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REVIEW

Hepatitis C in human immunodeficiency virus co-infected individuals: Is this still a "special population"?

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Abstract

A substantial proportion of individuals with chronic hepatitis C virus (HCV) are co-infected with human immunodeficiency virus (HIV). Co-infected individuals are traditionally considered as one of the "special populations" amongst those with chronic HCV, mainly because of faster progression to end-stage liver disease and suboptimal responses to treatment with pegylated interferon alpha and ribavirin, the benefits of which are often outweighed by toxicity. The advent of the newer direct acting antivirals (DAAs) has given hope that the majority of co-infected individuals can clear HCV. However the "special population" designation may prove an obstacle for those with co-infection to gain access to the new agents, in terms of requirement for separate pre-licensing clinical trials and extensive drug-drug interaction studies. We review the global epidemiology, natural history and pathogenesis of chronic hepatitis C in HIV co-infection. The accelerated course of chronic hepatitis C in HIV co-infection is not adequately offset by successful combination antiretroviral therapy. We also review the treatment trials of chronic hepatitis C in HIV co-infected individuals with DAAs and compare them to trials in the HCV mono-infected. There is convincing evidence that HIV co-infection no longer diminishes the response to treatment against HCV in the new era of DAA-based therapy. The management of HCV co-infection should therefore become a priority in the care of HIV infected individuals, along with public health efforts to prevent new HCV infections, focusing particularly on specific patient groups at risk, such as men who have sex with men and injecting drug users.

Key words: Human immunodeficiency virus; Hepatitis C; Coinfection; Antiviral agents; Anti-retroviral agents; Natural history; Epidemiology; Pathogenesis; Therapy

Core tip: This manuscript focuses on hepatitis C virus/human immunodeficiency virus (HIV) co-infection, two intersecting epidemics with great global health interest. It reviews the epidemiology, pathogenesis and natural history of chronic hepatitis C in HIV infected individuals. It also reviews the impact of antiretroviral therapy on the natural history of chronic hepatitis C and the liver. Moreover, it shows that the outcomes of treatment with the newer direct acting antivirals against hepatitis C are similar in the mono-infected and co-infected patients, providing informative data extracted from relevant clinical trials. It argues that HIV infected individuals should no longer be designated as a "special population" among those with chronic hepatitis C, as this could delay their access to the new treatments.

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INTRODUCTION

Co-infection with the blood-borne hepatitis C Virus (HCV) and human immunodeficiency virus (HIV) is common due to their shared routes of transmission and the fact that individuals with HIV are at higher risk of contracting HCV. Estimates of HCV prevalence in the general population overall vary from 0.3% in Austria, England and Germany to 8.5% in Egypt[1]. However, in the HIV population, the prevalence of HCV/HIV co-infection has been reported between 9.2%-37.3%[2,3]. This population has long been considered a special risk population both in terms of disease progression and subsequent mortality, and in terms of their inferior responses to traditional HCV therapies. However, in the ever-evolving era of direct-acting antivirals (DAAs) we ask the question "Is this still a special population?".

EPIDEMIOLOGY OF HCV/HIV CO-INFECTION

Following its discovery 25 years ago and until recently, HCV was considered a disease of parenteral transmission, affecting people who inject drugs (PWIDs) who share needles or drug-taking equipment and of individuals who received infected blood products prior to the introduction of reliable screening in the 1990s. Largely this is still the case in less developed regions such as sub-Saharan Africa where HCV/HIV co-infected individuals tend to be older than those with HIV mono-infection, likely reflecting improvements to healthcare sterility and blood screening[4]. In almost all countries in the world there is a male preponderance for HCV infection overall, in keeping with higher levels of intravenous drug use in men, except in France and Germany where more women are affected, with the risk factor for acquisition being blood transfusion after childbirth[1].

It is estimated that in 2010 around 10 million PWIDs (range 6.0-15.2 million) were HCV seropositive. This is over three and a half times higher than the 2.8 million people estimated to be infected with HIV[5]. A review of worldwide systematic reviews demonstrated that the midpoint prevalence of co-infection in PWIDs varies greatly between countries ranging from 9.8% in Paraguay to 97% in Mexico. Those countries with the highest estimated populations of PWIDs were China, Russia and the United States with HCV prevalence of 67%, 72.5% and 73.4%, respectively. However, these statistics under-represent the total burden of HCV from drug use as they do not include former PWIDs who have previously been infected with HCV.

Blood-borne viruses account for much of the morbidity and cost associated with intravenous drug use and many countries around the world have invested in programmes to both treat drug addiction and promote safe injection practices. This may partly account for the reduction in HCV incidence in HIV-infected PWIDs that is currently being seen. The Swiss Cohort reported a decrease in incidence from 13.89 (95%CI: 8.20-22.39) per 100 person-years in 1998 to 2.24 (95%CI: 0.55-10.66) in 2011[6]. However, European surveillance data shows that although the number of newly diagnosed HIV infections related to intravenous drug use is decreasing following its peak in 2001-2002, only half the twelve countries with available data show decreases in HCV prevalence during 2005-2010[7]. These data however report prevalence rather than incidence and do not take into account probable increases in awareness and testing over the past decade. The economic recession that has struck countries like Greece worsens the efforts for tackling the HIV and HCV epidemics amongst PWIDs[8].

Transmission of HCV outside of these populations with healthcare-associated risks and intravenous drug-use has always been considered to be negligible and restricted to low numbers of new cases in regular sexual partners of individuals with HCV infection. However, a few years ago clinicians began to notice a significant rise in new HCV among men who have sex with men (MSM) and denied intravenous drug use and had no healthcare-associated risks. One survey of United Kingdom urban centre-based HIV clinics revealed a doubling of new HCV in MSM from 6.86 cases/person-years in 2002 to 11.58 in 2006, without an apparent change in testing policy[9].

