Clinical utility of ledipasvir/sofosbuvir in the treatment of adolescents and children with hepatitis C

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Abstract: Chronic infection with hepatitis C virus (HCV) affects an estimated 0.1%–2% of the pediatric population in the United States. While the clinical course in young children is indolent, adolescents who contract HCV have a disease course similar to adults, with a 26-fold increased risk of chronic liver disease-associated mortality, hepatocellular carcinoma, and need for curative liver transplantation. Furthermore, adolescent patients are entering childbearing age and carry a risk of passing HCV to their offspring via vertical transmission. Pegylated-interferon (PEG-IFN) with ribavirin was previously the only treatment option for pediatric patients with chronic hepatitis C (CHC), but the high likelihood of adverse reactions and subcutaneous route of administration limited its use and efficacy. Recently, the direct-acting antivirals (DAAs) ledipasvir (LDV) and sofosbuvir (SOF) were approved for adolescents with CHC. This review discusses the natural history of CHC in pediatric patients, data supporting LDV/SOF in adolescents, and ongoing studies evaluating DAAs in pediatric patients.

Keywords: hepatitis C virus, chronic hepatitis C, adolescent, pediatric, direct-acting antivirals

Introduction
Hepatitis C virus (HCV) is an RNA virus that affects more than 180 million people worldwide.1 The HCV seroprevalence rate is 1%–1.5% in North America, with 0.17% in 6–11-year-olds and 0.39% in 12–19-year-olds. HCV is the primary cause of chronic hepatitis of infectious etiology in children in industrialized countries2 and is estimated to affect 0.1%–2% of children in the United States.3 Chronic HCV infection (CHC) is defined by the presence of serum HCV RNA for at least 6 months after the onset of infection and includes the ensuing complications from liver injury that may develop.1 In the USA, it is estimated 23,000–46,000 children have CHC,4 and who are thus at risk for cirrhosis, hepatocellular carcinoma, and death.5

HCV virology
HCV is from the Flaviviridae family and hepacivirus genus and is a single-stranded, positive sense RNA virus. There are six genotypes, as well as 100 subtypes, which are denoted by lower-case letters.6 The six genotypes follow a geographic distribution. Genotype 1 is the most prevalent worldwide and accounts for the majority of HCV infections in North America (genotype 1a) and Europe (genotype1b). Genotype 2 is found in regions of Africa. Genotype 3 is commonly found in Asia, Europe, and Australia. Genotype 4 is mostly found in North Africa and the Middle East. Genotype 5 is found in Southern Sub-Saharan Africa. Lastly, genotype 6 is found mainly in...
Clinical course of HCV infection in pediatric patients
The transmission of HCV is through blood contact. Before widespread blood screening efforts were established in 1992, transmission of HCV to pediatric patients occurred mostly through blood transfusions and organ transplantations. After 1992, vertical transmission has become the most common means of HCV transmission in children. Approximately 7,500 new cases of CHC occur annually in the US from vertical transmission. There is increasing concern for horizontal transmission through injection drug use, especially among adolescents. HCV infection rates are rising among adolescents and young adults in the US, especially in eastern rural regions of the country. This is associated with the opioid epidemic and increased use of injected opiates. As these individuals are entering childbearing age, the risk of vertical transmission will also increase. Spontaneous clearance of infection occurs in 25%–40% of infected infants but occurs far less frequently in older children (6%–12%). Thus, the majority of children (54%–86%) exposed to HCV will progress to develop CHC.

For CHC acquired in childhood, the clinical course is indolent and usually asymptomatic. However, adolescents who acquire CHC have a clinical course similar to adults, with at 26-fold increased risk of liver-associated mortality, hepatocellular carcinoma, and need for liver transplantation, compared to age-matched controls. Additionally, the 10-year cost associated with pediatric HCV infection is estimated to be $199–336 million as pediatric patients with CHC have decreased quality of life from learning disorders, developmental delay, and cognitive deficits reflective of decreased executive function. Thus, it is critical to treat HCV infection in pediatric patients, in order to prevent progression of liver disease, development of hepatocellular carcinoma, transmission to subsequent generations, and to improve childhood development.

