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Commentary

Towards hepatitis C eradication from the HIV-infected population ☆

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ABSTRACT

Around 10–15% of the 35 million people living with HIV worldwide have chronic hepatitis C virus (HCV) infection and are prone to develop liver-related complications. Exposure to HCV is almost universal among injecting drug users and is on the rise among homosexual men. Response to peginterferon-ribavirin therapy is generally lower in coinfection compared to HCV monoinfection. For this reason, the advent of direct-acting antivirals (DAA) is eagerly awaited for this population. The results of trials using DAA in coinfection show that treatment response rates are similar to those obtained in HCV monoinfection. Thus, HIV should no longer be considered as a "special" population, as long as antiretroviral therapy is given and drug interactions are taken into account. Envisioning HCV eradication from the HIV population faces major challenges ahead, including identification of the large number of undiagnosed individuals, and ensuring wide access to the best but often expensive HCV medications. This article forms part of a symposium in Antiviral Research on "Hepatitis C: next steps toward global eradication".

1. Introduction

Because shared transmission routes, HIV–HCV coinfection is relatively common. Recent estimates suggest that around 4 million people worldwide are HIV–HCV coinfected, which represents 10–15% of the 35 million living with HIV, but less than 3% of the 150 million infected with HCV (Hanafiah et al., 2013). The rate of chronic hepatitis C is particularly high in HIV-positive individuals infected parenterally, such as injecting drug users (IDUs) or recipients of contaminated blood products (Naggie and Sulkowski, 2012; Barreiro et al., 2012). More recently, outbreaks of acute hepatitis C among HIV-infected homosexual men have been reported in Western cities, often associated with sexually transmitted infections (e.g., syphilis) and/or unsafe traumatic sexual activities (Witt et al., 2013; Sánchez et al., 2013).

HIV infection increases the chances for HCV persistence following exposure, and HIV–HCV coinfected patients depict greater HCV-RNA levels, experience faster liver fibrosis progression and more frequent hepatic decompensation events (Macías et al., 2009; Konerman et al., in press). On the other hand, the presence of chronic hepatitis C increases the risk of antiretroviral-related liver toxicity (Soriano et al., 2008b; Vispo et al., 2013), and treatment-induced HCV eradication may reduce the hepatotoxicity of HIV medications (Labarga et al., 2007).

Highly active antiretroviral therapy has led to a dramatic reduction in complications and death in HIV-infected patients (Palella et al., 2006), which has turned out chronic hepatitis C as a leading cause of morbidity and mortality in coinfected patients (Weber et al., 2006). As the REVEAL-C study pointed out (Lee et al., 2012), the spectrum of HCV-associated complications goes beyond the liver, and HIV coinfection seems to magnify this effect, increasing the rates of kidney disease, metabolic abnormalities, cardiovascular events and even bone disease (Wyatt et al., 2008; Peters et al., 2012; Kakinami et al., 2013; Gillis et al., in press; Lo Re et al., 2012).

HCV infection is mainly prevented by avoiding parenteral exposure to contaminated material. In this regard, opioid substitution and needle exchange programs in IDUs and application of universal precautions in medical procedures has proven to be quite efficacious (Soriano and Gallego, 2013; Hauri et al., 2004; Abdul-Quader et al., 2013; Robaeys et al., 2013). Prevention of hepatitis C has been further enhanced by HCV antibody testing, leading to exclusion of infected blood donors since 1990. If HCV-positive persons disregard preventive measures and continue to be engaged

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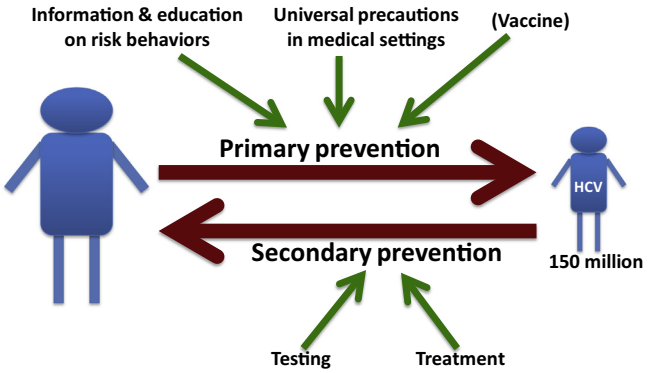

Fig. 1. The path towards HCV eradication requires multiple interventions.

in risk behaviors, treatment might help to prevent further transmissions. This secondary prevention has already been shown to be effective among IDUs (Robaeys et al., 2013; Martin et al., in press). Fig. 1 summarizes the strategies that may help to reduce HCV transmission.

