 24 weeks after the completion of antiviral therapy.

^b Since one publication⁷⁷ reported one study fully and gave the preliminary outcomes of a second study, the figures here could differ by 1 from those in the text.

^c The level of economic development of the study country was categorized using The World Bank classification.¹⁶

Table 2. **Serious adverse events leading to treatment discontinuation in patients with a chronic hepatitis C virus infection in low- and middle-income countries, 1996–2011**

Publication	Year	Country	No. of patients affected	Type of event (No. of patients affected)
Sood ⁵⁸	2002	India	3	Psychiatric illness (2), hypotension (1)
Sood ⁸⁷	2006	India	3	Agitated behaviour (1), liver decompensation (2)
Gupta ⁷¹	2006	India	1	Weakness (1)
Ahmed ²⁷	2011	Pakistan	14	Thrombocytopenia, ascites, depression, arthralgia, weight loss, rash, fever, hair loss, epistaxis ^a
Khan ⁴⁶	2009	Pakistan	12	Extreme weakness (6), severe depression (2), thyroid dysfunction (3), recurrent leukopenia (1)
Khokhar ⁴⁷	2002	Pakistan	2	Myalgia (1), psychosis (1)
Khalid ⁴⁵	2009	Pakistan	1	Severe depression (1)
Idrees ⁴²	2009	Pakistan	6	Psychosis (6)
Butt ⁷⁵	2009	Pakistan	5	Thrombocytopenia and neutropenia (2), refractory anaemia (2), ascites and hepatic encephalopathy (1)
Lerias de Almeida ⁷⁶	2009	Brazil	33	Not stated
Lerias de Almeida ⁹⁰	2010	Brazil	7	Not stated
Goncalves ⁷⁸	2006	Brazil	10	Depression (6), neutropenia (2), anaemia (1), low platelet count (1)
Narciso-Schiavon ⁸¹	2010	Brazil	22	Anaemia (2), thrombocytopenia (2), not stated (18)
Khattab ⁹¹	2010	Egypt	4	Not stated
El Makhzangy ⁹²	2009	Egypt	2	Psychiatric disorder (1), haemolytic anaemia (1)
El-Zayadi ²²	1996	Egypt	8	Not stated
El-Zayadi ³⁸	2005	Egypt	4	Neutropenia (1), thyroid dysfunction (1), depression (1), neutropenia (1)
Yu ¹¹¹	2009	China	1	Severe anaemia (1)
Gheorghe ¹⁰⁰	2007	Romania	11	Severe psychiatric side-effects, severe haematological abnormalities, severe reactivation of previously controlled rheumatoid arthritis, cardiac death ^a
Gheorghe ⁹⁹	2009	Romania	20	Severe psychiatric side-effects (2), severe haematological abnormalities (9), occurrence or reactivation of auto-immune disease during antiviral therapy (7), cardiac death (1), not stated (1)
Gheorghe ⁹⁸	2005	Romania	10	Severe haematological abnormalities, severe and protracted skin rash, acute cytomegalovirus hepatitis ^a
Gallegos-Orozco ³⁹	2005	Mexico	1	Thyrotoxicosis (1)
Ridruejo ¹⁰⁶	2010	Argentina	18	Not stated
Laufer ¹⁰⁴	2011	Argentina	2	Thrombocytopenia (2)
Seow ¹⁰⁷	2005	Malaysia	1	Excessive lethargy (1)
Pramoolsinsap ⁵⁰	1998	Thailand	3	Thrombocytopenia (2), hyperthyroidism (1)
Kalantari ⁴⁴	2007	Islamic Republic of Iran	2	Thrombocytopenia (1), major depression (1)
Petrenkiene ⁴⁹	2004	Lithuania	11	Anaemia (1), thrombocytopenia (5), irritability (1), exacerbation of concomitant disease (1), not stated (3)
Belhadj ⁹⁵	2008	Tunisia	5	Not stated
Sombie ¹⁰⁸	2011	Burkina Faso	2	Not stated
Njoun ¹⁰⁵	2008	Cameroon	6	Neutropenia, encephalitis, pancytopenia and thrombopenia ^a

^a Detailed data were not available.

all low- and middle-income countries. It does, however, illustrate the range of treatment outcomes that can be achieved in settings with limited resources.

With currently available regimens, the treatment success rate achievable in patients infected with an HCV genotype other than 1 and 4 is in line with or better than the success rate achieved with other chronic infections that cause sub-

stantial morbidity in resource-limited settings, such as multidrug-resistant tuberculosis.¹¹⁸ However, currently the cost of treatment is a major barrier: a 48-week course of pegylated interferon and ribavirin costs as much in Thailand as in the United Kingdom of Great Britain and Northern Ireland (i.e. around 17 000 United States dollars). Treatment with recently approved protease inhibitors

substantially improves success rates and these drugs are now the standard of care for patients with HCV genotype 1 infections in resource-rich settings, but they are even more expensive.¹¹⁹ In a recent survey in low-income countries, four out of five ministries of health identified the need for financial assistance to increase access to treatment for viral hepatitis as a priority.³ Future research

on barriers to obtaining medicines for the treatment of HCV infection in resource-limited settings should be encouraged.

