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News on Viral Hepatitis in HIV: Update from the 2016 GEHEP Conference

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Abstract

The II Conference of the Group for the Study of Viral Hepatitis (GEHEP) (29 September-1 October, Spain) updated epidemiological, diagnostic and treatment aspects on viral hepatitis. The conference was mostly focused on the latest news related to HCV infection, including the successes achieved since the implementation of direct-acting antiviral agents for HCV therapy, but also in the new, future challenges for a real HCV eradication. The scenario for chronic HCV infection has dramatically changed in the last two years and most patients have been cured after 12 weeks of therapy with minimal side effects. However, as the experience of treatment increases, new challenges have emerged for the maximum optimization and success of therapy. Moreover, different issues need to be resolved for a real HCV eradication (i.e. unmasking HCV infection, prevention and diagnosis of HCV reinfections, diagnostic tools for treatment optimization). The latest advances in the knowledge on these topics were presented and discussed at this conference. Also, some interesting studies related to viral hepatitis E were addressed. This review summarizes some of the major findings reported and discussed during the GEHEP Conference. **(AIDS Rev. 2017;19:47-53)**

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Key words

Hepatitis C. HEV. HIV. GEHEP.

Introduction

The widespread use of direct-acting antiviral (DAA) agents for HCV therapy has dramatically changed the scenario of chronic HCV infection in the last two years. Current DAA combinations are highly effective and safe, allowing shortened treatment duration for most patients. Therefore, many HCV-infected patients have been treated and cured after 12 weeks of DAA-based therapies with minimal side effects[1,2]. However, despite these high rates of cure (> 90%) for most HCV-infected patients, the accumulated experience since the beginning of this new era for HCV treatment have identified specific profiles of patients for which the efficacy of these new therapies might be compromised. This is the case of specific genotypes such as genotypes 1a and 3 with advanced fibrosis stage (cirrhotic), previously exposed to HCV therapy or harboring baseline NS5A

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resistance-associated variants related with a poor response to NS5A inhibitors[3,4]. Hence, the latest updates of HCV treatment guidelines record specific recommendations for patients with these profiles, considering currently available drugs[5-7].

Moreover, there are several issues that need to be resolved for a real HCV eradication: unmasking HCV infection in the whole population and linking to care, preventing and diagnosing HCV reinfections among individuals already cured, or the implementation of diagnostic tools for treatment optimization. This is the case of the use of resistance testing to guide HCV therapy with some NS5A inhibitors and for specific patient populations (i.e. genotypes 1a or 3 and advanced fibrosis), or genotyping tools for monitoring patients with high risk of reinfection. Re-treatment of HCV-infected patients who failed DAA-based therapies is another issue that currently deserves special attention and therefore it is important to know the new upcoming therapeutic options for the design of optimal rescue therapies[8-10].

New data from real world experience using DAA-based therapies among different cohorts of patient populations, such as HIV-coinfected, the elderly, or HCV-infected patients with uncommon HCV genotypes or mixed genotypes, are still necessary for the maximum optimization and success of these therapies. Moreover, the identification of single nucleotide polymorphisms (SNP) associated with liver disease progression/regression are relevant in the current scenario for treatment prioritization strategies and optimization of clinical follow-up of patients after HCV cure[11,12].

Unlike HCV infection, cure is rare in the case of hepatitis B infection (HBV) due to the persistence of viral DNA in the form of covalently closed circular DNA (cccDNA) within the nucleus of infected cells[13]. During the conference, the state of the art in HBV drug research and progress made in the development of new compounds, such as immune modulators, inhibitors of gene expression, and potent inhibitors of ccDNA for chronic HBV eradication, were reviewed.