This observed shift of new HCV infections from PWIDs to MSM was confirmed in analysis of the Swiss Cohort showing an alarming 18-fold increase in the incidence of new cases in MSM from 0.23 (95%CI: 0.08-0.54) per 100 person-years in 1998 to 4.09 (95%CI: 2.57-6.18) in 2011. This resulted in an increase in the proportion of MSM among incident HCV from 20% prior to 2006

to 75% after ($P < 0.001$)[10]. Significant increases were also shown in the Amsterdam MSM cohort from 2000 to 2005 (incidence rate ratio 3.41, 95%CI: 1.58-7.34), though there was a levelling off of new HCV infections in MSM from 2005 onwards[11].

Virus sequencing and phylogenetic analysis of 226 HIV-infected MSM diagnosed with acute HCV from urban centres in England, Netherlands, Germany, France and Australia revealed that the independently reported European outbreaks were actually part of a large European MSM-specific transmission network[12]. A second MSM-specific transmission network was found in Australia, with very little overlap with the European network. In contrast to the European network, only 18% of transmissions in this cohort were thought to be from sexual exposure, with intravenous drug exposure still the predominate risk factor (73%)[13]. Eighty-six percent of sexual transmissions were in MSM and all of those were HIV-positive. In this cohort social networks exist in HIV-infected MSM that contain both PWIDs and non-PWIDs.

In the European transmission networks of MSM the predominant HCV genotype has been shown to be genotype 1a (59%), with an unexpectedly high proportion of genotype 4d (23%)[12]. Thus, the difficult-to-treat genotypes 1 and 4 accounted for 90% of infections compared to 67% of the Australian cohort. This has clear implications for treatment and healthcare planning.

The cause of this epidemic of HCV in MSM is likely to be multi-factorial. There is certainly some evidence that risk of HCV transmission in HIV-infected MSM is associated with non-intravenous recreational drug taking. Recreational drug use may increase the risk of unprotected sex and may be associated with group sex or with more traumatic sexual practices. In the Multicenter AIDS Cohort Study (MACS) non-intravenous recreational drug use was found to double risk, however, in the Swiss cohort no association was found[6,14].

Risk of HCV acquisition in MSM has, unsurprisingly been found to be related to multiple sexual partners, receptive anal sex and inconsistent condom use[6,14]. The spread of HCV may in part, be related to the practice of serosorting. Though men may select sexual partners on the basis of HIV status, they may well be at risk of HCV; almost a third of HIV-positive individuals are unknowingly infected with HCV[15]. However, if HCV transmission among MSM was solely due to behavioural factors, higher rates would be expected in the HIV-negative MSM population, even taking into account serosorting. Interestingly, there has been no increase in HCV in HIV-negative MSM observed, and risk has been shown to be comparable or lower than the risks in the heterosexual population[16]. More recently, however, there are emerging reports of HCV infection amongst HIV-negative MSM, so this may well represent an emerging epidemic[17].

In both the Swiss and the MACS cohorts, risk was associated with past or recent syphilis infection, confirming either a shared route of acquisition or suggesting that potentially ulcerative sexually transmitted infection could increase the risk of HCV transmission[6,14]. Individuals with HCV/HIV co-infection have been shown to have higher HCV viral loads than HCV mono-infected individuals, which may well increase the risk of transmission, particularly in the presence of ulcerative lesions, as recognised in HIV transmission[18]. A change in the virulence of circulating HCV does not appear to account for the HCV epidemic is not supported by phylogenetic analysis showing strains in the populations belong to several different genotypes and subtypes[12]. There has also been the suggestion that transmission risk may increase with decreasing CD4 count. In the MACS cohort every 100 cells/mm^3 decrease was associated with a 7% increase in risk of transmission below 500, though no association was shown in other studies[6,14].

The reports of HCV outbreaks in MSM around 2000, shortly followed the introduction of combination antiretroviral therapy (cART) in 1996. It was thought that individuals on cART had increased their sexual risk taking as a result of having suppressed HIV viral loads and reduced risk perception from HIV and there is some data to support this[19]. However, no association with HCV seroconversion and use of cART has been found, and cohort analyses have shown incident infections since the 1980s, and increases in incidence since the 1990s, well before the introduction of cART[6,14,20]. Furthermore, in the phylogenetic studies described, for each cluster of new HCV infections, the date of the common ancestor was calculated using the molecular clock approach. In the Australian networks the earliest events were estimated to have occurred around 1989 and in the European clusters 15% of transmissions were estimated to have occurred prior 1996, though the majority of infections (63%) did occur after 2000[13,20].

NATURAL HISTORY OF HCV/HIV CO-INFECTION

Acute hepatitis C is usually asymptomatic or minimally symptomatic and rarely causes severe hepatitis. Depending on the characteristics of the population examined, around 80% of patients with newly acquired hepatitis C mono-infection will develop chronic hepatitis C[21]. Most of the chronically mono-infected hepatitis C are asymptomatic, but 20%-30% will progress to develop cirrhosis over about 30 years[22]. The risk of progression from advanced fibrosis to cirrhosis has been estimated at about 10% per year[23]. Individuals with compensated cirrhosis have approximately a 4% annual risk for hepatic decompensation and a 1%-2% annual risk for development of hepatocellular carcinoma[24,25]. Among those with a first episode of hepatic decompensation, almost half will die within the next 5 years[24,26].

Higher HCV plasma viral loads are seen in HIV co-

infected individuals[27]. The level of HCV viraemia has been inversely correlated with CD4 counts[28]. Although HCV viraemia is not thought to play a role in the rate of progression of liver disease, it is important in the treatment response to pegylated interferon (PegIFN)/ribavirin (RBV) therapy and may also play a role in the length of therapy required for likelihood of response to PegIFN-free therapy[29,30].

