Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2017;19:167-172

Generics for the Treatment of Hepatitis C in Monoinfected and HIV-coinfected Patients: Pros and Cons

Dario Cattaneo[1], Alessandro Fossati[2], Chiara Resnati[3], Massimo Galli[3] and Cristina Gervasoni[3]

Departments of [1]Laboratory Medicine, [2]Cardiovascular Surgery, and [3]Infectious Diseases, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy

Abstract

The treatment of hepatitis C virus in monoinfected and HIV-coinfected patients has greatly changed over recent years as a result of the introduction of direct-acting antiviral agents (DAAs), which have revolutionized clinical outcomes and led to sustained virological response rates above 90-95%. The discovery of new molecules and the subsequent competition between pharmaceutical companies, together with the negotiated price policies pursued by many national health systems, have led to a gradual reduction in the cost of DAAs, and expand their use to an increasing number of patients, including those with mild liver damage. However, the cost of branded DAAs is still too high for many developing countries, and many patients are still left without therapy. In this context, the availability of generic DAAs certainly provides a major opportunity for further cost savings in industrialized countries and will ensure broader access to treatment elsewhere. However, their more widespread use must not lead to a reduction in pharmaceutical quality because this could result in serious clinical consequences, including high rat failures, and selection of drug resistance. It is therefore essential that all generic formulations of DAAs are pre-qualified by the World Health Organization, and that real-life studies are carried out to verify their pharmacokinetic bioequivalence (ideally in patients, and not just in healthy volunteers) and clinical effectiveness. In this regard, lessons from expanding access programs in the HIV field would be very helpful. **(AIDS Rev. 2017;19:167-172)**

Key words

Direct-acting antivirals. Generics. Bioequivalence. Pharmacology.

Introduction

Hepatitis C virus (HCV) infection is a serious public health problem throughout the world: It is estimated that a total of about 130-170 million people are affected and known that its prevalence is markedly higher in developing countries, especially China, Pakistan, Egypt, Nigeria, and India[1,2]. Roughly, 20-30% of chronic hepatitis C patients' progress toward cirrhosis, and the yearly rate of liver cancer is 2-3% in cirrhotics. Not surprisingly, HCV infection is the main cause for liver transplantation in many countries[3], and about

Correspondence to:
Dario Cattaneo
Unit of Clinical Pharmacology
ASST Fatebenefratelli Sacco
Via Grassi 74, 20157 Milano, Italy
E-mail: dario.cattaneo@asst-fbf-sacco.it

Received in original form: 26/09/2016
Accepted in final form: 07/06/2017
DOI: 10.24875/AIDSRev.M17000002

500,000 people every year die of HCV-related liver diseases[2]. This scenario is more dramatic in HCV/HIV coinfected patients. Indeed, evidence is now available showing that HIV coinfection is associated with accelerated hepatic fibrosis progression and higher rates of liver decompensation and death compared to HCV monoinfection, and liver disease is one of the leading causes of non-AIDS-related mortality among HIV-infected patients[4].

Over the past 3-5 years, the treatment of HCV infection has radically changed as a result of the introduction new direct-acting antiviral agents (DAAs), which have revolutionized clinical outcomes and led to sustained virological response (SVR) rates of more than 90-95%[5]. DAAs block viral replication by inhibiting proteases (grazoprevir and paritaprevir), polymerases (dasabuvir and sofosbuvir), or non-structural protein 5A (NS5A: daclatasvir, elbasvir, ledipasvir, ombitasvir, and velpatasvir)[6], and are used in various combinations with and without ribavirin depending on the disease genotype[2]. In addition to these drugs, it will not be long before other molecules characterized by pangenotypic activity and a lower risk of pharmacological interactions will become available: The protease inhibitors glecaprevir and voxilaprevir; the polymerase inhibitor uprifosbuvir; and the NS5A inhibitors pibrentasvir and ruzasvir[7].

As might be expected, the main limitation of these innovative and highly efficacious treatments is their cost[8,9]. At the time they entered the market, their estimated average price varied from €25,000 to €80,000 per patient (12-24 weeks of treatment), with often significant differences from one country to another, which meant that their use was limited to patients with advanced liver disease[8,9]. However, the marketing of new molecules and the consequent competition between pharmaceutical companies, together with the cost reduction/containment policies of national health services, has led to a gradual decrease in prices and it is now possible to extend their use to patients in earlier disease stages.