Medical therapy for pediatric patients with CHC
Prior to 2017, the only US Food and Drug Administration (FDA) approved therapy for CHC in pediatric patients aged three and older was pegylated-interferon-alpha (PEG-IFN) given in combination with ribavirin. However, in 2017, both the European Medicines Agency (EMA) and the FDA approved the use of fixed-dose ledipasvir/sofosbuvir (LDV/SOF) 90 mg/400 mg once daily to treat adolescents (ages 12–17 or weight >35 kg) with CHC with genotypes 1 and 4. Treatment duration is 12 weeks, unless patients have cirrhosis and previously failed therapy with PEG-IFN/ribavirin, in which case treatment duration is 24 weeks. Sofosbuvir with ribavirin is also approved to treat adolescents with CHC with genotypes 2 and 3. For patients with genotype 2, treatment is SOF 400 mg once daily with weight-based ribavirin (15 mg/kg in two divided doses) for 12 weeks. For patients with genotype 3, doses are the same but duration is 24 weeks (Table 1). There are ongoing trials for treatment with these agents for younger children. The current recommendation from the Hepatology Committee of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) is to consider waiting until younger children are old enough to receive approved therapy, or use these medications off-label in young children with severe disease (Table 2).

LDV and SOF are small molecules classified as direct-acting antivirals (DAAs). DAAs target a variety of viral enzymes, which are responsible for different parts of the HCV life cycle. The HCV genome encodes a precursor polyprotein, which is then processed by host peptidases and HCV proteases into structural (core, envelope E1, E2/p7) and non-structural (NS2: protease, NS3: protease, NS4A: NS3 cofactor, NS5A: involved in viral replication, NS5B: RNA polymerase) proteins. DAAs attack non-structural proteins, and are classified based on the non-structural proteins they inhibit.

LDV is an NS5A inhibitor and SOF is an NS5B nucleoside analog polymerase inhibitor. NS5A is an RNA binding

Table 1 Drugs approved by the EMA and FDA for the treatment of children with CHC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age (years)</th>
<th>HCV genotype</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>12–17</td>
<td>1, 4, 5, 6</td>
<td>90/400 mg PO daily</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>12–17</td>
<td>2, 3</td>
<td>400 mg PO daily</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>1–18</td>
<td>1–6</td>
<td>15 mg/kg PO daily divided in two doses</td>
</tr>
<tr>
<td>Interferon α–2b</td>
<td>3–18</td>
<td>1–6</td>
<td>six × 10^8 IU/m^2 SQ three times weekly</td>
</tr>
<tr>
<td>Pegylated interferon α–2b</td>
<td>3–18</td>
<td>1–6</td>
<td>1.5 mg/kg SQ once weekly</td>
</tr>
<tr>
<td>Pegylated interferon α–2a</td>
<td>5–18</td>
<td>1–6</td>
<td>100 mg/m^2 SQ once weekly</td>
</tr>
</tbody>
</table>

Abbreviations: CHC, chronic hepatitis C; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HCV, hepatitis C virus; PO, per os; SQ, subcutaneous.
Sofosbuvir/ledipasvir for adolescents with hepatitis C

Table 2 Current recommendations from ESPGHAN’s hepatology committee for the treatment of CHC in adolescents (children >12 years or weight >35 kg)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Quality of evidence and strength of recommendation per GRADE system</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotypes 1 and 4 should be treated with LDV/SOF 90/400 mg once daily for 12 weeks</td>
<td>C1</td>
</tr>
<tr>
<td>HCV genotype 1 with cirrhosis should be treated with LDV/SOF 90/400 mg once daily for 24 weeks</td>
<td>C2</td>
</tr>
<tr>
<td>HCV genotype 2 should be treated with SOF 400 mg once daily and weight-based ribavirin (15 mg/kg in two divided doses) for 12 weeks</td>
<td>C1</td>
</tr>
<tr>
<td>HCV genotype 3 should be treated with SOF 400 mg once daily and weight-based ribavirin (15 mg/kg in two divided doses) for 24 weeks</td>
<td>C1</td>
</tr>
<tr>
<td>IFN-free regimens are the best options for HCV-infected adolescents, regardless of liver disease stage and co-morbidities, and PEG-iFN with ribavirin is no longer recommended as of 2017 for the treatment of HCV in adolescents</td>
<td>C1</td>
</tr>
</tbody>
</table>

