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A Brief Update on the Treatment of Hepatitis C

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Abstract

Hepatitis C virus was discovered nearly 30 years ago, and for the first two decades, treatment was limited to agents with low response rates and substantial side effects. Since the introduction of direct-acting antivirals, there have been rapid advances made toward even higher sustained virologic responses (SVRs) and fewer side effects. This chapter provides a review of the newer agents for treatment of hepatitis C and highlights special populations, including those coinfecting with HIV or hepatitis B, previously treated patients, and post-liver transplant patients.

Keywords: hepatitis C, direct-acting antivirals, protease inhibitors, HIV, hepatitis B

1. Introduction

Hepatitis C virus (HCV) infects approximately 185 million individuals worldwide and is the leading indication for liver transplant in the United States (US) [1]. In 2014, the centers for disease control and prevention (CDC) reported an estimated 30,500 new cases of HCV in the US, while the estimated number of chronic cases was approximately 2.7–3.9 million. HCV was first discovered in 1989, and there have been numerous advances in medical therapies available for the treatment and cure of HCV infection. Cure is defined as a sustained virologic response (SVR), which means undetectable levels of plasma HCV RNA for 12 or 24 weeks after completion of therapy.

The first agents available for treatment of HCV were the alfa interferons, which are immunomodulatory agents administered subcutaneously. The initial treatment regimen with interferon monotherapy resulted in SVR rates of only approximately 15% [2]. Ribavirin was subsequently added, which improved SVR rates to 33 and 41% for 24- and 48-week treatment regimens, respectively [3]. With the introduction of pegylated interferon (peg-IFN), SVR rates

increased up to an estimated 50% [4]. Despite significant side effects, a suboptimal SVR rate, the need for prolonged therapy, and parenteral injections, Peg-IFN and ribavirin were the standard of care for over a decade.

The most recent development in treatment of HCV was the introduction of direct-acting antivirals (DAAs), which target various stages in the HCV life cycle. In 2014, an all-oral combination regimen was approved, and trials have demonstrated SVR rates approaching 100% [5–9]. With their unprecedented efficacy and improved tolerability, they have revolutionized the approach to treatment of chronic hepatitis C.

2. Direct-acting antivirals

2.1. First-generation NS3/4A protease inhibitors

The HCV RNA genome encodes a single polyprotein consisting of 3000 amino acids, which is cleaved by host and viral-encoded proteases to yield the functional structural and non-structural components of the virus [10]. The NS3/4A is composed of a serine protease (NS3) and cofactor (NS4A) and is involved in posttranslational processing or cleavage of the non-structural components at the NS3/NS4A, NS4A/NS4B, NS4B/NS5A, and NS5A/NS5B sites. The NS3/4A protease is essential to the processing of the HCV polypeptide and is critical for replication of the virus [10].

In 2011, boceprevir and telaprevir were the first DAAs, and the first NS3/4A inhibitors to be approved for the treatment of chronic hepatitis C, genotype 1. The mechanism of action is to inhibit the NS3/4A protease by forming a reversible covalent bond with the NS3/4A active site [11]. Both boceprevir and telaprevir were found to have significant side effects, including anemia and anemia plus rash, respectively [11]. In addition, their use was complicated by significant drug-drug interactions (both boceprevir and telaprevir are potent cytochrome p450 inhibitors), inconvenient dosing requiring multiple daily doses, and low barriers to resistance [11].

2.2. Second-generation protease inhibitors

A second generation of protease inhibitors was designed to contain macrocycles, or cyclic macromolecules, which resulted in improved antiviral potency [12]. Simeprevir was the first macrocyclic protease inhibitor to be approved for HCV treatment [13]. Simeprevir forms a noncovalent bond with the NS3/4A active site rather than the reversible covalent bond that boceprevir and telaprevir formed [14]. Paritaprevir is a protease inhibitor given in combination with three other medications (ombitasvir, paritaprevir, and dasabuvir), which comprise Viekira Pak, approved by the FDA in 2014 for HCV genotype 1. This was the second all-oral, interferon-free, fixed-dose combination for treatment of chronic HCV genotype 1 to be approved in the US [15]. Grazoprevir is another second-generation protease inhibitor that was FDA approved in 2016 in combination with an NS5A inhibitor [16]. Asunaprevir is a potent, selective NS3 protease inhibitor with activity against HCV genotypes 1, 4, 5, and 6 *in vitro* and is given in combination with daclatasvir, discussed in the next section [17]. Benefits of

second-generation protease inhibitors include reduced dosing, improved side effect profiles, and fewer drug-drug interactions [18].