Although it must be remembered that pharmacological treatment is only one of the factors in the more complex framework of managing HCV infection, which necessarily involves early patient screening, making a correct diagnosis, and deciding on the most appropriate treatment (which is now possible in the majority of cases), the aim of this review is to discuss the clinical and economic advantages of generic DAAs, and their possible limitations.

Generic DAAs: Pharmacokinetic Bioequivalence Data

The current definition of generic medications can be found in Article 10 of Directive 2001/83/CE, which not only states that they must have the same pharmaceutical form and the same qualitative and quantitative composition of active substances as the reference drugs but also lays down that their bioequivalence must be demonstrated by means of appropriate bioavailability studies[10]. The European Medicines Agency guideline says that two formulations can be defined bioequivalent if the 90% confidence interval of the ratio between the area under the concentration-time curve and maximum concentration falls within the acceptability interval of 80-125%.

There are only five published scientific articles describing the results of bioequivalence studies of sofosbuvir, ledipasvir, and daclatasvir[11-15]. As shown in table 1, all of the studies involved healthy volunteers and had a cross-over design with the administration of a single dose, and all of them demonstrated the bioequivalence of the generic formulations on the basis of the acceptability interval. However, they have been criticized on methodological grounds, mainly in terms of their experimental design (the pharmacokinetic evaluations were not made at steady-state) and the subjects involved: With the exception of oncological drugs, almost all bioequivalence studies are carried out using young, healthy volunteers who are not taking any concomitant drugs and have optimal excretory organ function[16,17]. These methodological biases often make it difficult to generalize the results of pharmacokinetic/bioequivalence studies to participants with HCV infection (or HCV/HIV coinfection), who are frequently elderly, have comorbidities such as renal and hepatic insufficiency, and are also taking other drugs. It is therefore still unknown whether the bioequivalence of the generic formulations found in healthy volunteers will be confirmed in HCV-infected patients.

Generic DAAs: Clinical Evidence

At the time of writing (April 2017), only one published full-length paper has described the results of a scientific study evaluating the safety and efficacy of a generic coformulation: Ledipasvir/sofosbuvir (Hepcinat LP, marketed by Natco Pharma Limited)[18]. This open-label observational study was conducted in China and involved 192 HCV-postive patients with genotyps 1b:

Table 1. Published bioequivalence studies of generic DAAs

Evaluated drug	Participants	Study design	Ratio (90% CI)
Sofosbuvir 400 mg (Mpiviropack Marcyrl Pharmaceutical Industries, Egypt) versus Sovaldi®[10]	24 healthy adult volunteers	Cross-over, randomized, open-label, single dose in two sequences (fasting)	AUC_{0-t}: 96.5% (85.8-108.6%) $AUC_{0-\infty}$: 96.4% (85.7-108.4%) C_{max}: 100.2% (83.1-120.8%)
Sofosbuvir 400 mg (Sobiovir, Bakhtar Bioshimi) versus Sovaldi®[11]	24 healthy adult volunteers	Cross-over, randomized, open-label, single dose in two sequences (fasting)	AUC_{0-t}: 107.0% (99-119%) $AUC_{0-\infty}$: 107.7% (102-122%) C_{max}: 117.6% (100-132%)
Sofosbuvir 400 mg (Sofovirotal, Future Pharmaceutical Industies, Egypt) versus Sovaldi®[12]*	28 healthy adult volunteers	Cross-over, randomized, open-label, single dose in two sequences (fed)	AUC_{0-t}: 98.2% (93.2-103.4%) $AUC_{0-\infty}$: 98.2% (93.2-103.4%) C_{max}: 103.3% (86.7-122.9%)
Daclatasvir 60 mg (Daclavirocyrl Marcyrl Pharmaceutical Industries, Egypt) versus Daklinza®[13]	26 healthy adult volunteers	Cross-over, randomized, open-label, single dose in two sequences (fasting)	AUC_{0-t}: 100.6% (92.5-109.5%) $AUC_{0-\infty}$: 100.7% (92.6-109.5%) C_{max}: 97.0% (84.7-111.0%)
Sofosbuvir/ledipasvir 400/90 mg (Mpiviropack plus Marcyrl Pharmaceutical Industries, Egypt) versus Harvoni®[14]	28 healthy adult volunteers	Cross-over, randomized, open-label, single dose in two sequences (fasting and fed) The ledipasvir $AUC_{0-\infty}$ was not calculated	Sofosbuvir (fasting) AUC_{0-t}: 101.2% (89.0-115.2%) $AUC_{0-\infty}$: 101.2% ((89.0-115.2%) C_{max}: 104.6% (96.9-112.9%) Sofosbuvir (fed) AUC_{0-t}: 107.7% (98.0-118.5%) $AUC_{0-\infty}$: 108.2% (98.0-119.4%) C_{max}: 106.1% (97.6-115.4%) Ledipasvir (fasting) AUC_{0-t}: 106.1% (95.8-117.4%) C_{max}: 98.2% (88.4-109.1%) Ledipasvir (fed) AUC_{0-t}: 104.4% (94.6-115.3%) C_{max}: 93.5% (86.5-101.0%)

