Report

# Hepatitis C Virus Infection among Hematopoietic Cell Transplant Donors and Recipients: American Society for Blood and Marrow Transplantation Task Force Recommendations

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## INTRODUCTION

In recent years, management of hepatitis C virus (HCV) infection has changed dramatically because of the approval of new antiviral therapies. The purpose of the American Society for Blood and Marrow Transplantation (ASBMT) Task Force on HCV infection in hematopoietic cell transplant (HCT) recipients is to provide guidance regarding diagnosis and management of HCV infection in donors and recipients of hematopoietic cells.

Limited data are available on treating HCV infection in HCT recipients. A group of experts in infectious diseases, hepatology, and HCT worked together to compile this document with 2 goals: to summarize the currently available data in the field and to provide evidence-based and expert opinion recommendations regarding early identification and treatment of HCV-infected donors and recipients to minimize barriers to HCT and improve care and outcomes in this population. In preparing this report, the committee recognizes that in the absence of data in donors and recipients

of hematopoietic cells, clinicians would benefit from preliminary guidance while awaiting the completion of appropriate studies.

The recommendations herein are based on synthesis of limited evidence, theoretical rationales, practical considerations, and author opinion. When appropriate, the level of the evidence and the strength of the recommendation have been rated by applying the system used for the Hepatitis C Guidance of the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) (http://hcvguidelines.org) (Table 1) [1]. However, for some individual recommendations, the level of the supporting evidence and strength of the recommendation could not be rated.

For this report, HCT is defined as transplant of any blood- or marrow-derived hematopoietic progenitor cells, regardless of whether the transplant is allogeneic or autologous and regardless of the cell source (ie, bone marrow, peripheral blood, or umbilical cord blood). The recommendations in this document are based on data from the following sources: research published in the peer-reviewed literature or presented at major national and international scientific conferences, safety warnings from the US Food and Drug Administration (FDA) or other regulatory agencies or from manufacturers, drug interaction data, and prescribing information for FDA-approved products.

**Table 1**
Grading System used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

| Classification | Description |
| --- | --- |
| Class I | Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective |
| Class II | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment |
| Class IIa | Weight of evidence and/or opinion is in favor of usefulness and efficacy |
| Class IIb | Usefulness and efficacy are less well established by evidence and/or opinion |
| Class III | Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful |
| Level of Evidence | Description |
| Level A* | Data derived from multiple randomized clinical trials, meta-analyses, or equivalent |
| Level B* | Data derived from a single randomized trial, nonrandomized studies, or equivalent |
| Level C | Consensus opinion of experts, case studies, or standard of care |

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (I, II, or III) that represents the level of the evidence that supports the recommendation and a letter (A, B, or C) that represents the strength of the recommendation.

\* In some situations, such as for IFN-sparing HCV treatments, randomized clinical trials with an existing standard-of-care arm cannot ethically or practically be conducted. The FDA has suggested alternative study designs, including historical control subject or immediate versus deferred, placebo-controlled trials. For additional examples and definitions see the FDA link (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf). In those instances for which there was a single predetermined, FDA-approved equivalency established, panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B. Adapted from the American College of Cardiology and the American Heart Association Practice Guidelines. (American Heart Association, 2011); (Shiffman, 2003)

Literature searches were conducted using medical subject headings and free text terms combined to maximize retrieval of relevant citations from the PubMed, Scopus, EMBASE, and Web of Science databases; search terms included "HCV and Bone Marrow Cell Transplantation" and "HCV and Hematopoietic Stem Cell Transplantation." Only articles published in English from 1990 to the present were considered for inclusion. The ASBMT Task Force on HCV Infection plans to review these recommendations periodically and update them to include advances in the published evidence.

**EXECUTIVE SUMMARY**

For more than a decade the mainstay of treatment for HCV infection was a combination regimen of pegylated interferon (IFN) and ribavirin, but this regimen was associated with a poor rate of sustained virologic response (SVR) and poor tolerability, especially in cancer patients and HCT recipients [2,3]. Furthermore, almost 30% of infected HCT recipients could not be treated with pegylated IFN and ribavirin because of contraindications to the treatment combination [3]. The management of HCV infection in the general population has recently changed as a result of FDA approval of several direct-acting antiviral agents (DAAs), which have rendered IFN-containing regimens obsolete for almost all HCV genotypes.

This report, developed by the ASBMT Task Force on HCV Infection, is specifically devoted to diagnosis and management of HCV infection in donors and HCT candidates and recipients. There are few data that answer important clinical questions for such donors or recipients. The online document from the AASLD-IDSA, "Recommendations for Testing, Managing, and Treating Hepatitis C" (http://www.hcvguidelines.org), which is updated regularly throughout the year, was used as a resource in the development of this report but had no specific recommendations for these populations. Thus, this document was developed to provide expert opinion for clinicians who must make management decisions while awaiting adequately powered trials dealing with donors and HCT recipients.

Evidence is summarized, and, where possible, recommendations are provided. This report replaces the 2009 ASBMT-IDSA guideline [4]. Several topics are new or expanded from that document (Table 2).

**NATURAL HISTORY OF HCV INFECTION IN HCT RECIPIENTS**
**George B. McDonald, Marcos De Lima**
*Recommendations*

- In all HCT survivors with active HCV infection, cofactors that can lead to fibrosis should be addressed. Patients should be counseled to avoid excessive weight gain, ethanol and medications or herbal supplements that are hepatotoxic, as well as on treatment of other causes of liver disease (nonalcoholic fatty liver disease, hepatitis B virus, HIV, and extrahepatic obstruction) (class I, level C), and mobilization of excess iron (class II, level C).

- All HCV-infected long-term HCT survivors should be evaluated for progression of liver disease every 6 to 12 months with a hepatic function panel, complete blood cell count, and evaluation of prothrombin time/international normalized ratio (class I, level C). If fibrosis is suspected in long-term HCT survivors, noninvasive tests such as serologic panels and transient elastography can be used to evaluate for the presence of advanced fibrosis (Scoring System for Histological Stage Metavir score $\geq$ F3) and cirrhosis (Metavir score F4).

- HCV-infected HCT recipients should be vaccinated against hepatitis A virus and hepatitis B virus following HCT immunization protocols [4].

- Donors and HCT candidates with HCV infection should be counseled to use appropriate precautions to prevent transmission of HCV to others (class I, level C).

- For HCV-infected HCT long-term survivors with advanced fibrosis (Metavir score $\geq$ F3), surveillance for hepatocellular carcinoma (HCC) with ultrasonography every 6 months is recommended (class I, level C). For patients with cirrhosis, endoscopic surveillance for esophageal varices is recommended (class I, level A).

- HCT recipients who develop end-stage liver disease can be considered for liver transplant; in rare cases, a living donor liver transplant from the original hematopoietic cell donor may be feasible (class I, level C).