2.3. NS5A inhibitors

The NS5A phosphoprotein has no known enzymatic activity and its detailed function remains unclear [19]. NS5A inhibitors are thought to interact with NS5A and block formation of the “membranous web” that houses HCV RNA replication. They interfere with several functions of NS5A in the HCV life cycle, and disrupt the establishment of replication sites, which in turn prevents continued HCV RNA replication [19]. NS5A inhibitors include daclatasvir, ombitasvir, ledipasvir, elbasvir, and velpatasvir. Daclatasvir can be given in combination with sofosbuvir +/- RBV for the treatment of HCV genotypes 1–4. Ombitasvir is approved for treatment of genotype 1 in combination with paritaprevir, ritonavir, and dasabuvir. Ledipasvir is approved for genotypes 1, 3, and 4 in combination with sofosbuvir +/- RBV [20]. Velpatasvir in combination with sofosbuvir was approved in June 2016 by the FDA and became the first regimen approved for genotypes 1–6 [21].

2.4. Polymerase NS5B inhibitors

Polymerase inhibitors are another class of DAAs and are comprised of nucleoside analog and nonnucleoside analog inhibitors. Both types bind to the NS5B polymerase to terminate replication of the virus. The enzyme has a catalytic site for nucleoside binding and at least four other sites at which a nonnucleoside compound can bind and induce allosteric alterations in conformation [22].

Nucleoside analog inhibitors are incorporated into the HCV RNA chain and lead to direct chain termination. The advantage of this mechanism of action is that it is potentially active against all HCV genotypes, and the potential for viral resistance is low. This is because the NS5B active site has a low tolerance for amino acid substitutions. Any NS5B active site mutation that would potentially confer resistance to a polymerase inhibitor would likely also impair the RNA polymerase activity. Sofosbuvir is an example of a nucleoside analog inhibitor for use in treatment of HCV. It is given orally once a day, has pan-genotypic antiviral activity, and has a high barrier to viral resistance with no virologic breakthrough reported thus far [23].

Nonnucleoside analog inhibitors bind to discrete sites outside of the polymerase active center and induce a conformational protein change. Dasabuvir is an example of a nonnucleoside inhibitor of the NS5B polymerase [24].

In comparison with the nucleoside analog inhibitors, nonnucleoside polymerase inhibitors are more genotype-specific and have a lower barrier to resistance. This class of drugs is used in combination with other classes that are more potent with higher barriers to resistance.

2.5. Role of ribavirin in the era of direct-acting antivirals

Ribavirin was a critical component of hepatitis C treatment in the era of interferon-based therapy; however, its role in DAA regimens was initially unclear. At this time, guidelines

do recommend the use of ribavirin in combination with DAAs, depending on genotype and presence or absence of cirrhosis. For example, there is evidence to support the use of ribavirin in specific situations, such as patients using sofosbuvir-based regimens who are either HCV genotype 1, treatment-experienced, and cirrhotic, or HCV genotype 3 with cirrhosis [25]. SVR rates tend to be lower among HCV genotype 3 patients with advanced liver disease (as low as 62% in patients with cirrhosis who were null responders to IFN-RBV therapy) [26]. In the ALLY-3+ study, ribavirin was investigated in combination with daclatasvir and sofosbuvir in patients who were HCV genotype 3, both treatment-naïve and treatment-experienced, and with advanced fibrosis or compensated cirrhosis. They achieved an overall SVR rate at 12 weeks of 90% [27]. These results, in combination with other studies, support the addition of ribavirin to achieve higher rates of SVR, allow shortening of treatment, and decrease the cost of treatment.

3. Treatment strategies

The ultimate goal of antiviral therapy for patients with chronic hepatitis C is achieving SVR. Refer to **Table 1** for additional terminology used to define treatment responses.

Monitoring viral levels during treatment with the new DAA regimens has minimal value, as the viral level is typically undetectable after 4 weeks of treatment. The more important assessment of virologic response is measuring the viral load at 12–24 weeks after therapy is completed or stopped.

