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Retreatment Options Following HCV Direct Acting Antiviral Failure

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OPINION STATEMENT

Despite the excellent efficacy of direct acting antivirals (DAA) for hepatitis C virus (HCV), treatment failures do occur. Until recently, retreatment decisions after DAA failure were influenced by the number of available agents, concerns about HCV drug resistance, and lack of data regarding retreatment. Recommended treatment approaches previously depended on limited clinical trials and expert opinion. In this article, we review the current state of the evidence for HCV retreatment after DAA failure. Based on recent clinical trial data, most patients who fail HCV treatment with DAA agents now have excellent retreatment options. While some patients may benefit from resistance testing after DAA therapy failure to select the optimal treatment and duration, newly approved salvage therapies are not significantly impacted by common mutations and have been approved by the Food and Drug Administration for HCV retreatment without regard for the presence of resistance associated substitutions. While prior retreatment efforts were limited to longer courses of therapy, the addition of ribavirin, or novel combinations of approved therapies based on expert guidance, current DAA options make HCV retreatment in the DAA era more streamlined and evidence-based.

Keywords

Direct acting antiviral (DAA); Hepatitis C virus (HCV); Relapse; Retreatment; Treatment

INTRODUCTION

Direct acting antiviral (DAA) treatment of hepatitis C virus (HCV) results in high rates of sustained virologic response (SVR). For the small number of patients failing DAA treatment, there has been limited data to guide retreatment. Until recently, no available agent was approved by the Food and Drug Administration (FDA) in this population.[1] Due to limited data and retreatment options, the AASLD/IDSA Guidelines previously recommended deferral of retreatment in many cases unless the need to retreat was urgent.[2]

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COMPLIANCE WITH ETHICS GUIDELINES

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors. Dr. Naggie co-chairs the current HCV Guidance Panel AASLD/IDSA committee responsible for HCV guideline recommendations.

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Reasons for DAA failure have been linked to host, virus, and treatment factors.[3] The best strategies to address these factors have yet to be determined.[1, 3–5]

While current treatment regimens have high efficacy, the need for retreatment strategies persists. As more persons with HCV are treated with DAAs, treatment failures inevitably occur and salvage options remain an important priority. In this review, we discuss the current regimens recommended for retreatment as well as the data supporting retreatment strategies after DAA failure. (Tables 1 and 2)

CURRENT STRATEGIES FOR RETREATMENT

Retreatment of Genotype 1 After DAA Failure

NS3/4A Protease Inhibitor plus Pegylated Interferon plus Ribavirin Failures— First generation nonstructural protein (NS) 3/4A protease inhibitors (PI) boceprevir (BOC) and telaprevir (TPV) were the first DAAs to be FDA approved, substantially increasing SVR rates when combined with pegylated interferon (peg-IFN) and ribavirin (RBV) in genotype (GT) 1 infection as compared to the historical standard of care.[6] Multiple retreatment strategies exist for this patient population based on clinical trial data.

Ledipasvir/sofosbuvir: Ledipasvir (LDV), a NS5A inhibitor, in combination with sofosbuvir (SOF), a first in class NS5B polymerase inhibitor, with or without RBV, has been evaluated as a retreatment regimen after first generation NS3/4A PI failures.[7] The largest trial, ION-2, was a phase 3 study that included patients infected with HCV GT1 who had failed peg-IFN plus RBV with or without a first generation PI.[8] Two hundred and eleven study participants (52%) had previously failed a PI-based DAA regimen. Patients were treated with multiple LDV/SOF durations with or without RBV. SVR rates were 94–100% across all arms. Although the 12-week regimen had the lowest SVR rate, this was primarily driven by failures in patients with cirrhosis and/or baseline NS5A resistance associated substitutions (RASs). Out of the 11 relapses observed after retreatment with LDV/SOF with or without RBV, six had baseline NS5A RASs prior to retreatment with LDV/SOF. All patients who failed this retreatment regimen had NS5A RASs after relapse. Two smaller phase 2 studies using LDV/SOF with or without RBV for retreatment in this population reported similar SVR rates.[9, 10]

