

Public–Private Partnership: Targeting Real-World Data for Hepatitis C Direct-Acting Antivirals



The era of direct-acting antivirals (DAAs) has transformed the treatment landscape for chronic hepatitis C virus (HCV) infection. Primarily this is due to the approval of multiple DAAs that are highly efficacious with improved safety profiles that became available within a short time span.¹ Regulatory agencies have a public health responsibility to ensure the safety and efficacy of approved drug products. Although the demonstrated safety and efficacy of the drugs in registrational trials is paramount, the continued safety and effectiveness of drugs and treatment outcomes in diverse clinical care settings after a drug's approval are of great importance. This paper describes an innovative collaborative platform using real-world clinical practice settings to gather safety and effectiveness data for DAAs approved for the treatment of chronic HCV infection.

Background

The US Food and Drug Administration (FDA) strives to balance the timely access of novel therapies to patients in need with gathering additional data in subgroups in the postmarketing phase. A current approach is to request drug sponsors to conduct postmarketing phase IV studies or clinical trials to expand our knowledge and understanding of novel therapies. However, sometimes results from these postmarketing studies and trials may be outdated by the time final results become available owing to rapid advancements in the scientific field. This was particularly observed with first-generation HCV DAAs, boceprevir and telaprevir, which received regulatory approval in 2011. By the time some of the postmarketing trials for

these drugs were completed, the results were outdated because the HCV treatment landscape rapidly moved into the interferon-free era.² In such a rapidly evolving treatment landscape, innovative solutions are required to obtain “real-world data” at the earliest time points feasible.

An alternative approach can involve use of a systematic observational cohort evaluating new drugs or therapies that leverage real-world evidence. This approach could help the FDA to strike a balance between premarket evaluation and postmarket data collection to facilitate identification of emerging safety signals in the postmarketing setting. Using real-world evidence to enhance the safety and effectiveness of new drugs can be achieved through robust public–private partnerships. This approach has been used by the FDA's Center for Drug Evaluation and Research, Division of Antiviral Products in partnership with Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET).³

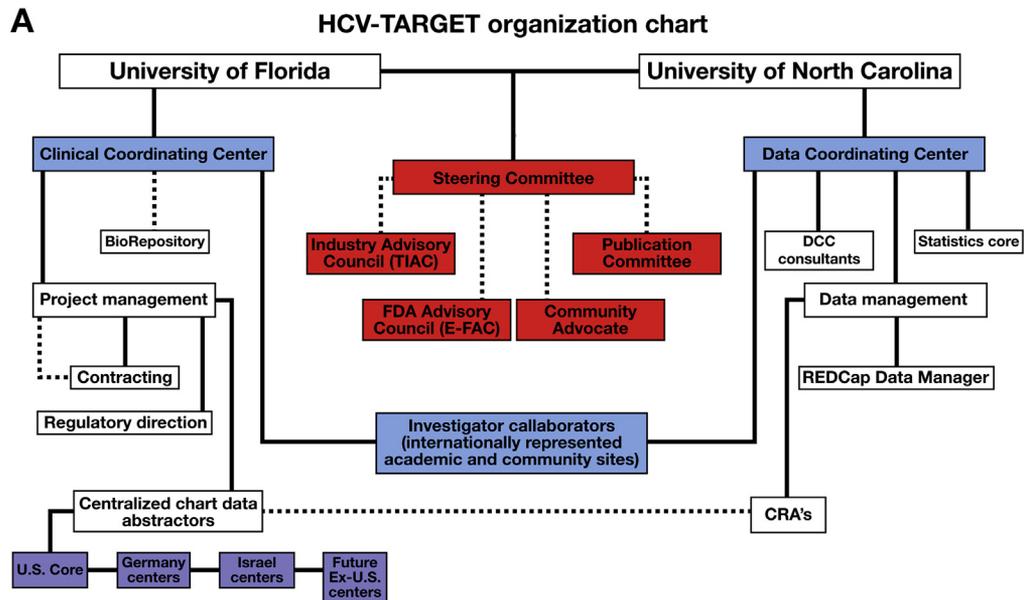
There are specific disease characteristics of chronic hepatitis C and its treatment that make it amenable to using real-world evidence for further informing safety and effectiveness. First, chronic hepatitis C is a disease that progresses over a long period of time and, if left untreated, chronic HCV infection is rarely associated with spontaneous cure.⁴ As such, there is a negligible placebo effect and clearance of the virus is attributed to the treatment intervention. Second, the clinical assessment of virologic cure, sustained virologic response (SVR), is an objective and reliable endpoint of treatment efficacy that correlates with improvement in clinical outcomes and is routinely assessed by practicing physicians.⁵ Finally, chronic hepatitis C treatment durations are relatively short and highly effective interventions, limiting the extent of missing data from real-world observational studies.

