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Update on HIV/HCV Coinfection

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Abstract Liver disease is currently one of the leading causes of hospitalization and death in HIV-positive individuals. Coinfection with the hepatitis C virus (HCV) is a major contributor to this trend. Besides hepatic damage, which is enhanced in the presence of HIV-associated immunosuppression, HCV may contribute to disease in coinfected individuals by potentiating immune activation and chronic inflammation, which ultimately account for an increased risk of cardiovascular events, kidney disease, and cancers in this population. Fortunately, hepatitis C therapeutics has entered a revolutionary era in which we hope that most patients treated with the new oral direct-acting antivirals (DAA) will be cured. However, many challenges preclude envisioning a prompt elimination of HCV from the coinfected population. Issues that should be addressed include the following: (1) rising incidence of acute hepatitis C in men who have sex with men, and expansion/recrudescence of injection drug use in some settings/regions; (2) adverse drug interactions between antiretrovirals and DAA; and (3) high cost of DAA, which may lead many to defer or fail to access appropriate therapy.

Keywords Hepatitis C · HIV · Coinfection · HIV/HCV coinfection · Sofosbuvir · Telaprevir · Boceprevir · Antiviral therapy

Introduction

During the last decade, liver-related complications have become a leading cause of hospitalization and death in HIV-infected individuals living in Western countries [1, 2], representing 9 % of deaths in HIV-positive persons in the latest D:A:D survey. This phenomenon largely reflects the high prevalence of viral hepatitis in the HIV population, during an era in which successful antiretroviral therapy has virtually halted the development of opportunistic complications [3]. Coinfection with the hepatitis C virus (HCV) occurs in 25 % of HIV-positive individuals [3, 4] although rates vary widely in different patient populations. In the absence of successful treatment for hepatitis C, coinfected patients are at increased risk for developing end-stage liver disease, including hepatocellular carcinoma, compared with HCV-monoinfected individuals [5–7]. Interestingly, whereas serum HCV-RNA increases over time in the absence of antiretroviral therapy [8], no association has been found between HCV viremia or genotype and liver disease progression in coinfected patients [9].

End-stage hepatic events and drug-induced liver injury are the major determinants of liver-related complications in HIV-positive patients with chronic hepatitis C [10, 11, 12•]. The most recently approved antiretroviral agents, however, are associated with improved hepatic safety profile in coinfected individuals [13–15]. Regardless, eradication of HCV with antiviral therapy before prescribing antiretroviral drugs may further reduce the chances of liver injury [16] and, therefore, hepatitis C therapy must be prioritized in the coinfected population. It is hoped that the advent of direct-acting antivirals (DAA) as therapy for hepatitis C will soon help to reverse the harmful impact of HCV in coinfected individuals [17].

Updated Epidemiology of HIV/HCV Coinfection

The efficient parenteral transmission of HCV explains why coinfection with HIV is so common (>75 %) in persons who have used drugs intravenously or received contaminated

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blood products [3]. While intravenous drug use has declined dramatically in Western Europe, after peaking in the eighties [18], it is still ongoing in some cities and prisons in North America and Western Europe [19], and is rapidly expanding in Eastern Europe and South East Asia [20].

With respect to the risk of blood transfusions, universal screening for both HIV and HCV has blunted this route of transmission in developed countries; however, it continues to be an important source of contagion in resource-poor regions [21]. Finally, a rising incidence and outbreaks of acute hepatitis C among HIV-positive homosexual men during the last decade have highlighted that HCV can also be transmitted efficiently in this population [22–24, 25•, 26]. Recognition of acute hepatitis C is important because treatment response is more efficacious shortly after infection than in chronic hepatitis C [27, 28].

Although irrelevant until recent years, there is evidence stressing that HCV re-infection is relatively common among certain HIV-infected individuals, such as injecting drug users [29] and homosexual men with many sexual partners [30]. This should be kept in mind, since liver enzyme elevations in patients already treated for hepatitis C and cured may be falsely attributed to other causes. For these reasons, education and prevention strategies should remain a key aspect of HIV-HCV coinfection care.

HCV-Related Liver and Extrahepatic Disease in HIV Patients

Despite well-established evidence for faster liver disease progression in HIV/HCV-coinfected patients [7], only a small fraction of these individuals has been treated with peginterferon/ribavirin [31]. Low response rates and frequent side effects of the medication have mainly contributed to discourage its prescription by doctors [32–35]. On the other hand, a high proportion of coinfected patients are ineligible for interferon (ie, serious neuropsychiatric conditions) or particularly difficult to access (ie, homeless, alcoholics, prisoners, etc.) [31, 36•]. Interestingly, in the few places where hepatitis C therapy has been widely used in coinfected individuals, the remaining pool of those still infected is filled with particularly difficult-to-cure characteristics, such as advanced liver fibrosis, unfavorable IL28B alleles, HCV genotypes 1 or 4, and comorbidities (ie, diabetes) [37].

The development of reliable noninvasive tools for staging liver fibrosis during the last decade has allowed universal and periodic monitoring of the severity of liver disease in HIV/HCV-coinfected patients. The advent of transient elastography has been particularly helpful in this population [38], where serum fibrosis indexes often perform less well due to interferences caused by some antiretroviral agents (ie, GGT and nevirapine/efavirenz, or bilirubin and atazanavir) or HIV-associated immune activation [39]. Despite being widely used worldwide, FibroScan only received FDA approval in April 2013. Several studies have highlighted the predictive value of liver fibrosis stage using either liver biopsy or hepatic stiffness for developing liver-related related events and mortality in coinfected patients [40, 41]. Likewise, reductions in liver stiffness after successful eradication of HCV with therapy have been noticed [42–44], which indirectly reflect the improved prognosis and survival of hepatitis C cured patients [45, 46]. Although a residual clinical and histological benefit of interferon was suggested for HIV/HCV-coinfected patients who relapsed after a course of interferon therapy [47], more recent information has attributed this observation to the transient antiviral effect of interferon, whereas it remains clear that liver fibrosis progression resumes when the virus comes back [48].