Reddy et al performed a post-hoc integrated safety and efficacy analysis on seven trials (including the above three cited trials) evaluating LDV/SOF in treatment naïve and treatment-experienced patients with cirrhosis.[11] In the analysis, 240 patients (47%) had failed an HCV regimen containing a first generation PI. An overall SVR12 rate of 96% (230/240) was reported for all PI-experienced patients after retreatment with LDV/SOF with or without RBV. However, SVR12 rates were lower in treatment-experienced patients retreated with LDV/SOF without RBV for only 12 weeks (90%), suggesting that extending treatment duration to 24 weeks or adding RBV to the shortened 12-week duration may be beneficial, particularly in treatment experienced patients with cirrhosis. Also, SVR12 rates were lower among participants treated with LDV/SOF without RBV for 12 and 24 weeks (SVR12 88% and 85%, respectively) who had baseline NS5A resistance as compared to LDV/SOV + RBV for 12 or 24 weeks (SVR12 94% and 100%, respectively). This suggested

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that the impact of NS5A RASs is greater when other negative baseline predictors, such as prior treatment failure, are present.

Elbasvir/grazoprevir: Retreatment strategies of first generation NS3/4A PI failures with a second generation NS3/4A PI have also been studied. Grazoprevir (GZP), a next-generation NS3/4A PI that maintains *in vitro* activity against many treatment-emergent first generation PI RASs, has been combined with elbasvir (EBR), a NS5A inhibitor, in a fixed dose combination.[12] This combination regimen plus RBV achieved an SVR24 rate of 96% (76/79) when used for retreatment of first generation PI failures.[13, 14] Though small in number, six of the eight patients (75%) with baseline NS5A RASs and four of the six patients (66.7%) with both NS3 and NS5A RASs achieved SVR12, suggesting a role for NS5A RASs in relapse. The impact of NS5A RASs was primarily noted in patients with genotype 1a infection; thus, NS5A RAS testing is recommended prior to use of this regimen in genotype 1a infection, and extension to 16 weeks should be considered to optimize retreatment response. This regimen is contraindicated in patients with decompensated cirrhosis (Child Pugh B or C liver disease).[12]

Sofosbuvir/velpatasvir: SOF in combination with velpatasvir (VEL), a NS5A inhibitor, has also been evaluated in patients infected with HCV GT1 who previously failed peg-IFN plus RBV plus a first generation NS3/4A PI.[15] Pianko et al included 111 patients who received VEL at a dose of 25 mg or 100 mg in combination with SOF with or without RBV for 12 weeks.[16] SVR12 rates were 96–100% across all arms, with a 100% (27/27) SVR12 rate in the treatment arm containing the VEL dose (100 mg) approved by the FDA. The subsequent phase 3 ASTRAL-1 study, which evaluated SOF/VEL for 12 weeks, included 56 patients with prior PI failure, all of whom (100%; 56/56) achieved SVR12.[17] While the number of PI-experienced patients with baseline NS5A resistance testing was not reported, 255 of the 257 participants with baseline NS5A resistance achieved SVR12.

Glecaprevir/pibrentasvir: Co-formulated glecaprevir (GLE; NS3/4A inhibitor) and pibrentasvir (PIB; NS5A inhibitor) are two agents that were recently FDA approved for pangenotypic treatment of HCV in treatment naïve adults with or without cirrhosis as well as for retreatment in select cases.[18] GLE/PIB's efficacy in retreatment after DAA failure was demonstrated by the phase 2 MAGELLAN-1 study.[19] GLE/PIB at various doses with and without RBV for 12 weeks was studied in 50 HCV GT1 infected patients without cirrhosis who had previously failed DAA therapy. Twenty-five had prior PI exposure in combination with peg-IFN and/or SOF; of these patients, 92% (23/25) achieved SVR12. Additionally, this regimen was studied further in MAGELLAN-1, Part 2.[20] This study evaluated patients infected with GT1 or GT4 who had failed a NS3/4A PI and/or a NS5A inhibitor. Patients were treated with GLE/PIB for 12 or 16 weeks. Twenty-seven patients had previously failed a NS3/4A PI without a NS5A inhibitor. All patients (100%; 27/27) achieved SVR12. Thus, GLE/PIB for 12 weeks is recommended for GT1 patients who previously failed a NS3/4A inhibitor. This regimen is contraindicated in patients with decompensated cirrhosis (Child Pugh B or C liver disease).[18]