The FDA and HCV-TARGET

HCV-TARGET is a cooperative academic consortium that is partially

supported through a National Institutes of Health Clinical and Translational Science Award, augmented with substantial support from pharmaceutical sponsors. The organization, headed by a Steering Committee of hepatology experts including a Clinical Coordinating Center based at the University of Florida and a Data Coordinating Center based at the University of North Carolina, has forged key partnerships between academic centers, community sites, and private industry (Figure 1). The Steering Committee provides oversight and guidance to HCV-TARGET. The HCV-TARGET Industry Advisory Council, composed of 1 representative from each industry sponsor, serves in a nonvoting advisory capacity to the Steering Committee and provides input on the use of network data and new initiatives consistent with the goals of HCV-TARGET. The FDA Advisory Council advises the HCV-TARGET Network as part of their ongoing charge to protect and improve public health by ensuring the safety, and efficacy of drugs, biological products, and medical devices related to HCV. The Community Advocate Representatives provide input on the needs and ideas of the HCV community in framing new initiatives and long-term goals for HCV-TARGET. A formal memorandum of understanding formed the basis for development of scientific collaborations, outreach, and educational initiatives, and intellectual partnerships between FDA and HCV-TARGET. Last, the Publications Committee oversees the activities of the scientific publications and presentations of HCV-TARGET. This committee assures the appropriate public dissemination of HCV-TARGET Network data, the completion of manuscripts, and adherence to principles of authorship and conflicts.

HCV-TARGET established a common research database to be able to conduct a longitudinal observational study to evaluate use of approved DAAs for the treatment of hepatitis C in clinical practice to (1) rapidly inform strategies for better management of populations represented and underrepresented in clinical trials, (2) identify and remediate gaps relative to



HCV-TARGET

B HCV-TARGET: clinical sites

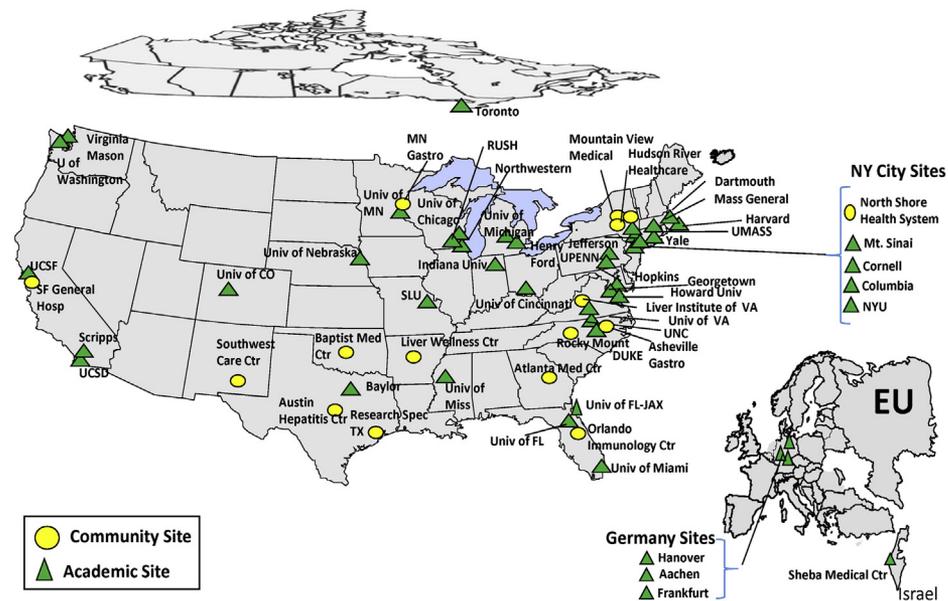


Figure 1.(A) The Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) is led by University of Florida and the University of North Carolina. The Clinical and Data Coordinating Centers (*blue*) are responsible for the overall management of the study. The Steering Committee (*red*) is consulted on all matters having network-wide scientific or operational impact. (B) HCV-TARGET clinical sites across North America, Europe, and Israel including academic sites (*green triangle*) and community sites (*yellow circle*).