**Table 2**
Summary of Changes Compared with the Guidelines Published in 2009 [4]

| Major Change | Starting Page |
| --- | --- |
| Updated background on natural history of HCV infection in HCT recipients | 2 |
| New recommendations regarding HCV screening: | |
|   1. Screening of all hematopoietic cell donors within 30 days before cell harvest with FDA-approved HCV antibody and RNA testing in accordance with the FACT standards and FDA guidance (class I, level C) | 3 |
|   2. Screening of all long-term survivors of HCT, especially those with epidemiologic risk factors including those transplanted in the era before routine donor and blood product screening (class I, level C) | |
| Updated background on impact of HCV infection on eligibility to donate hematopoietic cells or undergo HCT | 4 (Table 3) |
| New section regarding monitoring of HCV in chronically infected HCT recipients: | |
|   1. ALT level should be evaluated at entry into care, 2 to 8 weeks after completion of the conditioning regimen, every 2 to 8 weeks during maintenance chemotherapy or immunosuppressive treatment, and every 3 to 6 months thereafter (class II, level C) | 6 |
|   2. In HCT recipients with chronic HCV infection, routine monitoring of HCV RNA is not recommended. However, viral load should be considered for patients who have an unexplained elevation of ALT (class II, level C). HCV RNA should be measured in all patients at entry into care, and monitoring of viral load should be performed in patients receiving HCV treatment according to the AASLD-IDSA HCV guidance (http://www.hcvguidelines.org/) (class I, level C). | |
| New section regarding fibrosis assessment in HCV-infected HCT candidates and recipients using serologic markers and ultrasound-based VCTE | 7 |
| New recommendations regarding antiviral therapy for donors and HCT candidates and recipients: | |
|   1. Timing of antiviral therapy | 7 |
|   2. Treatment interruption is not recommended (class I, level C) | 8 |
|   3. IFN-based regimens should be avoided because of their suboptimal efficacy and safety (class I, level B) | 8 |
|   4. DAA combinations of potential use in HCV-infected HCT recipients extrapolated from studies in other patient populations | 9 |
| New section and table on drug–drug interactions in HCV-infected HCT candidates and recipients receiving DAAs and conditioning regimens or immunosuppressive agents | 9 Table 4 |

## Evidence Summary

### Course of HCV infection to 1 year after HCT

HCV infection has hepatic and extrahepatic manifestations. Hepatic manifestations in HCT recipients in addition to those seen in immunologically normal hosts include (1) an increased risk of fatal sinusoidal obstruction syndrome (previously known as veno-occlusive disease) among patients with chronic HCV infection who receive sinusoidal endothelial cell toxins (eg, cyclophosphamide, etoposide, melphalan, thiotepa, total body irradiation ≥12 Gy) as part of the conditioning therapy [5]; (2) hepatic inflammation occurring 3 to 6 months after HCT, coincident with immune reconstitution and discontinuation of immunosuppressive drugs [5]; (3) liver decompensation among patients who had cirrhosis at the time of transplant [6,7]; and (4) rarely, fatal fibrosing cholestatic hepatitis C before day 100 in patients receiving mycophenolate mofetil [8]. Fibrosing cholestatic hepatitis is an aggressive form of viral hepatitis caused by either hepatitis B virus or HCV that causes rapid clinical deterioration, characterized histologically by extensive fibroblastic portal-to-portal bridging, ductular proliferation, cholestasis, high intrahepatocyte viral load, and inflammation [8].

Extrahepatic manifestations of HCV infection after HCT have been suggested by epidemiologic studies and include greater 1- to 2-year nonrelapse-related mortality than in HCV-negative control subjects, including an excess of deaths related to bacterial infections [6,7]. It is not clear if the higher mortality is due to HCV per se, the presence of undetected hepatic fibrosis and portal hypertension, or chronic viral coinfections (such as hepatitis B virus infection or HIV infection) at the time of transplant.

### Course of HCV infection between 1 and 10 years after HCT

Coincident with immune reconstitution after HCT, serum alanine aminotransferase (ALT) levels wax and wane in most HCV-infected patients. The course of this chronic hepatitis is usually uncomplicated for 10 years after HCT, but, rarely, patients may progress to cirrhosis. Serum aminotransferase elevations can be seen in 57% of HCV-infected patients

between 5 and 10 years after HCT [5]. In several series no excess mortality was noted in HCV-infected patients up to 10 years after HCT [5,9,10]. In some patients, however, the duration of HCV infection before HCT can only be estimated, and the extent of fibrosis is unknown at the time of HCT; such patients may experience progressive liver disease that only becomes apparent after HCT [6,7].

### Course of HCV infection 10 to 40 years after HCT

Chronic HCV is the leading cause of cirrhosis after HCT, and the time to cirrhosis is shorter in patients with chronic HCV infection who undergo HCT than in patients with chronic HCV infection who do not undergo HCT [11,12]. About one third of HCV-infected 40-year survivors of HCT develop end-stage liver disease (cirrhosis, HCC, or disease requiring liver transplant). HCT recipients who develop end-stage liver disease can be considered for liver transplant; living donor liver transplant from the original hematopoietic cell donor has been described [13,14].

## Knowledge Gaps

- What is the natural history of HCV in HCT in the era of current immunosuppressive regimens?
- What are the predictors of liver disease progression in HCT recipients?
- Do effective antiviral drugs alter the course of HCV-related fibrosing cholestatic hepatitis, hepatic fibrosis, and cirrhosis in HCV-infected survivors of HCT?

## HCV SCREENING IN DONORS OF HEMATOPOIETIC STEM CELLS, HCT CANDIDATES, AND LONG-TERM SURVIVORS
Sarah P. Hammond, John R. Wingard
### Recommendations

- All hematopoietic cell donors should be screened for HCV within 30 days before cell harvest with FDA-approved HCV antibody (anti-HCV) and RNA testing in

accordance with the Foundation for the Accreditation of Cellular Therapies (FACT) standards and FDA guidance (class I, level C).

- All HCT candidates should be screened for HCV with FDA-approved anti-HCV testing (class I, level C).
- All long-term survivors of HCT should be screened for HCV infection based on the current recommendations for screening in non-HCT recipients, with special attention to those with epidemiologic risk factors, including those transplanted in the era before routine donor and blood product screening (class I, level C).

### Evidence Summary

In the general US population, risk-based screening for HCV infection with anti-HCV testing (with reflex HCV RNA testing for individuals with positive results) is recommended by the Centers for Disease Control and Prevention [15], US Preventive Services Task Force [16], and AASLD, IDSA, and International Antiviral Society–USA [1]. Individuals considered at high risk include not only intravenous drug users but also individuals born between 1945 and 1965 [15].

Transmission of HCV from HCV-infected bone marrow donors to uninfected recipients was first documented in the early 1990s [17]. FACT has issued standards for US centers performing HCT that include HCV screening of allogeneic donors within 30 days before stem cell harvest using tests required by applicable laws and regulations [18]. The FDA has issued guidelines recommending that such donors be screened with FDA-licensed antibody and nucleic acid tests [19]. A positive test result for anti-HCV (using third-generation tests) in the setting of undetectable serum HCV RNA indicates past infection (resolved spontaneously or therapeutically), acute HCV infection during a period of low-level viremia, or a false-positive test result [1,20].