New protease and polymerase inhibitors currently under investigation offer the potential for oral therapy that will further improve the SVR rate in patients with HCV infection and may also reduce both treatment complexity and adverse events.¹²⁰ These drugs will be particularly useful in resource-limited settings where the disease burden

is greatest. Given that HCV treatment can be successful in these settings, the early introduction of new therapies in countries with limited resources should be an important consideration during drug development. In the past, mechanisms for decreasing the cost of and improving access to medicines for chronic infections such as multidrug-resistant tuberculosis and HIV/AIDS have been established; similar mechanisms should be considered for HCV infection.

In summary, our review found that patients with an HCV infection in resource-limited settings have treatment success rates similar to those in developed countries. This observation provides further justification for increasing efforts to improve access to HCV treatment in low- and middle-income countries. ■

Competing interests: None declared.

ملخص

نتائج علاج التهاب الكبد C المزمن في البلدان منخفضة ومتوسطة الدخل: استعراض منهجي وتحليل وصفي
الغرض تقييم فعالية علاج عدوى فيروس التهاب الكبد C (HCV) في البلدان منخفضة ومتوسطة الدخل وتحديد العوامل المرتبطة بالنتائج الناجحة. الطريقة أجرينا استعراضاً منهجياً وتحليلاً وصفيًا لدراسات برامج علاج فيروس التهاب الكبد C في البلدان منخفضة ومتوسطة الدخل. وكانت النتيجة الأولية استجابة فيروسية مستديمة (SVR). وتم تحديد العوامل المرتبطة بنتائج العلاج من خلال تحليل الارتداد الوصفي للأثار العشوائية. النتائج اشتملت التحليل على بيانات حول 12213 مريضاً تم إدراجهم في 93 دراسة من 17 بلداً. وكان المعدل الكلي للاستجابة الفيروسية المستديمة 52٪ (95٪، فاصل الثقة: 48-56). وبخصوص الدراسات التي ضمت مرضى مصابين بشكل عام بعدوى فيروس التهاب الكبد C بالنمط الجيني 1 أو 4، كان المعدل المجمع للاستجابة الفيروسية المستديمة 49٪ (95٪، فاصل الثقة: 43-55). وكان هذا المعدل منخفضاً بدرجة كبيرة عن معدل 59

摘要

在中低收入国家慢性丙型肝炎治疗的效果：系统性回顾和元分析

目的 评估中低收入国家治疗丙型肝炎病毒 (HCV) 感染的效果并确定成功结果的相关因素。

方法 我们对中低收入国家的丙型肝炎病毒治疗方案研究进行了系统性回顾和元分析。主要成果是治疗持续病毒学响应 (SVR)。随机效应元回归分析确定与治疗效果相关的因素。

结果 分析来自17个国家93个研究中涉及12213例病患的数据。总体SVR率为52% (95%置信区间, CI: 48-56)。对于患者主要感染基因型1或4丙型肝炎病毒的研究, 合并的SVR率为49% (95% CI: 43-55); 在患者主要感染其

他基因型病毒 ($p = 0.012$) 的研究中发现的SVR率为59% (95% CI: 54-64), 前者比率显著低于后者。与成功结果关联的因素包括使用聚乙二醇干扰素和利巴韦林治疗、感染非基因型1或4的基因型丙型肝炎病毒、无肝损害或者基线艾滋病毒感染。在权重调整和固定剂量的利巴韦林治疗之间未观察到SVR率的显著差异。总体而言, 17% (95% CI: 13-23) 的不良事件导致治疗中断或剂量调整, 而4% (95% CI: 3-5) 的不良事件导致治疗终止。**结论** 中低收入国家丙型肝炎病毒感染治疗的效果与高收入国家报道的效果相似。

Résumé

Résultats du traitement de l'hépatite C chronique dans les pays à revenu faible et moyen: évaluation systématique et méta-analyse

Objectif Évaluer l'efficacité du traitement de l'infection par le virus de l'hépatite C (VHC) dans les pays à revenu faible et moyen et identifier les facteurs associés aux résultats positifs.

Méthodes Nous avons effectué une évaluation systématique et une méta-analyse des études sur les programmes de traitement du VHC dans les pays à revenu faible et moyen. Le résultat principal consistait en une réponse virologique soutenue (RVS). Les facteurs liés aux résultats du

traitement ont été identifiés à l'aide d'une analyse de méta-régression des effets aléatoires.