When deciding on an appropriate DAA regimen, several factors must be taken into account, particularly HCV genotype, prior treatment history, stage of liver disease, presence of decompensation in patients with known cirrhosis, renal function, and other medications the patient is taking that could interact with the DAAs.

3.1. Treatment-naïve patients

Refer to **Table 2** for an overview of treatment regimens recommended based on American association for the study of liver diseases (AASLD) and infectious diseases society of America

Nonresponse	Detectable HCV RNA after 12 weeks of HCV therapy
Partial response	>2 log decline in HCV RNA but detectable HCV RNA after 12 weeks of HCV therapy
Null response	<2 log decline in HCV RNA after 12 weeks of HCV therapy
Viral breakthrough	Detectable HCV RNA after previously undetectable
Relapse	Undetectable HCV RNA on therapy with detectable HCV RNA after stopping therapy
Sustained virologic response	Undetectable HCV RNA 12 or 24 weeks after stopping therapy

Table 1. Definitions of treatment response to HCV treatment.

(IDSA) guidelines from April 2017. Compared to previous guidelines from July 2016, there is now a subcategory of patients who qualify for treatment of 8 weeks duration. Otherwise, the remainder of treatment regimens are all at least 12 weeks. This recommendation was based

Genotype 1a	Without cirrhosis	<ul style="list-style-type: none"> • Daily elbasvir/grazoprevir* • Daily ledipasvir/sofosbuvir** • Daily paritaprevir/ritonavir/ombitasvir plus twice-daily dosed dasabuvir with weight-based ribavirin • Daily simeprevir plus sofosbuvir • Daily sofosbuvir/velpatasvir • Daily daclatasvir and sofosbuvir
	With compensated cirrhosis	<ul style="list-style-type: none"> • Daily elbasvir/grazoprevir* • Daily ledipasvir/sofosbuvir • Daily sofosbuvir/velpatasvir
Genotype 1b	Without cirrhosis	<ul style="list-style-type: none"> • Daily elbasvir/grazoprevir • Daily ledipasvir/sofosbuvir** • Daily paritaprevir/ritonavir/ombitasvir plus twice-daily dosed dasabuvir • Daily simeprevir plus sofosbuvir • Daily sofosbuvir/velpatasvir • Daily daclatasvir plus sofosbuvir
	With compensated cirrhosis	<ul style="list-style-type: none"> • Daily elbasvir/grazoprevir • Daily ledipasvir/sofosbuvir • Daily paritaprevir/ritonavir/ombitasvir plus twice-daily dosed dasabuvir • Daily sofosbuvir/velpatasvir
Genotype 2	Without cirrhosis	<ul style="list-style-type: none"> • Daily sofosbuvir/velpatasvir
	With compensated cirrhosis	<ul style="list-style-type: none"> • Daily sofosbuvir/velpatasvir
Genotype 3	Without cirrhosis	<ul style="list-style-type: none"> • Daily daclatasvir plus sofosbuvir • Daily sofosbuvir/velpatasvir
	With compensated cirrhosis	<ul style="list-style-type: none"> • Daily sofosbuvir/velpatasvir • Daily daclatasvir plus sofosbuvir for 24 weeks with or without weight-based ribavirin
Genotype 4	Without cirrhosis	<ul style="list-style-type: none"> • Daily paritaprevir/ritonavir/ombitasvir and weight-based ribavirin • Daily sofosbuvir/velpatasvir • Daily elbasvir/grazoprevir • Daily ledipasvir/sofosbuvir
	With compensated cirrhosis	<ul style="list-style-type: none"> • Daily paritaprevir/ritonavir/ombitasvir and weight-based ribavirin • Daily sofosbuvir/velpatasvir • Daily elbasvir/grazoprevir • Daily ledipasvir/sofosbuvir
Genotype 5/6	With and without cirrhosis	<ul style="list-style-type: none"> • Daily sofosbuvir/velpatasvir • Daily ledipasvir/sofosbuvir

Dosing: elbasvir 50 mg, grazoprevir 100 mg, ledipasvir 90 mg, sofosbuvir 400 mg, paritaprevir 150 mg, ombitasvir 25 mg, dasabuvir 250 mg, simeprevir 150 mg, ritonavir 100 mg, velpatasvir 100 mg.*In whom no baseline NS5A RAVs for elbasvir are detected.