Abbreviations: C1, low quality of evidence, strong recommendation; C2, low quality of evidence, weak recommendation; CHC, chronic hepatitis C; ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HCV, hepatitis C virus; IFN, interferon; LDV/SOF, ledipasvir/sofosbuvir; PEG-iFN, pegylated interferon.

LDV/SOF use in adults

The introduction of DAAs in 2011 revolutionized CHC treatment in adults, and nowadays CHC in adults is considered curable. There are currently ten different oral regimens licensed by the EMA and FDA for treatment of CHC in adults. All regimens achieve high (>90%) sustained virologic response (SVR) rates with 12 weeks of therapy, regardless of genotype, stage of fibrosis, or presence of human immunodeficiency virus (HIV) infection. SVR is defined as undetectable HCV RNA after completion of therapy, usually evaluated 12 weeks after treatment completion and coined “SVR12”. Certain populations can even achieve equally high SVR rates with only 8 weeks of therapy.

The efficacy of LDV/SOF in treating adults with CHC genotype 1 was established in multiple Phase III trials, including ION-1,28 –2,29 and –3,27 along with a Japanese Phase III trial.30 The oral, once daily fixed dose pill of LDV/SOF 90 mg/400 mg was used in all four trials that ranged from 341 to 865 patients. These trials found SVR12 rates of ≥93% in both treatment-naïve and treatment-experienced patients, regardless of treatment duration (8, 12, or 24 weeks), as well as whether it was administered with or without ribavirin. Rates of virologic breakthrough ( reappearance of HCV RNA while on therapy) or relapse ( reappearance of HCV RNA after completion of therapy) were low in all four studies, ranging from 0%–6%.31 These findings have been corroborated in several large real-world observational and registry studies ranging from 600 to 14,000 patients.32–40 The efficacy of LDV/SOF for treating adults with CHC from other genotypes has also been supported by multiple Phase II trials,41–47 a Japanese Phase III trial, and real-world data from a French cohort.31

LDV/SOF has shown great safety and in treatment-naïve and treatment-experienced adult patients with CHC with all genotypes. Pooled analysis of the ION trials found that treatment-emergent adverse events (TEAEs) occurred in 74% of 1,080 LDV/SOF patients, and 85% of LDV/SOF with ribavirin patients, with most TEAEs mild to moderate in severity.48 Very few (0%–2%) of patients discontinued treatment due to TEAEs. The most common treatment-related adverse events (TRAEs) were fatigue (13%–18%), headache (11%–17%), nausea (6%–9%), diarrhea (3%–7%), and insomnia (3%–6%), most of which were grade 1 in severity.31 Treatment-emergent serious adverse events (SAEs) occurred in 2% of LDV/SOF patients and 3% of LDV/SOF with ribavirin patients; of these, ≤0.4% were considered treatment-related.33

LDV/SOF use in adolescents

In children, SVR24 (sustained virologic response 24 weeks after completion of therapy) corresponds to definitive cure
in 98%–100% of cases. With the successful use of DAA
in adults with CHC, there is now great interest in their use
in children. In the US, there are currently eight clinical trials
evaluating DAA in pediatric patients (Table 3).10