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Current Retreatment Recommendations: While a number of retreatment strategies have been studied in patients failing IFN-based regimens containing a first generation PI, the four regimens reviewed above have the strongest evidence to support their use in this population. Three of these regimens (LDV/SOF, SOF/VEL, and GLE/PIB) are recommended for GT1 retreatment in patients without cirrhosis, while two (SOF/VEL and GLE/PIB) are recommended for GT1 retreatment in patients with cirrhosis. In patients with cirrhosis, LDV/SOF is an alternative GT1 retreatment regimen due to the recommendation to add RBV to optimize treatment outcomes. EBV/GZP is an alternative GT1 retreatment regimen in patients with or without cirrhosis due to the recommendation to add RBV regardless of fibrosis status to optimize treatment outcomes.[2]

Non-NS5A Inhibitor, Sofosbuvir-containing DAA Regimen Failure

Sofosbuvir/velpatasvir/voxilaprevir: The combination of SOF, VEL, and voxilaprevir (VOX), a NS3/4A protease inhibitor, was FDA approved for retreatment of GT1-6 after failure of a HCV regimen containing an NS5A inhibitor as well as for retreatment of GT1a and GT3 after failure of a HCV regimen containing SOF without an NS5A inhibitor.[21] The POLARIS-4 trial evaluated the efficacy of this combination for retreatment in patients infected with GT1-4 who had failed a prior non-NS5A DAA regimen.[22] Patients were excluded if their only DAA exposure was a NS3/4A inhibitor; as such, the majority of patients were treated with a SOF-based regimen in combination with peg-IFN, RBV, and/or simeprevir (SMV), a second generation NS3/4A protease inhibitor. Among prior DAA failures, 69% of patients were previously exposed to SOF plus RBV with or without peg-IFN, and 11% were exposed to SOF plus SMV. Patients were retreated with either SOF/VEL or SOF/VEL/VOX for 12 weeks. Patients receiving SOF/VEL/VOX for 12 weeks had a numerically higher SVR12 rate of 98% overall compared to 90% in the SOF/VEL arm, and the SOF/VEL/VOX arm was the only intervention to meet the prespecified efficacy (SVR12) threshold of 85%. Of note, of the four patients who did not achieve SVR12 in the SOF/VEL/VOX arm, two withdrew consent after starting the trial and one was lost to follow-up. The single relapse in this arm did not develop treatment emergent RASs. Of the 15 virologic failures (14 relapses), five occurred with GT1a, one occurred with GT1b, one occurred with GT2, and eight occurred with GT3. Across the study, baseline RASs did not impact SVR12 in patients receiving SOF/VEL/VOX, as 100% of patients with baseline RASs achieved SVR12. Thus, the study results suggested that SOF/VEL/VOX offers the most benefit over SOF/VEL in GT1a patients where RASs have appeared to impact treatment outcomes. Thus, SOV/VEL/VOX may be most useful in GT1a patients who previously failed non-NS5A inhibitor, sofosbuvir-containing regimens. This regimen is contraindicated in patients with decompensated cirrhosis (Child Pugh B or C liver disease).[21]

Sofosbuvir/velpatasvir: As noted above, the POLARIS-4 study randomized patients who had previously failed non-NS5A inhibitor-based DAA regimens to either SOF/VEL or SOF/VEL/VOX for 12 weeks.[22] Patients receiving SOF/VEL/VOX for 12 weeks had a numerically higher SVR12 rate as compared to SOF/VEL, and SOF/VEL/VOX was the only arm to meet the prespecified efficacy (SVR12) threshold of 85%. However, the relapses in the SOF/VEL arm primarily occurred in patients with GT1a or GT3 infection. For GT1b

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infection, the SVR12 rate with SOV/VEL (95%) was comparable to the SVR12 rate with SOF/VEL/VOX (96%). Based on this study, SOF/VEL for 12 weeks is a recommended retreatment option in this GT1b patient population.