treatment guidelines, (3) describe adverse event management to optimize treatment, and (4) serve as the core resource for collaborative translational studies using biospecimens and clinical data from diverse patient populations. Through this collaboration, the FDA has access to the HCV-TARGET resources to further inform use of newly approved HCV drugs in an actual clinical practice setting. The collaboration provides a robust platform for FDA scientists to learn from study data to inform areas for improvement in clinical trial design.

The HCV-TARGET model allows rapid data acquisition across multiple regimens being used in a disease population receiving care in routine clinical practice. Thus, the study design is disease focused, and not drug specific. This allows for continuous acquisition of data as new drugs enter the market.

Data Collection Methods and Standards

HCV-TARGET uses innovative approaches related to bioinformatics,

epidemiology, biostatistics, and health care data systems integration. Patients at participating sites are consented prospectively for participation. HCV-TARGET uses a centralized data abstraction process that minimizes burden on research sites and reduces data variability owing to difference in interpretation of medical records. The site redacts protected health information from the entire electronic medical record and transmits it electronically to the Clinical Coordinating Center where the data are entered in a

Table 1. Selected Demographics and Baseline Characteristics of Enrolled Patient Population

	TARGET 1.0	TARGET 2.0	TARGET 3.0
Timeframe	December 2011–November 2013	November 2013–December 2014	December 2014–present
Enrollment (n)	2774	2453	5226
Regimens	Boceprevir/pegylated interferon/ ribavirin Telaprevir/pegylated interferon/ ribavirin	Sofosbuvir/ribavirin Sofosbuvir/pegylated interferon/ ribavirin Simeprevir/pegylated interferon/ ribavirin Simeprevir/sofosbuvir with or without ribavirin	Ledipasvir/sofosbuvir ± ribavirin Daclatasvir/sofosbuvir ± ribavirin Paritaprevir/ritonavir/ombitasvir/ dasabuvir ± ribavirin Grazoprevir/elbasvir Sofosbuvir/velpatasvir
Demographics (%)			
Age > 65 y	7.3	19.3	22.8
Race (black)	16.2	11.3	23.9
HCV genotype 1	97.0	70.0	89.6
Treatment naïve	40.9	48.4	57.5
Treatment experienced	59.1	51.6	42.4
Presence of cirrhosis	39.1	50.3	35.3
Hepatic decompensation	7.8	24.1	15.7
Liver transplantation	1.8	11.4	8.9

HCV, hepatitis C virus; TARGET, Hepatitis C Therapeutic Registry and Research Network.

standardized format into the HCV-TARGET research electronic data capture database. The database was established to be compliant with Title 21 of the Code of Federal Regulations Part 11 governing electronic records and adherent to Clinical Data Interchange Standards Consortium standards that facilitate data exchange to both sponsors and the FDA. HCV-TARGET's comprehensive, observational cohort uses meticulous data collection methods that have <2% missing data elements and <5% loss to follow-up.

Notable Outcomes

Since inception in 2011, HCV-TARGET has enrolled >10,000 patients treated with HCV DAA-based regimens approved by the FDA (Table 1). The HCV-TARGET protocol allows for enrollment of populations that may have been underrepresented in premarket clinical trials; this data may be useful in understanding the safety and/or effectiveness in these subpopulations. Thus, patients from underrepresented minorities, those with cirrhosis, decompensated cirrhosis, and those undergoing liver transplant, for example, have been oversampled compared with the general population of patients treated for hepatitis C and

those enrolled in clinical trials (Table 1).