False-positive anti-HCV tests are more common with earlier generation testing, especially if confirmation with the recombinant immunoblot assay was not included in the method. In such a case the HCV-treating providers should retest the donor for anti-HCV and HCV RNA to exclude the presence of active infection and seek guidance from an infectious disease or hepatology expert.

The presence of serum HCV RNA indicates current and active infection. If the viremia persists for more than 6 months postexposure, the infection is considered chronic and is not likely to resolve spontaneously.

FACT and FDA guidance on HCT donor screening does not extend to HCT candidates and recipients. Overall, HCV screening in HCT candidates establishes a pretransplant baseline and identifies patients who might benefit from HCV treatment after transplant. There is usually insufficient time to complete a course of HCV therapy before HCT. Chronic HCV can be associated with false-negative anti-HCV test results in immunosuppressed patients [20], including HCT recipients [21]. Such patients have a positive serum HCV PCR test.

In a prospective study in allogeneic HCT recipients from 15 European transplant centers, data on pretransplant HCV RNA were available for 182 patients, and 11 were found to have viremia, including 6 anti-HCV–negative patients [21]. In HCT candidates and recipients, screening with HCV RNA testing in addition to anti-HCV serologic testing is advocated by many experts (class IIb, level C). In 1 study, 13% of HCV-infected patients with a positive anti-HCV test result before HCT had a negative anti-HCV test result after HCT [22].

### Knowledge Gap

- How frequently are HCT candidates or HCV recipients seronegative for HCV with third-generation tests despite serum nucleic acid evidence of active infection?
- What is the most cost-effective algorithm for screening HCT candidates and recipients?

## IMPACT OF HCV INFECTION ON ELIGIBILITY TO DONATE HEMATOPOIETIC STEM CELLS OR UNDERGO HCT
### Harrys A. Torres, John R. Wingard
### Recommendations

- HCV infection in donors or potential HCT recipients should not be an absolute contraindication for HCT (class I, level C) (Table 3).
- The risk of HCV transmission is extremely low when seronegative and HCV RNA–negative HCT candidates receive HCT from donors of hematopoietic stem cells with positive anti-HCV and undetectable HCV RNA (class I, level C).
- HCV-infected donors should be assessed for advanced chronic liver disease and other extrahepatic manifestations of HCV to recommend an optimal management of their disease (class I, level C).
- HCV-infected donors should be screened for other coinfections (eg, HIV). HIV-HCV–coinfected individuals should not be considered as donors for HIV-seronegative recipients, according to standard HCT guidelines [4].
- HCV-infected HCT candidates requiring HCT and for whom there is no alternative donor can proceed with HCT from a donor also infected with HCV provided the recipient has full understanding of the potential consequences given the viral characteristics of the donors' HCV infections (class IIa, level C).
- If the donor is HCV RNA positive and transplantation to an HCV-infected or -uninfected recipient is considered, the donor should start antiviral therapy immediately with the goal of reducing the infectious potential of the donor, ideally attaining undetectable plasma HCV RNA in the donor before stem cell harvest (class I, level C).
- Selection of HCV-infected candidates for HCT should be based on the extent of liver fibrosis and degree of portal hypertension (class I, level C).

### Evidence Summary
#### Donors with positive HCV screening test results

As recommended for the general population [1], donors (or HCT recipients) found to have positive results for anti-HCV and negative results for HCV RNA by PCR using an FDA-approved sensitive HCV RNA test should be informed they do not have evidence of current (active) HCV infection. Repeat HCV RNA testing at a later date (eg, 1 to 2 months) is typically unnecessary but can be performed when there is strong suspicion of acute infection or in patients with ongoing risk factors for HCV infection [1].

Up to 100% of infected donors transmit HCV to uninfected HCT recipients [17]. If no alternative donor is available and if time does not permit treatment of the infected donor to eliminate HCV from the infusion product, the use of HCV-infected hematopoietic cells for an HCV-uninfected recipient is not contraindicated. New DAAs could potentially provide a virologic cure after HCT in most patients and may

**Table 3**
Eligibility to Donate Hematopoietic Stem Cells or Undergo HCT according to Different Clinical Scenarios

| Clinical Scenario | Donor Anti-HCV | Donor HCV RNA | HCT Candidate/ Recipient Anti-HCV | HCT Candidate/Recipient HCV RNA | Recommendation for Donor | Recommendation for HCT Candidate/Recipient |
|---|---|---|---|---|---|---|
| 1 | Negative | Negative | Negative | Negative | Proceed with stem cell harvest. | Proceed with HCT. |
| 2 | Negative | Positive | Negative | Negative | Proceed with stem cell harvest. When possible, start antivirals and proceed with cell harvest once HCV PCR is undetectable.* | Proceed with HCT. Monitor HCV RNA managing acute infection per HCV guidance.† |
| 3 | Negative | Positive | Positive | Negative | Proceed with stem cell harvest. When possible, start antivirals and proceed with cell harvest once HCV PCR is undetectable.* | Proceed with HCT. Monitor HCV RNA managing acute infection per HCV guidance.† |
| 4 | Negative | Positive | Positive | Positive | Proceed with stem cell harvest.‡ | Proceed with HCT.‡ Start antiviral therapy, when possible.§ |
| 5 | Negative | Positive | Negative | Positive | Proceed with stem cell harvest.‡ | Proceed with HCT.‡ Start antiviral therapy, when possible.§ |
| 6 | Negative | Negative | Positive | Negative | Proceed with stem cell harvest. | Proceed with HCT.‖ |
| 7 | Negative | Negative | Positive | Positive | Proceed with stem cell harvest. | Proceed with HCT. Start antivirals, when possible.§ |
| 8 | Negative | Negative | Negative | Positive | Proceed with stem cell harvest. | Proceed with HCT. Start antivirals, when possible.§ |
| 9 | Positive | Negative | Negative | Negative | Proceed with stem cell harvest.‖ | Proceed with HCT. |
| 10 | Positive | Positive | Negative | Negative | Proceed with stem cell harvest. When possible, start antivirals and proceed with cell harvest once HCV PCR is undetectable.* | Proceed with HCT. Monitor HCV RNA managing acute infection per HCV guidance.† |
| 11 | Positive | Positive | Positive | Negative | Proceed with stem cell harvest. When possible, start antivirals and proceed with cell harvest once HCV PCR is undetectable.*,‖ | Proceed with HCT.† Monitor HCV RNA managing acute infection per HCV guidance.† |
| 12 | Positive | Positive | Negative | Positive | Proceed with stem cell harvest.‡ Manage infection per HCV guidance. | Proceed with HCT.‡ Start antivirals, when possible.§ |
| 13 | Positive | Positive | Positive | Positive | Proceed with stem cell harvest.‡ Manage infection per HCV guidance. | Proceed with HCT.‡ Start antivirals, when possible.§ |
| 14 | Positive | Negative | Positive | Positive | Proceed with stem cell harvest.‖ | Proceed with HCT. Start antivirals, when possible.§ |
| 15 | Positive | Negative | Negative | Positive | Proceed with stem cell harvest.‖ | Proceed with HCT. Start antivirals, when possible.‡,§ |
| 16 | Positive | Negative | Positive | Negative | Proceed with stem cell harvest.‖ | Proceed with HCT.‖ |

* When possible, start antiviral therapy immediately, attaining viral clearance before stem cell harvest to reduce the risk of HCV transmission. If HCT must be done urgently, stem cell harvest from a viremic donor should be considered.