Résultats L'analyse portait sur les données de 12 213 patients inclus dans 93 études provenant de 17 pays différents. Le taux de RVS général était de 52% (intervalle de confiance de 95%, IC: 48-56). Pour les études dans lesquelles les patients étaient principalement atteints par le VHC de génotype 1 ou 4, le taux de RVS groupé était

de 49% (IC de 95%: 43-55). Ce taux était largement inférieur à celui de 59% (IC de 95%: 54-64) présenté dans les études dans lesquelles les patients étaient principalement atteints par d'autres génotypes ($P=0,012$). Les facteurs liés aux résultats positifs incluaient le traitement à l'interféron pégylé et à la ribavirine, l'infection à un VHC de génotype autre que 1 ou 4 et l'absence de lésions au foie ou d'infection par le virus de l'immunodéficience humaine initialement. Aucune différence significative dans le taux de RVS n'a été observée entre les traitements

de ribavirine adaptés au poids et ceux à dose fixe. Dans l'ensemble, 17% (IC de 95%: 13-23) des effets indésirables ont entraîné une interruption du traitement ou une modification des doses, tandis que 4% (IC de 95%: 3-5) d'entre eux ont entraîné un abandon du traitement.

Conclusion Les résultats du traitement de l'infection du VHC dans les pays à revenu faible et moyen étaient similaires à ceux qui étaient indiqués dans les pays à revenu élevé.

Резюме

Результаты лечения хронического гепатита С в странах с низким и средним уровнем дохода: систематический обзор и мета-анализ

Цель Оценить эффективность лечения вируса гепатита С (ВГС) в странах с низким и средним уровнем дохода, а также определить факторы, влияющие на достижение успешных результатов.

Методы Мы провели систематический обзор и мета-анализ исследований, посвященных программам лечения ВГС в странах с низким и средним уровнем дохода. В качестве основного параметра оценки было выбрано получение устойчивого вирусологического ответа (УВО). Факторы, связанные с результатами лечения, идентифицировались с помощью мета-регрессионного анализа на основе модели случайных эффектов.

Результаты Были проанализированы данные о 12 213 пациентах, участвовавших в 93 исследованиях в 17 странах. Общий уровень УВО составил 52% (доверительный интервал, ДИ 95%: 48-56). Для исследований, в которых пациенты были инфицированы преимущественно ВГС с генотипом 1 или 4, агрегированное значение УВО составило 49% (ДИ 95%: 43-55). Это было

значительно ниже уровня 59% (ДИ 95%: 54-64), выявленного в исследованиях, в которых пациенты были инфицированы преимущественно другими генотипами ($P=0,012$). Факторы, влияющие на достижение успешных результатов, включали лечение пегилированным интерфероном и рибавирином, инфицирование генотипом, отличным от 1 и 4, а также отсутствие повреждения печени или вируса иммунодефицита человека на начальном этапе. Не наблюдалось каких-либо существенных различий в уровне УВО между дозировкой рибавирина в зависимости от массы тела и фиксированной дозировкой. В целом, 17% (ДИ 95%: 13-23) нежелательных реакций приводили к прерыванию лечения или изменению дозировки, а 4% (ДИ 95%: 3-5) – к прекращению лечения.

Вывод Результаты лечения инфекции ВГС в странах с низким и средним уровнем дохода были схожи с теми, о которых отчитываются в странах с высоким уровнем доходов.

Resumen

Resultados del tratamiento de la hepatitis C crónica en países de ingresos medios y bajos: examen sistemático y meta-análisis

Objetivo Determinar la efectividad del tratamiento para la infección por el virus de la hepatitis C (VHC) en países de ingresos medios y bajos e identificar los factores asociados con unos resultados satisfactorios.

Métodos Realizamos un examen sistemático y un meta-análisis de estudios de programas de tratamiento del VHC en países de ingresos medios y bajos. El resultado fundamental fue una respuesta viral sostenida (RVS). Los factores asociados con los resultados del tratamiento se identificaron mediante un análisis de metarregresión de efectos aleatorios.

Resultados El análisis incluyó datos sobre 12 213 pacientes en 93 estudios de 17 países. La tasa global de RVS fue del 52% (intervalo de confianza, IC del 95%: 48-56). Para estudios en los que los pacientes estaban predominantemente infectados con VHC del genotipo 1 o 4, la tasa de RVS combinada fue del 49% (IC del 95%: 43-55). Esta fue significativamente menor que la tasa del 59% (IC del 95%:

54-64) encontrada en estudios en los que los pacientes estaban predominantemente infectados con otros genotipos ($P=0,012$). Los factores asociados con los resultados satisfactorios incluyeron el tratamiento con interferón pegilado y ribavirina, la infección del VHC de un genotipo distinto al 1 o al 4 y la ausencia de lesión hepática o de infección por el virus de la inmunodeficiencia humana en el inicio. No se observaron diferencias significativas en la tasa de RVS entre el tratamiento de ribavirina adaptado al peso del paciente y el de dosis fijas. En conjunto, el 17% (IC del 95%: 13-23) de los eventos adversos provocó la interrupción del tratamiento o la modificación de la dosis, mientras que el 4% (IC del 95%: 3-5) causó el abandono del tratamiento.

Conclusión Los resultados del tratamiento de la infección del VHC en países de ingresos bajos y medios fueron similares a los de países de ingresos elevados.

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