The recognition that chronic HCV infection, through persistent immune activation and inflammatory phenomena, may contribute to extrahepatic manifestations and mortality has further increased the interest for treating hepatitis C as early as possible, without limiting therapy to individuals with advanced liver disease [49, 50]. In this regard, the results of the REVEAL-C study are an important hallmark [51•]. The rate of kidney disease, cardiovascular events, and some cancers were increased in chronic hepatitis C patients compared with controls. More importantly, this effect was driven by persistent HCV replication and vanished in subjects who cleared the virus spontaneously. The presence of HCV-RNA has similarly been associated with an increased risk of renal and cardiovascular disease in large HIV cohorts, such as EuroSIDA [52] or US Veterans [53]. Altogether, appreciation of the indirect damage that HCV may further cause in HIV-infected carriers should refresh the need for treating hepatitis C as early as possible in this population [54, 55].

Similar to what has occurred in the HIV field [56, 57], once less toxic and easy to take HCV medications become available, more hepatitis C patients will be treated. In this regard, the major difference between these viruses is the prominent role of treatment for halting sexual HIV transmission, an issue that only marginally applies to HCV (Fig. 1). On the other hand, the possibility of true eradication of HCV with therapy is a unique goal that does not apply to HIV [58]. Enthusiasm unabated, a more open consideration of treatment for chronic hepatitis C in HIV patients has unveiled important gaps that must be filled properly if we want advances in therapeutics to be translated into significant public health benefits. Whereas HCV has surpassed HIV in total annual deaths in the United States (15,000 vs 13,000), more than 50 % of HCV and 20 % of HIV cases remain undiagnosed [59, 60••]. Thus, active policies of HCV and HIV screening of adults should be encouraged, promoting universal testing of persons who come into contact with the health system for any reasons. In this regard, since early 2013 the US government recommends anti-HCV testing of

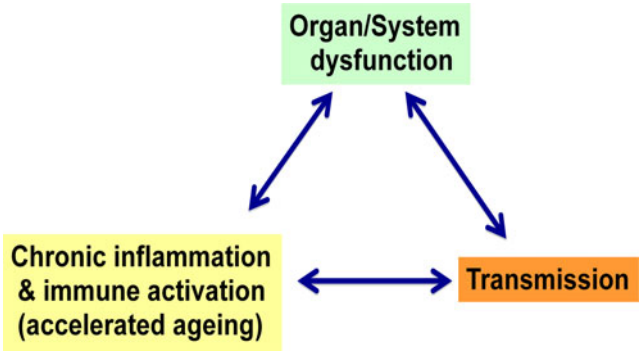

Fig. 1 Rationale for "*Test & Treat*" strategies for HIV and HCV. Successful therapy may halt patient's damage caused by the virus either at the target organ/system (ie, liver for HCV or immunity for HIV). A further benefit of successful therapy derives from preventing new virus transmission events

all persons born between 1945 and 1965 ("baby-boomers") and anti-HIV testing of all persons aged 18 to 65 years-old.

New Oral DAA in HIV/HCV Coinfection

The advent of molecules that specifically target different key life cycle elements of HCV replication has been eagerly awaited for treating the HIV-HCV coinfected population. However, the complexities using first-generation HCV protease inhibitors is being negatively perceived by many, discouraging triple therapy particularly in the HIV setting, where drug-drug interactions, overlapping toxicities and adherence issues derived from polypharmacy are even more challenging (Table 1) [17, 49, 50].

In the HIV/AIDS field there has been a shift in the attention of patients. Hospitalizations due to severe opportunistic infections or cancers in the eighties and nineties have been largely replaced today by periodic visits to specialized HIV outpatient clinics. As antiretroviral treatment has progressively become simpler, increasing its success rate, the management of HIV/AIDS has begun to be analogous to other chronic conditions (ie, diabetes, hypertension, etc.), and most likely there will be a gradual shift back to care provided by more general practitioners. Telemedicine would probably play a major role providing assistance when difficult management issues are present [61]. In the meantime, we will review the information available with the first approved and the next coming DAAs in HIV/HCV-coinfected patients.

Table 1 Challenges treating hepatitis C with DAA in HIV/HCV-coinfected patients

- Drug interactions between ARV and DAA
- Lower drug adherence due to polymedication
- Overlapping side effects of ARV and DAA
- Frequent HCV re-infections
- Frequent liver-related comorbidities (hepatitis B, hepatitis delta, alcohol, steatohepatitis)
- More frequent HCV subtype 1a than 1b
- More frequent advanced liver fibrosis
- Higher serum HCV-RNA load

Telaprevir

Telaprevir was one of the first approved HCV protease inhibitors as therapy for genotype 1 infections. The Vertex study C110 was an exploratory phase II trial that examined the efficacy and safety of telaprevir along with peginterferon-ribavirin in comparison with standard dual therapy in 60 HIV-positive patients coinfected with HCV genotype 1 [62]. All were interferon-naïve. Overall there was a 74 % SVR rate in the triple therapy arm compared with 45 % in the dual arm. There were no significant differences between individuals on antiretroviral therapy with either efavirenz or atazanavir and those not treated for HIV, although the small study population precluded definitive conclusions in this regard. Three individuals discontinued triple therapy prematurely due to side effects. Rash developed in one third of telaprevir treated patients. Given the induction of telaprevir metabolism by efavirenz, higher telaprevir dosing (1125 mg q8h) was used in subjects receiving efavirenz. Hyperbilirubinemia was exacerbated in patients on atazanavir/r due to increased atazanavir exposure in the presence of telaprevir.