† Per HCV guidance, monitor HCV RNA (eg, every 4 to 8 weeks) for 6 to 12 months after the time of infection to determine spontaneous viral clearance versus active HCV. Detectable HCV RNA at 6 months after onset of infection will identify most persons who need HCV therapy (http://hcvguidelines.org/full-report/management-acute-hcv-infection).

‡ HCV-infected HCT candidates requiring HCT and for whom there is no alternative donor can proceed with HCT from a donor also infected with HCV (see text for details).

§ HCV-infected HCT candidates should be started on therapy and should complete HCV therapy before transplant, when possible.

‖ HCT donors and candidates with positive anti-HCV in the setting of undetectable HCV RNA should have repeat HCV RNA testing when there is strong suspicion of acute infection or in patients with ongoing risk factors for HCV infection (see text for details).

halt liver disease progression in HCT survivors. The risk of dying from the underlying hematologic malignancy without the transplant outweighs the risk of acquiring potentially curable HCV. However, the donor should be assessed for advanced chronic liver disease per current HCV guidance [1] as well as extrahepatic manifestations of HCV (eg, lymphoproliferative diseases) and coinfections (eg, HIV) that might contraindicate donation (class I, level C) [4].

The risk of transmission of HCV was decreased to nearly 0 if HCV RNA was undetectable at the time of hematopoietic cell donation [17]. In viremic donors, viral clearance with DAAs before cell harvest may be attempted if feasible to reduce the risk of HCV transmission, because most donors will attain undetectable HCV PCR within 4 weeks of starting currently available DAAs [4,23,24]. The timing of HCV therapy is further discussed below (see When to Treat HCV Infection in Donors and Autologous or Allogeneic HCT Candidates and Recipients).

*HCT candidates with positive HCV screening test results*

Similar to what is recommended for donors, HCT candidates with positive test results for anti-HCV in the setting of undetectable HCV RNA should be evaluated to exclude acute infection by repeating HCV RNA. HCV-infected HCT candidates requiring HCT and for whom there is no alternative donor can proceed with HCT from a donor also infected with HCV, provided the recipient has full understanding of the potential consequences (class IIa, level C) [5]. The potential consequences include infections with different genotypes (eg, genotype 3) or resistance-associated variants (such as NS5A variants) potentially associated with a higher rate of virologic failure. Treatment recommendations in HCT candidates are further discussed below (see When to Treat HCV Infection in Donors and Autologous or Allogeneic HCT Candidates and Recipients). All individuals (donors and recipients) with HCV infection should be referred to a practitioner able to provide comprehensive management of HCV [1].

### Knowledge Gaps

- Studies are needed to determine the magnitude of risk for HCV transmission when HCV-infected donors have achieved undetectable HCV RNA but have not completed their recommended treatment course.

## MONITORING HCV IN HCT RECIPIENTS WITH CHRONIC HCV INFECTION
**Harrys A. Torres, Marcos De Lima**
### Recommendations

- In HCT recipients with chronic HCV infection, ALT level should be evaluated at entry into care, 2 to 8 weeks after completion of the conditioning regimen, every 2 to 8 weeks during maintenance chemotherapy or immunosuppressive treatment, and every 3 to 6 months thereafter (class II, level C).
- In HCT recipients with chronic HCV infection, routine monitoring of HCV RNA is not recommended. However, viral load should be considered for patients who have an unexplained elevation of ALT (class II, level C). HCV RNA should be measured in all patients at entry into care, and monitoring of viral load should be performed in patients receiving HCV treatment according to the

AASLD-IDSA HCV guidance (http://www.hcvguidelines.org/) (class I, level C).

### Evidence Summary

Acute exacerbation of chronic HCV infection, indicated by a significant elevation of serum aminotransferase levels over the baseline level in the absence of other potential causes of acute hepatitis, can occur in both immunocompetent [25] and immunocompromised cancer patients [26]. However, there are no standard definitions for this phenomenon. In a retrospective study of 308 patients with cancer and chronic HCV infection, 11% were identified as having acute exacerbation of chronic HCV infection, defined as a 3-fold or greater increase in serum ALT level from baseline in the absence of (1) infiltration of the liver by cancer, (2) use of hepatotoxic medications, (3) blood transfusion within 1 month of elevation of ALT level, or (4) other systemic infections affecting the liver (including hepatitis A virus, hepatitis B virus, cytomegalovirus, adenovirus, herpes simplex virus, varicella-zoster virus, and HIV infections) [26]. In that study, acute exacerbation (significant ALT elevation) of HCV infection during chemotherapy prompted clinicians to discontinue chemotherapy in nearly half of affected patients [26].

Enhanced HCV replication (also known as HCV reactivation [26]) has been defined as an increase in HCV RNA viral load of at least 1 $\log_{10}$ IU/mL over baseline after chemotherapy or immunosuppressive therapy [26] because chronically infected patients have stable HCV RNA levels that may vary by approximately .5 $\log_{10}$ IU/mL [27]. The increased replication of HCV appears to be associated with a more indolent course than hepatitis B virus reactivation [28]; only a few reports of deaths have been associated with increased HCV replication [8,29]. Regrettably, the published data on simultaneous changes in ALT levels and HCV viral load are limited and not sufficient for examination of whether a correlation exists between enhanced viral replication and hepatocellular injury [26], as has been described for patients with chemotherapy-induced hepatitis B virus reactivation.

Little is known about acute exacerbation of HCV infection in HCT recipients, with emerging data after autologous and allogeneic HCT recently presented [22,30]. However, such studies should be considered preliminary because most were retrospective analyses of small numbers of patients. In 1 prospective study, aspartate aminotransferase (AST) levels were compared between HCV-infected and HCV-negative HCT recipients [5]. A severe acute flare of hepatitis (AST >10 times the upper limit of normal) developed in 11 of 36 HCV-infected patients (31%) who survived at least 1 year after HCT but only 6 of 115 HCV-negative patients (5%) (P < .0001). Data on HCV RNA were not presented; thus, it was not possible to determine whether the increase in AST level in patients receiving chemotherapy resulted from coinfections, drugs, or enhanced HCV replication in the setting of immunosuppression.

Patients with significant ALT elevations (eg, ≥3-fold increase from the upper limit of normal) should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury. HCV-treating physicians should participate in the diagnostic workup of acute exacerbation of HCV to exclude other potential explanations for ALT increase (eg, infiltration of the liver by cancer, hepatotoxic medications, blood transfusion within 1 month, the hepatitic presentation of liver graft-versus-host disease [GVHD], or other systemic infections affecting the liver).

### Knowledge Gaps

- Prospective studies are needed to determine the incidence, clinical implications, and outcome of acute exacerbation of chronic HCV infection in HCT recipients.
- What is the best strategy for monitoring HCV infection around the time of HCT?