Boceprevir and Telaprevir

HCV-TARGET analyzed the experiences of >2000 patients who were among the first patients in the United States to receive triple therapy with telaprevir or boceprevir in combination with pegylated interferon (PEG-IFN) and ribavirin.^{6,7} The results demonstrated that patients treated in clinical practice with these agents had high rates of advanced disease (38% cirrhosis), had lower SVR rates, and were more likely to sustain significant adverse events than participants in the registrational trials. Rates of anemia and treatment discontinuations in the HCV-TARGET analysis were higher than reported for the pivotal registrational trials, although the HCV-TARGET population had more advanced liver disease.^{8–11} The lower SVR rates in HCV-TARGET could be explained by the higher proportion of patients with cirrhosis and of African American patients, factors that have all been associated with lower SVR.¹²

Sofosbuvir and Simeprevir

The usefulness of the HCV-TARGET model was apparent in 2013 when 2 new “triple therapy” regimens became available: simeprevir in combination

with PEG-IFN and ribavirin, and sofosbuvir in combination with PEG-IFN and ribavirin. Given that PEG-IFN, the backbone of HCV treatment for more than a decade, had numerous side effects and contraindications for use in many patients, physicians were seeking all-oral, well-tolerated, and highly effective alternatives. A small phase II study that combined simeprevir plus sofosbuvir, without PEG-IFN, demonstrated remarkably high SVR rates with only 12 to 24 weeks of therapy in difficult-to-cure populations.¹³ Shortly thereafter, the “off-label” all-oral regimen of simeprevir plus sofosbuvir became one of the most frequently prescribed regimens for patients in the United States. The HCV-TARGET network accrued data on safety and effectiveness of this unapproved regimen in nearly 1000 patients in routine clinical practice.¹⁴

The FDA also became aware of the extent of “off-label” use of the simeprevir and sofosbuvir combination regimen and reviewed the FDA's Adverse Event Reporting System database to identify any safety signals for this off-label combination use. However, a major limitation of the Adverse Event Reporting System is a reliance on passive reporting of adverse events by health care professionals or consumers, which unfortunately may include incomplete

information on relevant patient characteristics, baseline disease information, comorbid conditions, or concomitant medications.¹⁵ Selective reporting also makes it difficult to assess the incidence of unexpected adverse events when medications are used in a broader population outside of clinical trials.

Coinciding with this “off-label” use of the simeprevir and sofosbuvir combination regimen, an efficacy supplement was submitted to the FDA in 2014 to support the use of these 2 drugs together based on the previously mentioned phase II results.¹⁶ The sponsor approached the HCV-TARGET group to obtain the overall safety and effectiveness data evaluated in the HCV-TARGET database and submitted the summary data to the FDA to provide supportive evidence and reassurance in terms of safety of the combination regimen. Based on a comprehensive review of the available data, the simeprevir indication was expanded to include its use in combination with sofosbuvir providing an all-oral treatment option for patients. Final results from 2 phase III confirmatory trials, specifically submitted to fulfill the postmarketing commitments, are comparable with the results generated from HCV-TARGET in a real-world setting.^{17,18}

Sofosbuvir and Ledipasvir

The HCV-TARGET consortium continued to accrue data as other approved therapeutic regimens entered clinical practice. A phase III study of sofosbuvir plus ledipasvir suggested that patients with favorable treatment characteristics at baseline when treated for an 8-week duration had similar SVR rates compared with those treated for 12 weeks.¹⁹ FDA labeling of the sofosbuvir plus ledipasvir regimen states that treatment for 8 weeks could be considered for patients who were genotype 1 without cirrhosis, treatment naïve, with pretreatment HCV RNA viral load of <6 million IU/mL. As a cost savings measure, payers frequently mandated the shortened duration regimen, which raised concerns for practitioners, particularly when patients had

advanced fibrosis or levels of viremia at the upper boundary of 6 million IU/mL. HCV-TARGET performed a detailed analysis of patients who met the labeled criteria for shortened duration therapy and who subsequently received only 8 weeks treatment compared with similar patients who received 12 weeks of therapy.²⁰ The SVR12 rate was 96% (95% CI, 94-99) in the group that received 8 weeks (244/255) and 98% (95% CI, 95-99) in the group that received 12 weeks (289/296). These results suggest that the shortened duration of treatment in usual clinical practice paralleled the results obtained in phase III clinical trials.