*Results presented without decimal figures. CI: confidence interval; AUC: area under the concentration-time curve; C_{max}: maximum concentration; DAAs: direct-acting antiviral agents.

63 cirrhotic (group 1) and 65 non-cirrhotic patients (group 2) treated with the generic coformulation in combination with ribavirin (1000-1200 mg/day) for, respectively, 12 and 8 weeks, and a further 64 non-cirrhotic patients (group 3) treated with ledipasvir/sofosbuvir alone for 8 weeks. The primary endpoint, which was defined as the presence of an SVR 12 weeks after the end of the treatment, was reached by 96.8% of the patients in group 1, 96.9% of those in group 2, and 96.9% of those in group 3. Only one patient (in group 3) experienced a relapse (4 weeks after stopping treatment). The treatment was well tolerated: The most frequent adverse events were asthenia (17.8%), diarrhea (10.9%), and headache (9.9%). Four patients had to discontinue treatment prematurely because of nausea and vomiting.

Similar findings were observed in the Australian REDEMPTION study in which generic DAAs purchased through the FixHepC website led to results that were clinically equivalent to their branded counterparts[19]. The study was presented at the 2016 International Liver Congress, but it has not yet been published in full.

Likewise, studies presented at the 2016 International Congress on Drug Therapy in HIV infection have also found that the efficacy of generic DAAs is similar to that of the branded drugs[20-22]. These examined the virological outcomes of patients who obtained the DAAs with the aid of buyers' clubs in Australia, Southeast Asia, and Eastern Europe, and were asked to provide their virological data through their attending specialists with the aim of discovering how many achieved an SVR. The greatest amount of data was obtained from the FixHepC Buyer's Club: A 12-week SVR was achieved by 87% of the patients who took sofosbuvir/ledipasvir and 81% of those who took sofosbuvir/daclatasvir (the response rate was lower among the latter because the combination was taken by patients with genotype 3, the most difficult genotype to treat). Fewer data were obtained concerning

the patients in the buyers' clubs of South-east Asia and Russia because fewer patients had reached the end of treatment, but virological response rates were also high in these groups.

Generic DAAs: Quality of Pharmaceutical Formulations

In 2001, the World Health Organization (WHO) confirmed the right of the least developed countries to take action to overcome the patent barriers hindering drug access by importing generic drugs from producing countries. This right had previously been foreseen in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) signed by the members of the World Trade Organization (WTO) in 1994 and was reaffirmed in the 2001 Doha Declaration on the TRIPS Agreement and Public Health adopted by the WTO Ministerial Conference[23].

This opened the door to the manufacturers of generic drugs (mainly from India and China) that not only cost less than innovative drugs but also raised doubts concerning their real pharmaceutical quality that also apply to DAAs[24].

To confront these doubts, the WHO presented its Prequalification Medicines Programme (PMP) which, on the basis of an evaluation of documentation submitted by the manufacturers, "pre-qualifies" the active ingredients used to produce generic drugs[25]. Until a few weeks ago, no DAA had been pre-qualified by the PMP and there were still concerns about the quality of the generic DAAs on the market[24]. However, extremely importantly, a press release issued by the WHO on 31 March 2017 announced that Mylan Laboratories Ltd., India, had obtained the pre-qualification of its sofosbuvir (www.who.int/medicines/news/2017/1st_generic-hepCprequalified_active_ingredient/en/), the first generic DAA to be formally pre-qualified by the WHO. However, this is only the first step in the process of guaranteeing the quality of the final pharmaceutical compound which, as indicated in the PMP, also requires bioequivalence data. Table 2 shows the WHO requirements for the design of bioequivalence studies of generic sofosbuvir/ledipasvir coformulations.