Glecaprevir/pibrentasvir: There is limited data about the GLE/PIB regimen in prior non-NS5A inhibitor, SOF-containing regimen failures. The EXPEDITION-1 study evaluated GLE/PIB for 12 weeks in GT1 infected patients with cirrhosis and 11 patients had previously failed a SOF + RBV regimen with or without peg-IFN.[23] The ENDURANCE-1 study evaluated 8 versus 12 weeks of GLE/PIB in patients without cirrhosis, but only 3 patients had previously failed a non-NS5A inhibitor, sofosbuvir-containing regimen.[24] Lastly, GLE/PIB for 12 weeks was evaluated in NS3/4A PI failures in the MAGELLAN-1 trial, which included SMV plus SOF failures.[19] All together these studies represent a small number patients (likely less than 20) who failed a non-NS5A inhibitor, sofosbuvir-containing regimen and were retreated with GLE/PIB for 12 weeks; however, the observed SVR rate in this small group was >90%. Although the FDA recommendation includes a short 8-week duration for GLE/PIB in GT1a patients who have failed a regimen of SOF plus RBV with or without IFN, this is supported by few observations and thus is not recommended until further data is available.[2] However, GLE/PIB for 12 weeks for other DAA failures is supported by larger numbers of patient outcomes and thus is recommended for this retreatment population, regardless of the presence of cirrhosis (provided that it is compensated).[2]

Current Retreatment Recommendations: SOF/VEL/VOX, SOF/VEL, and GLE/PIB provide fixed-dose combinations for 12-week courses of therapy. Furthermore, the recommendations for these regimens are the same regardless of presence of cirrhosis, although two of the regimens are contraindicated in patients with decompensated cirrhosis. GLE/PIB may be used regardless of GT1 subtype, while SOF/VEL/VOX is recommended in GT1a and SOF/VEL in GT1b. In patients without cirrhosis, LDV/SOF with RBV is considered an alternative regimen, but the need for RBV will likely limit its usage now that multiple other options are available; thus, the data supporting this recommendation are not reviewed here.[2]

NS5A Inhibitor DAA Failures

Sofosbuvir/velpatasvir/voxilaprevir: The recent approval of SOF/VEL/VOX has particularly impacted the landscape of HCV retreatment after for those who have failed a prior NS5A inhibitor-based regimen. The phase 3 POLARIS-1 trial compared SOF/VEL/VOX for 12 weeks to placebo in patients with GT1-6 infection who had previously failed a HCV regimen containing an NS5A inhibitor.[22] Overall, 96% of patients retreated with SOF/VEL/VOX achieved SVR12. Across the entire SOF/VEL/VOX arm (N=263), there was 1 virologic breakthrough and 6 relapses. Of those infected with GT1a, 96% (97/101) achieved SVR12. Of those infected with GT1b, 100% (45/45) achieved SVR12. Among all patients retreated regardless of genotype, baseline RASs did not significantly impact SVR12 rates, as 97% of patients with RASs and 98% without RASs achieved SVR12. Based on this data as well as the accompanying POLARIS-4 trial, SOF/VEL/VOX was approved for retreatment of HCV GT1-6 infections after failing a prior

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NS5A regimen.[21] This is the only recommended regimen for the retreatment of this particular patient population.

Glecaprevir/pibrentasvir: The GLE/PIB regimen was also approved by the FDA for the retreatment of HCV GT1 after failing a prior NS5A inhibitor regimen, provided that the prior treatment regimen did not include an NS3/4 protease inhibitor.[18] This approval and specificity to the type of prior DAA regimen was based on the MAGELLAN-1 study, which included 42 GT1 infected patients who had previously failed combination DAA therapy.[19] Seventeen patients failed a NS5A inhibitor based regimen that did not include a NS3/4 protease inhibitor. These patients were treated with GLE/PIB for 16 weeks, and 94% (16/17) achieved SVR12. The single patient with failure had an on-treatment viral breakthrough. The MAGELLAN-1, Part 2 study further studied this population.[20] Thirty patients who had previously been exposed to an NS5A inhibitor or had previously been exposed to both an NS5A inhibitor and an NS3/4A inhibitor were retreated with GLE/PIB for 12 weeks. Thirty-four patients who had previously been exposed to an NS5A inhibitor or had previously been exposed to both an NS5A inhibitor and an NS3/4A inhibitor were retreated with GLE/PIB for 12 weeks. Nearly all of these patients were GT1; only four GT4 patients were included in this study. In the 12-week retreatment arm, 83% (25/30) of those previously exposed to an NS5A inhibitor with or without an NS3/4A PI achieved SVR12. In the 16-week retreatment arm, 88% (30/34) of those previously exposed to an NS5A inhibitor with or without an NS3/4A PI achieved SVR12. Due to the limited data supporting its use, this regimen is recommended as an alternative therapy for retreatment in this population and is expected to primarily be used in patients who cannot tolerate SOF/VEL/VOX.