The likelihood of spontaneous clearance of acute hepatitis C infection appears to be lower in HIV-co-infected individuals[28]. This could correlate to weaker HCV-specific T-cell responses in individuals with HIV infection[31]. Immunogenetic factors, particularly a favourable interleukin-28B (IL28B) genotype, play a role in this regard, as in mono-infected individuals. Some high-risk HIV-infected individuals present with one or more reinfections after spontaneous clearance or successful treatment of hepatitis C. It has been suggested that the likelihood of clearance of a new episode of acute hepatitis C increases with the prior number of spontaneous clearances[32].

Numerous clinical studies have shown that HIV infection is an accelerator of hepatitis C related outcomes[33]. Whether the sequence of acquisition of the viruses is important in this regard has not been fully elucidated. Some experts argue that hepatitis C may progress more rapidly if acquired in a patient with pre-existing immunosuppression, as seen in the setting of the recurrence of hepatitis C after orthotopic liver transplantation[34]. There are case reports of HIV infected individuals developing decompensated cirrhosis and death within as soon as 2-8 years after HCV acquisition. Other studies, however, have not found such a malignant course after acute hepatitis C in HIV infected individuals[35].

The rate of fibrosis progression has been found to be faster in HCV/HIV co-infected individuals compared with HCV mono-infected ones. Lower CD4 counts and higher HIV viral load have been associated with a greater likelihood of fibrosis progression. Other risk factors for faster fibrosis progression among co-infected individuals include advanced age, alcohol use, viral co-infection, obesity, insulin resistance, and hepatic steatosis, the latter being more common with genotype 3 HCV infection[36-40].

In HCV/HIV co-infected individuals, as in those with HCV mono-infection, the likelihood of hepatic decompensation is associated with the stage of liver disease[41]. However, the likelihood of decompensation is higher for co-infected *vs* mono-infected individuals with a similar stage of liver disease, even if HIV control is achieved with antiretroviral therapy[42]. The prognosis following hepatic decompensation in co-infected individuals is generally poor. A median survival of 13 mo was noted in a prospective cohort of 153 HCV/HIV co-infected individuals after the first episode of hepatic decompensation[43]. The definitive treatment in decompensated cirrhosis is liver transplantation, the outcomes of which are less favourable for co-infected individuals[44]. HCV/HIV co-infected individuals have also a greater incidence of hepatocellular carcinoma than those with HCV mono-infection, which is observed at a younger age, is typically more advanced and more likely to be symptomatic at diagnosis, and has a worse prognosis[45].

With the effective control of HIV infection with potent antiretroviral therapy, non-AIDS related causes of death have become more prominent[46]. Among these, liver-related death, associated with chronic hepatitis, is one of the most common causes of death in the HIV-infected population[47,48]. Although the upwards trend of liver-related deaths among HIV infected individuals appears to be reversing, the proportion remains considerably high[46,48]. Liver-related death may be more likely in patients with lower CD4 counts[49]. The presence of HCV infection among HIV infected individuals has been associated with a negative impact on overall mortality[50].

All-cause hospitalization is also more likely in HCV/HIV co-infected compared with HIV mono-infected individuals[51]. Certain comorbid conditions have been observed more frequently in HCV/HIV co-infected individuals than those with HIV mono-infection. These include cardiovascular disease, neurocognitive disorders, chronic kidney disease, osteoporosis and bone fractures, as well as diabetes mellitus[52].

The achievement of a sustained virological response with anti-HCV treatment in HIV co-infected individuals has been associated with the same benefits on liver disease as those seen in HCV mono-infection, including decreases in fibrosis progression and greater likelihood for regression of fibrosis, as well as decreases in the rate of hepatic decompensation and liver-related mortality[39,53-55]. Although co-infected individuals with advanced fibrosis who have failed prior PegIFN/RBV therapy may fare better in terms of fibrosis progression than untreated individuals, maintenance PegIFN/RBV therapy in the setting of treatment failure has not proven beneficial[55,56]. Hepatocellular carcinoma can develop in individuals with cirrhosis despite effective treatment of chronic hepatitis C.

The effect of HCV infection on the natural history of HIV infection has not been well characterised[57]. Most studies suggest that chronic hepatitis C does not alter the course of HIV infection, however, in a multi-national HIV seroconvertor cohort, HCV appeared to increase risk of progression to AIDS and death[58].

PATHOGENETIC MECHANISMS

Several pathogenetic mechanisms could explain the faster liver disease progression rate in HCV/HIV co-infected individuals. Although HIV does not directly infect hepatocytes, it has been shown that HIV enhances the replication of HCV in hepatocytes *in vitro*. This effect could be mediated by the interaction between HIV and the co-receptors CCR5 and CXCR4 on hepatocytes, *via* a transforming growth factor (TGF)-β1-mediated pathway[59]. TGF-β1 is a key mediator in the process of

liver fibrosis, as it is one of the most pro-fibrinogenic cytokines. HIV can also promote fibrogenesis *via* the induction of production of reactive oxygen species by hepatocytes and hepatic stellate cells, *via* an nuclear factor kappa-B-dependent pathway; this effect is enhanced in the presence of HCV. HIV can also induce hepatocyte apoptosis through increased sensitivity to tumor necrosis factor-related apoptosis-inducing ligand[60]. The systemic immune activation in HIV-infection has been associated with activation of hepatic stellate cells, which have a central role in the development of fibrosis[61]. Direct infection of hepatic stellate cells by HIV has been documented, although the exact mechanism is unclear[62]. The activation of hepatic stellate cells may also relate to the diminished natural killer-cell cytotoxic responses against these cells that is seen in HIV infection, owing to loss and impaired function of $CD4^+$ cells[63].