## FIBROSIS ASSESSMENT IN HCV-INFECTED HCT CANDIDATES AND RECIPIENTS
### Maya Gambarin-Gelwan and Mark S. Friedman
### Recommendations

- All HCV-infected HCT candidates should undergo assessment of the stage of liver fibrosis and the presence of cirrhosis (class I, level C).
- The presence of cirrhosis may affect duration and type of HCV therapy and will identify patients who need to be screened for HCC and the presence of esophageal varices (class I, level C).
- The decision to perform a liver biopsy should be made only after careful consideration of the risks and benefits of the procedure (class I, level B).
- Serologic marker panels for detection of fibrosis have not been studied in HCV-infected HCT candidates, and their use is not recommended (class IIb, level C).
- Ultrasound-based vibration-controlled transient elastography (FibroScan VCTE; Echosens, Paris, France) has not been studied in HCT recipients, and thus results should be interpreted with caution (class II, level C).

### Evidence Summary

All HCV-infected HCT candidates should undergo assessment of the stage of liver fibrosis and the presence of cirrhosis (class I, level C). The presence of advanced fibrosis (Metavir $\geq$ F3) or cirrhosis (Metavir F4) may have a significant impact on HCT eligibility, the choice of conditioning regimen, HCV therapy, and risk of HCC.

*Liver biopsy*

Liver biopsy has been the gold standard for histopathologic assessment of fibrosis in patients with chronic HCV infection, particularly when the stage of fibrosis and presence or absence of cirrhosis may guide subsequent management. However, liver biopsy is an imperfect gold standard because it is associated with sampling limitations and error, is invasive, and carries a risk of complications. Individuals with hematologic malignancies requiring HCT may be at particular risk for complications [31] and often require a transjugular approach because of severe thrombocytopenia [32]. The decision to perform a liver biopsy should be made only after careful consideration of the risks and benefits of the procedure (class I, level B) [33].

*Serologic marker panels for detection of fibrosis*

Tests for serologic markers of fibrosis have become widely available in the past several years and are used extensively in patients with chronic HCV infection. The AST-to-platelet ratio index (APRI) and FIB-4 index (combines platelet count, ALT, AST, and age) are easy to calculate using data available on routine laboratory testing and can be used to assess for presence of advanced fibrosis and cirrhosis. Four commercial serum marker panels have been validated in the general

population of patients with chronic HCV infection: FibroTest/FibroSure (LabCorp, Burlington, NC, USA), Hepascore (Quest Diagnostics, Madison, NJ, USA), FibroSpect (Prometheus Laboratories, San Diego, CA, USA), and the European Liver Fibrosis Study Group panel (not available in the United States). No panel has yet emerged as standard of care or is FDA approved; however, all 4 panels have demonstrated accuracy in distinguishing patients with significant fibrosis (Metavir score F2 to F4) from those without significant fibrosis (Metavir score F0 or F1) [34]. Because individual markers in these panels include aminotransferases, platelets, coagulation parameters, γ-glutamyl transferase, total bilirubin, haptoglobin, gamma globulins, and so on, the results might be unreliable in HCT candidates and recipients because of cytopenias, ongoing systemic inflammation, drug-related liver damage, and infection. These panels have not been studied in candidates for HCT or in HCT recipients, and their use is not recommended in either population.

*Vibration-controlled transient elastography*

Ultrasound-based elastography in the form of FibroScan VCTE was approved by the FDA in April 2013. This procedure has been endorsed by the AASLD "to be used by clinicians providing care for patients with liver disease to evaluate liver fibrosis at the point of care" [35]. VCTE is quick, is done at the time of the clinic visit, is noninvasive, has good reproducibility, is relatively inexpensive, and provides information about a large area of the liver. VCTE has been extensively studied in patients with chronic HCV infection. In a recent US multicenter study, VCTE demonstrated a positive predictive value of 75.6% to 80.8% and a negative predictive value of 55.0% to 84.7% for diagnosis of significant fibrosis (F $\geq$ 2) and an estimated positive predictive value of 41.6% to 60.4% and negative predictive value of 95.6% to 97.6% for diagnosis of cirrhosis [36]. VCTE would plausibly be useful for assessment of advanced fibrosis, particularly *to rule out* cirrhosis in HCT candidates and recipients, although these patient populations have not been extensively studied [37,38].

### Knowledge Gaps

- Reliability of serologic markers of fibrosis and FibroScan VCTE in predicting the presence of advanced fibrosis and cirrhosis in HCT candidates and recipients.
- Effect of leukemic infiltration of hepatic sinusoids, lymphoma of the liver, or extramedullary hematopoiesis with sinusoidal fibrosis on the accuracy of VCTE.
- Role of VCTE as a predictor of hepatotoxicity in HCT recipients.

## WHEN TO TREAT HCV INFECTION IN DONORS AND AUTOLOGOUS OR ALLOGENEIC HCT CANDIDATES AND HCT SURVIVORS
### Maya Gambarin-Gelwan, Sergio Giralt, George B. McDonald
### Recommendations

- HCV-infected donors should be evaluated for HCV therapy and treated before cell harvest to prevent transmission of HCV to uninfected recipients, if possible (class I, level C).
- All HCT candidates with HCV infection should be evaluated for HCV therapy before the start of conditioning therapy; after transplant, HCV-infected survivors should also be evaluated for therapy (class I, level B).

- When possible, HCV-infected HCT candidates should be started on therapy and should complete therapy for HCV before transplant (class IIa, level C).
- After HCT, the following patients should be treated for HCV without delay: HCV-infected patients who develop fibrosing cholestatic hepatitis C, patients with cirrhosis whose condition is deteriorating, and patients who underwent HCT for HCV-related lymphoproliferative disorders (class I, level C).
- After HCT, treatment for HCV can be deferred until after immune reconstitution for patients not meeting the criteria above (class I, level C).
- All HCV-infected long-term survivors of HCT should be offered antiviral therapy (class I, level C).
- HCV therapy should be undertaken only with the intention of completion of the full course of therapy as defined in the AASLD-IDSA Hepatitis C Guidance (http://www.hcvguidelines.org/). Treatment interruption is not recommended (class I, level C).
- IFN-based regimens should be avoided in donors and HCT candidates/recipients with HCV infection because of their suboptimal efficacy and safety (class I, level B).
- HCV therapy should be undertaken by providers experienced in management of HCV in HCT recipients in close collaboration with transplant teams (class I, level B).

### Evidence Summary

*Treatment of HCV-infected donors before HCT*

Several case reports have described successful prevention of HCV transmission through treatment of HCV-infected donors before cell harvest [5,24,39,40]. When there are oncologic imperatives for moving quickly to transplant, DAAs should be able to clear extrahepatic HCV from donors more quickly than IFN and ribavirin can without significant toxic effects on the donor marrow. Once initiated, a full course of antiviral therapy should be completed in donors based on the current treatment recommendations for individuals with HCV infection [1].

The risk of HCV transmission at various time points during HCV therapy has not been studied. Plausibly the risk of transmission should be sharply reduced if serum HCV RNA levels are below the level of detection for the assay.