Current Retreatment Recommendations: SOF/VEL/VOX is approved based on Phase 3 registration trials, and thus it is the sole recommended regimen for this difficult to treat population. Twelve weeks of therapy is sufficient, as cirrhosis was well represented in supporting trials and since cirrhosis does not appear to impact the SVR rate in GT1 infection. GLE/PIB's approval for NS5A salvage has a smaller scope, excluding patients who failed a combination regimen including both a NS5A inhibitor and a NS3/4A PI. This was based on higher relapse in patients exposed to both drug classes. Thus, this regimen is an alternative regimen for NS5A salvage within the same limited scope as the FDA approval. While there are other small pilot studies of other salvage regimens, these are off label, supported by small numbers of patients, and are no longer discussed in detail in the AASLD/IDSA Guidance.

Retreatment of Genotype 2 After DAA Failure

Sofosbuvir/velpatasvir—The first DAA standard of care for GT2 therapy was SOF plus RBV (with peg-IFN in select cases). Use of other DAA combination regimens for GT2 infection was uncommon, usually because it was unnecessary. More recently, SOF/VEL has become the recommended treatment for GT2 infection in both treatment naïve and treatment experienced patients. The Phase 3 registration trial for SOF/VEL excluded SOF failures because the comparator arms in the ASTRAL-2 trial was SOF plus RBV.[25] No GT2 infected patient failed the SOF/VEL therapy in ASTRAL-2, making SOF/VEL the preferred regimen for GT2 infection upon its approval. The phase 3 registration trial for SOF/VEL/

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VOX, POLARIS-4, randomized patients who previously failed non-NS5A inhibitor DAA regimens to either SOF/VEL or SOF/VEL/VOX for 12 weeks.[22] Among patients with GT2 infection, 97% (32/33) who received SOF/VEL for 12 weeks achieved SVR12. While the number of GT2 patients who previously failed a SOF-containing regimen is not clear, it is most likely that the majority of the GT2 study participants had previously failed a SOF-containing regimen. This study supported the efficacy and safety of SOF/VEL for GT2 infection, including for SOF treatment failures, and it demonstrated no clear benefit in adding VOX to SOF/VEL.

Glecaprevir/pibrentasvir—GLE/PIB has limited data to support use in GT2 infected patients who have failed prior DAA regimens. The phase 3, randomized, placebo-controlled ENDURANCE-2 study enrolled treatment-naive and treatment-experienced GT2 infected patients without cirrhosis to treatment with either GLE/PIB for 12 week or a placebo study arm.[26] Of the 61 treatment-experienced patients, six had previously failed a SOF-based regimen, and all (100%; 6/6) achieved SVR12. In addition, the phase 3 EXPEDITION-1 study enrolled patients with cirrhosis across multiple genotypes (including 31 patients infected with HCV GT2) to GLE/PIB for 12 weeks.[23] Within the overall study, 36 patients were treatment experienced, 11 of which were SOF failures. All patients with GT2 achieved SVR12 in the intention-to-treat analysis. The only study to evaluate GLE/PIB for 8 weeks in GT2 infection was the phase 2 SURVEYOR study, and no sofosbuvir failures were included; thus, there is no data to support the 8-week regimen for retreatment of GT2 infection.[27] However, GLE/PIB for 12 weeks is highly efficacious across multiple genotypes and treatment failure groups; for this reason, it is a recommended regimen for HCV-infected GT2 patients who previously failed a SOF-containing DAA regimen.