Hepatitis E virus (HEV) infections represent an emerging problem in Europe and the main cause of acute hepatitis in developing countries. Pigs and wild boar are the main reservoirs, and most autochthonous infections are probably caused by the consumption of uncooked or undercooked infected meat. Although most HEV infections are subclinical, in some groups of patients (i.e. immune-suppressed, transplant patients) they can progress to chronic infection[14,15]. Epidemiological studies evaluating the prevalence and the potential reservoirs for this infection are necessary to establish its magnitude and optimal prevention strategies. An interesting case report of an outbreak of HEV due to wild boar consumption has been described in the south of Spain during the GEHEP conference[16].

The latest advances in the knowledge on all these topics were presented at the II Conference of the Group for the Study of Viral Hepatitis (GEHEP, 29 September-1 October, Spain). This review summarizes the main issues discussed at this event.

HCV epidemiology

In the current DAA treatment era, HCV genotype and subtype must still be properly assessed and considered prior to treatment initiation because it continues to be one of the main factors driving the choice of therapy[5-7]. Although pan-genotypic treatment combinations are available, these are not equally effective in all cases[4]. Therefore, updated information on HCV genotype/subtype prevalence and distribution in specific populations[17,18] is very useful and needed at this moment to optimize diagnosis and treatment strategies. Moreover, there are scarce updated data regarding HCV seroprevalence in the general population, but also in specific populations (i.e. prisons). This is a key point on the road to HCV eradication as well as for unmasking HCV infection in the whole population and linking to care to treat and cure. Several relevant studies on these topics were presented at the conference.

Navarro, et al.[19] reported updated data of the GEHEP-005 study evaluating HCV prevalence and the distribution of HCV genotypes in Spain during the period 2000-2015. This was a retrospective study recruiting 48,947 patients from 29 hospitals from 11 different geographic regions in Spain. The annual distribution of HCV genotypes and subtypes, as well as, gender, age, transmission route, HIV and/or HBV coinfection and treatment, were recorded. The most prevalent genotype was G1 (68.4%), G1a (26.2%), and G1b (38.3%), followed by G3 (17.3%) and G4 (11.4%). The less represented genotypes were G2 (2.8%) and G5 and 6 (0.1%). HCV G1a, 3, and 4 were closely associated with male gender, parenteral route of transmission, and coinfection with HIV and/or HBV. Conversely, G1b was associated with female gender, non-parenteral route of transmission, and monoinfection. A different genotype distribution was observed based on age and

Table 1. Clinically relevant NS5A resistance-associated substitutions for specific direct-acting antiviral regimens

NS5A substitutions	DAA regimen
M28A/G/T	Sofosbuvir/ledipasvir Grazoprevir/elbasvir
Q30E/G/H/K/R	Sofosbuvir/ledipasvir Grazoprevir/elbasvir
Q30D/L	Grazoprevir/elbasvir
L31M/V	Sofosbuvir/ledipasvir Grazoprevir/elbasvir
L31F	Grazoprevir/elbasvir
P32L/S	Sofosbuvir/ledipasvir
H58D	Sofosbuvir/ledipasvir Grazoprevir/elbasvir
Y93C/H/N/S	Sofosbuvir/ledipasvir Grazoprevir/elbasvir
Y93H	Sofosbuvir/velpatasvir

DAA: direct-acting antiviral.

geographic region in Spain (center vs. north/south). Of note, a significantly higher prevalence of G1b was observed in individuals older than 69 years compared with those under 50 years (76.2 vs. 26.0%). Moreover, a significantly higher prevalence of G1a, 3, and 4 was observed in subjects under 50 years (31.3, 20.6, and 14.7%, respectively). Regarding the geographic distribution, a higher prevalence of G1b was observed in central Spain (46%) compared with the north (32.2%).

Another interesting study was presented by Daivozadeh, et al.[20], showing data describing the situation of HCV infection in several prisons in the south of Spain during 2016. They observed an HCV seroprevalence of 17.59% and 11.5% of chronic infection. Of them, 30% were HIV/HCV coinfected and most of them (92.2%) were naive for HCV therapy. A high proportion of patients had advanced fibrosis (F3-F4), especially those HIV/HCV coinfected (> 46%). These data show the urgent need for the implementation of treatment strategies in this population to reduce differences related with healthcare between prisoners and the general population.