*Treatment of HCV-infected candidates before HCT and recipients after HCT*

Data are lacking regarding treatment of HCV-infected HCT candidates. DAA therapy before HCT should be considered.

Prompt treatment of HCV infection after transplant is urgent for 3 groups: patients with fibrosing cholestatic HCV [8], patients with cirrhosis whose condition is deteriorating [41], and patients who underwent HCT for HCV-related lymphoproliferative disorders [22,42]. It is not known, however, whether the efficacy of DAA therapy is affected by dysfunctional immunity after therapy for cancer. It is also not known whether eliminating HCV before HCT improves the outcome of transplant by, for example, reducing the risks of post-HCT fatal sinusoidal obstruction syndrome, liver decompensation, fibrosing cholestatic hepatitis, or recurrent lymphoma [43,44]. Once HCV therapy is started in either HCT candidates or recipients, treatment interruption is not recommended, because it is associated with increased risk of treatment failure [2].

The alternative to pre-HCT therapy for HCV is to treat after HCT using DAAs after immune reconstitution [22]. Although published data are limited on outcomes of DAA therapy in HCT recipients, SVR rates of 70% to 96% have been observed in patients who received DAAs during immunosuppressive therapy after liver transplant [43,44].

A preliminary observational study suggested that IFN-sparing regimens were well tolerated and effective in 10 HCT recipients and have potential to improve patient outcomes [22]. Combination DAA therapy appears to be safe and effective in HCV-infected allogeneic and autologous HCT recipients after a follow-up period of 6 months after transplant [22]. Some experts advocate waiting for 6 months after the transplant to allow tapering of immunosuppression agents and GVHD prophylaxis, which might result in higher SVR rates and reduction of drug–drug interactions.

Flare of GVHD that occurs after tapering immunosuppressive therapy could be confused for HCV exacerbation and/or medication toxicity in those receiving antivirals. Some clinicians may still choose to defer DAA therapy until immunosuppressive treatment has been discontinued to avoid drug–drug interactions.

IFN-based regimens should be avoided in donors and HCT candidates with HCV infection because of their suboptimal efficacy and safety (class I, level B). Data are not available regarding the impact of treatment regimens consisting of ribavirin plus DAA in HCV-infected HCT recipients.

*Treatment of HCV-infected long-term HCT survivors*

About one third of HCV-infected long-term HCT survivors develop end-stage liver disease or HCC [11,12]. Thus, all HCV-infected long-term HCT survivors should be offered DAA therapy. The rationale for universal treatment of infected survivors is that it can prevent transmission of HCV, delay the development of cirrhosis, and reduce long-term consequences of chronic HCV infection, including development of HCC, extrahepatic manifestations of HCV, and possible need for liver transplantation.

### Knowledge Gaps

- Should all HCV-infected donors and HCT candidates be treated with antivirals before HCT?
- What is the optimal timing of antiviral therapy for HCT candidates?
- How effective and safe are DAAs given to HCT candidates or recipients?
- What is the effect of virologic cure of HCV on the risk of sinusoidal obstruction syndrome and other liver-related complications of HCT in HCV-infected individuals?
- Does antiviral therapy prevent post-HCT liver disease progression and relapse of HCV-associated non-Hodgkin lymphoma?
- Does recovery of a full immunologic repertoire after HCT affect the efficacy of antiviral treatment?

## ROLE OF DAA COMBINATIONS IN HCV-INFECTED HCT RECIPIENTS
**Pearlie P. Chong, Mark S. Friedman, Henry Masur**
*Recommendations*
*Recommendations by HCV genotype as of August 2015*

- For infection with genotypes 1a or 1b HCV, treatment with one of the following four DAA combinations is recommended:
  (1) Daily daclatasvir and sofosbuvir with or without ribavirin

(2) Daily fixed-dose combination of ledipasvir and sofosbuvir
(3) Daily fixed-dose combination of ombitasvir, paritaprevir, ritonavir, and twice-daily dasabuvir with or without ribavirin
(4) Daily sofosbuvir plus simeprevir with or without ribavirin

- For infection with genotype 2 HCV, the preferred regimen is sofosbuvir plus weight-based ribavirin; those who cannot tolerate ribavirin should be treated with daily daclatasvir and sofosbuvir.
- For infection with genotype 3 HCV, treatment with one of the following DAA combinations is recommended:
  (1) Daily daclatasvir and sofosbuvir with or without ribavirin
  (2) Daily sofosbuvir and ribavirin plus weekly pegylated-interferon
- For infection with genotype 4 HCV, treatment with one of the following the three DAA combinations is recommended:
  (1) Daily fixed-dose combination of ledipasvir and sofosbuvir
  (2) Daily fixed-dose combination of ombitasvir, paritaprevir, ritonavir, and ribavirin
  (3) Daily sofosbuvir and ribavirin.
- For infection with genotypes 5 or 6 HCV, the preferred regimen is daily fixed-dose combination of ledipasvir and sofosbuvir (class IIa, Level B).
- Monotherapy with a DAA is not recommended for any patient with HCV infection (class III, level A).
- The choice of regimen should be individualized on the basis of patient-specific data, including potential drug interactions.

*Treatment considerations in specific patient populations*

- HCT recipients often receive multiple drugs that could have pharmacologic interactions with DAAs or toxic effects that overlap with those of DAAs. Treating physicians should be mindful of potential drug interactions and/or side effects, although this has not been extensively studied in HCT recipients.
- In patients with mild (creatinine clearance 60 to 89 mL/min) to moderate (creatinine clearance 30 to 59 mL/min) renal impairment, no dosage adjustment is required for daclatasvir, sofosbuvir plus simeprevir, ledipasvir plus sofosbuvir, or ombitasvir, paritaprevir, ritonavir, and dasabuvir (class I, level A). The total daily dose of ribavirin should be reduced for patients with creatinine clearance ≤50 mL/min [45].
- In patients with severe renal impairment (creatinine clearance 15 to 29 mL/min) or with end-stage renal disease, safety and efficacy data for DAAs are not available; treatment can be contemplated after consultation with an expert (class IIb, level C) or as new data in this patient population become available. If ribavirin is used, dose should be reduced [45].
- Patients coinfected with HIV and HCV should be treated like HCV-monoinfected patients, except that interactions with antiretroviral medications must be recognized and managed (class I, level B).

### Evidence Summary

DAAs are oral agents that target various HCV-encoded proteins vital to the replication of the virus. When used in combination, DAAs are capable of curing HCV infection; DAAs have demonstrated excellent rates of SVR and favorable safety profiles in multiple phase III clinical trials [46-52].

Unfortunately, the efficacy and safety of DAAs in HCV-infected HCT recipients have not been extensively studied or documented. The recommendations above are extrapolated from studies in other patient populations. The optimal therapy for HCV is evolving rapidly and will continue to evolve as multiple new drugs are approved and as more studies are reported. The recommendations above should be compared with the online AASLD-IDSA Hepatitis C Guidance for the management of HCV infection, which are updated frequently as new data emerge (http://www.hcvguidelines.org/news/hcv-guidance).