Peginterferon-ribavirin therapy generally results in lower response rates in HIV–HCV coinfected patients than in HCV-monoinfected individuals. This is particularly true for HCV genotypes 1 or 4 (25–40% cure rates), which are the most prevalent. The recent availability of HCV protease inhibitors has filled with optimism the expectations for this population (Soriano et al., 2013a); however, hepatitis C triple therapy in coinfected individuals is subject to further challenges derived from drug interactions with antiretrovirals, overlapping toxicities, high pill burden, etc. (Soriano et al., 2011). For this reason, the advent of interferon-free, all-oral regimens will represent a huge step for eradicating HCV from the HIV population. However, major efforts would require the identification of the large number of people who are unaware of their infection status and to ensure access to the new therapies (Fig. 2). Enthusiasm unabated, the example of hepatitis B should remind us that despite good antivirals and even a vaccine, the benefits derived from the implementation of these tools in the real world are far from desired, as HBV infection continues to be among the most frequent human chronic viral diseases.

2. Lessons from HIV and opportunities

Despite the harmful effects of HIV on hepatitis C, the fact that HCV testing is mandatory in all HIV-infected persons, makes easier the diagnosis of coinfection. All practitioners taking care of HIV patients must exclude hepatitis C by HCV antibody screening and by HCV-RNA testing when seroreactive. Moreover, HCV testing must be repeated periodically in persons that remain engaged in high-risk practices, such as IDUs and promiscuous homosexual men, as recommended by European HIV guidelines (European AIDS Clinical Society (EACS), 2013).

Although major biological and clinical differences exist between HIV and HCV (Soriano et al., 2008a), both epidemics share many aspects and consideration of steps taken to fight HIV/AIDS may shed light on how to proceed in the path for HCV eradication. At the end of 2013 a conference on HIV eradication was held in San Francisco, where world experts discussed what it will take to achieve an AIDS-free world (Fauci and Marston, 2013). Attenders concluded that less than 10 of the 35 million people living with HIV are currently receiving antiretroviral therapy. Despite many efforts, another 16 million in need do not have access to treatment. There is a need for optimization of treatment and to find more potent, less toxic, and longer acting antiretrovirals. Ideally, a cure for HIV would need to be safe, administered with no tertiary care needed, and most definitely scalable. There are enormous political, economic, and structural forces that press the questions about maintaining funding and neglecting key populations and geographies. Ultimately, the hope is for low endemic levels of HIV.

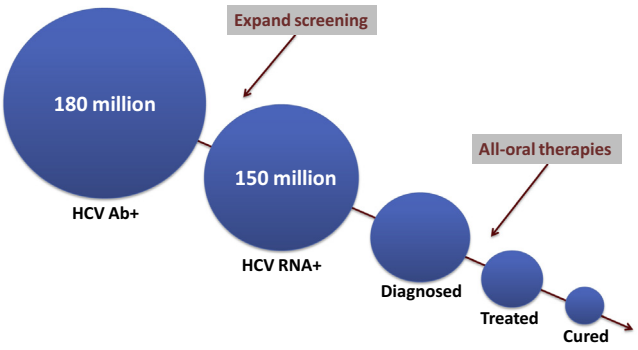

Fig. 2. The long roadmap for HCV eradication.

3. Treatment and prevention in the path for HCV eradication

Given that HCV can be eradicated from infected persons, in contrast with HIV (Soriano et al., 2008a), treatment efforts should be more cost-effective in hepatitis C than in HIV/AIDS. Table 1 summarizes and compares the main benefits expected from treatment of HIV and HCV infections. Successful hepatitis C therapy would produce a double benefit. On one hand, it will prevent patients from developing HCV-related hepatic and extrahepatic complications. On the other hand, new HCV infections will be prevented as the number of viral sources is reduced.

Although the efficacy of hepatitis C therapy is currently taking huge steps forward, it is clear that the path to global HCV eradication will require the contribution of further interventions, including identification of the large number of infected carriers unaware of their infection by expanding HCV testing (Thomas, 2013) (Fig. 3). Moreover, all prevention efforts need to be intensified, including implementation of universal precautions in all medical settings and ensuring adequate information and education to people engaged in high-risk behaviors, such as active IDUs or promiscuous homosexual men. As with HIV, the immunologic correlates of protective immunity are only incompletely understood in HCV, and therefore a vaccine is still far on the horizon (Cox and Thomas, 2013).