**For patients who are nonblack, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL, treatment duration is 8 weeks.

Table 2. Regimens for treatment-naïve patients (dosing for 12 weeks unless specified).

on the ION-3 trial, which compared SVR rates in patients treated for 8 weeks versus 12 weeks and found no difference. However, relapse rates were higher in patients with certain characteristics. Thus, the recommendation of 8 weeks of treatment is indicated in patients with HCV genotype 1a/1b without cirrhosis who are nonblack, human immunodeficiency virus (HIV)-uninfected, and whose HCV RNA level is 6 million IU/mL.

3.2. FDA-approved regimens

While the direct-acting antivirals have been discussed up to this point as separate categories, it is clear based on the guidelines that most regimens include drugs from many categories. Pharmaceutical companies manufacture the drugs as combination pills, which makes dosing convenient.

Brand Name	Components	Year approved by FDA
Sovaldi	Sofosbuvir (NS5B)	2013
Harvoni	Ledipasvir (NS5A) Sofosbuvir (NS5B)	2014
Viekira Pak	Ombitasvir (NS5A) Paritaprevir (NS3/4A) Ritonavir (booster) Dasabuvir (NS5B)	2014
Technivie	Ombitasvir (NS5A) Paritaprevir (NS3/4A) Ritonavir (booster)	2015
Zepatier	Elbasvir (NS5A) Grazoprevir (NS3/4A)	2016
Epclusa	Sofosbuvir (NS5B) Elpatasvir (NS5A)	2016

Table 3. Hepatitis C treatment regimens and their components.

GT1	GT2	GT3	GT4	GT5	GT6
Harvoni ^a	Sovaldi/RBV	Sovaldi/Daklinza	Harvoni	Harvoni	Harvoni
Zepatier ^f	Peg-IFN/RBV ^d	Sovaldi/RBV ^d	PegIFN/Sovaldi/RBV		
Viekira +/- RBV ^c		Peg-IFN/RBV ^e	Technivie ^b		
Peg-IFN/Sovaldi/RBV			Zepatier		
Epclusa ^g	Epclusa	Epclusa	Epclusa	Epclusa	Epclusa

^aTreatment experienced: 24-week course.
^bContraindicated in cirrhotics.
^cGenotype 1a: add ribavirin, 12-week course; genotype 1a cirrhotics, add ribavirin, 24-week course.
^d24-week course.
^e48-week course.
^fGenotype 1a with polymorphism: add ribavirin, 16-week course.
^gAdd ribavirin for Child-Pugh class B and C.

Table 4. FDA-approved regimens based on genotype (12-week course except where indicated).

Refer to **Table 3** for the brand names of hepatitis C treatment regimens and their components. **Table 4** provides the approved regimens based on the genotype.

4. Special populations

4.1. Coinfection with HIV

Approximately 10–30% of patients with human immunodeficiency virus (HIV) also have HCV [28], with a global prevalence estimated at 2.5–5 million people [29]. With the improved lifespan of HIV patients attributable to effective antiretroviral therapy, the focus is now shifting to treatment of concurrent infections that afflict HIV patients, with HCV-related liver complications being a leading non-HIV cause of death [30].

A meta-analysis study examined the survival benefit of achieving SVR, looking at a total of 33,360 patients with HCV and HIV/HCV coinfection [31]. Achieving HCV SVR was associated with a 50% reduction in the risk of all-cause mortality compared with not achieving SVR in the general HCV population. This result was markedly higher for the coinfecting subgroup (79%), highlighting the importance and potential impact HCV cure has on patients also co-infected with HIV.

The *ION-4* study studied outcomes for patients with HIV/HCV coinfection that were given DAAs while on antiretroviral therapy for HIV [32]. There were 335 patients enrolled in the study, most of which were genotype 1 (98%). In addition, 55% of the patients were treatment experienced. They were administered ledipasvir and sofosbuvir (Harvoni). After 12 weeks of therapy, 96% were HCV RNA negative, and SVR rates of >94% were observed. None of the patients discontinued treatment due to adverse events.