HIV infection has been associated with higher hepcidin blood levels than HCV mono-infection or HCV/HIV co-infection[64,65]. Hepcidin is a peptide hormone that regulates iron homeostasis. Whether increased hepcidin results in increased liver iron stores in co-infected individuals than HCV mono-infected ones, remains to be proven. Of note, liver iron has been shown to stimulate hepatic stellate cells and negatively affects fibrosis progression in HCV mono-infected individuals[66].

The immune responses against HCV are compromised in HIV co-infected individuals. Lower CD4 counts lead to attenuated $CD8^+$ T cell HCV-specific immune responses[31,67]. The HCV infecting viral population appears to be genetically more diverse in co-infection[31,68]. This reflects weaker selection pressure from the immune system. Higher quasispecies heterogeneity might negatively affect the response to interferon-based treatment[69].

HIV leads to a state of immune activation and dysregulation. Decrease in CD4 cells in gut-associated lymphoid tissue, which occurs early in the course of HIV infection, leads to increase in microbial translocation through the intestinal mucosa[70]. This is evident by increase in the circulating lipopolysaccharide (LPS) and other relevant markers. Higher levels of circulating LPS have been associated with a higher likelihood of development of cirrhosis in HCV/HIV co-infected individuals[71].

THE IMPACT OF CART ON HCV/HIV CO-INFECTION

Since the introduction of cART, life expectancy for individuals living with HIV has become comparable to that associated with other long term conditions, though it is still lower than the general population[3,72]. Less people with HIV are dying from HIV/AIDS-related causes and with the increasing length of survival, the relative importance of comorbidities such as viral hepatitis has increased[73]. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study found that since the introduction of cART, there has been a proportional increase in liver-related deaths (LRD) and that this was the most common cause of non-AIDS related death[49]. There was initial concern that this was a consequence of ART-related hepatotoxicity, however, in subsequent analyses it became clear that this excess liver-related mortality is largely a product of viral hepatitis, and that half of those that died in the D:A:D study had active HCV[73,74].

Individuals with HCV/HIV continue to do significantly worse in terms of mortality when compared with their HIV mono-infected peers. In a Spanish cohort, all cause mortality reduced by almost 50% in HIV mono-infected individuals, but no significant change was found in HCV/HIV co-infection[75]. A meta-analysis of cohort studies showed no increased risk of mortality associated with HCV/HIV co-infection in the pre-cART era, but since the introduction of cART the risk ratio was 1.12 (95%CI: 0.82-1.51) for AIDS-defining events and 1.35 (95%CI: 1.11-1.63) for overall mortality among co-infected patients, compared with that among patients with HIV mono-infection[50].

Though there is a risk of hepatitis flare when first initiating cART, there is no evidence that cumulative exposure to cART in itself is related to increased mortality[76,77]. The increased number of deaths in co-infected individuals after the introduction of cART is likely to reflect those individuals who would not have previously survived from HIV/AIDS related events rather indicating a hepatotoxic effect of cART. Moreover, any potential risk is outweighed by the benefits of treatment.

Though the benefits of cART to HIV disease are clear, its impact on liver disease progression in co-infected individuals has been debated. A meta-analysis in 2008 failed to show that cART had any significant effect on fibrosis progression or risk of cirrhosis. However, it did show that the risk of cirrhosis in the post-cART era was slightly lower than pre-cART[78]. Other studies since then have shown an association between the use of cART and a slower rate of liver fibrosis[79,80]. One study of 638 co-infected individuals, 69% of whom were on cART, showed that both current cART and HIV viral suppression were independently associated with decreased incidence of all-cause events and a 66% reduction in liver-related events such as end-stage liver disease (ESLD), hepatocellular carcinoma (HCC) and LRD[41]. Another study found evidence that cART reduces the risk of hepatic decompensation in those with advanced liver disease[81].

As a result of these benefits, national and international guidelines have changed to recommend initiation of cART in HCV/HIV co-infection at earlier stages of HIV disease[82,83]. One mathematical model has been used in South Africa to estimate the benefit of expanding cART eligibility from those with CD4 < 350 cells/mm^3 to those with CD4 < 500 cells/mm^3. Factoring in the assumptions that co-infection accelerates liver disease 2.5-fold and

that cART reduces progression by one third, this model simulated disease progression in both HIV mono-infection and individuals co-infected with viral hepatitis. Significant benefits were shown in hepatitis B virus (HBV)/HIV co-infection, and HIV mono-infection in terms of deaths averted and disability-adjusted life-years (DALY). However, in HCV/HIV co-infection, expanding eligibility of cART actually increased the share of LRD by 34% as individuals survive for longer. Expanding eligibility was estimated to avert only 3.9 DALYs compared to 4.8 for HIV mono-infection and 5.1 for HBV/HIV co-infection. Authors estimated cART would need to reduce liver disease progression by 70% to show any significant benefit[84].

The obvious reason for this discrepancy in the benefit of cART between HBV/HIV and HCV/HIV co-infections is that while HBV can be easily controlled with well tolerated anti-hepatitis B containing cART, HCV has, until now, required long courses of poorly-tolerated subcutaneous PegIFN with RBV. The EuroSIDA study demonstrated that from 1998 to 2007, 22% of patients with at least F2 fibrosis remained untreated and that there were significant variations of treatment uptake across Europe and across transmission groups[85]. There has been a rise observed in HCV treatment uptake in co-infected individuals from 22% in 1991 one study to 88% in 2012[10]. However, a decline in 2013 was noted as individuals with less advanced disease inevitably await the availability of newer treatments[1].