Telaprevir has to be given as 2 pills thrice daily (although 3 pills twice daily may work as well) for the first 3 months of triple therapy. The main side effects associated with telaprevir use are anemia, rash, and anal pruritus. Given its metabolism by the cytochrome P450, pharmacokinetic interactions are common with a wide number of drugs, including antiretroviral agents [63]. Nucleos(t)ide analogues, atazanavir, and raltegravir can be safely used with telaprevir. The interaction between methadone and telaprevir is not considered to be clinically significant.

Boceprevir

This HCV protease inhibitor was approved by the FDA in mid 2011. The Merck phase II trial that tested boceprevir triple therapy in HIV/HCV coinfection included 98 patients [64]. As in the telaprevir trial, all were interferon naïve and infected by HCV genotype 1. Patients were randomized 2:1 to triple therapy vs pegIFN/RBV. It is intriguing that the peak of maximal response in the triple arm occurred at week 24 and not at earlier time points, perhaps indirectly reflecting a limited activity of boceprevir in comparison with other HCV protease inhibitors, including telaprevir. Although the crude response rates might appear to be lower for boceprevir than telaprevir, the response in the control arm was lower in the boceprevir study (26 %) and perhaps closer to "real world

conditions" than in the telaprevir trial (45 %). Overall the added benefit of triple therapy over standard of care was around 29-35 %. Unfortunately, drug interaction studies thereafter concluded that HIV protease inhibitors reduce boceprevir exposure and therefore their combination should be avoided [65]. Fortunately, raltegravir, rilpivirine and etravirine can safely be used along with boceprevir [66, 67].

Recent reports from observational studies suggest that telaprevir may exhibit greater early antiviral activity than boceprevir [68–70]. Thus, telaprevir might the first choice in the subset of patients particularly difficult-to-cure [71], such as those with HIV, cirrhosis, infection with HCV subtype 1a [72], high serum HCV-RNA, unfavorable IL28B alleles [73], and/or prior partial or null response to interferon.

Simeprevir

This HCV protease inhibitor is given as 1 pill once daily during the first 3 months of treatment. Study C212 is an ongoing phase III trial that compares 24 or 48 weeks of triple therapy with peginterferon, ribavirin, and simeprevir in 106 HIV-positive patients coinfected with HCV genotype 1 [74]. Most patients (93 %) were on antiretroviral therapy (mostly on raltegravir- or rilpivirine-based regimens) and had undetectable plasma HIV-RNA and favorable CD4 counts. Most patients (86 %) harbored HCV subtype 1a, which is less responsive to therapy. The favorable IL28B CC alleles were present in 21 % of patients. The proportion of patients with undetectable HCV-RNA at week 4 of treatment was 66 % (in 89 % viremia was unquantifiable). As expected, better results were obtained in naïve and relapsers than in prior partial or null responders. Preliminary results in 13 interferon-naïve and relapsed patients that had completed at least 12 weeks after ending therapy showed a 77 % SVR rate. Interestingly, all patients that relapsed (15 %) were infected with HCV subtype 1a. Hyperbilirubinemia was the most common adverse event associated with simeprevir therapy.

Faldaprevir

Like simeprevir, faldaprevir is a second-generation HCV protease inhibitor, with more favorable dosing, higher potency, and less drug interactions than first-generation molecules within this class. Faldaprevir has proven its high potency along with peginterferon/ribavirin and as part of an interferon-free combination in HCV-monoinfected patients [75]. STARTVerso 4 is an ongoing phase III trial that compares 12 or 24 weeks of 2 doses of faldaprevir along with peginterferon-ribavirin therapy in 308 HIV-positive patients with HCV genotype 1 coinfection [76]. HCV subtype 1a was present in 78 % of patients. Up to 17 % were cirrhotics. Most (89 %) were on antiretroviral therapy, with raltegravir, efavirenz, darunavir, or atazanavir the most common third agents. A high proportion of patients achieved undetectable or unquantifiable serum HCV-RNA at weeks 4 and 12 of therapy. As expected, outcomes were better in the 69 prior relapsers than in the 239 interferon-naïve patients. Hyperbilirubinemia was the most frequent side effect associated to faldaprevir therapy. Rash developed in 18 % of patients. Recent pharmacokinetic studies have not revealed any significant interaction between faldaprevir and most frequently used antiretroviral agents [77].

Sofosbuvir

Sofosbuvir is a uridine analog nucleotide. It exhibits potent antiviral activity across all HCV genotypes, a high barrier to resistance, good safety profile, and is given as a single 400 mg pill once daily [78]. Furthermore, no significant pharmacokinetic drug interactions have been reported so far [79]. The results of phase III trials have recently been reported in both interferon-naïve [80] and interferon-experienced or intolerant patients with Hepatitis C mono-infection [81]. Along with peginterferon-ribavirin for 12 weeks, 90 % SVR_{12} were obtained in the NEUTRINO trial, testing 327 naïve patients infected with HCV genotypes 1 or 4 [80]. When sofosbuvir was given only with ribavirin in patients with HCV genotypes 2 or 3, it becomes clear that HCV genotype 3, cirrhosis, non-CC IL28B alleles, and/or shorter duration of therapy may all impair treatment outcomes. This was reproduced in distinct patient's populations, such as interferon-naïve (FISSION trial) [80], interferon-experienced (FUSION trial) [81], or interferon-intolerant (POSITRON trial) [81]. It is noteworthy that failures in all these trials were relapses as there were no single viral breakthroughs during sofosbuvir therapy. Moreover, selection of drug resistance was absent in all cases. Based on this information, it seems reasonable that extension of therapy to 24 weeks could be the best way to enhance SVR rates. An alternative option could be the addition of another active DAA.