Data from a Phase II, multicenter open-label study (NCT
02249182) evaluating safety and efficacy of LDV/SOF in 100
adolescent patients aged 12–17 years with CHC genotype 1
showed an excellent SVR rate of 98%. In this study, patients
received fixed-dose LDV/SOF 90 mg/400 mg once daily for
12 weeks. Patient demographics were: 37% were males and
63% were females, 90% were white, and average weight was
61 kg (range 33–126 kg). HCV history was: average baseline
HCV RNA log10 IU/mL 6.0 (range 4.7–7.0) with 55% hav-
ing HCV RNA >800,000 IU/mL, 81% genotype 1a, 80%
treatment-naive, 1% with cirrhosis, and 84% infected through
vertical transmission. Pharmacokinetic evaluation of LDV,
SOF, and the SOF metabolite GS-331007 was comparable
to those of adult patients receiving the same dose in Phase II
and III trials. The primary efficacy endpoint was percentage
of patients achieving SVR12, which occurred in 98/100
(98%) patients, including the one patient with cirrhosis. The
two patients in which SVR12 was not achieved were lost to
follow-up either during or after treatment, but both had
undetectable viral loads at the time of their last visit. None of
the 98 patients achieving SVR experienced virologic break-
through or relapse. Adverse reactions were similar to the adult
population, including headache (27%), diarrhea (14%), and
fatigue (13%), with no serious adverse events or treatment
discontinuation reported. Nine patients developed transient
grade 3–4 (severe or life threatening) laboratory abnormali-
ties which later resolved after treatment completion. There
was no effect on child development through the 12 weeks of
treatment.17 Currently, follow-up to evaluate for SVR24 after

treatment is in process, as are studies in other age groups
(3–11 years) and genotypes (4, 5, and 6). Estimated date of
study completion is July 2018.10

A prospective, multicenter open-label study in Egypt
of 144 adolescents (mean age 14 years, range 12–16 years,
69% males) with CHC with genotype 4 treated with fixed
dose LDV/SOF 90 mg/400 mg once daily for 12 weeks also
showed promising results. In this cohort, 128/144 (89%)
were treatment-naive with mean baseline HCV RNA log10
IU/mL 5.26 (range 3.70–6.73). Transient elastography mea-
surements revealed 96/144 (67%) had F0/F1 fibrosis, 48/144
(33%) had F2 fibrosis, and there were no patients with F3–4
fibrosis or cirrhosis. Virologic monitoring was performed
before treatment, at weeks 4 and 12 of treatment, and 12
weeks after treatment. SVR12 was achieved in 142/144 (99%)
of patients. The two patients that did not achieve SVR12 were
treatment naive and had early virologic response to LDV/
SOF but relapsed. No serious adverse events were observed,
and no patients discontinued therapy due to adverse events.
Headache was the most common side effect (20%), and
treatment-experienced patients had significantly higher rates
of pruritus (31%, P=0.007), diarrhea (44%, P<0.001), and
rash (19%, P=0.002) compared to treatment-naive patients.
One treatment-naive patient developed hyperbilirubinemia
and anemia, and one treatment-experienced patient developed
anemia. Both of these laboratory abnormalities resolved after
the end of treatment.14

Other published DAA data in
adolescents
SOF and ribavirin use in adolescents
Data from a Phase II, multicenter, open-label study (NCT
02175758) evaluating safety and efficacy of SOF with riba-
virin in 52 patients aged 12–17 years (median age 15 years)
with CHC with genotype 2 or 3 also showed promising
results.13 Thirteen patients genotype 2 (25%) and 39 with
genotype 3 (75%) infection were recruited from 30 study sites

<table>
<thead>
<tr>
<th>Drug</th>
<th>HCV genotype</th>
<th>Study identifier</th>
<th>Estimated completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glecaprevir/pibrentasvir</td>
<td>1–6</td>
<td>NCT 03067129</td>
<td>May 2022</td>
</tr>
<tr>
<td>Gratitsovir + ribavirin</td>
<td>1–6</td>
<td>NCT 02486406</td>
<td>June 2018</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>1, 4</td>
<td>NCT 02869242</td>
<td>April 2019</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir + ribavirin</td>
<td>1, 4, 5, 6</td>
<td>NCT 02249182</td>
<td>July 2018</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin</td>
<td>1, 4</td>
<td>NCT 02486406</td>
<td>September 2019</td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir</td>
<td>4</td>
<td>NCT 03080415</td>
<td>June 2018</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin</td>
<td>2, 3</td>
<td>NCT 02175758</td>
<td>April 2018</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>1–6</td>
<td>NCT 03022981</td>
<td>December 2019</td>
</tr>
</tbody>
</table>