Several studies have confirmed that PWIDs are less likely to receive treatment for their HCV than MSM[10,85]. Intravenous drug use is independently associated with poorer outcome in terms of all-cause mortality, LRD, ESLD and HCC[3,41,49]. Barriers to treatment in PWIDs include persistent drug or alcohol addiction, difficulties accessing care, concerns over drug side effects, poverty, discrimination and general poor health. Co-infected PWIDs are less likely to complete HCV treatment compared to mono-infected PWIDs. Adherence however, can be improved with addiction treatments, though coverage of opioid substitution and needle/syringe programmes is very variable across Europe with particularly low coverage in central and south-east Europe[7,86]. Addiction treatment can also have benefits for HIV treatment in terms of compliance and improved virological success[87]. After the roll-out of shorter, oral treatments for HCV with fewer side effects, requiring less intensive monitoring, it is hoped that uptake of HCV treatments will improve, but particular focus must still given to the hard-to-reach PWID population.

TREATMENT OF HCV IN CO-INFECTED INDIVIDUALS

The response to PegIFN alpha plus RBV for the treatment of chronic hepatitis C in individuals with HIV co-infection is lower than in those with HCV mono-infection[88,89]. The basis of the viral clearance of HCV with PegIFN/RBV therapy is immunologic. PegIFN acts primarily by enhancing the innate antiviral immune response and can also potentiate adaptive immune responses[90]. Ribavirin is thought to exert various, not well characterised antiviral effects and to potentiate the effect of PegIFN[91]. An important predictor of the treatment success with PegIFN/RBV against chronic hepatitis C genotype 1 or 4 infection is a favourable interleukin 28B genotype[29,92].

The integrity of the immune system appears to be less important when direct acting antivirals are used for the treatment of HCV infection. The introduction in 2011 of the direct acting antivirals boceprevir and telaprevir, which are first generation, first wave NS3/4A protease inhibitors, has allowed for a substantial increase in the likelihood for sustained virological response (SVR) in genotype 1 HCV/HIV co-infected patients (Table 1). The absolute treatment benefit achieved with these agents is similar to that observed in HCV mono-infected individuals[93,94]. In a recently published study, telaprevir in combination with PegIFN/RBV had high effectiveness (SVR24 80%) in PegIFN/RBV treatment-experienced genotype 1 HCV/HIV co-infected individuals[95]. This population would have been considered to be a "difficult-to-treat" one in the era before DAAs. The likelihood of treatment success did not differ by the fibrosis stage, IL28B genotype, HCV 1a or 1b genotype, CD4 cell count, type of previous response to HCV treatment, baseline HCV-RNA level or the rapidity of HCV-RNA response.

Despite their antiviral activity, boceprevir and telaprevir have many limitations including the requirement for a long course of therapy in combination with PegIFN/RBV, a high rate of adverse effects, the need for multiple daily dosing including the requirement for co-administration with food, high pill burden, low barrier to resistance, and a high potential for drug-drug interactions[96]. Some of these issues are particularly important in the context of HIV co-infection and concomitant antiretroviral therapy.

Newer DAAs have now been marketed and numerous others are in the later stages of clinical development[97]. The drug targets include the NS3/4A serine protease, the NS5A replication complex, and the NS5B RNA polymerase; the latter enzyme can be targeted by nucleos(t)ide or non-nucleoside inhibitors. Following the paradigm of combination antiretroviral therapy, the combination of two or more antiviral agents (depending on potency, genetic barrier to resistance and activity against the different HCV genotypes), has made interferon-free therapy possible[98,99]. As of this writing, sofosbuvir (NS5B RNA polymerase nucleotide inhibitor), simeprevir (NS3/4A protease inhibitor), daclatasvir and ledipasvir (NS5A inhibitors) have been approved by the European Medicines Agency.

Table 1 presents the characteristics and findings of the main trials of direct acting antivirals, with or without PegIFN, in HCV/HIV co-infection[95,100-110]. The newer interferon-free regimens are expected to allow for a high likelihood (> 90%) of achieving SVR, with shorter

Table 1 Trials of direct-acting antivirals for chronic hepatitis C infection in human immunodeficiency virus co-infected patients