4. Peginterferon plus ribavirin in coinfection

Treatment of hepatitis C with peginterferon–ribavirin has been the gold standard during the last decade for all HCV genotypes. There are several reasons accounting for the lower treatment response rate in HIV-positive patients as compared with HIV-negative individuals (Torriani et al., 2004; Carrat et al., 2004; Nuñez et al., 2007; Labarga et al., 2012), including greater HCV-RNA levels, impaired cellular immunity and more prevalent advanced liver disease. Moreover, treatment-related adverse events (e.g., neuropsychiatric symptoms and anemia) generally tend to be more common in the HIV population.

With dual therapy, a full course of 48 weeks of peginterferon-ribavirin is warranted in HIV patients harboring HCV genotypes 1 or 4. Extending therapy up to 72 weeks may reduce relapses in the subset of patients that does not attain rapid virological response (European AIDS Clinical Society (EACS), 2013; Nuñez et al., 2007). Fig. 4 records the results of dual therapy in 148 coinfected patients at several European clinics. The authors pointed out that lack of achievement of undetectable viremia at week 4 might

Table 1
Differential effects of antivirals used in HIV and HCV infections.

	Antiretrovirals (HIV)	Direct-acting antivirals (HCV)
Viral replication	Suppression without clearance	Eradication
Major clinical benefit	Immune restoration	Reversion of liver fibrosis
Chronic inflammation and persistent immune activation	Amelioration	Elimination
Transmission	Reduction	Elimination
Drug-related toxicity	Long-lasting, cumulative	Short-term, reversible

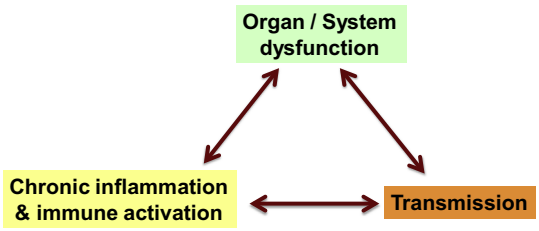

Fig. 3. Rationale for "*Test & Treat*" strategies in HIV and HCV.

allow either switching to triple therapy or recommend extension of dual therapy for 72 weeks (Mandorfer et al., in press). In contrast, shortening the length of therapy to 24 weeks could be recommended in coinfected patients with HCV genotypes 2 or 3 that reach rapid virological response, as long as they do not have cirrhosis. A daily dose of 1000–1200 mg of ribavirin instead of flat 800 mg doses should be used in coinfection (European AIDS Clinical Society (EACS), 2013; Nuñez et al., 2007).

Given the current economic restrictions, some regulatory authorities have restricted the use of triple therapy, advocating to still consider dual therapy as the first choice in specific patient subsets, such as in HCV genotype 1 patients naïve to interferon or prior relapsers with good baseline predictors of response, such as favorable IL28B alleles, null-minimal liver fibrosis and low viral load (Camma et al., 2012). All these variables are included in the Prometheus index (www.fundacionies.prometheusindex.php), a freely available website that may assist in treatment decision making, accurately predicting the likelihood of achieving HCV clearance with peginterferon-ribavirin alone in coinfected patients (Medrano et al., 2010).

5. First-generation DAA in coinfection

The addition of boceprevir or telaprevir to peginterferon–ribavirin significantly increases treatment response rates in patients with HCV genotype 1 infection, including those coinfected with HIV (Sulkowski et al., 2013a,b). The benefit is seen despite relatively high rates of serious adverse events, particularly anemia (Cachay et al., in press; Arends et al., 2013). Results in coinfection overall have reproduced what is obtained in HCV-monoinfected patients, as long as drug interactions with antiretrovirals are avoided (Sulkowski et al., 2013a,b). Outside clinical trials, there is some evidence of outperformance of telaprevir over boceprevir in HCV monoinfection (Backus et al., in press) and this is also our experience in coinfection, where telaprevir is associated with more pronounced antiviral effects than boceprevir (Benito et al., in press). However, so far no controlled trials have compared head-to-head boceprevir and telaprevir.