Abbreviations: CHC, chronic hepatitis C; DAA, direct-acting antivirals; HCV, hepatitis C virus.
in Australia, Germany, Italy, New Zealand, Russia, the UK, and the US. Most patients (43/52, 83%) were treatment-naïve, 60% (31/52) were male, and 90% (47/52) were white. No patients had known cirrhosis; 21/52 (40%) were documented as not having cirrhosis, and the remainder were not assessed for presence or absence of cirrhosis. All received SOF 400 mg once daily, and weight-based ribavirin (15 mg/kg divided into two doses), either for 12 weeks (genotype 2) or 24 weeks (genotype 3). The adult dose of SOF 400 mg was given as pharmacokinetic results showed similar plasma exposure and safety profiles. Pharmacokinetic studies for SOF and GS-331007 were also done at day seven in the first 10 patients enrolled, as well as with sparse sampling throughout treatment, and were found to be comparable to prior SOF studies with adults. The primary efficacy endpoint was the percentage of patients achieving SVR12, which was achieved in 98% (51/52) of patients. The single patient who did not achieve SVR12 had HCV genotype 3 and was lost to follow-up after 4 weeks of treatment during which the viral load was already undetectable. The most common adverse events were nausea (27%) and headache (23%), and no patients discontinued treatment due to adverse events. Only one patient reported a grade 3 (severe) adverse event, which was a shoulder joint injury that was not considered related to the study drug. The study is ongoing in younger children. The dose of SOF for patients aged 6–11 will be 200 mg. This dosing is from pharmacokinetic data in adults, along with a lead-in group of patients in the 6–11 age group. Pharmacokinetic lead-in results for patients aged 3–5 are pending.

In addition, there is an ongoing study Phase II/III in Egypt evaluating the safety and efficacy of gratisovir (a generic of sofosbuvir) and ribavirin in pediatric patients with CHC 10–18 years in age (NCT 02985281). Generic versions of sofosbuvir have been studied in adults with CHC genotype 4 in Egypt. One study found no significant difference in SVR12 rates between patients treated with ribavirin and either gratisovir or gradeziano, which are both generic versions of sofosbuvir. Another study found that dual gratisovir/daclatasvir treatment duration tailored according to vRVR at 8 or 12 weeks was non-inferior compared to a fixed 12-week treatment duration.

**Sofosbuvir and daclatasvir use in adolescents**

Sofosbuvir and daclatasvir therapy for 12 weeks is an option for the treatment of CHC (all genotypes) in adults. Furthermore, a study in adults who achieved very rapid virologic response (vRVR, defined as undetectable serum HCV RNA by week 2 of treatment) showed that decreasing the duration of therapy to 8 weeks was non-inferior to the standard 12-week treatment course. In adolescents, there has been a pilot study of a cohort of 10 adolescents from Egypt with CHC from any genotype treated with SOF and daclatasvir. The first ten consecutive adolescent patients who fulfilled eligibility criteria were treated with weight-based SOF and weight-based daclatasvir; as all patients weighed >40 kg, they all received the adult doses of 400 mg and 60 mg once daily, respectively. All achieved vRVR at week 2, thus all received 8 weeks of treatment instead of 12 weeks. All patients completed 8 weeks of treatment, and SVR12 was achieved in all patients. Six patients reported adverse events, including nausea, abdominal pain, fatigue, and headache; all were mild to moderate in severity.

**LDV/SOF use in children**

There is preliminary data from 90 children (aged 6–11 years) treated with SOF/LDV 45 mg/200 mg, with or without ribavirin. Of the 90 children, there were 86, 3, and 2 with genotypes 1, 3, and 4 respectively; 59% were male, 79% were whites, and 80% were treatment-naïve. Median age was 9 years, median weight was 33 kg, and median BMI was 18 kg/m². Pharmacokinetic evaluation was done on day 10 in the first 12 participants, and found that LDV, SOF, and GS-331007 exposures were equivalent to those in adults. At the time of this review, 88/90 patients had completed therapy, and the rate of SVR at 4 weeks post-treatment (SVR4) in these 88 patients was 99% (87/88); one genotype 1a patient relapsed at 12 weeks of LDV/SOF therapy. No patients experienced grade 3 or 4 adverse events, and the only serious adverse events reported were a tooth abscess, abdominal pain, and gastroenteritis not believed to be related to the study drug. The most common adverse events were abdominal pain, headache, diarrhea, vomiting, nausea, fatigue, fever, cough, and oropharyngeal pain.