Study	GT	Tx regimen	Tx duration (wk)	Hepatitis C characteristics	SVR12		
					GT	Fibrosis stage	Treatment status
P05411[100]	1	PegIFNα-2b + RBV wb (600-1400 mg) + BOC *vs* placebo	BOC: 44 PegIFN/RBV: 48	Tx naïve Metavir F0-4 Cirrhosis: 3%	BOC GT1: 42/64 (66%) GT1a: 32/51 (63%) GT1b: 7/12 (58%) Placebo GT1: 9/34 (26%)		
VX08-950-110[101]	1	PegIFNα-2a + RBV 800 mg or wb (1000-1200 mg) + TVR *vs* placebo	TPV: 12 PegIFN/RBV: 48	Tx naïve Metavir F0-4	TPV GT1: 28/38 (74%) GT1a: 20/27 (74%) GT1b: 7/11 (64%) Placebo GT1: 10/22 (45%) GT1a: 4/14 (29%) GT1b: 4/6 (67%)		
ANRS HC26 TelapreVIH[95]	1	PegIFNα-2a + RBV wb (1000-1200 mg) + TVR	TPV: 12 PegIFN/RBV (RGT): 44 or 72	Tx exp Metavir F0-4 Both cirrhosis and prior null-response excluded	GT1: 55/69 (80%) GT1a: 36/48 (75%) GT1b: 19/21 (90%)	F1-2 34/42 (81%) F3-4 21/27 (78%)	Relapse 20/27 (74%) Breakthrough 5/6 (83%) Partial response 15/15 (100%) Null response 15/21 (71%)
P7977-1910[102]	1-4	SOF + PegIFNα-2a + RBV wb (1000-1200 mg)	12	Tx naïve No cirrhosis	All GTs: 21/23 (91%) GT1: 17/19 (89%) [GT1a: 13/15 (87%) GT1b: 4/4] GT2: 1/1 GT3: 2/2 GT4: 1/1		
STARTVerso4[103,104]	1	FDV 240 mg (EFV) or 120 mg (ATV/r or DRV/r) or 120 *vs* 240 mg (RAL or MVC or no ART) + PegIFNα-2a + RBV wb (1000-1200 mg)	FDV: 24 or (12 *vs* 24), PegIFN/RBV (RGT): 48 or 24 wk *vs* 48 wk	PegIFN/RBV Tx naïve or prior relapse Compensated cirrhosis: 15%	GT1: 221/308 (72%) GT1a: 171/242 (71%) GT1b: 50/66 (76%)	No Cirrhosis 187/261 (72%) Cirrhosis 33/45 (73%)	Tx naïve 164/239 (69%) Relapse 57/69 (83%)
C212[105]	1	SMV + PegIFNα-2a + RBV wb (1000-1200 mg)	SMV: 12 PegIFN/RBV RGT: (24 *vs* 48) for Tx naïve or prior relapse or 48 for partial- or null-response or cirrhosis	PegIFN/RBV Tx naïve or Tx exp Metavir F0-4; Cirrhosis: 6%-30% by Tx arm	GT1: 78/106 (74%) GT1a: 62/88 (70%) GT1b: 16/18 (89%)	F0-2 36/45 (80%) F3-4 14/22 (64%)	Tx naïve 42/53 (79%) Relapse 13/15 (87%) Partial response 7/10 (70%) Null response 16/28 (57%)
PHOTON-1[106]	1-3	SOF + RBV wb (1000-1200 mg)	GT 1: 24 GT 2-3 Tx naïve: 12 GT 2-3 Tx exp: 24	Tx naïve (GT1-3) or exp (GT2-3) Cirrhosis ⩽ 20%	GT1: 87/114 (76%) [GT1a: 74/90 (82%) GT1b: 13/24 (54%)] GT2: 44/50 (88%)	No Cirrhosis GT1: 84/109 (77%) GT2: 22/25 (88%) GT3: 24/36 (67%)	Tx naïve GT1: 87/114 (76%) GT2: 23/26 (88%) GT3: 28/42 (67%)

					GT3: 44/59 (75%)	Cirrhosis GT1: 3/5 (60%) GT2: 1/1 GT3: 4/6 (67%)	Tx exp GT2: 22/24 (92%) GT3: 16/17 (94%)
PHOTON-2[107]	1-4	SOF + RBV wb (1000-1200 mg)	GT 1, 3, 4: 24 GT 2 Tx naïve: 12 GT 2 Tx exp: 24	Tx naïve (GT1-4) or exp (GT 2-3) Compensated cirrhosis: 20% of patients	GT1: 95/112 (85%) [GT1a: 84/100 (84%) GT1b: 10/11 (91%)] GT2: 22/25 (88%) GT3: 94/106 (89%) GT4: 26/31 (84%)	No Cirrhosis GT1: 84/95 (88%) GT2: 19/22 (86%) GT3: 73/80 (91%) GT4: 19/23 (83%) Cirrhosis GT1: 11/17 (65%) GT2: 3/3 GT3: 21/26 (81%) GT4: 7/8 (88%)	Tx naïve GT 1: 95/112 (85%) GT2: 17/19 (89%) GT3: 52/57 (91%) GT4: 26/31 (84%) Tx exp: GT2: 5/6 (83%) GT3: 41/49 (84%)
TURQUOISE-I[108]	1	Paritaprevir/r/Ombitasvir + Dasabuvir + RBV wb (1000-1200 mg)	12 or 24	Tx naïve or PegIFN/RBV exp Cirrhosis ⩽ 30%	Tx for 12 wk GT1: 29/31 (94%) Tx for 24 wk 19/20 (95%)		
ERADICATE[109]	1	SOF/LDV	12	Tx naïve Knodell F0-3	Untreated HIV Infection GT1: 10/10		
C-WORTHY[110]	1	Grazoprevir + MK-8742 +/- RBV	12	Tx naïve No cirrhosis Metavir F0-3	With RBV 28/29 (97%) Without RBV 26/29 (90%)		

/: Indicates co-formulation; +/-: With or without; GT: HCV genotype and subtype; RGT: Response guided therapy; Tx (exp): Treatment (experienced); *vs*: Indicates randomisation; wb: Weight based; ATV: Atazanavir; BOC: Boceprevir; DRV: Darunavir; EFV: Efavirenz; FDV: Faldaprevir; LDV: Ledipasvir; PegIFN: Pegylated Interferon; r: Ritonavir boosted; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; TVR: Telaprevir.

treatment duration, a favourable side-effect profile (similar to that observed in mono-infected individuals), and convenient dosing schedules. The genotype 3 now appears as the most challenging HCV genotype to treat, as few of the newer DAAs have potent specific antiviral activity. This is important as genotype 3 is more common amongst PWIDs, who also have a substantial rate of HIV co-infection[111,112].

The effectiveness of DAA-based therapy does not appear to differ between HCV mono-infected and HCV/HIV co-infected individuals according to data from different trials, as shown in Figure 1[93,94,100-103,105-110,113-126]. For that reason, experts recommend that the same DAA-based regimens should be used in HCV/HIV co-infected individuals as those used in HCV mono-infected individuals[127,128]. The same position is held by the European Association for the Study of Liver, with a note for attention to potential drug-drug interactions[129]. In the United States, the pertinent guidelines consider HIV co-infected patients as one of four "unique patient populations"[130]. The United States Food and Drug Administration regards the HCV/HIV co-infected population as "a population with unmet medical needs"[131]. It warrants that industry sponsors for the development of DAAs to present specific clinical trial data on drug-drug interactions with the antiretroviral agents and the safety for HIV infection. In our opinion, drug developers must make sure that such recommendations do not lead to unnecessary delay in the licensure and availability of the newer agents for HCV/HIV co-infected individuals.