Current Retreatment Recommendations—The recommendation for retreatment of GT2 infected patients who have failed prior SOF-containing regimens includes SOF/VEL as well as GLE/PIB, both for 12 weeks of therapy, regardless whether cirrhosis is present. Based on the POLARIS-4 data, there does not appear to be a benefit in adding VOX to SOF/VEL. Furthermore, there is not sufficient data to support an 8-week regimen in this patient population at this time.[2]

Retreatment of Genotype 3 After DAA Failure

Sofosbuvir/velpatasvir/voxilaprevir—Infection with HCV GT3 has been identified as the most difficult to treat successfully in the DAA era. SOF/VEL/VOX has demonstrated efficacy in other difficult to treat groups, such as GT1 infection that have failed NS5A inhibitor DAA therapy. The phase 2 program of SOF/VEL/VOX included 35 patients infected with GT3, 17 of which had failed a prior DAA regimen. Among all GT3 patients in this study treated with SOF/VEL/VOX (including both treatment naïve and treatment experienced), 97% (34/35) achieved SVR12, with the single relapse being a patient with GT3 infection, cirrhosis, and a Y93H mutation. [28] In the POLARIS-1 and POLARIS-4 trials, 74/78 (95%) and 52/54 (96%) of GT3 infected patients receiving SOF/VEL/VOX for 12 weeks achieved SVR12, respectively.[22] In the POLARIS-1 trial, all four patients who had GT3 and failed SOF/VEL/VOX had cirrhosis. The patients in these studies represent

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some of the most difficult to treat patients with poor treatment prognostic factors including GT3 infection, cirrhosis, and prior treatment failure after DAA regimens.

Glecaprevir/pibrentasvir—The role of GLE/PIB for the retreatment of GT3 infection is under ongoing study. SURVEYOR-II, Part 3 is phase 3 study evaluating GLE/PIB in GT3 infected patients who are treatment naïve with cirrhosis or treatment experienced with or without cirrhosis.[29] This study included patients who had been treated with SOF plus RBV with or without peg-IFN but excluded DAA regimens that were not SOF-based. Forty-two patients who had previously failed SOF plus RBV with or without peg-IFN were included in treatment arms including GLE/PIB for 12 or 16 weeks. Though specific outcomes in these SOF-experienced patients are not available, 96% (87/91) of treatment experienced patients achieved SVR12. Among these five treatment failures, one had baseline PI resistance, and one additional patient developed PI RASs. Among these same five treatment failures, three had baseline NS5A resistance, and all five had evidence of NS5A RASs after failure. Further study of this regimen is ongoing.

Current Retreatment Recommendations—SOF/VEL/VOX for 12 weeks is the currently recommended regimen for the treatment of GT3 after prior DAA failure, including failure with prior NS5A inhibitor-based regimens. Due to concerns that GT3, DAA-experienced patients with cirrhosis remain at high risk for relapse, there may be benefit in adding RBV to optimize response rates.

Retreatment of Genotypes 4, 5, and 6 after DAA Failure

Previously, the AASLD/IDSA Guidance Panel have not provided recommendations on retreatment strategies in patients with HCV GT4-6 who have previously failed DAA therapy. These genotypes are less common in the United States and Europe, and prior DAA regimens have had high efficacy rates in these populations.[17, 30–33] Furthermore, there has been minimal data to help guide retreatment in this population. With the approval of SOF/VEL/VOX and GLE/PIB, there are now retreatment options for these genotypes. In the POLARIS-1 and POLARIS-4 trials, 41 patients infected with GT4, 1 patient infected with GT5, and 6 patients infected with GT6 were enrolled to receive SOF/VEL/VOX for 12 weeks.[22] Of the 41 infected with GT4, 95% (39/41) achieved SVR12, while the single GT5 (100%; 1/1) and all six GT6 patients (6/6; 100%) achieved SVR12 with retreatment. While retreatment studies utilizing GLE/PIB have sought to enroll patients with multiple genotypes, there have been few patients with GT4, 5, or 6. For example, the MAGELLAN-1, Part 2 study only enrolled 4 patients with GT4 and none with GT5 or GT6.[20] GLE/PIB has minimal data to support use in DAA failures in GT4, 5 and 6; further study is ongoing.

Current Retreatment Recommendations—Based on currently available data, SOF/VEL/VOX is the recommended regimen for retreatment of GT4-6. As future data becomes available, additional agents may be recommended in the future.