**Ongoing DAA trials for pangenotype CHC in pediatric patients**

Of the ongoing clinical trials evaluating DAAs in pediatric patients with CHC, there are two which are evaluating CHC from all genotypes: sofosbuvir/velpatasvir and glecaprevir/pibrentasvir.

**Sofosbuvir/velpatasvir (SOF/VEL)**

Velpatasvir (VEL) is an NSSA inhibitor and is given with SOF as a single-tablet combination DAA. This was the first...
single-tablet pangenotype DAA therapy for CHC. In adults, SVR12 rates range between 95% and 100% in a variety of populations, including those with compensated cirrhosis and prior treatment failures. Duration of treatment is 12 weeks, regardless of genotype, prior treatment, cirrhosis, or presence of NS5A-resistant mutations. Patients with uncompensated cirrhosis are also treated with ribavirin. Adverse reactions include fatigue, headache, nausea, and nasopharyngitis, but it is overall well tolerated.61 The pediatric clinical trial (NCT03022981) is ongoing and is a Phase II trial with two parts: pharmacokinetics lead-in phase and treatment phase. The pharmacokinetic phase will evaluate pediatric SOF/VEL dosing; the treatment phase will evaluate safety and efficacy of a 12-week course of treatment. Patients will be divided into three cohorts for the pharmacokinetic phase (ages 12 to <18, 6 to <12, and 3 to <6 years), and two cohorts for the treatment phase (ages 12 to <18, and 3 to <12 years). Estimated enrollment is 200 patients, with estimated primary completion date December 2019.62

**Glecaprevir/pibrentasvir (GLE/PIB)**

Glecaprevir is an NS3/4A protease inhibitor, and pibrentasvir (PIB) is an NS5A inhibitor. GLE/PIB is effective across all HCV genotypes, including patients with chronic kidney disease (as it is minimally excreted by the kidneys), HIV infection, and compensated cirrhosis, as well as those who have failed a previous NS5A treatment regimen. In addition, treatment duration is shortened to 8 weeks in treatment-naïve patients without cirrhosis.63,64 The pediatric clinical trial (NCT03067129) is a Phase III trial evaluating the pharmacokinetics, safety, and efficacy of GLE/PIB. Patients will be divided into four age groups: 12 to <18, 9 to <12, 6 to <9, and 3 to <6 years. Some patients in all age groups will undergo pharmacokinetic evaluation to determine the pharmacokinetics of GLE/PIB in each age group, with the rest undergoing evaluation of safety and efficacy of GLE/PIB. Estimated enrollment is 110 patients, with estimated primary completion date September 2019.65

**Conclusion**

The development of DAAs has dramatically changed the landscape of HCV treatment in adults with CHC. LDV/SOF and SOF with ribavirin are now approved treatments for adolescents with CHC. There are few published studies examining DAAs in the pediatric population, and none with long-term follow-up. Furthermore, currently there is no data from controlled trials regarding DAA use in children with coinfections (such as hepatitis B virus or HIV), co-morbidities, or those who are nonsustained virological responders to DAAs.10 However, the results of DAAs in the adult population are encouraging for their expanded use in the younger population, and there have been promising cases of children successfully treated with DAAs who had cirrhosis.10,66,67 There are several ongoing clinical trials evaluating LDV/SOF and SOF with ribavirin in younger children. It is anticipated that more treatment options will become available to treat CHC in pediatric patients in the upcoming years.

**Disclosure**

Aijaz Ahmed is a consultant and advisory board member for AbbVie Pharmaceuticals, Gilead Sciences, and Janssen Pharmaceutical. Aijaz Ahmed has research funding/grant from Gilead Sciences. The authors report no other conflicts of interest in this work.

**References**