The PHOTON studies are ongoing phase II trials that examine the efficacy and safety of sofosbuvir in HIV/HCV-coinfected patients. The drug is given along with ribavirin without interferon. No information is yet available. In a phase I trial, 19 HIV-positive patients on antiretroviral therapy and coinfected with HCV genotypes 1 to 3 received sofosbuvir 400 mg once daily for 1 week [82]. An encouraging maximal reduction in serum HCV-RNA of 4 log IU/ml was recognized. The drug was well tolerated without any impact on plasma HIV-RNA nor CD4 counts.

Upon cell entry, nucleoside analogs like lamivudine or emtricitabine must first be phosphorylated to the active triphosphate species. The first step, a conversion of the nucleoside to a nucleotide monophosphate (NMP) by cellular kinases, often is inefficient and the rate limited step. Sofosbuvir is a second-generation nucleoside analog; it is designed as a nucleotide prodrug, which bypasses this rate-limiting NMP conversion by delivering the nucleoside as a

monophosphate prodrug. Moreover, this prodrug is liver-targeted. The first step of its metabolism is the removal of the prodrug moiety by cellular enzymes within hepatocytes followed by the activation of the nucleoside monophosphate analog by cellular kinases. CES1/CatA are the enzymes running on the first step of sofosbuvir metabolism. Whereas these 2 enzymes are highly active in the liver, poor activity has been reported at other body compartments [83].

Both sofosbuvir and lamivudine (or emtricitabine) utilize UMP-CMP kinase and DMPK on the last steps of its activation and theoretically could compete for these enzymes. Inhibitory competition phenomena could cause concentration increases in their metabolites (MP or DP) along with concentration reduction of the active triphosphate form, potentially impairing antiviral activity. Thus, it seems important to check the toxicity of drug metabolites and the antiviral activity before prescribing these drugs in combination. However, abacavir, didanosine, zidovudine, stavudine, and tenofovir utilize different kinases and accordingly inhibitory competition phenomena with sofosbuvir are less probable [78, 83].

Daclatasvir

NS5A inhibitors are molecules that block viral RNA synthesis and virus assembly/secretion across all HCV genotypes [84]. However, daclatasvir, the first drug within this class to be developed, is more active against HCV genotype 1b than 1a. Daclatasvir is given as a pill once daily, exhibits a good safety profile, and lacks significant drug interactions. The drug has proved to be efficacious in combination with peginterferon as well as part of interferon-free regimens [85, 86]. A trial is currently exploring the safety and efficacy of the triple combination of peginterferon, ribavirin, and daclatasvir in HIV/HCV-coinfected individuals, and the release of preliminary results are expected late in 2013.

Predicted Off-Label Use of DAAs and Untested Therapeutic Strategies

A next wave of approvals for new DAAs is expected for sofosbuvir and simeprevir before the end of year 2013. This could be followed early in 2014 by faldaprevir and daclatasvir licensing. All these drugs will be registered based on their good performance in HCV-monoinfected individuals given as triple therapy along with peginterferon-ribavirin, increasing the overall efficacy (~80 %) and shortening the duration of therapy for most patients (6 months). A second wave of approvals is expected for the second half of 2014 and will make all-oral, interferon free regimens potentially feasible, including co-formulations such of sofosbuvir-ledispavir or ABT450/ritonavir-ABT267. Despite this rapid pace, it should be highlighted that FDA has not approved yet any DAA for HIV-HCV coinfected patients.

As the HCV armamentarium expands, prescription of single medications as part of untested innovative combinations, for distinct lengths of therapy or exploring new strategies (ie, simeprevir intensification for the first month along with sofosbuvir, followed by 3–6 months of sofosbuvir alone) will be tried based on individual provider's opinions and/or patient's own choices. Table 2 summarizes the main characteristics of DAA already approved and of those expected to be licensed soon. It would be worthwhile to set up mechanisms to collect this information and update properly and periodically the therapeutic roadmap for hepatitis C. Investigator-driven clinical trials should be encouraged by both pharmaceutical companies and governments, testing innovative strategies, combinations, dosing, and/or special patient populations. This could be particularly important for HIV/HCV-coinfected individuals, for whom inadequate DAA use could be more harmful because of drug interactions and faster liver disease progression.

Who Will Treat Hepatitis C in HIV and Beyond?

In the past, the face of hepatitis C was mainly represented by end-stage liver disease complications, such as ascites, encephalopathy, and variceal bleeding. For this reason, HCV patients were largely managed in hepatology units. Frequent visits and rapid hospitalization gave the best chances to manage cirrhosis decompensation events, hepatocellular carcinoma, or access to liver transplantation. However, as hepatitis C has become a more common diagnosis among asymptomatic individuals, based on simple serologic tests, infectious diseases specialists rather than hepatologists have increasingly taken over the management of these patients. Lessons learned from HIV are very helpful for HCV care. This is the case for concepts such as viral load, drug resistance, combination therapy, viral kinetics, genotypes, and subtypes, etc.

Following the approval of the first DAA on May 2011, the interest for treating HCV patients has been awakened. The promotion of "test and treat" strategies will further increase the identification of unaware HCV-infected individuals. Given the complexities surrounding the use of first-generation HCV protease inhibitors, a growing number of HCV patients are being referred to specialized outpatient clinics. However, the current shift of hepatitis C patients from family/general medicine to specialized outpatient clinics must be viewed as temporary. Within the next several years, interferon-free regimens will be available and HCV therapeutics will become easier, using more potent, safer, and convenient drugs. We could envision the development of single tablet regimens, resembling what has occurred for HIV infection. Being asymptomatic most of the new diagnosed HCV patients, we