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Retreatment of Mixed Genotypes after DAA Failure

A paucity of data is available on patients with mixed genotypes requiring retreatment after relapse. The AASLD/IDSA Guidance Panel have recommended using a pangenotypic regimen and obtaining expert guidance in these situation.[2]

SPECIFIC POPULATIONS

The emergence of new HCV treatment options has altered the retreatment approach among many specific populations. In the DAA era, HIV/HCV co-infected individuals have clinical outcomes similar to HCV mono-infected individuals. As such, these populations are treated similarly. HIV/HCV co-infected individuals should be retreated as if they were HCV mono-infected, though with special attention to drug-drug interactions between HCV DAAs and HIV antiretroviral therapy. HCV-infected individuals with severe renal dysfunction, end stage renal disease, or on renal replacement therapy may be retreated with regimens that have demonstrated efficacy for retreatment but are also safe in those with severe renal dysfunction, including EBV/GZP and GLE/PIB. Those with decompensated cirrhosis may be treated and/or retreated with regimens found to be safe in these populations; SOF/VEL is a regimen that is currently recommended for use in this population, and it is an appropriate choice for retreatment for some clinical situations as noted above. Of note, PI-based regimens should be avoided in patients with decompensated cirrhosis as noted previously. Patients with recurrent HCV after liver transplantation require an individualized treatment plan to address the appropriate choice of therapy and to mitigate drug-drug interactions. Additional recommendations regarding retreatment as well as treatment and retreatment of specific populations is available in the AASLD/IDSA guidelines.[2, 34]

CONCLUSION

A number of retreatment strategies have been described in patients who have previously failed DAA therapies. While previously data was only available for retreatment after first generation NS3/4A PI failures, many trials now address retreatment outcomes among those who relapsed after second generation NS3/4A PI, NS5A inhibitor, and other DAA combinations. Recently approved DAA regimens have demonstrated high SVR rates when used for HCV retreatment regardless of genotype, cirrhosis status, RASs, or prior retreatment regimen. While those who have failed DAA therapy remain a challenging population to treat, providers have new pharmaceutical tools as well as frequently updated guidance from the AASLD/IDSA when considering retreatment after DAA failure.

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Conflict of Interest

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Table 1

HCV DAA Regimens Recommended for Retreatment After Prior DAA Treatment Failure [2]

Regimen	DAA Type	Retreatment Recommendation	Pharmacologic Considerations
Elbasvir/grazoprevir (EBV/GZP) [12]	NS5A inhibitor NS3/4A protease inhibitor	GT1 after NS3/4A PI plus peg-IFN plus RBV[#]	Indicated for GT1 Contraindicated in decompensated cirrhosis (Child Pugh Class B and C) Safe for use in patients with severe renal dysfunction
Glecaprevir/pibrentasvir (GLE/PIB) [18]	NS3/4A protease inhibitor NS5A inhibitor	GT1 after NS3/4A PI plus peg-IFN plus RBV GT1 after SOF-based without NS5A inhibitor GT1 after NS5A inhibitor with or without SOF[$] GT2 after SOF-containing regimen	Pangenotypic Contraindicated in decompensated cirrhosis (Child Pugh Class B and C) Safe for use in patients with severe renal dysfunction
Ledipasvir/sofosbuvir (LDV/SOF) [7]	NS5A inhibitor NS5B polymerase inhibitor	GT1 after NS3/4A PI plus peg-IFN plus RBV[%] GT1 after SOF-based without NS5A inhibitor[&]	Indicated for GT 1, 4, 5, and 6 May require RBV to optimize SVR rates in some groups
Sofosbuvir/velpatasvir (SOF/VEL) [15]	NS5B polymerase inhibitor NS5A inhibitor	GT1 after NS3/4A PI plus peg-IFN plus RBV GT1b after SOF-based without NS5A inhibitor GT2 after SOF-containing regimen	Pangenotypic May be used for treatment in decompensated cirrhosis
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) [21]	NS5B polymerase inhibitor NS5A inhibitor NS3/4A protease inhibitor	GT1a after SOF-based without NS5A inhibitor GT1 after NS5A inhibitor with or without PI or SOF GT3 after prior DAA failure	Pangenotypic Contraindicated in decompensated cirrhosis (Child Pugh Class B and C)

Abbreviations:
EBV= elbasvir; GLE= glecaprevir; GT= genotype; GZR= grazoprevir; LDV= ledipasvir; NS= nonstructural protein; Peg-IFN: pegylated interferon; PI= Protease Inhibitor; PIB= pibrentasvir; RBV= ribavirin; SOF= sofosbuvir; VEL= velpatasvir; VOX= voxilaprevir.