Routine screening for hepatitis C infection in HIV-infected individuals allows for many cases of acute hepatitis C infection to be recognised. This is important given the rising incidence of HCV acquisition among HIV-infected MSM in many countries seen over the past 10 years and the high incidence of HCV acquisition among PWIDs. Treatment of acute HCV infection with PegIFN results in a high likelihood of treatment success in mono-infected individuals, although in HIV co-infected individuals the addition of RBV is recommended[132]. Trials are under way for testing new DAA-based regimens for this indication, which might allow for a shorter duration of treatment, fewer side effects and great treatment effectiveness[133].

Reinfection with hepatitis C is not infrequent in certain HIV infected populations, particularly those with ongoing sexual risk-taking behaviour and illicit drug use[134].

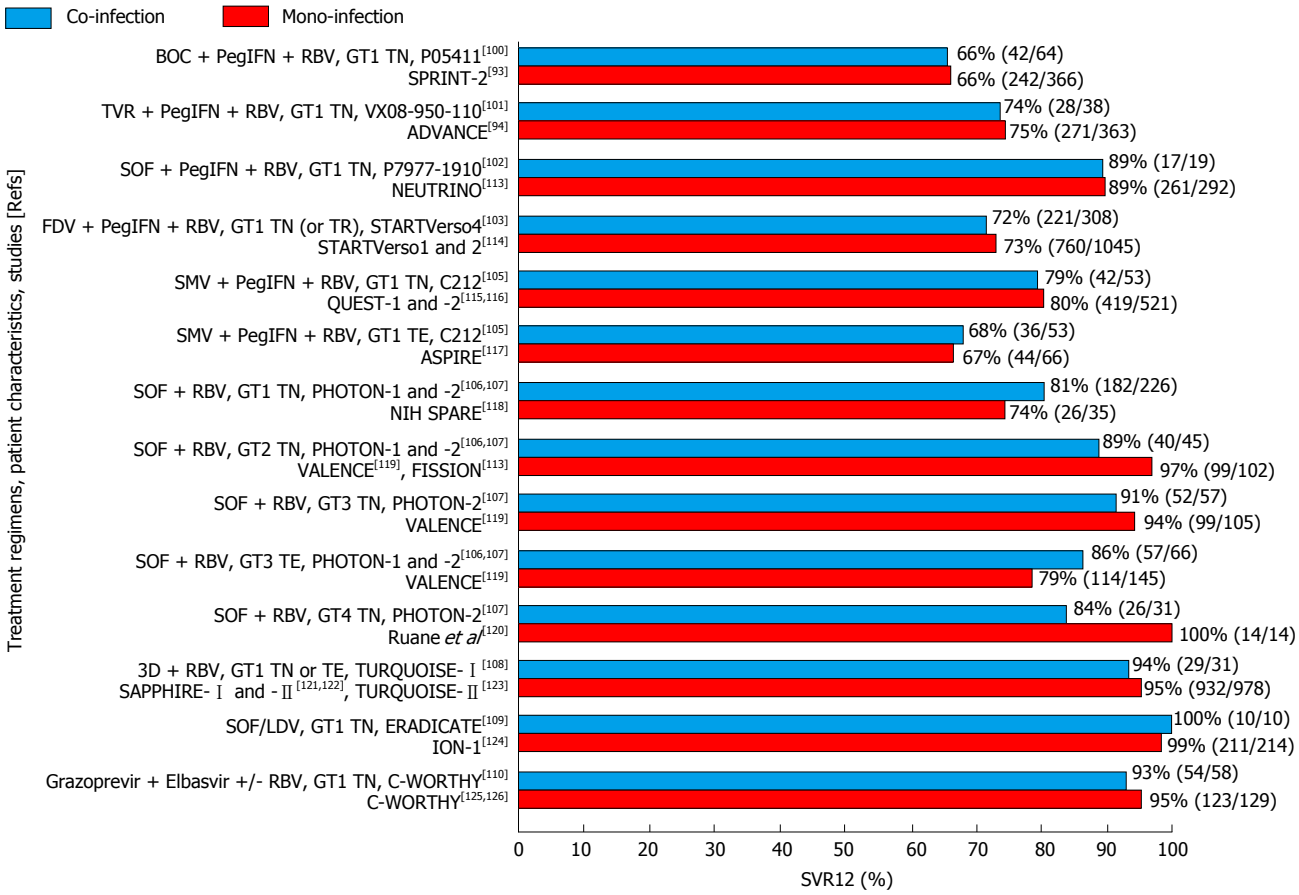

Figure 1 Comparison of week-12 sustained virological response rates between patients co-infected with hepatitis C virus and human immunodeficiency virus mono-infected patients treated with the same regimens containing direct acting antivirals in clinical trials (Data from similar studies were arithmetically pooled). 3D: Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir; BOC: Boceprevir; FDV: Faldaprevir; GT: HCV genotype; LDV: Ledipasvir; PegIFN: Pegylated Interferon; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; TE: Treatment experienced; TN: Treatment naïve; TR: Prior relapse after treatment; TVR: Telaprevir; /: Indicates co-formulation; +/-: With or without.

Reinfection with a new HCV strain can in some cases complicate the assessment of the effectiveness of treatment against hepatitis C if it occurs during or shortly after the completion of treatment[135]. Data from phylogenetic analyses of paired samples from the same individuals are reassuring that true late relapses are generally rare in co-infected individuals, as is the case for mono-infected individuals[136].