Drug interactions of boceprevir and telaprevir with certain antiretrovirals should be taken into careful consideration, especially for drugs metabolized throughout the cytochrome P450. Overall, HIV protease inhibitors must be avoided, as co-administration results in significant underexposure to either boceprevir or telaprevir (Hulskotte et al., 2013; van Heeswijk et al., 2013). However, atazanavir can be safely used with telaprevir, although bilirubin levels may increase further. Efavirenz is generally avoided along with telaprevir, as it forces an increase in its dosage, requiring more pills and increasing cost. HIV nucleos(t)ide analogues, raltegravir, dolutegravir, etravirine and rilpivirine can be safely used either with boceprevir or telaprevir (Soriano et al., 2011).

6. Second-generation DAA in coinfection

Although both telaprevir and boceprevir improves treatment responses compared to former dual therapy, their relatively poor safety profile, inconvenient dosing and wide range of drug interactions largely limit their global benefit for HIV–HCV coinfected patients.

Simeprevir is an HCV protease inhibitor with activity against all HCV variants but genotype 3. The C212 study recruited 106 HIV–HCV coinfected patients that received one daily pill of simeprevir 150 mg for 12 weeks along with peginterferon-ribavirin (Dieterich et al., 2013). Cirrhotics, prior partial or null responders and subjects without rapid virological response (negative serum HCV-RNA at week 4 of therapy) were treated for 48 weeks; whereas interferon-naïve and prior relapsers with rapid virological response were randomized to either 24 or 48 weeks of therapy. Simeprevir was allowed with nucleos(t)ide analogues plus either rilpivirine, raltegravir or maraviroc. The overall sustained virological response rate was 74%; slightly better in interferon-naïve (79%) and prior

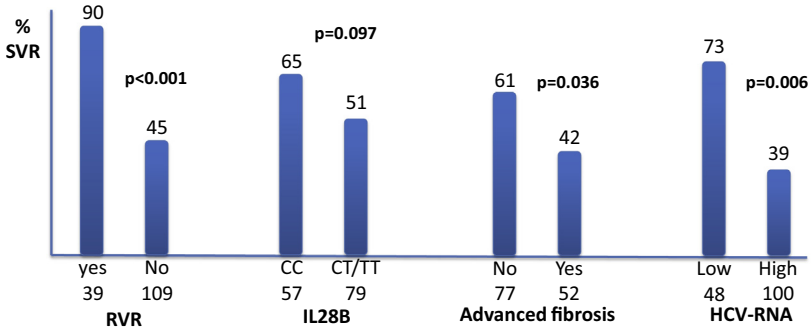

Fig. 4. Determinants of sustained virological response to peginterferon-ribavirin in HIV-positive patients with HCV G1 (Mandorfer et al., 2014).

relapsers (87%) as compared with prior partial (70%) or null responders (57%). There was a harmful influence on treatment response by advanced liver fibrosis, high baseline HCV-RNA, non-CC IL28B alleles and HCV subtype 1a. Interestingly, results supported 24 weeks length of therapy in interferon-naïve patients with rapid virological response, which occurred in 80% of instances. No serious adverse events attributable to simeprevir were recorded.

The STARTVerso 4 study compared 12 or 24 weeks of the HCV protease inhibitor *faldaprevir* along with peginterferon-ribavirin in 308 HIV-positive patients with HCV genotype 1 coinfection that were interferon-naïve or prior relapsers (Rockstroh et al., 2013). Faldaprevir benefits from very few drug interactions (Sabo et al., 2013) and accordingly efavirenz, darunavir, atazanavir and maraviroc were allowed in this trial. The overall rate of sustained virological response was 74%, with no significant differences by treatment arms. Moreover, HCV subtype or cirrhosis did not affect results. However, patients with IL28B CC alleles had higher response than the rest (89% vs 67%, respectively). Overall 80% of patients achieved rapid virological response and could be treated for only 6 months. Rash and hyperbilirubinemia were the most common side effects attributable to faldaprevir.

Sofosbuvir is an uridine analogue that blocks HCV replication, acting as a chain terminator of the nascent RNA strand by the RNA polymerase. The drug is highly active against all HCV genotypes (but G3), exhibits a high barrier to resistance and excellent safety profile, lacks drug interactions and is given as a once daily pill (Soriano et al., 2013b). A pilot study of sofosbuvir 400 mg/day plus peginterferon–ribavirin for 12 weeks provided 91% sustained virological response rates in 23 interferon-naïve HIV–HCV coinfected patients on antiretroviral therapy (Rodriguez-Torres et al., 2013). Sofosbuvir was overall well tolerated without any impact on plasma HIV-RNA nor CD4 counts. Table 2 summarizes the main results obtained with distinct triple therapy regimens in HIV–HCV G1 coinfected patients.