[#]Alternative in patients without and with cirrhosis due to need for RBV

[$]Excludes patients previously treated with NS5A inhibitor and NS3/4A PI in combination

[%]Recommended in patients without cirrhosis but alternative in patients with cirrhosis due to need for RBV.

[&]Alternative in patients without cirrhosis due to need for RBV. Not recommended nor alternative for patients with cirrhosis.

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Table 2

Selected Clinical Trials of HCV Retreatment After DAA Failure

Study	Genotypes Included	Prior DAA Treatment Failure Included	Retreatment Regimen Studied	SVR12[#]
ION-2 [8]	1	NS3/4A PI plus peg-IFN plus RBV	LDV/SOF +/− RBV for 12−24 weeks	94–100%
LONESTAR [9]	1	NS3/4A PI plus peg-IFN plus RBV	LDV/SOF +/− RBC × 12 weeks	95–100%
SIRIUS [10]	1	NS3/4A PI plus peg-IFN plus RBV	LDV/SOF +/− RBV × 12−24 weeks	96–97%
C-SALVAGE [13, 14]	1	NS3/4A PI plus peg-IFN plus RBV	GZR/EBV + RBV × 12 weeks	96%
Clinical Trial NCT01909804 [16]	1 and 3	NS3/4A PI plus peg-IFN plus RBV	SOF/VEL +/− RBV × 12 weeks[$]	96–100%
ASTRAL-1 [17]	1, 2, 4, 5, and 6	NS3/4A PI plus peg-IFN plus RBV	SOF/VEL × 12 weeks	100%
MAGELLAN-1 [19]	1	NS3/4A PI plus peg-IFN plus RBV	GLE/PIB +/− RBV[%] × 12 weeks	92%
		SOF-based without NS5A inhibitor		
		NS5A inhibitor with or without PI or SOF		
MAGELLAN-1, Part 2 [20]	1 and 4	NS3/4A PI plus peg-IFN plus RBV	GLE/PIB × 12−16 weeks	79–100%
		NS5A inhibitor with or without PI or SOF		
POLARIS-4 [22]	1, 2, 3, and 4	SOF-based without NS5A inhibitor	SOF/VEL × 12 weeks	90%
		NS5A inhibitor with or without PI or SOF	SOF/VEL/VOX × 12 weeks	98%
EXPEDITION-1 [23]	1,2,4,5 and 6	SOF-based without NS5A inhibitor	GLE/PIB × 12 weeks	99%
ENDURANCE-1 [24]	1	SOF-based without NS5A inhibitor	GLE/PIB × 8−12 weeks	99–100%
POLARIS-1 [22]	1	NS5A inhibitor with or without PI or SOF	SOF/VEL/VOX × 12 weeks	96%
ASTRAL-2 [25]	2	SOF-based without NS5A inhibitor	SOF/VEL × 12 weeks	99%
ENDURANCE-2 [26]	2	SOF-based without NS5A inhibitor	GLE/PIB × 12 weeks	99%
SURVEYOR-II, Part 3 [29]	3	SOF-based without NS5A inhibitor	GLE/PIB × 122013;16 weeks	96%

Abbreviations:
EBV= elbasvir; GLE= glecaprevir; GZR= grazoprevir; LDV= ledipasvir; NS= nonstructural protein; Peg-IFN: pegylated interferon; PI= Protease Inhibitor; PIB= pibrentasvir; RBV= ribavirin; SOF= sofosbuvir; VEL= velpatasvir; VOX= voxilaprevir.

[#]Some studies included treatment naïve or non-DAA treatment experienced arms. SVR rates reported reflect DAA failure retreatment only when possible.

[$]Variable doses of VEL were used.

[%]Variable doses of GLE and PIB were used.