The WHO's pre-qualification programme is not enough to prevent the circulation of counterfeit medicines, most of which are purchased online. The world-

Table 2. The WHO criteria for bioequivalence studies of sofosbuvir/ledipasvir coformulations

Factors to be considered	The WHO comments
Dose	Consider the oral administration of a single tablet containing sofosbuvir 400 mg and ledipasvir 90 mg
Fasting/fed	The bioequivalence study should be carried out under fasting conditions as there no restrictions concerning the administration of sofosbuvir/ledipasvir with or without food
Participants	The study may be carried in healthy adult volunteers. It is not necessary to include patients when assessing bioequivalence
Sample size	On the basis of the information contained in the PMP, the intra-patient variability of ledipasvir and sofosbuvir is, respectively, 45% and 35%. This information will facilitate the calculation of sample size when designing bioequivalence studies
Washout	As the elimination half-life of sofosbuvir is about 47 h, it is estimated that a washout period of 14 days is sufficient to prevent a carry-over effect
Blood sampling	Blood sampling must be frequent during the first five hours after drug administration to be able to characterize adequately the C_{max} of sofosbuvir (within 2 h) and ledipasvir (3-5 h after taking the drug). It is not necessary to take blood samples more than 72 h after the drug has been administered
Analytical considerations	On the basis of the information contained in the PMP, it is possible to measure sofosbuvir and ledipasvir levels in human plasma using LC-MS/MS. The bioanalytical method must be sufficiently sensitive to quantify concentrations that are 5% of C_{max}
Metabolite data	It is not necessary to quantify metabolites when assessing bioequivalence
Statistical considerations	The 90% confidence intervals of the AUC_{0-t}, AUC_{0-72h} and C_{max} ratios between the tested generic drugs and their branded reference drugs must fall within the range 80-125%

PMP: pre-qualification medicines programme; LC-MS/MS: high-performance liquid chromatography in tandem with mass spectrometry; WHO: World Health Organization; AUC: area under the concentration-time curve; C_{max}: maximum concentration.

wide existence of counterfeit formulations of sofosbuvir, pegylated interferon, and ribavirin has been reported by the specialist press since 2015[24] and, in 2016, the WHO issued alerts concerning the circulation of counterfeit formulations containing sofosbuvir or daclatasvir alone, or sofosbuvir in combination with ledipasvir or daclatasvir (see the editorial by Ravinetto et al.)[24]. Furthermore, in March 2016, the Swiss Medicines Agency (Swissmedic) reported the presence of counterfeit formulations of Harvoni (a coformulation produced by Gilead that contains ledipasvir 90 mg and sofosbuvir 400 mg) in Israel (www.swissmedic.ch/aktuell/00673/03287/index.html?lang=en). These formulations, which were produced in India and imported by a Swiss trading company, consisted of white tablets instead of the characteristic diamond-shaped orange tablets of the original formulation of Harvoni.

Generic DAAs: Economic Implications

The most significant consequences of the availability of generic DAAs are certainly economic in nature. A recent analysis by van de Ven et al.[26] has estimated that the cost of synthesising the amounts of the active ingredients necessary for 12 weeks' treatment is in the range of $100-400 per person, whereas the average cost borne by national health services for the purchase of the branded medicinal products is about €25,000-80,000 per person (more recently reduced to about €9,000-15,000). These figures highlight the enormous disproportion between the production costs and sales prices of the originator DAAs. Although it is true that a part of the difference is due to the pharmaceutical companies' need to cover their research and development costs, a recent analysis by Freeman and Hill has shown that, even when this is taken into account, DAA prices are still disproportionately high[27]. These high prices, and the consequent restrictions on prescribing DAAs imposed by various governments in an attempt to limit their global pharmaceutical expenditure, have encouraged patients to seek alternative channels through which to obtain the drugs, above all on-line purchasing. Setting aside the sites that supply counterfeit drugs, one of the most widely used sites is FixHepC, a web-based platform that specializes in importing generic DAAs (mainly from India and Bangladesh) and offers a 12-week course of treatment at an average price of about $1500-2000 per patient[2]. According to Hill et al., the massive use of generic DAAs could further reduce the cost of antiviral therapy to $100-200/patient[28].