Specific Populations

Often, the safety and efficacy data to inform treatment decisions in specific subpopulations such as transplant recipients or those with advanced liver disease such as decompensated liver disease becomes available at some point after approval. The HCV-TARGET network was instrumental in systematically collecting these data as clinicians were using these regimens after approval in subpopulations with unmet needs (Table 1).²¹⁻²⁴ From the data on early DAA regimens assessed in HCV-TARGET database, treatment for genotype 3 patients with decompensated cirrhosis was identified as an unmet need.²²

Monitoring of Serious Adverse Events

The FDA is committed to ensuring safety throughout the life cycle of a drug from premarket testing and clinical development through postmarketing surveillance and risk management.²⁵ The FDA may identify a new safety signal or identify more serious or more frequent reports of a known safety risk from various sources during the postmarketing period once a drug is used in a real-world setting. The HCV-TARGET platform characterizes and tabulates all adverse events abstracted from redacted medical records provided by clinicians throughout treatment and posttreatment follow-up. Serious adverse events

are monitored and queried to generate a complete understanding of the event and the results are reported to sponsors and the FDA. Both regulatory authorities and sponsors have access to HCV-TARGET resources that have been used to evaluate reports of unexpected adverse events for a variety of situations, including (1) the interactions of sofosbuvir and amiodarone causing bradyarrhythmia, (2) the safety of specific regimens in patients with decompensated cirrhosis, (3) the prevalence of baseline resistant-associated variants in usual clinical practice, and (4) the incidence of hepatocellular carcinoma recurrence after SVR with a DAA regimen. Thus, HCV-TARGET uses an evidence-based approach to evaluate the postmarketing experience of these drugs. These data are reviewed as part of the comprehensive assessment of the identified safety risk.

In general, the interpretation of postmarketing safety data involves a benefit–risk assessment based on the review of data from multiple sources such as spontaneous adverse event reports, observational studies, clinical trials, published literature, and estimates of drug usage and background rates of the adverse event. The relevant data are interpreted in the context of the known safety and efficacy profiles, as demonstrated in clinical trials supporting approval. The totality of the existing information is taken into consideration when assessing the public health risks of an approved drug. Based on appropriate scientific data, the FDA may require certain postmarketing studies and clinical trials to further assess a known serious risk, and/or to assess signals of serious risk, and/or to identify an unexpected serious risk when available data indicate the potential for a serious risk.²⁶ Nontraditional sources of information, such as that generated by HCV-TARGET, have demonstrated usefulness as an important component in informing the postmarketing safety of new HCV treatments.

Limitations

There are several limitations to HCV-TARGET database. First, there is

no control group of untreated hepatitis C patients. Without an unexposed control group, the causality assessment of adverse outcomes cannot always be ascertained; uncertainty may remain as to whether the observed adverse reactions are due to the treatment regimen, progression of underlying disease, other comorbid conditions and/or effects secondary to concomitant medications. Second is the issue of selection bias; it cannot be determined how the proportion of patients who enrolled (received treatment) is different from nonenrollees who did not receive treatment. In addition, the demographics of the enrolled population may change over time based on criteria used by third-party payers for coverage of available treatment options.

Moving Forward

Comparative effectiveness trials are important and informative to compare the safety profile and the efficacy of various approved regimens. Although the approved DAA regimens have demonstrated robust efficacy and reasonable safety across a range of genotypes, most of the regimens have been approved using placebo-controlled, historic-controlled, or dose- and duration-controlled trials with limited direct comparison against other approved regimens. This information gap is important for practitioners who may be interested in a direct comparison between these approved regimens to best inform the ideal regimen based on a patient demographics and viral genotype and subtype. When comparative trials are not feasible to conduct before approval, effectiveness data can be collected postmarketing as demonstrated in HCV-TARGET database.

This use of systematically collected observational cohort data to demonstrate clinical effectiveness holds promise. Real-world effectiveness data could provide supportive evidence if included as a component of an overall benefit-risk assessment with other studies and can contribute to the totality of data available for regulatory decision making. Longitudinal follow-up

cohort studies provide a means to assess long-term outcomes in the setting of SVR and obtain much needed safety data once a drug is used more widely and under more diverse conditions in a real-world setting. The data generated will help to provide important safety and effectiveness information on how the drugs performed in the more diverse populations in which they are intended for use. In addition, the results may further guide providers and patients to assure safe and effective use of drugs. This public-private partnership provides a neutral platform for academia, pharmaceutical companies, and regulatory agencies to collaborate and work effectively to reach mutual goals of responding to public health needs in a timely manner.