Table 2 Characteristics of direct-acting antivirals

DAA	HCV genotype activity	Dosing	Length of therapy	Resistance barrier	Contraindicated antiretrovirals
Telaprevir	1	3 pills bid	3 months	Low	PIs (but atazanavir); all NNRTIs[1]
Boceprevir	1	4 pills tid	6 to 12 months	Low	All PIs; NNRTIs (but rilpivirine and etravirine)[2]
Simeprevir	1b >1a[3] 2,4	1 pill qd	3 months	Low	No
Faldaprevir	1b >> 1a 2 to 4	1 pill qd	3 months	Low	No
ABT-450/r	1	1 pill qd[4]	3 months	Low	Caution with all CYP450 substrates
Sofosbuvir	All (1 to 6)	1 pill qd	3 to 6 months	Very high	No
Daclatasvir	1b>1a 2 to 6	1 pill qd	3 to 6 months	Low	No

[1] Efavirenz may be combined with telaprevir increasing telaprevir dosing. Etravirine reduces telaprevir exposure by 25 % and increases rilpivirine exposure by 90 %, which may potentially cause QT prolongation

[2] Rilpivirine and etravirine does not interact significantly with boceprevir

[3] Around 30 % of HCV subtype 1a strains harbor a polymorphism at protease codon 80 (Q→K) that reduces simeprevir susceptibility

[4] ABT-450 is planned to be co-formulated with ABT-267, a NS5A inhibitor

should expect that general practitioners will put hands on hepatitis C, prescribing curative therapies for periods no longer than 6 months. Then, specialized units with HCV experts will only be required for patients refractory to standard medications and/or those with decompensated hepatic disease.

Treatment of hepatitis C in HIV most likely will remain in the hands of HIV care providers, given that HIV is not curable and antiretroviral therapy must be life-long. The lack of improvement in liver function tests or hepatic fibrosis in coinfected patients following therapeutic HCV eradication should alert providers about the presence of other conditions, such as coinfection with hepatitis B, delta or E viruses, nonalcoholic steatohepatitis, alcohol abuse, and antiretroviral-related liver injury [11, 12•, 87]. The reports of noncirrhotic portal hypertension associated to didanosine exposure [88–92] represent a good example of unsuspected conditions that may preclude recognition of the hepatic improvement that should always result from HCV clearance [93].

Future Prospects

Several public health implications of rapid and wide use of DAA can be envisioned. First, constraints in cost and availability of well-trained personnel will limit the use of new hepatitis C drugs in the short term. Second, the benefit of the new HCV therapies in terms of reduced liver decompensation episodes and the need for liver transplantation will be significant, but only in the long term. Third, selection of drug resistance in HCV in patients treated with most of the new drugs will require the design of second-line or rescue regimens, as cross-resistance may jeopardize the success of recycling drugs within the same family. In this regard, a recent study has shown very promising results combining daclatasvir plus sofosbuvir and/or ribavirin as rescue therapy for boceprevir or telaprevir prior triple failures [94]. Four, as previously mentioned, a shift in HCV care providers must be expected, with more involvement of infectious diseases specialists, because of the new way hepatitis C is managed, targeting asymptomatic infected individuals instead of end-stage liver disease patients and making decisions largely based on virological parameters, for which infectious disease providers are more familiar than hepatologists and gastroenterologists.

Finally, because of economic constraints and access to health care, a shift in HCV populations will occur, with indirect marginalization of patients. In rich countries, homeless, illegal immigants, alcohol abusers, mentally disabled, prisoners, and active intravenous drug users, among others, will not benefit from the new HCV therapies in the short and mid term [36•]. On the other hand, the high cost of DAA will represent a huge barrier for their wide use in resource-limited regions [95, 96]. Reminding what is happening in the oncology field, where new unprecedented chemotherapeutic agents have been discovered, the most important barrier for its use is price [97]. There is a need for dialogue between pharmaceutical companies, physicians, governmental agencies, insurance companies, and patients' advocates to establish objective measures of benefit for patients and drug developers that allow to maximize benefits of health at the lowest cost.

Conclusions

Chronic hepatitis C is an important modifier of health in persons with HIV infection, contributing to both liver and extrahepatic illnesses. Mercifully, hepatitis C has entered the stage when safe and very effective curative therapies will

soon become available. Efforts have to be made to extend this benefit to large segments of the HIV-HCV coinfected population.