Another DAA regimen combining elbasvir, an NS5A inhibitor, with grazoprevir, a second-generation NS3/4A protease inhibitor (Zepatier), was approved by the FDA for the treatment of chronic HCV genotypes 1 and 4, including those with HIV-1 coinfection. This indication was based on the C-EDGE CO-INFECTION study, which studied 218 patients with HIV/HCV coinfection who were treated with the elbasvir-grazoprevir combination [33]. Study results demonstrated an SVR rate of 96% at 12 weeks.

4.2. Coinfection with HBV

In the US, about 800,000–1.4 million people have chronic hepatitis B virus (HBV) infection. Around 2–10% of patients with chronic HCV are coinfecting with HBV [34–36]. It has been shown that the presence of HBV coinfection with HCV accelerates the progression of liver damage, and is associated with a higher probability of liver cirrhosis and hepatic decompensation, higher incidence of hepatocellular carcinoma, and death [36, 37].

A potentially serious complication of stable HBV infections is the phenomenon of reactivation in which viral replication and liver damage suddenly increase. HBV reactivation can occur in patients who are hepatitis B surface antigen (HBsAg) (+), patients who have HBV DNA (+) active infection, or in patients with inactive infections, i.e., who are HBsAg (–), HBV DNA (–),

but anti-HB virus core antibody (HBcAb) (+) and/or anti-HB virus surface antibody (HBsAb) (+) [38]. Reactivation can occur spontaneously, but more commonly occurs as a complication of medically induced changes in immune status. This has been clearly observed in patients with HBV infection who received antitumor necrosis factor (TNF) biologicals.

For this reason, the FDA has issued a black box warning concerning the risk of HBV reactivation in patients receiving anti-TNF and anti-CD20 monoclonal antibodies [39]. HBV reactivation has also been reported in patients with HBV/HCV coinfections treated with the combination of daclatasvir and asunaprevir. [40]. Accordingly, the FDA has issued a Drug Safety Communication about the risk of HBV reactivation in patients with current or previous infection who are to be treated with direct-acting antiviral (DAA) agents for HCV. The FDA is considering a boxed warning for nine DAAs in addition to Harvoni including Sovaldi, Viekira Pak, Viekira Pak XR, Daklinza, Epclusa, Olysio, Technivie, and Zepatier.

It is important that health-care professionals screen and monitor for HBV in all patients before initiating treatment with DAAs [41]. Coinfected HBV patients should receive anti-HBV therapy prior to and during anti-HCV treatment as prophylaxis against reactivation. Antiviral therapy started after HBV reactivation may not be effective to prevent hepatitis and/or hepatitis flares. The possible interaction of DAAs with some anti-HBV agents must also be considered [40, 42, 43].

4.3. Previously treated patients

There have been many studies that investigated retreatment strategies after lack of SVR with either an IFN-based regimen or an IFN-free regimen.

In the combination of simeprevir and sofosbuvir in HCV-infected patients (COSMOS) study (COSMOS) study trial, there were 80 HCV genotype 1 patients who were null responders to previous treatment with pegylated interferon and ribavirin. They were subsequently treated with simeprevir and sofosbuvir +/-ribavirin for 24 weeks, and achieved a mean SVR of 90%. In the ION-2 study, 440 HCV genotype 1 patients who were previously treated with an IFN-based regimen were given sofosbuvir + ledipasvir +/- RBV for 12–24 weeks, and achieved a SVR rate of greater than 94%.

In the retreatment of patients with genotype 1a and 1b who previously failed peg-interferon and ribavirin therapy, current guidelines recommend the same 12-week regimens used as initial treatment for genotype 1a and 1b patient without cirrhosis [44].

There have been a few small studies examining treatment failure with IFN-free regimens, and results have been promising, demonstrating that retreatment can successfully achieve SVR, by either prolonging the duration of treatment to 24 weeks or by adding ribavirin [45]. The retreatment regimen should include sofosbuvir with 1–3 other DAAs with different mechanisms of action.