Poveda, et al.[21] presented very interesting data related with unmasking HCV infection among primary care centers in the northwest of Spain among individuals born between 1960 and 1969, the range of age with the highest HCV seroprevalence in this medical area[22]. HCV testing was done in a total of 765 individuals using the OraQuick® HCV test in saliva. They found an HCV seroprevalence of 0.26% allowing an estimation of unmasking HCV infection in this region and considering the population born between 1960 and 1969 in 1,068 subjects. These results must be considered for the implementation of optimal strategies for HCV diagnosis in this population to advance to HCV eradication.

HCV resistance to direct-acting antivirals and prognosis factors

The accumulated experience since the introduction of DAAs for HCV treatment and the approval of new highly potent and pan-genotypic combinations have been modifying the recommendations for HCV resistance testing to guide the use of DAAs[5-7].

In the current treatment scenario, the relevance of HCV resistance is mainly focused on the NS5A region for genotypes 1a and 3. Several studies have shown that the presence of resistance-associated substitutions (RAS) at NS5A might compromise the virological response among genotypes 1a and 3 HCV-infected patients[3,4,23]. The latest recommendations from the European Association for the Study of the Liver (EASL) highlight that, in case of access to a reliable resistance

Table 2. Treatment recommendations for HCV-monoinfected and HIV/HCV-coinfected patients with NS5A resistance-associated substitutions

	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Grazoprevir/ elbasvir	Sofosbuvir/ daclatasvir
Genotype 1a				
Treatment-experienced* and/or cirrhosis	12 weeks with ribavirin or 24 weeks without ribavirin	12 weeks without ribavirin	16 weeks with ribavirin if HCV RNA > 800,000 IU/ml	12 weeks with ribavirin or 24 weeks without ribavirin
Genotype 3				
Treatment-experienced* and/or cirrhosis		12 weeks with ribavirin or 24 weeks without ribavirin		12 weeks with ribavirin or 24 weeks without ribavirin. If cirrhosis, 24 weeks with ribavirin

*HCV-infected patients who failed a treatment based on pegylated interferon/ribavirin, naive to direct-acting antivirals.

tests, the results of HCV resistance to NS5A inhibitors can be useful to guide physicians' decisions[6]. The presence of RAS that are clinically relevant (i.e. M28A/G/T, Q30D/E/G/H/K/L/R, L31F/M/V, P32L/S, H58D, Y93C/H/N/S) may influence decisions on the treatment regimen (Table 1). The presence of these variants would make necessary the use of ribavirin or prolonged treatment duration (16 or 24 weeks) for genotypes 1a and 3 under a NS5A-based regimen (Table 2).

Several studies evaluating the prevalence of RAS to DAAs were presented at the conference. One of the most relevant was presented by Pérez, et al.[24], assessing the prevalence of RAS among 255 patients with virological failure after a DAA-based therapy within the HepCREsp-GEHEP-004 cohort. The results confirm the high genetic barrier of sofosbuvir for the development of resistance; less than 2.6% of patients had RAS at NS5B. Conversely, they found a high prevalence of RAS at NS5A and NS3 in patients failing a DAA-based therapy, especially for genotypes G1a and 1b (> 78% had RAS). Interestingly, a high proportion of genotype 3 and 4 HCV-infected patients failed without RAS (53.6 and 68.5%, respectively). These data must be considered for re-treatment strategies.

Neukam, et al.[25] highlighted, in a prospective study performed in the GEHEP-MONO and the HEPAVIR-DAA national cohorts, the predictive value of HCV RNA levels at week 4 to predict sustained virological response (SVR) among HCV genotype 3-infected patients under DAA-based therapies without interferon (IFN). These findings might be useful for treatment monitoring in genotype 3 patients.