More recently, a combination of sofosbuvir plus weight-based ribavirin without peginterferon has been tested in the PHOTON-1 trial, that recruited 179 HIV–HCV coinfected patients either naïve or with prior interferon experience (Sulkowski et al., 2013c). Patients were treated for either 24 weeks (114 G1) or 12 weeks (26 G2 and 42 G3). Sustained virological response rates were 76% for G1, 88% for G2 and 67% for G3. Although most failures were relapses (22% for G1 and 29% for G3), 5 patients experienced viral breakthrough during therapy (four G1 and one G3). Interestingly, response rates were not influenced by IL28B alleles, cirrhosis, baseline HCV-RNA or age; however, patients infected with HCV subtype 1b responded less than those with 1a.

Daclatasvir is an inhibitor of the NS5A protein active across all HCV genotypes, although HCV subtype 1a escapes inhibition more easily than 1b. The drug is given as 60 mg once a day. While tenofovir, efavirenz or atazanavir do not require dose adjustments, the daclatasvir daily dose may need to go down to 30 mg when given with atazanavir and be increased to 90 mg when given with efavirenz (Bifano et al., in press). Daclatasvir has shown potent efficacy along with peginterferon–ribavirin or as part of all-oral interferon-free regimens with either asunaprevir or sofosbuvir (Lok et al., 2012; Suzuki et al., 2013). A trial with daclatasvir and peginterferon–ribavirin in HIV/HCV-coinfected individuals is currently ongoing.

ABT-450, which needs pharmacokinetic enhancement with ritonavir, is another potent HCV protease inhibitor. It has been tested with the NS5A inhibitor ABT-267 and the non-nucleoside NS5B polymerase inhibitor ABT-333, with or without ribavirin. More than 90% of HCV G1 monoinfected patients treated with the 4-drug regimen for 12 weeks achieved sustained virological response (Sulkowski et al., 2014; Poordad et al., 2013; Kowdley et al., 2014). A similar trial is currently being conducted in HIV–HCV coinfected patients.

7. Future hepatitis C therapy in coinfection

Triple therapy with peginterferon-ribavirin plus HCV protease inhibitors still fails in one-third or more of patients (Soriano et al., 2012), especially in those with unfavorable IL28B alleles, advanced liver fibrosis, HCV subtype 1a or prior interferon failure. Unfortunately, this subset of patients has been on the rise in places were hepatitis C therapy has been widely used in coinfected patients, since those with a more favorable profile already have been treated and cured (Poveda et al., 2012; Soriano et al., 2013c).

New all-oral DAA regimens will soon displace unpleasant subcutaneous interferon (Lok et al., 2012; Suzuki et al., 2013; Sulkowski et al., 2014; Poordad et al., 2013; Kowdley et al., 2014; Zeuzem et al., 2013). These regimens will be needed to confront the large proportion of hepatitis C patients unwilling to take peginterferon and/or ribavirin or in whom these drugs are contraindicated (i.e. due to low platelet or CD4 counts, serious neuropsychiatric conditions, decompensated cirrhosis or prior severe toxicity). The combination of simeprevir and sofosbuvir already has been shown to be effective in a large proportion of patients in the COSMOS study (Jacobson et al., 2013). Moreover, oral co-formulations are being developed rapidly, such as sofosbuvir plus ledipasvir (Lawitz et al., in press), or ABT-450 plus ABT-267 (Kowdley et al., 2014; Afdhal et al., 2013). Duration of therapy will be no longer than 24 weeks, and as short as 8–12 weeks in specific subsets of patients. Success rates above 90% are envisioned for HCV-monoinfected patients and there is no reason to expect lower success rates in HIV/HCV-coinfected patients, at least in those with a preserved immune status.

The current challenges with triple therapy include a relatively low success rate, need for good adherence to high pill burden, significant drug-drug interactions, and pricing. For the coming fu-

Table 2
Triple therapy with pegIFN + RBV plus DAA in IFN-naive HIV–HCV G1 coinfected patients. SVR, sustained virological response; RGT, response guided therapy; pegIFN, peginterferon; RBV, ribavirin.