Conclusions

The recent availability of various DAAs has radically changed the natural history of both HCV-monoinfected and HIV coinfected patients. It is now possible to eradicate the virus in more than 90% of treated cases, thus preventing many of the long-term complications associated with the disease. The continuing introduction of new molecules and the consequent competition among pharmaceutical companies, together with price reduction policies, has meant that costs have progressively decreased and allowed DAAs to be used for an ever-increasing number of patients. However, branded drugs are still too expensive for many countries, and many patients go untreated.

The availability of generic DAAs is certainly an important opportunity for further containing costs in industrialized countries and a fundamental means of extending treatment access in poorer countries. However, it has to be said that their more widespread use must not be allowed at the expense of pharmaceutical quality because this could have major clinical consequences. It is therefore essential to verify that all of the generic formulations of DAAs on the market are prequalified by the WHO's PMP, clinically efficacious, and pharmaceutically bioequivalent (ideally in patients and not just in healthy volunteers).

It is our personal opinion that, however secure they might be, the use of on-line sites to purchase DAAs should only be considered a sort of "palliative" measure while awaiting national governments to establish their own cost-containment strategies in such a way as to guarantee the dispensing of these treatments through more conventional, safer, and more controllable channels. Although it may be considered unique of its kind, one emblematic example is that of Egypt, whose government has managed to obtain branded sofosbuvir with a 99% discount on the reference price.

Conflict of Interest

Dr. Dario Cattaneo, Dr. Alessandro Fossati, Dr. Chiara Resnati, Dr. Massimo Galli and Dr. Cristina Gervasoni have nothing to disclose.

References

1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61 1 Suppl: S45-57.
2. Ghinea N, Lipworth W, Day R, Hill A, Dore GJ, Danta M. Importation of generic hepatitis C therapies: Bridging the gap between price and access in high-income countries. Lancet. 2017;389:1268-72.