4.4. Post-liver transplant patients

For patients with untreated recurrent hepatitis C after liver transplantation, disease progression is accelerated, with approximately 20% developing graft cirrhosis by 5 years

posttransplantation [46]. DAA regimens have significantly improved SVR rates in post-transplant patients. The CORAL-I study looked at recurrent HCV genotype 1 infection in patients who had received liver transplants. These patients were treated with combination ombitasvir/paritaprevir/ritonavir plus dasabuvir with ribavirin for 24 weeks, and they achieved an SVR rate of 97% after 24 weeks of therapy [47].

5. Resistance to DAAs

NS5A inhibitors, NS3/4A protease inhibitors, and nonnucleoside polymerase inhibitors have low barriers to resistance. Prior to any antiviral treatment, resistance-associated variants (RAV) may preexist at varying frequencies and these variants may be selected rapidly during treatment with DAAs. However, with a few exceptions, HCV drug resistance testing is not recommended in naïve patients, because SVR rates were not affected by the presence of baseline NS3/4A or NS5A RAVs [45]. Moreover, the majority of treatment failures with DAAs are usually related to relapse rather than on-treatment viral breakthrough [48].

Although resistance testing is not routinely recommended for all DAAs at this time, it is an important focus of research because it could guide regimen choices if patients at high risk for treatment failure were identified early. However, there are many conditions to be met prior to the widespread use of HCV resistance testing including a standardized assay, interpretation and reporting of the data [45].

At this time, these criteria have not been met. As discussed above, not all RAVs are clinically significant, and the level of resistance conferred by a preexisting RAV needs to be further delineated.

6. Barriers to treatment

With the recent success of DAA regimens and their exceptional SVR rates demonstrated in most recent trials, the prospect of eradicating HCV infection seems near. However, there still exist multiple barriers to treatment. The most obvious barrier is the high cost associated with treatment.

Drug pricing is impacted by many factors, including market competition, presence of generic versions, existing prices of effective treatment, and business negotiations. There is very little transparency in the process, particularly in the negotiations between pharmaceutical companies and payers. However, the basis for negotiation starts with a list price set by the pharmaceutical company, called the Wholesale Acquisition Cost (WAC). Refer to **Table 5** for the wholesale acquisition costs of the current HCV regimens on the market.

In the US, sofosbuvir was approved in 2013, and the WAC was set at \$84,000 for a 12-week course of treatment [49]. The more recent development of market competition has created opportunity for greater discounts and rebates. When Viekira Pak (ombitasvir/paritaprevir/ritonavir + dasabuvir)

Direct-acting antiviral	Pharmaceutical company	WAC for 12-week course
Sofosbuvir (Sovaldi)	Gilead sciences	\$84,000
Ledipasvir/Sofosbuvir (Harvoni)	Gilead sciences	\$94,500
Ombitasvir/paritaprevir/ritonavir + Dasabuvir (Viekira Pak)	AbbVie	\$83,319
Daclatasvir (Daklinza) + Sofosbuvir (Sovaldi)	Bristol-Myers Squibb and Gilead	\$147,000
Grazoprevir/Elbasvir (Zepatier)	Merck	\$54,600
Sofosbuvir/Velpatasvir (Epclusa)	Gilead sciences	\$74,760

Table 5. Wholesale Acquisition Cost of direct-acting antivirals.

was approved, it was made available for \$51,000–\$66,000 [50]. Currently, 80% of the market is exclusive to either Harvoni (Ledipasvir/Sofosbuvir) or Viekira Pak, and the average negotiated discount is 46% off of the WAC [51].

Until DAAs become widely affordable, there will be restrictions, and priority will be given to those who have failed previous IFN-based therapies with evidence of disease progression, patients ineligible for IFN-based therapy with progressive disease, patients with established cirrhosis, patients on the liver transplant waiting list, and those who have had a liver transplant.

7. Conclusions

This is a pivotal time in which there have been major advances in the treatment of hepatitis C. Patients have the option of an all-oral regimen with high tolerability and convenient dosing. With SVR nearing 100%, the prospect of limiting HCV treatment failures appears to be promising. It is important to recognize the potential of these current regimens and minimize the emergence of resistant HCV. Avoidance of development of drug resistant virus is best achieved by using HCV regimens that incorporate agents with different mechanisms of action. Some strides have been made in accessibility and affordability, but there remains a large proportion of HCV-infected patients for which treatment needs to be made available prior to disease progression. Finally, there needs to be continued screening and education to reduce the prevalence.

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