	Boceprevir (Sulkowski et al., 2013a)	Telaprevir (Sulkowski et al., 2013b)	Simeprevir (Dieterich et al., 2013)	Faldaprevir (Rockstroh et al., 2013	Sofosbuvir (Sulkowski et al., 2013c)
No.	64	38	53	239	114
SVR	63%	74%	79%	69%	76%
Regimen	44 weeks of triple therapy preceded by 4 weeks pegIFN/RBV lead-in	48 weeks of triple therapy	12 weeks of triple therapy followed by either 12 or 36 additional weeks with pegIFN/RBV	12 or 24 weeks of triple therapy; additional pegIFN/RBV up to weeks 24 or 48	Sofosbuvir plus RBV for 24 weeks
Comments	48 weeks of triple therapy; all HIV protease inhibitors discouraged	12 weeks of triple therapy plus 36 weeks dual therapy. SVR was unexpectedly high (45%) in controls	82% G1a RGT (24 weeks length) in 80%	79% G1a Negative impact of non-CC IL28B; but not for cirrhosis nor for G1a. RGT (24 weeks length) in 80%	24 weeks therapy. No influence of IL28B nor cirrhosis. Most failures were relapses.

ture with all-oral DAA regimens, the global challenges for hepatitis C therapies in HIV-infected patients would be re-directed to underdiagnosis and access to the newest expensive drugs. On the long road toward the dream of HCV eradication, pools of difficult-to-reach populations will be created, preventing rapid global success (Fig. 5). These marginalized populations must be identified in advance. It will be worth to build new and appropriate strategies to confront them at due time. Only with a huge commitment, hepatitis C may follow the path of smallpox, the only infectious disease so far eradicated from the earth. Clearly, we have the means, but we need the will.

8. Treatment of hepatitis C as prevention in HIV-infected patients

Besides the contribution of treatment to reduce the number of HCV carriers as result of cure, treatment may contribute globally to hepatitis C eradication by preventing new infections. In the HIV field, several studies have demonstrated that early initiation of antiretroviral therapy not only improves survival rates but significantly reduces HIV transmission (Cohen et al., 2011; Barreiro et al., 2006). Parenteral exposure, especially amongst IDUs, remains the most frequent transmission route for HCV in developed countries (Hagan et al., 2010; Williams et al., 2011), although an increase of acute hepatitis C amongst HIV-positive homosexual men has been noticed during the last decade (Mohd-Hanafiah et al., 2013). Since an important proportion of HCV-infected patients are unaware of their serologic status, expanding HCV screening will identify a large number of asymptomatic hepatitis C carriers. Given the scaling-up of treatment success for hepatitis C, it is clear that "*test-and-treat*" strategies would be cost-effective. It makes sense to identify all individuals unaware of their infection, since simple and short treatment courses will eradicate HCV from most carriers. As a general policy, universal HCV testing of those born between 1945 and 1965 has been recommended in the United States (CDC, 1945), and similar pro-active policies will soon be adopted in Europe (Deuffic-Burban et al., 2012; Mathurin, 2013).

On the other hand, strategies pursuing "*treatment-as-prevention*" may certainly decrease HCV incidence in major high-risk populations, such as IDUs (Grebely et al., 2013). Mathematical models have estimated the benefit of DAA on HCV prevalence in IDUs living in different geographic areas, acknowledging the counter-effect of HCV re-infections (Martin et al., in press). Reductions of up to 75% in HCV prevalence rates at 15 years might be expected if access to DAA becomes widely available. Integrating harm reductions programs with hepatitis C treatment is crucial in IDUs. Opioid substitution and social support must be linked to maximize the success of any HCV therapy, as recently pointed out by the Greece experience, where the recent collapse of social and medical services to IDUs has led to an unprecedented rise of HIV and HCV infections (Paraskevis et al., 2013). An additional challenge in treating IDUs is poor medication compliance, raising the risk of developing drug-resistant HCV strains that could be transmitted to others.