The influence of host genomics on HCV outcomes and progression of liver disease has been extensively evaluated in recent years. Indeed, the identification of the strong association of the SNPs within the interleukin 28 (IL28B) gene with both natural clearance and treatment responses of HCV to pegylated interferon alpha-ribavirin (pegIFNα-RBV)[26] has been one of the great milestones in the field of HCV infection. There are other SNPs under evaluation and some of them have been associated with liver disease progression, steatosis, hematological side effects, and metabolic disorders (i.e. PNPLA3, ITPA, mitochondrial haplogroups)[11,12].

In this field of research, Real, et al.[27] presented at the conference an interesting study demonstrating the association of the polymorphism rs738409 at the PNPLA3 gene with cirrhosis progression among 322 HIV/HCV-coinfected patients, and identified this variant as a prognostic factor for the development of hepatic fibrosis. Therefore, this information might be useful for prioritization of HCV treatment, especially for F0-F1 patients for whom there is no urgency for treatment.

Moreover, Álvarez-Osorio, et al.[28] identified the IL28B genotype as a predictive marker of sustained virologic response (SVR) at week 12 after the end of treatment among 190 genotype 4 patients under DAA-based therapies. Lack of SVR at week 12 was associated with CT and TT genotypes.

HCV therapy

In the last two years, many HCV-infected patients have been treated with DAA-based therapies with high efficacy (> 90%) and minimal side effects[1,2]. However, despite these high rates of cure for most HCV-infected patients, new challenges remain to obtain an overall benefit of HCV therapy for all chronic HCV-infected patients and for a maximum optimization and success of these therapies. During the conference, new data about these topics, including real world experience using DAA-based therapies among different cohorts of patient populations such as HIV-coinfected, chronic kidney disease, or among HCV-infected patients with uncommon HCV genotypes or mixed genotype populations, were presented.

A retrospective and observational study including 17 patients with chronic kidney disease exposed to DAAs was presented by Monzó, et al.[29] This study demonstrates the overall safety and efficacy of these antivirals; nine of them under sofosbuvir-based therapies and eight receiving ombitasvir/paritaprevir with or without dasabuvir.

Casas, et al.[30] highlighted the need to promote the implementation of alert systems and monitoring strategies for newly diagnosed HCV patients to avoid the lack of a link between primary and specialized care. They found high rates of HCV-diagnosed patients (> 43.52%) at the microbiology service not linked to physicians specialized in HCV infection. This issue represents an important challenge to HCV eradication.

Mancebo, et al.[31] presented new data from the GEHEP-MONO cohort, analyzing the situation of this cohort after the implementation of the Spanish Strategic Plan to cure HCV infection (April 2015-2016). A total of 574 chronic HCV-monoinfected patients from 27 infectious diseases units in Spain started DAA-based therapy during the study period. HCV genotype 1a was the most prevalent (44.9%) and 42 of them had cirrhosis. The most used DAA combination was sofosbuvir/ledipasvir for G1a and 1b followed by ombitasvir/dasabuvir/paritaprevir/r with or without ribavirin. For genotype 3, the most commonly used combination was sofosbuvir/daclatasvir, and for genotype 4 it was ombitasvir/paritaprevir/r plus ribavirin. This is very good news since most patients have been treated using IFN-free DAA-based therapies in Spain.

There is scarce data regarding the effectiveness of DAA-based therapies against infrequent HCV genotypes in western countries (i.e. genotype 5 and 2) and among mixed HCV genotype infections. Navarrete, et al.[32] reported novel data regarding this issue, evaluating the efficacy of DAA-based therapies among patients infected with HCV genotype 5 treated with sofosbuvir/ribavirin (n = 4) and sofosbuvir/ledipasvir, and HCV genotype 2 treated with sofosbuvir/ribavirin (n = 9). Moreover, they presented results among several mixed HCV genotype infections: genotypes 1 and 3 treated with sofosbuvir/daclatasvir; genotypes 1 and 4 treated with sofosbuvir/ledipasvir: genotypes 1a and 4 treated with sofosbuvir/ledipasvir/ribavirin; and genotypes 1b and 4 treated with sofosbuvir/ledipasvir. All patients harboring these infrequent genotypes or mixed HCV infections achieved SVR 12 weeks after the end of treatment.