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References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Weber R, Sabin C, Friis-Moller N, et al. Liver-related deaths in persons infected with the HIV: the D:A:D study. Arch Intern Med. 2006;166:1632–41.
2. Ruppik M, Ledergerber B, Rickenbach M, et al. Changing patterns of causes of death: SHCS, 2005 to 2009. 18th CROI, Boston, MA. Feb 27-March 2, 2011. [Abstract 789].
3. Puoti M, Moioli MC, Travi G, Rosootti R. The burden of liver disease in HIV-infected patients. Semin Liver Dis. 2012;32:103–13.
4. Soriano V, Puoti M, Sulkowski M, et al. Care of patients coinfected with HIV and HCV: 2007 updated recommendations from the HCV-HIV International Panel. AIDS. 2007;21:1073–89.
5. Lacombe K, Rockstroh J. HIV and viral hepatitis coinfections: advances and challenges. Gut. 2012;61 Suppl 1:47–58.
6. Barreiro P, Vispo E, Labarga P, Soriano V. Management and treatment of chronic hepatitis C in HIV patients. Semin Liver Dis. 2012;32:138–46.
7. Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in HIV-infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis. 2004;38:128–33.
8. Grint D, Peters L, Reekie J, et al. Stability of HCV RNA levels among interferon-naïve HIV/HCV-coinfected individuals treated with combination antiretroviral therapy. HIV Med. (in press).
9. Rockstroh J, Peters L, Grint D, et al. Does hepatitis C viremia or genotype predict the risk of mortality in individuals co-infected with HIV? J Hepatol. (In press).
10. Sulkowski M, Thomas D, Chaisson R, Moore R. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection. JAMA. 2000;283:74–80.
11. Soriano V, Puoti M, García-Gascó P, et al. Antiretroviral drugs and liver injury. AIDS. 2008;22:1–13.
12. • Jones M, Nuñez M. Liver toxicity of antiretroviral drugs. Semin Liver Dis. 2012;32:167–76. *This review updates the most recent knowledge on the mechanisms of antiretroviral-associated liver injury and propose strategies for rapid recognition and proper management.*
13. Vispo E, Mena A, Maida I, et al. Hepatic safety profile of raltegravir in HIV-infected patients with chronic hepatitis C. J Antimicrob Chemother. 2010;65:543–7.
14. Rockstroh J, Teppler H, Zhao J, et al. Safety and efficacy of raltegravir in patients with HIV-1 and hepatitis B and/or C virus coinfection. HIV Med. 2012;13:127–31.
15. Vispo E, Fernandez-Montero JV, Labarga P, Barreiro P, Soriano V. Low risk of liver toxicity using the most recently approved antiretroviral agents but still increased in HIV-HCV coinfected patients. AIDS. 2013;27:1187–8.
16. Labarga P, Soriano V, Vispo E, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. J Infect Dis. 2007;196:670–6.
17. Soriano V, Sherman K, Rockstroh J, et al. Challenges and opportunities for hepatitis C drug development in HIV-HCV coinfected patients. AIDS. 2011;25:2197–208.
18. Perez-Cachafeiro S, del Amo J, Iribarren JA, et al. Decrease in serial prevalence of coinfection with HCV among HIV-infected patients in Spain, 1997–2006. Clin Infect Dis. 2009;48:1467–70.
19. Ward J. The hidden epidemic of hepatitis C virus infection in the United States: occult transmission and burden of disease. Top Antivir Med. 2013;21:15–9.
20. Samet J. Russia and HIV – beyond crime and punishment. Addiction. 2011;106:1883–5.
21. Javaraman S, Chalabi Z, Perel P, Guerriero C, Roberts I. The risk of transfusion-transmitted infections in Sub-Saharan Africa. Transfusion. 2010;50:433–42.
22. Van der Helm J, Prins M, del Amo J, et al. The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007. AIDS. 2011;25:1083–91.
23. Boesecke C, Rockstroh J. Acute hepatitis C in patients with HIV. Semin Liver Dis. 2012;32:130–7.
24. Witt M, Seaberg E, Darilay A, et al. Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis from 1984 to 2011. Clin Infect Dis. (in press).
25. • AIDS European Treatment Network (NEAT). Acute hepatitis C in HIV-infected individuals: recommendations from the NEAT. AIDS. 2011;25:399–409. *This article records the major conclusions reached by a group of European experts regarding the diagnosis and treatment of acute hepatitis C in HIV-infected persons. It particularly provides comprehensive and updated information on acute hepatitis C outbreaks among HIV-positive MSM.*
26. Sanchez-Parra C, Plaza Z, Vispo E, et al. Scaling up epidemics of acute hepatitis C and syphilis in HIV-infected men who have sex with men in Spain. Liver Int. (in press).
27. Deterding K, Grüner N, Buggisch P, et al. Delayed vs immediate treatment for patients with acute hepatitis C: a randomized controlled noninferiority trial. Lancet Infect Dis. (in press).
28. Webster D, Wojcikiewicz T, Keller M, et al. Spontaneous clearance and treatment of acute hepatitis C infection in HIV-positive men