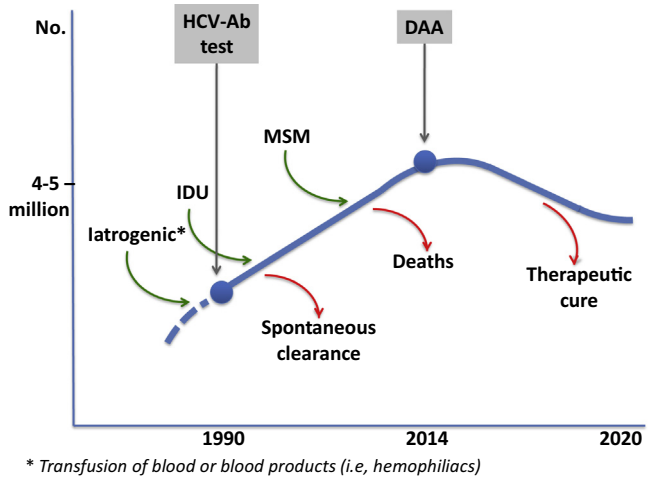

Fig. 5. Global HCV population dynamics.

9. Atypical HCV clearance behaviors in HIV coinfection

In contrast with human retroviral infections caused by HIV or HTLV, or with chronic hepatitis B, the replication of HCV only takes place within the cytoplasm of infected cells, in close association with the membranous intracellular web system, so that there is no integration of the virus genetic material into the nucleus of infected cells (Soriano et al., 2008a; Scheel and Rice, 2013). In this way, any antiviral therapy with enough potency and given for enough time should lead to HCV elimination, by blocking the synthesis of new HCV-RNA strands, and considering that the already existing HCV-RNA molecules are rapidly degraded by cellular RNases (Guedj et al., 2013).

This simple scenario, however, has been confronted with several observations that indirectly suggest that HCV reservoirs might exist, where the virus could remain hidden and escape antiviral and/or immune pressure for long periods. One concern with these "occult" (aviremic) HCV infections (Sugden et al., 2012) is the risk of very late HCV relapses following the achievement of sustained virological response with HCV therapy, as recently highlighted by several authors (Lawitz et al., 2013; Soriano et al., in press; Hara, in press; Tillma, in press). Although anatomical or cellular compartments where antivirals do not reach adequate levels may exist, these reservoirs should permit rapid virus replication once therapy is discontinued. Thus, long persistence of HCV-RNA should more likely be explained by establishment of null or minimally replicative HCV-RNA forms in long-life infected cells (Tillma, in press; Ralston et al., 2011) along with an immune-mediated contention of HCV replication once antiviral therapy is interrupted.

A second note of caution to the view of hepatitis C as a dichotomous acute or chronic process derives from reports of cases of spontaneous cure in patients with well-documented chronic hepatitis C. Interestingly most have been reported in HIV-HCV coinfected patients undergoing antiretroviral therapy (De Rosa et al., 2006; Endo et al., 2009; Falconer et al., 2008; Fialaire et al., 1999; Perez-Olmeda et al., 2000; Ranieri et al., 2003; Torti et al., 2004; Zeitoun et al., 2007; Weissbrich et al., 2003; Manfredi et al., 2012; Yokozaki et al., 2000; Vispo et al., in press). An immune-mediated effect has been suspected for a while. In fact, most cases of cure in chronic HCV carriers without specific antiviral therapy have been reported in IL28B CC carriers and many have occurred following the introduction or discontinuation of antiretroviral therapy (Vispo et al., in press).

Despite the above concerns, there is strong evidence that undetectable HCV-RNA in the bloodstream for 6 months reflects cure from HCV infection in most cases (Manns et al., 2013). Furthermore, HCV rebounds have not been found in series of patients with prior sustained virological response that thereafter received chemotherapy or immunosuppression, indirectly arguing against any HCV reservoir (Mahale et al., in press).

10. Conclusions

The introduction of DAA is a major turning point for HIV-HCV coinfected individuals, in whom liver disease is particularly prevalent and more severe, and for whom treatment was until

now less effective. Removal of interferon will allow treatment of larger numbers of patients, such as those with advanced liver disease or serious neuropsychiatric conditions. As in HIV infection, "*test and treat*" strategies are now cost-effective for hepatitis C. Reducing prices of new HCV antivirals would be required for broader use, as it has been the experience with HIV (Hill et al., in press). All-oral regimens may be of further benefit by reducing new infections once the virus is eliminated from carriers. However, identifying the large number of people unaware of their infection, access to harder-to-reach populations and pricing will be major challenges ahead before dreaming on a hepatitis C-free world, even just limited to the HIV community.

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