SPECIAL ISSUES IN THE MANAGEMENT OF CO-INFECTED INDIVIDUALS

Despite the effectiveness of DAAs in achieving SVR in HCV/HIV co-infected individuals, there are several issues that should be considered in the management of this population. As discussed, the treatment regimens must be selected carefully in view of the potential for drug-drug interactions between several DAAs and antiretroviral agents. This might require changes in dosage, as is the case for daclatasvir when used with efavirenz or boosted HIV protease inhibitors, or even avoidance of certain combinations. Moreover, the pharmacokinetics of different agents might change with different degrees of hepatic insufficiency and there is clearly a need for more data in this field[137]. Polypharmacy is common in HIV-infected individuals and a careful review of all drugs is needed before the addition of DAAs.

The sequence of treatment against each infection in newly diagnosed HCV/HIV co-infection could have been important with regard to treatment with PegIFN/RBV. Although chronic hepatitis C treatment can be treated prior to the commencement of antiretroviral therapy in patients with a high (> 500 per mm^3) CD4 cell count, achieving HIV-RNA suppression first might increase the likelihood of SVR[138]. These considerations might not be important in the era of new DAAs.

Interferon alpha has been shown to reduce HIV-RNA plasma viral load by about 1 log_{10} after one week of therapy and to have sustained activity against HIV over a treatment period of 24-28 wk[139,140]. This effect might be protective in terms of control of HIV in the case that drug-drug interactions result in lower exposure to antiretroviral drugs. With the newer DAAs, interferon-free treatment courses as short as 12 wk have been used and even shorter courses are under investigation. Treatment for such a short duration can mitigate the effect of any potential drug-drug interactions of DAAs

with ARVs on the control of HIV infection.

Adverse drug reactions in patients receiving treatment for hepatitis C might be more common in those co-infected with HIV. This has been a problem with boceprevir and telaprevir, but newer DAAs appear to have a similar safety profile in mono-infected compared to co-infected individuals.

Many of the HIV-infected individuals who are engaged into care have built over time strong relationships with their treating physicians and are well educated about several health issues[141-143]. Their care generally includes screening and immunisation against hepatitis A and B (if at risk) and monitoring for drug adherence and substance abuse disorders. The healthcare structures for these individuals often provide social and psychological support for those with social/financial problems, substance abuse issues or psychiatric comorbidity. Thus, many HIV infected individuals could be well-prepared for receiving treatment for concomitant hepatitis C infection. In the case of MSM, preventing transmission of HCV to their sexual partners might be an additional incentive for a successful treatment outcome. Moreover, HIV-infected individuals receiving long-term antiretroviral therapy are familiar with the need of taking a long-term drug regimen[144]. It may be easier for them to incorporate DAAs in their daily schedule than individuals who have never taken long-term therapy.

TREATMENT PRIORITIZATION

The substantial drug costs of DAAs raise the issue of the access to the new treatments and of treatment prioritisation. Clearly those with advanced liver disease, whether mono-infected or HCV/HIV co-infected are in the greatest need for the new treatments.

In general, HCV/HIV co-infected individuals should be considered as a population in need for treatment of hepatitis C with the new DAAs. The uptake of PegIFN/RBV treatment has been low in this population, due to the presence of comorbidity or other conditions that render many patients ineligible, low treatment effectiveness, difficulties in staging of liver disease, or relative inexperience of some infectious diseases/HIV-medicine providers[145-147]. As mentioned above, the progression of HCV infection is accelerated in the presence of HIV co-infection and a not insignificant minority of individuals can progress rapidly after acute infection. The fact that the HIV population is ageing is another factor that makes treatment of hepatitis C important, as liver-related complications increase in the elderly[148]. HIV co-infected individuals may not have good access to liver transplantation in case that decompensated cirrhosis or HCC develops, while the management of these patients post-transplant is still challenging[149]. Thus, a decision to defer treatment for hepatitis C must be weighed against the above considerations.

The access to the new DAAs for the co-infected population is also important from a public health perspective in order to decrease the incidence of new infections, which is particularly high for certain subgroups[150]. In contrast, many mono-infected individuals have acquired HCV iatrogenically in the distant past, and are of relatively low risk of transmitting the virus to others. The ultimate goal would be the eradication of HCV[151]. Although this necessitates the allocation of substantial healthcare resources, the containment of the epidemic in certain high-risk subgroups through active screening and administration of effective and highly tolerable treatment can be a more feasible goal[150]. Treatment cannot however constitute the only form of prevention; public health efforts including reaching and educating high-risk populations about prevention and treatment, screening for HCV infection and providing good linkage to care are also important in this regard.

CONCLUSION

Although HIV co-infected individuals represent a substantial minority, they have traditionally been considered to be one of the "special populations" amongst the HCV infected ones. This was mainly attributed to the lower likelihood of cure from PegIFN/RBV therapy. Moreover, the uptake of this type of therapy has generally been low due to various complicating factors. The advent of newer DAA-based therapy offers the opportunity of a very high rate of treatment success with short treatment courses and a favourable side effect profile. Yet, the HCV/HIV co-infected population remains one with unmet medical needs, given the faster progression of liver disease compared with mono-infected individuals. Although successful cART ameliorates the course of chronic hepatitis C in HIV co-infected individuals, they retain increased liver-related risk when compared with the HCV mono-infected individuals. Specific issues relating to the treatment of hepatitis C in HIV co-infected individuals, particularly drug-drug interactions, should be addressed in a timely manner in the process of DAA drug development so that the newer treatment options become readily available to this population. Significant and sustained improvements in mortality and morbidity and control of the current HCV epidemic in HIV-infected subgroups could then become a feasible goal.

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