with 48 weeks of interferon-alpha and ribavirin. Int J STD AIDS. (In press).
29. Marco A, Esteban JI, Solé C, et al. Hepatitis C virus reinfection among prisoners with sustained virological response after treatment for chronic hepatitis C. J Hepatol. (In press).
30. Lambers F, Prins M, Thomas X, et al. Alarming incidence of HCV re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV MSM. AIDS. 2011;25:F21–7.
31. Mehta S, Genberg B, Astemborki J, et al. Limited uptake of hepatitis C treatment among injecting drug users. J Community. 2008;33:126–33.
32. Chung R, Andersen J, Volberding P, et al. Peginterferon alfa-2a plus ribavirin vs interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004;351:451–9.
33. Torriani F, Rodriguez-Torres M, Rockstroh J, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004;351:438–50.
34. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients. JAMA. 2004;292:2839–48.
35. Nuñez M, Miralles C, Berdún MA, et al. Role of weight-based ribavirin dosing and extended duration of therapy in the treatment of chronic hepatitis C in HIV-infected patients: the PRESCO trial. AIDS Res Human Retroviruses. 2007;23:972–82.
36. • Grebely J, Oser M, Taylor L, Dore G. Breaking down the barriers to HCV treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. J Infect Dis. 2013;207 Suppl 1:19–25. *This article records the opinion of several experts about the ways to improve access to hepatitis C therapy in HIV-positive individuals, with particular attention to intravenous drug users and other marginal populations*.
37. Poveda E, Vispo E, Barreiro P, et al. Predicted effect of direct acting antivirals in the current HIV-HCV-coinfected population in Spain. Antivir Ther. 2012;17:571–5.
38. Soriano V, Garcia-Samaniego J. Liver biopsy in HIV-infected patients with chronic hepatitis C: pros and cons. HIV Clin Trials. 2002;3:351–3.
39. Sanchez-Conde M, Montes-Ramirez ML, Miralles P, et al. Comparison of transient elastography and liver biopsy for the assessment of liver fibrosis in HIV/HCV-coinfected patients and correlation with noninvasive serum markers. J Viral Hepat. 2010;17:280–6.
40. Limketkai B, Mehta S, Sutcliffe C, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. JAMA. 2012;308:370–8.
41. Fernández-Montero JV, Barreiro P, Vispo E, Labarga P, Sánchez-Parra C, Soriano V. Liver stiffness predicts liver-related complications and mortality in HIV patients with chronic hepatitis C on antiretroviral therapy. AIDS. (in press).
42. Soriano V, Labarga P, Ruiz-Sancho A, Garcia-Samaniego J, Barreiro P. Regression of liver fibrosis in hepatitis C virus/HIV-coinfected patients after treatment with pegylated interferon plus ribavirin. AIDS. 2006;20:2225–7.
43. Macias J, del Valle J, Rivero A, et al. Changes in liver stiffness in patients with chronic hepatitis C with and without HIV coinfection treated with pegylated interferon plus ribavirin. J Antimicrob Chemother. 2010;65:2204–11.
44. Barreiro P, Labarga P, Martín-Carbonero L, et al. Sustained virological response following HCV therapy is associated with nonprogression of liver fibrosis in HCV/HIV-coinfected patients. Antivir Ther. 2006;11:869–77.
45. Soriano V, Maida I, Núñez M, et al. Long-term follow-up of HIV-infected patients with chronic hepatitis C virus infection treated with interferon-based therapies. Antivir Ther. 2004;9:987–92.
46. Berenguer J, Alvarez-Pellicer J, Martin P, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with HIV and hepatitis C virus. Hepatology. 2009;50:407–13.
47. Berenguer J, Alvarez-Pellicer J, Carrero A, et al. Clinical effects of viral relapse after interferon plus ribavirin in patients co-infected with HIV and hepatitis C virus. J Hepatol. (In press).
48. Labarga P, Fernandez-Montero JV, Barreiro P, et al. Changes in liver fibrosis in HIV/HCV coinfected patients following different outcomes with peginterferon plus ribavirin therapy. Clin Infect Dis. (In press).
49. Naggie S, Sulkowski M. Management of patients coinfected with HCV and HIV: a close look at the role for direct-acting antivirals. Gastroenterology. 2012;142:1324–34.
50. Soriano V, Labarga P, Fernandez-Montero JV, et al. The changing face of hepatitis C in the new era of direct-acting antivirals. Antivir Res. 2013;97:36–40.
51. • Lee M, Yang H, Lu S, et al. Chronic HCV infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. J Infect Dis. 2012;206:469–77. *This study represents a pivotal contribution on the long-term consequences of hepatitis C. Besides liver-related complications, it demonstrated that the rate of kidney disease, cardiovascular events, and some cancers increases in HCV carriers. Thus, as long as new more potent and safer curative drugs became available, treatment should not be restricted to those with advanced liver disease*.
52. Peters L, Grint D, Lundgren J, et al. Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients. AIDS. 2012;26:1917–26.
53. Bedimo R, Westfall A, Mugavero M, Drechsler H, Khanna N, Saag M. Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients. HIV Med. 2010;11:462–8.
54. Soriano V, Labarga P, Vispo E, Fernández-Montero JV, Barreiro P. Treatment of hepatitis C in patients infected with HIV in the direct-acting antiviral era. Infect Dis Clin North Am. 2012;26:931–48.
55. Sulkowski M. Current management of hepatitis C virus infection in patients with HIV coinfection. J Infect Dis. 2013;207(Suppl):26–32.
56. Thompson M, Aberg J, Hoy J, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA. 2012;308:387–402.
57. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Last accessed April 30, 2013.
58. Soriano V, Perelson A, Zoulim F. Why are there different dynamics in the selection of drug resistance in HIV and hepatitis B and C viruses. J Antimicrob Chemother. 2008;62:1–4.
59. Rein D, Smith B, Wittenborn J, et al. The cost-effectiveness of birth-control screening for hepatitis C antibody in US primary care settings. Ann Intern Med. 2012;156:263–70.
60. •• U.S. Preventive Services Task Force (USPSTF). New HIV guidelines. (in press). *The USPSTF has recently acted decisively to accelerate routine HIV testing of all adults, following the steps taken for HCV by the CDC calling for one time testing of all baby boomers (born from 1945-1965), who are five times more likely than other adults to have HCV. In both HIV and HCV infections, expanding access to a simple test, used just one time, will identify more unaware infected people and get them treated with effective therapies while also dramatically reducing virus spread.*
61. Saifu H, Asch S, Goetz M, Smith J, Graber C, Schaberg D, et al. Evaluation of HIV and hepatitis C telemedicine clinics. Am J Manag Care. 2012;18:207–12.
62. Sulkowski M, Sherman K, Dieterich D, et al. Telaprevir in combination with peginterferon and ribavirin for chronic HCV genotype 1 infection in HIV-infected patients. Ann Intern Med. (in press).
63. van Heeswijk R, Beumont M, Kauffman R, Garg V. Review of drug interactions with telaprevir and antiretrovirals. Antivir Ther. (in press).