The choice of DAA regimen and duration of DAA treatment for HCV-infected HCT recipients should be informed by prior treatment experience, HCV genotype, and the degree of fibrosis.

### Knowledge Gaps

- Efficacy and safety of various DAA regimens in HCT recipients.
- Optimal duration of DAA regimens in HCT recipients.

### DRUG–DRUG INTERACTIONS IN HCV-INFECTED HCT CANDIDATES AND RECIPIENTS RECEIVING DAAS AND CONDITIONING REGIMENS OR IMMUNOSUPPRESSIVE AGENTS
### Patrick J. Kiel
### Recommendations

*Recommendations for drug-drug interactions as of August 2015*

- Physicians should frequently assess for drug–drug interactions in HCV-infected HCT recipients (class I, level C).
- HCT candidates should not receive DAAs concomitantly with the chemotherapy preparative regimen if the potential for drug–drug interactions exists (class I, level C).
- In patients receiving tacrolimus concomitantly with paritaprevir and ritonavir, holding tacrolimus for one day with an approximate dose reduction of 75% may be required. Due to the prolonged half-life of tacrolimus with this combination more frequent blood level assessment of tacrolimus, such as twice to thrice weekly, may be indicated. Some patients may even require intermittent dosing of tacrolimus based on blood levels. In patients receiving concomitant cyclosporine, increased therapeutic drug monitoring and an 80% decrease of the cyclosporine dose may be required (class IIb, level B).
- In patients receiving sirolimus concomitantly with paritaprevir and ritonavir, increased therapeutic drug monitoring and a decrease of 90% or more in the sirolimus dose may be required (class IIb, level C).
- Direct acting antivirals simeprevir, sofosbuvir, ledipasvir/sofosbuvir, and daclatasvir are known to have the least clinically significant interactions with commonly administered immunosuppressive medications following HCT. In patients with multiple medication interactions or those in whom it is prudent to minimize such interactions based on clinical assessment preference may be given to the aforementioned treatment regimens (class I, level C).

**Table 4**
DAA Pharmacology and Potential Interactions with Drugs Used in HCT

| Antiviral Agent[*] | Metabolism/Elimination | Metabolism Effects | Transporter Substrate | Transporter Effects | Drugs with Which DAA Does or May Interact |
|---|---|---|---|---|---|
| Protease inhibitors | | | | | |
| Boceprevir | CYP3A4, aldoreductase | Inhibits CYP3A4 | P-gp | Potentially inhibits P-gp | Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels |
| Paritaprevir with ritonavir[†] | CYP3A4, CYP3A5 | Inhibits CYP3A4, UGT1A1 | ABCG2, OATP1B1/3, P-gp | Inhibits ABCG2, OATPB1/3 | Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels |
| Simeprevir | CYP3A4 | Inhibits CYP1A2, intestinal CYP3A4 | OATP1B1/3, P-gp | Inhibits OATP1B1/3, P-gp | Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels |
| Telaprevir | CYP3A4 | Inhibits CYP3A4 | OATP1B1, OATP2B1, P-gp | Inhibits OATP1B1, OATP2B1, P-gp | Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels |
| Ritonavir[†] | CYP3A4, CYP2D6 | Inhibits CYP3A4 | P-gp | Inhibits ABCG2 | Increase azoles, CSA, tacrolimus, sirolimus, etoposide, Cy levels |
| NS5A inhibitor | | | | | |
| Daclatasvir | CYP3A4 | No data | P-gp | Inhibitor of ABCG2, OATP1B1, P-gp | Increase CSA, tacrolimus levels[‡] |
| Ledipasvir | Oxidized by unknown mechanisms | N/A | ABCG2, P-gp | inhibits ABCG2, P-gp | Increase CSA, tacrolimus levels |
| Ombitasvir | Amide hydrolysis, then oxidation | Inhibits UGT1A1 | ABCG2, P-gp | substrate only | Unknown |
| Nonnucleos(t)ide polymerase inhibitor | | | | | |
| Dasabuvir | CYP2C8 (primary), CYP3A4, CYP2D6 | Inhibits UGT1A1 | ABCG2, P-gp | Inhibit ABCG2 | CYP2D6 inhibitors increase dasabuvir |
| Nucleos(t)ide polymerase inhibitor | | | | | |
| Sofosbuvir | Extensive hepatic metabolism[§] to active moiety GS-461203, then most is renally eliminated | N/A | ABCG2, P-gp | Substrate only | Unknown |
| Nucleoside analog | | | | | |
| Ribavirin | Unknown metabolism, 60% renal elimination | N/A | N/A | N/A | Increase myelotoxicity with azathioprine |

P-gp indicates P-glycoprotein; OATP1B1/3, organic anion-transporting polypeptides 1B1 and 1B3; OATP2B1, organic anion-transporting polypeptides 2B1; ABCG2, ATP-binding cassette subfamily G member 2; CSA, cyclosporine A; Cy, cyclophosphamide; N/A, not applicable.

[*] Boceprevir and telaprevir are no longer available in the United States but are still in use in other countries.

[†] Ritonavir is used to boost plasma concentrations of paritaprevir.

[‡] Based on the results of drug interaction trials, no clinically relevant changes in exposure were observed for cyclosporine or tacrolimus with concomitant use of daclatasvir [52].

[§] Metabolic pathway involves hydrolysis of carboxyl ester moiety catalyzed by human cathepsin A or carboxylesterase 1 and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway.

### Evidence Summary

The introduction of novel antiviral agents in the treatment of HCV has not eliminated the risk of drug interactions. Physicians should frequently assess for drug–drug interactions in HCV-infected HCT recipients. Many interactions may not be adequately documented but rather may have to be inferred on the basis of the isoenzymes responsible for drug metabolism. Current databases (eg, http://www.hep-druginteractions.org) should be consulted along with the product prescribing information to ensure the safety of concomitantly prescribed medications such as acid reducers, antidepressants, antihypertensives, phosphodiesterase inhibitors, novel oral anticoagulants, macrolide antibiotics, triazoles, and HMG CoA inhibitors [1]. However, these databases lack documentation of potential interactions between DAAs, commonly prescribed immunosuppressive agents, and chemotherapy. The pharmacology of DAAs and potential drug–drug interactions between DAAs and chemotherapy or immunosuppressive agents used in patients undergoing HCT are summarized in Table 4 [53-58].

Drug–drug interactions can be pharmacokinetic, resulting in changes in drug concentrations, or pharmacodynamic, resulting in additive, synergistic, or antagonistic effects on efficacy or toxicity. Metabolism by CYP450 enzyme, specifically the CYP3A4 isoform, is the major metabolic pathway of approved HCV therapies, including DAAs. Membrane transporters are also implicated in clinically relevant drug–drug interactions and may include P-glycoprotein, organic anion transporting polypeptides, and the ATP-binding cassette subfamily G member 2. Membrane transporters and the CYP isoenzymes can be induced or inhibited.