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References

- Mishra P, Murray J, Birnkrant D. Direct-acting antiviral drug approvals for treatment of chronic hepatitis C virus infection: scientific and regulatory approaches to clinical trial designs. *Hepatology* 2015; 62:1298–1303.
- Florian J, Mishra P, Arya V, et al. Direct-acting antiviral drugs for the treatment of chronic hepatitis C virus infection: interferon free is now. *Clin Pharmacol Ther* 2015; 98:394–402.
- HCV-TARGET. Hepatitis C Therapeutic Registry and Research

Network. Available at: <http://hcvtarget.org/index.php/2013/08/29/fda-news-release-aug-29-2013/>. Accessed December 8, 2016.

- Di Bisceglie AM. Natural history of hepatitis C: its impact on clinical management. *Hepatology* 2000; 31:1014–1018.
- US Food and Drug Administration (FDA). Guidance for industry chronic hepatitis C virus infection: developing direct-acting antiviral drugs for treatment (draft May 2016). Available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf. Accessed March 8, 2017.
- Sterling RK, Kuo A, Rustgi VK, et al. Virological outcomes and treatment algorithms utilisation in observational study of patients with chronic hepatitis C treated with boceprevir or telaprevir. *Aliment Pharmacol Ther* 2015;41:671–685.
- Gordon SC, Muir AJ, Lim JK, et al. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. *J Hepatol* 2015; 62:286–293.
- Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364:1195–1206.
- Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405–2416.
- Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364:1207–1217.
- Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; 364:2417–2428.
- Ghany MG, Nelson DR, Strader DB, et al. An Update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice Guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011;54: 1433–1444.
- Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir,

- with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *Lancet* 2014;384:1756–1765.
14. Sulkowski MS, Vargas HE, Di Bisceglie AM, et al. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. *Gastroenterology* 2016;150:419–429.
 15. US Food and Drug Administration (FDA). Adverse Event Reporting System (FAERS). 2016. Available at: www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm. Accessed December 8, 2016.
 16. US Food and Drug Administration (FDA). Supplemental New Drug Application Approval letter. Available at: www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/205123Orig1s002ltr.pdf. Accessed March 23, 2017.
 17. Kwo P, Gitlin N, Nahass R, et al. Simeprevir plus sofosbuvir (12 and 8 weeks) in hepatitis C virus genotype 1-infected patients without cirrhosis: OPTIMIST-1, a phase 3, randomized study. *Hepatology* 2016;64:370–380.
 18. Lawitz E, Matusow G, DeJesus E, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: a phase 3 study (OPTIMIST-2). *Hepatology* 2016;64:360–369.
 19. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014;370:1879–1888.
 20. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. *Gastroenterology* 2016;151:1131–1140.
 21. Brown RS Jr, O’Leary JG, Reddy KR, et al. Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: real-world experience from the hepatitis C therapeutic registry and research network. *Liver Transpl* 2016;22:224–2233.
 22. Feld JJ, Maan R, Zeuzem S, et al. Effectiveness and safety of sofosbuvir-based regimens for chronic HCV genotype 3 infection: results of the HCV-TARGET Study. *Clin Infect Dis* 2016;63:776–783.
 23. Reddy KR, Lim JK, Kuo A, et al. All-oral direct-acting antiviral therapy in HCV-advanced liver disease is effective in real-world practice: observations through HCV-TARGET database. *Aliment Pharmacol Ther* 2017;45:115–126.
 24. Saxena V, Khungar V, Verna EC, et al. Safety and efficacy of current DAA regimens in kidney and liver transplant recipients with hepatitis C: results from the HCV-TARGET Study. *Hepatology* 2017 May 15 [Epub ahead of print].
 25. US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Drug safety priorities 2016: initiatives and innovation. Available at: www.fda.gov/Drugs/DrugSafety/ucm522941.htm. Accessed June 5, 2017.
 26. US Food and Drug Administration (FDA). Guidance for industry post-marketing studies and clinical trials—implementation of section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. April 2011). Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf. Accessed June 2, 2017.

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Conflicts of interest

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