Recently, an unexpected high rate of cancer recurrence has been reported after DAA treatment in patients with prior hepatocellular carcinoma[33]. Similarly, Merchante, et al.[34] reported at the GEHEP conference an increase in hepatocellular carcinoma diagnoses among 295 HIV/HCV-coinfected patients who achieved SVR after DAA IFN-free therapies during the period 2014-2016 compared with 2002-2011. These findings require further research to identify the reasons for these observations.

Hepatitis E

Hepatitis E virus (HEV) infections represent an emerging problem in Europe and are the main cause of acute hepatitis in developing countries. The main reservoirs are pigs and wild boar, with the most autochthonous infections probably being caused by the consumption of uncooked or undercooked infected meat[14]. Special attention was paid to HEV infection at the last GEHEP conference in which several studies addressing different aspects of this infection were presented. Specific diagnostic tools for the detection of HEV infection and an interesting case report of an outbreak of HEV due to wild boar consumption has been described. All the studies were performed by research teams from the south of Spain, a geographical region that shows a high prevalence of HEV infection[35]. Brieva, et al.[36] evaluated, among 19 symptomatic patients with detectable HEV viral load, the presence of immunoglobulin M (IgM) against HEV, finding anti-IgM in only 26.3% of patients (n = 5). The high rate of false negative results suggests that the determination of anti-IgM may not be diagnostic during HEV acute infection. Zafra-Soto, et al.[37] described a new protocol for the diagnosis of HEV available for the identification of all HEV human genotypes showing high rates of sensitivity and specificity. Finally, Frías, et al.[16] identified an outbreak of HEV from an index case diagnosed for acute HEV infection due to wild boar consumption. After an epidemiologic questionnaire, all family members were confirmed to be exposed and infected. A molecular epidemiologic analysis finally confirms HEV transmission by wild boar consumption. All these data presented are critical to establish the magnitude of the HEV epidemic and for the implementation of diagnostic and preventive strategies to minimize HEV transmission.

Conclusions

The situation of HCV infection has dramatically changed in the last two years after the wide implementation of DAA treatments. A large number of HCV-infected patients have been treated and cured after 12 weeks of therapy with minimal adverse events. However, we are facing new challenges for a real HCV eradication in the field of HCV diagnosis and treatment. Some of these issues were approached in the II Conference of GEHEP. HCV screening programs are necessary to know the rates of unmasking HCV infection in the general population, and to establish strategies to promote the linkage to care for the new HCV-diagnosed patients. Moreover, there are specific population groups (i.e. prisoners) still with limited access to DAA treatment. This situation needs to be urgently resolved since most of them are HIV/HCV coinfected and with advanced liver fibrosis.

The implementation of HCV-resistance testing on the NS5A region for genotypes 1a and 3 can be useful to guide physician decisions and optimize DAA treatment, since it may be necessary to decide on the use of ribavirin or to prolong treatment duration (16 or 24 weeks) for DAA regimens including NS5A inhibitors. The recurrence of hepatocellular carcinoma among HCV-infected patients treated and cured with DAA needs further research.

Finally, Hepatitis E virus infection is an emergent pathogen in Europe and, therefore, appropriate diagnostic tools are required to establish the coverage of the epidemic and adequate prevention programs. Overall, all the data presented at the GEHEP Conference provide very relevant information that must be considered to establish optimal diagnosis and treatment strategies to win the battle against viral hepatitis.

Declaration of interest

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