The pharmacologic targets of the novel DAAs include NS3/NS4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. The protease inhibitors (paritaprevir, simeprevir, telaprevir, and boceprevir) prevent the NS3 viral protease from cleaving the enzymes responsible for viral replication. All 5 agents undergo CYP3A4 metabolism and are affected by inducers (ie, phenytoin, rifampin, carbamazepine, and phenobarbital) and inhibitors (ie, posaconazole and voriconazole) [18,54-58].

The protease inhibitors may also increase serum concentrations of chemotherapy or immunosuppressive agents commonly used for HCT that are substrates of CYP3A4, including cyclophosphamide, etoposide, tacrolimus, cyclosporine, and sirolimus. Paritaprevir is administered concomitantly with ritonavir, a potent CYP3A4 inhibitor, as a "boosting" agent and will also interfere with other CYP3A4 and CYP2D6 metabolized medications. Thiotepa is an inhibitor of CYP2B6 and has no interactions with DAAs.

The NS5A inhibitors (daclatasvir, ledipasvir, and ombitasvir) inhibit NS5A viral RNA replication and virion assembly. Daclatasvir is metabolized via CYP3A4, whereas ledipasvir and ombitasvir undergo oxidative metabolism [52,55,58]. Ledipasvir is an inhibitor and a substrate of intestinal P-glycoprotein; inducers of P-glycoprotein (ie, St. John's wort, rifabutin, phenobarbital) that are coadministered may lead to reduced plasma concentrations and therapeutic effects of ledipasvir [58].

The polymerase inhibitor sofosbuvir is renally eliminated, whereas dasabuvir is metabolized via CYP2C8 (major pathway), 3A4, and 2D6 [55,58]. Sofosbuvir is a substrate of intestinal P-glycoprotein, and inducers of P-glycoprotein (ie, St. John's wort, rifabutin, phenobarbital) that are coadministered may lead to reduced plasma concentrations and therapeutic effects of sofosbuvir [58].

Immunosuppression with cyclosporine, tacrolimus, and sirolimus is common after HCT. Cyclosporine has been observed to increase sofosbuvir area under the curve (AUC), but the interaction was not clinically significant in healthy volunteer [59]. Simeprevir can increase cyclosporine and tacrolimus AUC by 19% and 17%, respectively [60]. Telaprevir increases the dose-normalized exposure $AUC_{0-\infty}$ values of cyclosporine and tacrolimus approximately 4-fold and 70-fold, respectively [61]. The mean half-life of cyclosporine was increased from 12 hours to 42.1 hours, and the mean half-life of tacrolimus was increased from 40.7 hours to 195 hours. Boceprevir increases the $AUC_{0-\infty}$ values of cyclosporine and tacrolimus approximately 3-fold and 17-fold, respectively [62]. Experience with dosing of immunosuppressive agents after liver transplant concomitantly with telaprevir or boceprevir plus IFN and ribavirin suggests an empiric dose reduction of approximately 75% for tacrolimus and 35% for cyclosporine [63,64]. Telaprevir and boceprevir are no longer available in the United States. Sirolimus plasma concentrations with the use of DAAs have not been prospectively evaluated, but case reports in patients with liver transplant would suggest a 90% dose decrease [64].

Co-administration of ombitasvir, paritaprevir, ritonavir and dasabuvir with cyclosporine or tacrolimus results in clinically significant increased immunosuppression levels, presumably from the protease inhibitors.[65] Cyclosporine $AUC^{\infty}$ is increased 5.8 fold while the half-life may increase from 7.3 to 25 hours. Due to this increased exposure and decreased clearance it is recommended to empirically decrease the cyclosporine dose by 80% and potentially dosing on a daily basis followed by more frequent assessment of blood levels. Tacrolimus $AUC^{\infty}$ is increased 57 fold while the half-life may increase from 32 to 232 hours. When co-administering ombitasvir, paritaprevir, ritonavir and dasabuvir with tacrolimus, then tacrolimus should be held on at least on the first day of DAA dosing and may require a 75% dose decrease.[55] Tacrolimus and associated laboratory monitoring may require twice or thrice weekly monitoring as published dosing experience with this combination is limited to healthy volunteers and patients with a liver transplant suggesting that intermittent dosing based on blood levels may be required.[55,65,66]

When a calcineurin inhibitor or sirolimus is used with a protease inhibitor, it is reasonable to empirically reduce the dose of the immunosuppressive agents and monitor their levels more frequently because of major CYP3A4 and P-glycoprotein drug–drug interactions. Formal dosing recommendations and the degree of dose adjustments in HCT recipients are conservatively estimated because pharmacokinetic studies have not evaluated dosage changes; studies are limited to healthy volunteers or solid organ transplant recipients.

### Knowledge Gap

- Studies are needed on the potential interactions between DAAs, immunosuppressive agents, and chemotherapy used in HCT candidates.

### OVERLAP BETWEEN TOXIC EFFECTS OF DAAs AND OF CONDITIONING REGIMENS AND SYMPTOMS OF GVHD IN HCV-INFECTED HCT CANDIDATES AND RECIPIENTS
Sarah P. Hammond, Sergio Giralt
### Recommendations

- No recommendations can be made regarding overlap between the toxic effects of DAAs and the toxic effects

of HCT conditioning regimens or symptoms of GVHD because evidence is lacking.

### Evidence Summary

Historically, treatment of HCV with IFN and ribavirin in allogeneic HCT recipients was carried out with some trepidation because of concerns about exacerbation of GVHD, anemia, and neutropenia. However, a relatively large cohort study showed no overall increase in GVHD among allogeneic HCT recipients treated with IFN with or without ribavirin after transplant, and there was a trend toward a decrease in the risk of severe liver complications after transplant with HCV treatment [67].

Because DAAs have been approved by the FDA for treatment of HCV only since 2011, information about the use of these agents in allogeneic HCT candidates and recipients is largely anecdotal [1]. This paucity of data limits understanding of the overlap between the toxic effects of DAAs and the toxic effects of HCT conditioning regimens and symptoms of GVHD.

The first DAAs approved to treat genotype 1 HCV infection, telaprevir and boceprevir, were both associated with toxic effects that could be mistakenly attributed to GVHD (eg, rash) or HCT conditioning regimens (eg, anemia) in the appropriate clinical context [68,69]. However, the availability of potent alternatives with fewer side effects to treat genotype 1 HCV has made telaprevir and boceprevir less desirable than other agents (both telaprevir and boceprevir have been removed from the US market) [47,48]. Simeprevir, a more recently approved protease inhibitor, can cause mild hyperbilirubinemia, which could also be mistakenly attributed to GVHD in the appropriate clinical context, but this effect is typically transient [70].

In general, the observed toxic effects of newer DAAs approved for clinical use outside of clinical trials are minimal compared with the toxic effects of IFN, ribavirin, and even telaprevir and boceprevir. Further studies and more postmarketing experience with these medications, particularly in patients with hematologic disorders and patients who have undergone HCT, will be crucial for predicting potential toxic effects unique to HCT recipients.

### Knowledge Gap

- The toxicity profile of DAAs in HCT recipients, including the toxic effects on progenitor cells.

### ACKNOWLEDGMENTS

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