64. Mallolas J, Pol S, Rivero A, et al. Boceprevir plus peginterferon/ribavirin for the treatment of HIV-HCV coinfected patients: end of treatment week 48 interim results. 47th EASL, Barcelona April 2012. [Abstract 366].
65. Hulskotte E, Feng H, Xuan F, et al. Pharmacokinetic interactions between the hepatitis C virus protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, darunavir, and lopinavir. Clin Infect Dis. 2013;56:718–26.
66. de Kanter C, Blonk M, Colbers A, Schouwenberg B, Burger D. Lack of a clinically significant drug-drug interaction in healthy volunteers between the hepatitis C virus protease inhibitor boceprevir and the HIV integrase inhibitor raltegravir. Clin Infect Dis. 2013;56:300–6.
67. Hammond K, Wolfe P, Burton J, et al. Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers. J Acquir Immune Defic Syndr. 2013;62:67–73.
68. Benito JM, Sanchez-Parra C, Barreiro P, et al. Triple combination therapy for hepatitis C with telaprevir exhibits greater early antiviral activity than with boceprevir. Antivir Ther. (in press).
69. Cotte L, Braun J, Lascoux-Combe C, et al. High early virological response with telaprevir-pegylated interferon-ribavirin in treatment-experienced HCV genotype 1/HIV coinfected patients: ANRS HC26 TelapreVIH study. CROI 2013, Atlanta, GA, March 3–6 2013. [Abstract 36].
70. Poizot-Martin I, Bellissant E, Piroth L, et al. ANRS HC27 BocepreVIH interim analysis: high early virologic response with boceprevir+pegylated interferón+ribavirin in HCV/HCV coinfected patients with previous failure to pegylated interferon+ribavirin. CROI 2013, Atlanta, GA, March 3–6, 2013. [Abstract 37].
71. Medrano J, Neukam K, Rallon N, et al. Modeling the probability of sustained virological response to therapy with pegylated interferon plus ribavirin in patients coinfected with hepatitis C virus and HIV. Clin Infect Dis. 2010;51:1209–16.
72. Vispo E, Rallon N, Labarga P, Barreiro P, Benito JM, Soriano V. Different impact of IL28B polymorphisms on response to peginterferon-α plus ribavirin in HIV-positive patients infected with HCV subtypes 1a or 1b. J Clin Virol. 2012;55:58–61.
73. Rallon N, Naggie S, Benito JM, et al. Association of a single nucleotide polymorphism near the interleukin 28B gene with response to hepatitis C therapy in HIV/hepatitis C virus coinfected patients. AIDS. 2010;24:F23–9.
74. Dieterich D, Rockstroh J, Orkin C, et al. Simeprevir with pegylated interferon/ribavirin in patients coinfected with chronic HCV and HIV-1: week 24 interim analysis of the TMC435-C212 study. CROI 2013, Atlanta, GA, March 3–6 2013. [Abstract 154LB].
75. Zeuzem S, Soriano V, Asselah T, et al. Interferon-free treatment with faldaprevir and BI-207127 for genotype 1 HCV infection. N Engl J Med. (in press).
76. Dieterich D, Soriano V, Nelson M, et al. STARTVerso 4: high rates of early virologic response in HCV genotype 1/HIV coinfected patients treated with faldaprevir+pegylated interferon and ribavirin. CROI 2013, Atlanta, GA, March 3–6, 2013. [Abstract 40LB].
77. Sabo J, Kort J, Haschke M, et al. Pharmacokinetic interactions of darunavir/ritonavir, efavirenz, and tenofovir with the HCV protease inhibitor faldaprevir in healthy volunteers. CROI 2013, Atlanta, GA. March 3–6, 2013, [Abstract 35].
78. Soriano V, Vispo E, de Mendoza C, et al. Hepatitis C therapy with NS5B polymerase inhibitors. Exp Opin Pharmacother. (in press).
79. Vispo E, Barreiro P, Soriano V. Pharmacokinetics of new oral hepatitis C antiviral drugs. Expert Opin Drug Metab Toxicol. 2013;9:5–16.
80. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. (in press).
81. Jacobson I, Gordon S, Kowdley K, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. (in press).
82. Rodriguez-Torres M, Gonzales Rodriguez J, et al. HIV/HCV coinfected and HCV monoinfected patients have similar early HCV viral kinetics with the potent HCV nucleotide polymerase inhibitor sofosbuvir. ICAAC 2012, Sept 9–12 2012. [Abstract H–1921a].
83. Golitsina N, Danehy F, Fellows R, Cretton-Scott E, Standring D. Evaluation of the role of three candidate human kinases in the conversion of the HCV inhibitor 2'-C-methyl-cytidine to its 5'-monophosphate metabolite. Antivir Res. 2010;85:470–81.
84. Guedi J, Dahari H, Rong L, et al. Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the HCV half-life. Proc Natl Acad Sci U S A. 2013;110:3991–6.
85. Lok A, Gardiner D, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012;366:216–24.
86. Suzuki Y, Ikeda K, Suzuki F, et al. Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options. J Hepatol. (in press).
87. Soriano V, Barreiro P, Sherman K. The changing epidemiology of liver disease in HIV patients. AIDS Rev. 2013;15:25–31.
88. Maida I, Núñez M, Ríos MJ, et al. Severe liver disease associated with prolonged exposure to antiretroviral drugs. J Acquir Immune Defic Syndr. 2006;42:177–82.
89. Mallet V, Blanchard P, Verkarre V, et al. Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients. AIDS. 2007;21:187–92.
90. Kovari H, Ledergerber B, Peter U, et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case–control study. Clin Infect Dis. 2009;49:626–35.
91. Vispo E, Morello J, Rodriguez-Novoa S, Soriano V. Noncirrhotic portal hypertension in HIV infection. Curr Opin Infect Dis. 2011;24:12–8.
92. Vispo E, Cevik M, Rockstroh J, et al. Genetic determinants of idiopathic noncirrhotic portal hypertension in HIV-infected patients. Clin Infect Dis. 2013;56:1117–22.
93. Vispo E, Maida I, Barreiro P, Moreno V, Soriano V. Upper gastrointestinal bleeding may unmask didanosine-associated portal hepatopathy in HIV/HCV-coinfected patients. HIV Clin Trials. 2008;9:440–4.
94. Sulkowski M, Gardiner D, Rodriguez-Torres M, et al. Sustained virological response with daclatasvir plus sofosbuvir +/− ribavirin in chronic HCV genotype 1 infected patients who previously failed telaprevir or boceprevir. J Hepatol. 2013;58(Suppl):570. [Abstract 1417].
95. Ford N, Singh K, Cooke G, et al. Expanding access to treatment for hepatitis C in resource-limited settings: lessons from HIV/AIDS. Clin Infect Dis. 2012;54:1465–72.
96. Easterbrook P, Sands A, Harmanci H. Challenges and priorities in the management of HIV/HBV and HIV/HCV coinfection in resource-limited settings. Sem Liver Dis. 2012;32:147–57.
97. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML): a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood. (in press).