3. Lim SG. HCV management in resource-constrained countries. Hepatol Int. 2017;11:245-54.
4. Chen JY, Feeney ER, Chung RT. HCV and HIV co-infection: Mechanisms and management. Nat Rev Gastroenterol Hepatol. 2014;11:362-71.
5. Ferreira VL, Tonin FS, Assis Jarek NA, Ramires Y, Pontarolo R. Efficacy of interferon-free therapies for chronic hepatitis C: A systematic review of all randomized clinical trials. Clin Drug Investig. 2017.
6. McConachie SM, Wilhelm SM, Kale-Pradhan PB. New direct-acting antivirals in hepatitis C therapy: A review of sofosbuvir, ledipasvir, daclatasvir, simeprevir, paritaprevir, ombitasvir and dasabuvir. Expert Rev Clin Pharmacol. 2016;9:287-302.
7. Kardashian AA, Pockros PJ. Novel emerging treatments for hepatitis C infection: A fast-moving pipeline. Therap Adv Gastroenterol. 2017;10:277-82.
8. Lynch SM, Wu GY. Hepatitis C Virus: A review of treatment guidelines, cost-effectiveness, and access to therapy. J Clin Transl Hepatol. 2016;4:310-9.
9. Craxì L, Sacchini D, Refolo P, Minacori R, Daloiso V, Ricci G, et al. Prioritization of high-cost new drugs for HCV: Making sustainability ethical. Eur Rev Med Pharmacol Sci. 2016;20:1044-51.
10. European Medicines Agency. Guideline on Bioanalytical Method Validation; 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf. [Last accessed 2017 Apr 11].
11. Rezk MR, Basalious EB, Karim IA. Development of a sensitive UPLC-ESI-MS/MS method for quantification of sofosbuvir and its metabolite, GS-331007, in human plasma: Application to a bioequivalence study. J Pharm Biomed Anal. 2015;114:97-104.
12. Bahrami MT, Mohammadi B, Miraghaei S, Babaei A, Ghaheri M, Bahrami G, et al. Quantification of sofosbuvir in human serum by liquid chromatography with negative ionization mass spectrometry using the parent peak and its source-induced fragment: Application to a bioequivalence study. J Sep Sci. 2016;39:2702-9.
13. Rezk MR, Basalious EB, Amin ME. Novel and sensitive UPLC-MS/MS method for quantification of sofosbuvir in human plasma: Application to a bioequivalence study. Biomed Chromatogr. 2016;30:1354-62.
14. Rezk MR, Bendas ER, Basalious EB, Karim IA. Development and validation of sensitive and rapid UPLC-MS/MS method for quantitative determination of daclatasvir in human plasma: Application to a bioequivalence study. J Pharm Biomed Anal. 2016;128:61-6.
15. Rezk MR, Bendas ER, Basalious EB, Karim IA. Quantification of sofosbuvir and ledipasvir in human plasma by UPLC-MS/MS method: Application to fasting and fed bioequivalence studies. J Chromatogr B Analyt Technol Biomed Life Sci. 2016;1028:63-70.
16. Cattaneo D, Andreoni M, Carosi G, Cauda R, Lazzarin A, Rizzardini G. Generic antiretrovirals for the treatment of HIV: A novel challenge for Western countries? Int J Clin Pharmacol Ther. 2017;55:381-393.
17. Sarpel D, Dieterich D. The use of generics to treat chronic hepatitis C: not quite ready for the big stage. Liver Int. 2016;36:933-5.
18. Zeng QL, Xu GH, Zhang JY, Li W, Zhang DW, Li ZQ, et al. Generic ledipasvir-sofosbuvir for patients with chronic hepatitis C: A real-life observational study. J Hepatol. 2017;66:1123-9.
19. Freeman J, Sallie R , Kennedy A, Hieu PT, Jeffreys G, Hill AM, et al. High sustained virological response rates using generic direct acting antiviral treatment for hepatitis C, imported into Australia. EASL, International Liver Congress: Barcelona, Abstract LB03; 2016.
20. Hill A, Dragunova J, Korologou-Linden R, Golovin S. Efficacy of Generic Direct Acting Antiviral Treatment for Hepatitis C, Imported into Russia and Eastern Europe. Glasgow: International Congress on Drug Therapy in HIV Infection (HIV Glasgow), Poster P261; 2016.
21. Korologou-Linden R, Hill A, Wardhana A, Khwairakpam G. Efficacy of Generic Direct Acting Antiviral Treatment for Hepatitis C, Imported into South-East Asia and China. Glasgow: International Congress on Drug Therapy in HIV Infection (HIV Glasgow), Poster 262; 2016.
22. Hill A, Savage A, Jeffreys G, Freeman JA, Sallie R, Kennedy A, et al. High Sustained Virological Response Rates Using Imported Generic Direct Acting Antiviral Treatment for Hepatitis C, Imported into Australia, UK, Europe and North America. Glasgow: International Congress on Drug Therapy in HIV Infection (HIV Glasgow) Poster P256; 2016.
23. Declaration on TRIPS Agreement and Public Health: WT/MIN(01)/DEC/2, Ministerial Conference; 2001. Available from: http://www.who.int/medicines/areas/policy/doha_declaration/en. [Last accessed on 2017 Apr 11].
24. Ravinetto R, de Weggheleire A, Dorlo TP, Francque S, Sokkab A, Pouget C, et al. Predictable threats to public health through delaying universal access to innovative medicines for hepatitis C: A pharmaceutical standpoint. Trop Med Int Health. 2016;21:1490-5.
25. 't Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: The World Health Organization's prequalification of medicines programme. J Public Health Policy. 2014;35:137-61.
26. van de Ven N, Fortunak J, Simmons B, Ford N, Cooke GS, Khoo S, et al. Minimum target prices for production of direct-acting antivirals and associated diagnostics to combat hepatitis C virus. Hepatology. 2015;61:1174-82.
27. Freeman JA, Hill A. The use of generic medications for hepatitis C. Liver Int. 2016;36:929-32.
28. Hill A, Simmons B, Gotham D, Fortunak J. Rapid reductions in prices for generic sofosbuvir and daclatasvir to treat hepatitis C. J Virus Erad. 2016;2:28-31.